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EPA

AN SAB REPORT: HUMAN EXPOSURE ASSESSMENT: A GUIDE TO RISK RANKING, RISK REDUCTION AND RESEARCH PLANNING

PREPARED BY THE INDOOR AIR QUALITY/TOTAL HUMAN EXPOSURE COMMITTEE

March 31, 1995

EPA-SAB-DWC-95-005

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

Subject: Human Exposure Assessment: A Guide to Risk Ranking, Risk Reduction, and Research Planning

Dear Ms. Browner:

In July of 1993, through the Assistant Administrator of the Office of Office of Policy, Planning and Evaluation (OPPE), the Administrator of EPA requested that the Science Advisory Board (SAB) provide guidance to help EPA improve its readiness to anticipate problems and to develop and implement appropriate strategies for the protection of human health and the environment associated with future risks. The Indoor Air Quality and Total Human Exposure Committee (IAQTHEC) of SAB focused its report, which is attached, on anticipated developments in the science of exposure assessment, and how these developments can be advanced and harnessed to help EPA and the nation achieve substantial risk reductions related to environmental hazards.

Exposure assessments are indispensable for the conduct of effective risk assessments, for the success of epidemiologic research, for the surveillance of environmental and health stresses in populations and ecosystems, and for development and evaluation of the efficacy of risk management activities. Risk management, in fact, almost invariably relies on management of exposures. Current exposure assessment capabilities, however, are hampered by technical limitations in the currently available exposure measurement techniques, by severe limitations of the currently available databases containing exposure and exposure-relevant data, by reliance on numerous assumptions which have been proven incorrect or are not supported by common experience and/or direct observations, and by the current fragmentation and lack of coherence of available models for different media, pathways, chemicals, etc.

As the attached report indicates, however, anticipated developments in both the near-term and the long-term offer significant possibilities for advancement in exposure assessment capabilities in the areas of databases of exposure and exposure-related information, personal sampling technologies (e.g., sensor technologies), biomarkers of exposure and effect, questionnaires, and improved and validated exposure models.

By embracing a leadership role in catalyzing advances in these areas, the Agency can create new capabilities that would allow it to more credibly model population exposures from sources through health risks in support of its risk assessments and risk management activities. Based on the Committee's deliberations, the attached report makes five major recommendations to allow the Agency to play this leadership role:

1) Develop more integrated research programs that develop, validate with field data, and improve models for: a) measurements of total exposure and their determinants; b) exposure distributions across different populations; and c) exposure-dose relationships Biomarkers of exposure and dose will play increasingly important roles in these activities.

2) Develop a robust database that reflects the status and trends in national exposure to current and anticipated environmental contaminants. The contents of this database must match the data needs for modeling environmental fate and transport, for conducting exposure-dose assessments, and for surveillance of environmental and health effects in populations and ecosystems, and as measures of exposure control efficacy.

3) Develop sustained mechanisms and incentives to ensure a greater degree of interdisciplinary collaboration in exposure assessment, and, by extension, in the resulting risk assessment and risk management activities.

4) Develop a mechanism to support the research, validation and application of: a) more sensitive and specific microsensors and other monitoring technologies and approaches; b) the determinants of human exposures; and,

c) the determinants of susceptibility to adverse effects from environmental exposures.

5) Take advantage of exploding capabilities in monitoring technology, electronic handling of data, and electronic communications to establish early-warning systems of developing environmental stresses, so that actions can be taken that minimize environmental and health impacts.

In summary, we believe that an increased recognition of the importance of the exposure paradigm as a fundamental approach for early identification of environmental stresses and the human health and ecological problems they may cause is necessary within EPA in order to effectively and efficiently prevent the occurrence of adverse effects. To this end, we strongly recommend the adoption of the above recommendations.

Sincerely,

/Signed/
Dr. Genevieve M. Matanoski
Chair, Executive Committee
Science Advisory Board

/Signed/
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Science Advisory Board

/Signed/
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Seven reports were produced from the Environmental Futures Project of the SAB. The titles are listed below:

1) Environmental Futures Committee EPA-SAB-EC-95-007
[Title: "Beyond the Horizon: Protecting the Future with Foresight," Prepared by the Environmental Futures Committee of the Science Advisory Board's Executive Committee.]

2) Environmental Futures Committee EPA-SAB-EC-95-007A
[Title: Futures Methods and Issues, Technical Annex to the Report entitled "Beyond the Horizon: Protecting the Future with Foresight," Prepared by the Environmental Futures Committee of the Science Advisory Board's Executive Committee.]

3) Drinking Water Committee EPA-SAB-DWC-95-002
[Title: " Safe Drinking Water: Future Trends and Challenges," Prepared by the Drinking Water Committee, Science Advisory Board.]

4) Ecological Processes and Effects Committee EPA-SAB-EPEC-95-003
[Title: "Ecosystem Management: Imperative for a Dynamic World," Prepared by the Ecological Processes and Effects Committee, Science Advisory Board.]

5) Environmental Engineering Committee EPA-SAB-EEC-95-004
[Title: "Review of Environmental Engineering Futures Issues," Prepared by the Environmental Engineering Committee, Science Advisory Board.]

6) Indoor Air and Total Human Exposure Committee EPA-SAB-IAQ-95-005
[Title: "Human Exposure Assessment: A Guide to Risk Ranking, Risk Reduction and Research Planning," Prepared by the Indoor Air and Total Human Exposure Committee, Science Advisory Board.]

7) Radiation Advisory Committee EPA-SAB-RAC-95-006
[Title: "Report on Future Issues and Challenges in the Study of Environmental Radiation, with a Focus Toward Future Institutional Readiness by the Environmental Protection Agency," Prepared by the Radiation Environmental Futures Subcommittee of the Radiation Advisory Committee, Science Advisory Board.]

ABSTRACT

This report represents the findings of the Indoor Air Quality and Total Human Exposure Committee study of the opportunities for advances in the field of exposure assessment. The Committee noted that early recognition of the nature and extent of potentially adverse exposures could be of immense benefit in avoiding adverse effects to public health and ecological systems. Opportunities for advancement were noted in key areas of microsensor and microprocessor technologies, the development and understanding of biomarkers of exposure, and the expansion of federal and industry databases on human exposures to toxic substances in the work place and at home. They encourage the Agency to develop integrated research programs to track and apply these developments to monitoring and assessment models, to work constructively to improve and validate exposure assessment models, to collaborate widely with governments and industry, to promote improvements in databases, and employ interdisciplinary teams to address exposure problems. The Committee anticipates that the importance of the exposure paradigm will increase significantly in the future, leading to a combined approach for human health and ecological resource protection.

KEY WORDS: Exposure Assessment, Exposure Monitoring, Biomarkers, Epidemiological Data, Databases.

ENVIRONMENTAL PROTECTION AGENCY
SCIENCE ADVISORY BOARD
INDOOR AIR QUALITY/
TOTAL HUMAN EXPOSURE COMMITTEE

Human Exposure Assessment: A Guide to Risk Ranking,
Risk Reduction, and Research Planning

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1. EXECUTIVE SUMMARY

The Administrator of EPA, through the Assistant Administrator of the Office of Office of Policy, Planning and Evaluation (OPPE) requested that the Science Advisory Board develop a procedure for conducting a periodic scan of the future and choose a few future developments for an in-depth examination of environmental impacts. The SAB accepted the request, called it the Futures Project, and formed an Environmental Futures Committee (EFC) to lead the effort. The objective of the Project was to produce reports and guidance to help EPA improve its readiness to anticipate problems and to develop and implement an appropriate strategy for the protection of human health and the environment now and in the future.

The Environmental Futures Committee invited each of the SAB Standing Committees to write a report on future developments in their areas of expertise. The Indoor Air and Total Human Exposure Committee (IAQTHEC) focused its report on anticipated future developments in the science of exposure assessment, and how these developments can be advanced and harnessed to help EPA and the nation achieve substantial risk reductions related to environmental hazards.

The introductory chapter (chapter 2), summarizes the scope and recent history of the science of exposure assessments and EPA's role in them, the four major reasons why exposure assessments are conducted, i.e., risk assessment, epidemiologic research, surveillance, and risk management; and the basic rationale for the selection and use of the three current approaches to the conduct of assessments, namely direct measurements, indirect measurements, and mathematical modeling. For the near-term, i.e., 5 years, the report identifies rapid technological advances in sensor technologies, computer capabilities and communications networks as developments that will present many opportunities for improved quantitative exposure measurements, for assembly and analysis of large databases of exposure information (including time-activity pattern information), and for more highly integrated computer frameworks for modeling population exposures from source through health risks. For the longer-term, i.e., 20-30 years, the report postulates that advances in monitoring technology could provide real-time information to institutions and individuals in feedback loops that will be able to quickly affect controls and/or for individuals to modify personal behaviors affecting exposures. Advances in exposure assessment will help to provide a sound scientific basis for ranking environmental risk and for developing effective risk management policies.

Chapter Three discusses the constraints affecting current human exposure assessment. The weaknesses that are highlighted include the severe weaknesses of the currently available databases containing exposure and exposure-relevant data, the reliance by EPA on exposure assessments based on numerous assumptions which have been proven incorrect, or are not supported by common experience and systematic verification by direct observation, and the current fragmentation and lack of coherence of available models for different media, pathways, chemicals, etc.

Chapter Four focuses on developments and prospects for improvements in exposure assessment in five areas: databases, personal sampling, biomarkers, questionnaires, and improved and validated exposure models. The report emphasizes the need for more comprehensive exposure databases and outlines four steps that should be taken: 1) making exposure monitoring reflect a theoretical framework; 2) establishing an ongoing program of trend monitoring; 3) organizing exposure research to more effectively integrate models and measurements; and, 4) improving coordination between federal agencies. Targeted surveys and improved uses of regulatory compliance data are identified as two complementary technical approaches to meet some of the above goals. In the area of personal samplers and monitors, the report highlights the need to obtain measures of breathing rates or exercise patterns concurrent with air measurements, the need to develop personal monitoring devices for dermal exposures, and the need for techniques to obtain better information about contaminant ingestion. Biomarkers of exposure and of response are discussed as future tools for exposure assessment that will be technically valuable yet ethically thorny. Major advances in questionnaire technology are described as requiring substantial improvements in applications of behavioral science, although increasingly automated methods involving computer and video administration can be anticipated for collecting useful data on personal activities. Finally, the chapter emphasizes the need to validate exposure models, to link multiple models into comprehensive integrated models, and to improve the efficacy of models as tools for prioritizing the major routes and media of concern.

Chapter Five presents a number of findings. First, the report uses some emerging issues for which improved exposure measurement techniques are needed, i.e., environmental estrogens, electromagnetic fields, and particulate matter to illustrate exposure assessment issues. Using the inhalation route as an example, the report discusses a number of areas where substantial progress in monitoring capabilities can be anticipated, including passive monitors, electrochemical sensors, and optically-based particle sensors. In this route, as in others, the report emphasizes the recognition that monitoring of environmental concentrations always needs to be accompanied by monitoring of individual characteristics relevant to the uptake of environmental chemicals. Specific suggestions for EPA exposure research activities are also made. In a 5-year time frame, the report suggests that the Agency support a number of initiatives to facilitate advances in exposure assessment. These include an increased recognition of the central role of the exposure paradigm in risk assessment activities in general, greater linkage of health concerns to research priorities, development of models that can iteratively improve collection of useful data, a strengthening of the partnership between academic and federal scientific communities, and the completion of a scientifically credible design for the National Human Exposure Assessment Survey (NHEXAS). In a 10-30 year time frame, the report calls for developing methods to identify early warning signs of significant exposures by creating and exploiting a broad-based resource of computerized information about concentrations of contaminants and pathogenic agents in environmental media, and for improvement in the capabilities for measurement and analysis of inhalation exposures, especially through miniaturized monitors and other innovative technologies and in microprocessing, and other data storage and manipulation capabilities.

The final chapter of the report makes six fundamental recommendations. They are to : 1) establish a mechanism to develop, validate with field data, and iteratively improve models that *integrate* measurements of total exposure and their determinants, exposure distributions across different populations, and the most current understanding available of exposure-dose relationships, including full utilization of developments in the use of biomarkers of exposure and dose, which are expected to provide significant capabilities in the next decades; 2) establish a mechanism to validate with data, and iteratively improve, the available models for environmental fate and transport of substances; 3) develop a robust database that reflects the status and trends in national exposure and closely matches the data needs for modeling environmental fate and transport, for conducting exposure-dose assessments, and for surveillance for signs of environmental and health effects in populations and ecosystems; 4) develop sustained mechanisms and incentives to ensure a greater degree of interdisciplinary collaboration in exposure assessment; 5) develop a mechanism to support the research, validation and application of microsensors and other monitoring technologies and the determinants of human exposures; and, 6) take advantage of exploding capabilities in monitoring technology, electronic handling of data, and electronic communications, to establish early-warning systems of developing environmental stresses, so that actions can be taken that minimize environmental and health impacts.

In summary, the IAQTHEC has undertaken an examination of prospects for future developments in the field of exposure assessment over the next five to thirty years, and the implications of the expected advances on the quality and utility of procedures for risk assessments and risk management. We envision extensive and highly significant developments during this time frame in the approaches, protocols and technology for collecting and analyzing data on the exposure and related dosimetric factors influencing human health and ecological sustainability.

2. INTRODUCTION

2.1 The EFC Charge

On July 16, 1993, Mr. David Gardiner, Assistant Administrator for the Office of Policy, Planning and Evaluation (OPPE) at EPA, and EPA Administrator Carol Browner requested that the Science Advisory Board develop a procedure for conducting a periodic scan of the future horizon and also choose a few of the many possible future developments for an in-depth examination of environmental impacts.

The SAB accepted the request, called it the Futures Project, and formed an Environmental Futures Committee (EFC) to lead the effort. The Futures Project appeared to be a logical extension of the SAB's 1990 report, Reducing Risk, which stressed the importance of identifying future potential risks to human health and the environment.

The objective of the Futures Project was to produce reports and guidance to help EPA improve its readiness to anticipate problems, to develop an appropriate strategy for the protection of human health and the environment now and in the future, and to implement that strategy. The Environmental Futures Committee invited each of the SAB Standing Committees to consider writing a report on future developments in their areas of expertise and their implications to EPA's abilities to meet its mandates and responsibilities for environmental and public health protection. The Indoor Air Quality and Total Human Exposure Committee (IAQTHEC) accepted this challenge, and focussed its report on anticipated future developments in the science of exposure assessment, and how these developments can be advanced and harnessed to help EPA and the nation achieve substantial risk reductions related to environmental hazards.

2.2 Preparation of the Report

The IAQTHEC discussed the request of the EFC at its meeting on September 8 and 9, 1993, enumerated driving forces in the areas of indoor air and total human exposure, and considered the options for reports in those areas. At its next meeting, on October 28, 1993, the Committee decided to prepare a single report entitled: "Human Exposure Assessment: A Guide to Risk Ranking, Risk Reduction, and Research Planning" as its major contribution to the Futures project. It would focus on the anticipated developments in the science of human exposure assessment, and the implications of these developments for EPA's abilities to improve and broaden its mission and function. The Committee members accepted assignments for the preparation of "think pieces" on various aspects of technological developments, societal trends, and opportunities for improvements in exposure assessments and their applications in risk assessment.

The Committee reviewed the original drafts of the "think pieces" at its meeting on December 2, 1993, prepared a draft outline of its report, and agreed to additional writing assignments on specific topics in the outline. The drafts were reviewed at the next committee meeting on April 7 and 8, 1994, and additional assignments were agreed to. This report is the product of the cumulative efforts of the entire committee, as refined by correspondence and mail reviews of the subsequent drafts.

2.3 The Scope of Human Exposure Assessment

2.3.1 Reasons for Performing Exposure Assessments

There are a variety of reasons for performing human exposure assessments. The major environmental health applications of exposure assessment are:

Risk Assessment: A risk assessment for a population is the product of a hazard rating (e.g., unit risk for carcinogenesis, reference concentrations in environmental media) and an exposure assessment (e.g., one distribution of peak concentrations for acute toxicity and other distributions of long-term averages of concentrations and/or uptakes for chronic disease development). Sizable contributions to the overall uncertainties in the resulting risk assessment can typically arise from either the hazard rating or the exposure assessment. In most current cases, however, the exposures estimates are more uncertain and hence function as the limiting factor in the reliability of risk assessments.

Environmental Epidemiology: Studies of exposure-response relationships in human populations can provide the most direct and relevant data for establishing hazard ratings for environmental agents affecting human health. However, characterizing exposures of populations of interest to environmental agents is a complex task because exposure is usually variable in both time and space, and is influenced by the patterns of activities of the individuals within the population. Furthermore, humans are often subjected to other risk factors that influence their health status, such as cigarette smoke, diet, genetic predisposition, and pre-existing disease. Because of such complexities, and of resource limitations, exposure assessments for epidemiology have often been simplistic. In many cases, they have been limited to dichotomous comparisons between groups on the basis of known exposure to the substance of interest vs. no known exposures, and have been able only to determine if a hazard exists.

When epidemiology is to be used to obtain hazard ratings, it is necessary to obtain reliable and accurate quantitative data regarding the distribution of exposures to the agent(s) of interest, as is done for the development of the National Ambient Air Quality Standards, using both detailed measurement data and complex models for combining time-activity data with airborne concentrations in numerous microenvironments.

Risk Management: When criteria for environmental exposures exist, the EPA and others responsible for maintaining exposures within these criteria need to conduct exposure assessments in order to determine if excessive exposures are occurring and, if they are, to initiate programs that result in appropriate reductions in exposure.

Baseline or Trends Analysis: When operators of potential sources of environmental contaminants seek, and governmental agencies grant, permission to operate processes and facilities, it is often prudent to conduct baseline surveys and periodic re-surveys of exposure to the agents being discharged to the surrounding populated areas. The purpose of such surveys is to determine whether controls on emissions are adequate to avoid excessive exposures in both: 1) the short-term (e.g., imminent exceedance of standards), and 2) in the longer-term (e.g., trends indicating that continued operations will result in eventual exceedance of existing standards) or exposures that may warrant future standards.

2.3.2 Approaches to Performing Exposure Assessments

The three alternate approaches to performing exposure assessments are: 1) direct measurements; 2) indirect measurements, such as biomarkers; and 3) mathematical modelling. Modelling can be semi-empirical, with direct measurements of concentrations in environmental media coupled with measured or estimated exposures to those media through time-activity diaries or estimates, or by the use of more conjectural estimation techniques using models relating source strengths, dispersion models, and assumptions about contacts with environmental media.

Direct measurement entails analysis of contaminant concentrations in air in the breathing zone, the drinking water and diet consumed by the individual. These are generally only feasible for small numbers of people and are only performed when highly precise determinations of exposure or exposure potential are needed.

Indirect measurements consist of less direct estimations of exposure, such as measurements of biological markers based on analyses of biological fluids for the presence of environmental agents, their metabolites, adducts formed, or mediators mobilized. Their use is complicated by uncertainties concerning metabolic rates and pathways and the time intervals between environmental exposures an the collection of the biological fluid that is analyzed.

Another indirect approach is micro-environmental modelling, in which measured or available data on concentrations of the environmental agent of concern in ambient air in the community drinking water supply, in representative collections of diet components, etc., are combined with measured or estimated time-activity patterns and standard assumptions about ingestion are used to calculate peak and/or time-weighted average exposures. This approach assumes that the person of interest is not a source or sink for the agent, and that his/her activities do not perturb the local distribution of the agent. This assumption is clearly not always true. Furthermore, the more one relies on assumptions about transport and contacts with environmental media, the greater the uncertainty in the estimated exposure.

The indirect approaches cited above involve some simple modelling, but *mathematical exposure models*, as generally used and understood, require the use of source strength data, environmental fate and transport models, and population exposure distribution models. These models usually incorporate some broad assumptions and rely on a variety of nominal or default assumptions concerning estimated and derived constants for transport and transformation equations and coefficients. This modelling approach, although widely used, is only substantially justifiable for range-finding risk assessments, where one need to know the extent of the exposures within one-to-two orders of magnitude.

2.3.3 Selection of Approach for Specific Application

When there is less margin for acceptable uncertainty, then either direct measurement or indirect measurements with fewer degrees of uncertainty are needed, and decisions must be made about what to measure, with what sensitivity and specificity, as well as when and how often. The exposure assessor must be prepared to justify the sampling and analytical protocols in relation to the importance and value of the results as they relate to the decisions to be made using them, as well as the accuracy and precision that will be required to meet the data quality objectives.

In some cases where sample collection is relatively inexpensive, opportunities for follow-up sampling uncertain, and analytical costs are high, it may be desirable and cost-effective to collect many samples and submit only a small subset of carefully selected samples for detailed analyses. The balance of the samples collected can be archived for future reference and analyses, provided that sample stability, access, and protection again loss can be assured. These considerations apply to both environmental samples (air, drinking water, food) and biological samples (blood, urine, tissues, etc.), although the latter may require more elaborate storage and arrangements for access.

2.4 Human Exposure Assessment: Historical Development

The principles of Exposure Assessment and their application to environmental problems have evolved considerably over the past 40 years. The basic practice of measuring human contact with a contaminant over a period of time has matured, building upon its origins in the field of industrial hygiene. Historically, the concentrations of materials present in the community environment usually have been much lower than those found in the work place. However, for some pollutants, the duration of exposure in the community may be longer. These differences have limited the direct transfer of occupational exposure measurement techniques to community exposure assessments.

During the 1970s and early 1980s concerted efforts were made to improve the methods used to measure personal exposures within the general population. At the same time, it was recognized that individuals spend most of their time engaged in activities in which air contaminants generated indoors may dominate their overall exposures. Such contaminants could include unvented indoor combustion products, residues of sprayed materials such as personal care products, pesticides, cleaning materials, contaminated house dust, etc. There were also problems encountered when trying to apply conventional ambient sampling and analytical protocols and equipment to analyses of indoor environments, e.g., indoor air. A series of indoor air monitors was developed for application to the estimation of exposure within specific types of community "microenvironments," such as residences and public buildings. Devices for measuring personal and microenvironmental exposures also received attention for development and use within epidemiologic studies.

The application of risk assessment techniques to the identification and control of environmental problems began at EPA during the mid-1970's. One of the major elements of this process is exposure assessment. By 1980 it was realized that adequate databases for completing reliable assessments did not exist for any route of exposure, and that exposure assessment was one of the weakest links in the risk assessment process. This led a National Academy of Sciences - National Research Council (NAS-NRC) report to state, in 1983, that "current methods and approaches to exposure assessment appear to be medium-and route specific ... exposure assessment has very few components that could be applicable to all media." Fortunately, **this point is no longer true today**.

The first total human exposure assessments were led in the 1980's by the EPA-sponsored Total Exposure Assessment Methodology (TEAM) studies. The results of the TEAM studies pointed out that multi-disciplinary scientific analyses were needed to inter-relate and prioritize the components of an exposure assessment, including: time-activities, measurements, and biological markers. Further, it became clear to a number of individuals and organizations that, to truly advance exposure assessment within the risk assessment process and other venues, basic principles needed to be firmly established and presented in a systematic fashion. Such concerns led to a series of National Research Council (NRC) reports which outlined the needs and issues surrounding the development of biological markers of exposure. A publication in 1991, known as the "white book", provided one of the first comprehensive discussion of fundamental principles in exposure assessment (NRC, 1991). The conceptual framework presented in that document has led to mathematical presentations of individual and population based exposures. It has also led to the development of theoretical models for exposure assessment that link traditional environmental science with toxicology and the expression of disease. This evolution has helped to prime the field. A new professional society (the International Society of Exposure Analysis) was founded in 1989, and EPA has fostered the development of the technology and models, encouraged the measurement of human exposure via multiple media, reduced uncertainties in the exposure assessment process, and issued comprehensive Guidelines for Exposure Assessment (EPA, 1992b). The EPA Office of Research and

Development has formed a Division of Exposure Assessment which is leading the development of a National Human Exposure Assessment Survey (NHEXAS), discussed elsewhere in this report.

2.5 Current Roles of Exposure Data and Exposure Models in the Risk Assessment Process at EPA

When EPA must respond to risk related issues within quite limited timeframes, there are seldom feasible options for exposure assessment other than reliance on exposure models. At other times, there is reluctance to utilize exposure measurement data because of the need to make interpretive judgements about such data, or because of the extra time and effort required to do so in comparison to the time and effort needed to use standard models. Since the models tend to be, by design, conservative, the resulting exposure estimates tend to be greater, sometimes much greater, than the actual exposures. However, the extent to which exposures, and hence risks, are overestimated is unknown because of the almost complete absence of comparisons of exposure estimates derived from models to estimates based on direct measurements.

In this regard, the recent publication of the *Guidelines for Exposure Assessment* by EPA (EPA, 1992b), which foster more direct measurements, may help to create a suitable data base for model evaluation leading to validation or revision. With an increased reliance on exposure assessments based on valid measurements, progress can be made toward the goal of improving the accuracy of risk assessments, as well as providing opportunities for applications in epidemiology and intervention. It is also desirable to do follow-up exposure assessment whenever a problem has been identified and remediation has occurred, to ensure that the problem has been satisfactorily resolved. The additional data collection can also provide opportunities to reduce uncertainties about the efficacy of risk management procedures.

The use of exposure assessment in risk assessment has begun to include applications of pharmacokinetic modeling for predicting doses or reconstructing past exposures. This area holds promise as a way to reconcile the measurements of external markers, which show the potential for delivery of a biologically effective dose, with measurements of biological markers of exposure and/or effect.

2.6 Emerging Opportunities in the Near Term

During the last 10-15 years, there have been rapid technological advances in sensor technologies, computer hardware, software, networks, and communications. These advances present many new opportunities for development of technologies and methodologies for quantitative exposure measurements, for assembly and analysis of large databases of exposure information (including time-activity pattern information), and more highly integrated computer frameworks for modeling population exposures from source through health effect risks.

In the area of chemical sensors, there are multiple possibilities for developing automated and, in some cases, relatively inexpensive real-time microsensors that can be used for measuring gaseous and particulate pollutants in air, soil gases, and water, and for personal and microenvironmental measurements (see Table 1). New materials and coating technologies have the potential for providing the chemical specificity and selectivity needed for such sensors. These new technologies offer the means to do near real-time measurements to understand the variability of exposures over short and long time-periods. Such sensors could also be used to directly reduce exposures by providing immediate exposure information to monitored populations or through linkages to control systems, e.g., air quality monitoring in buildings coupled with ventilation controls or ground water quality.

In many research applications, sensed data from field measurements are already being transmitted over telecommunications lines directly to computer systems for analysis. Such direct transmission reduces chances for errors in recording data. Applications of this technology to measurements of human exposures are now possible.

Table 1. A FEW EXAMPLES OF NEW SENSOR TECHNOLOGIES WITH POTENTIAL APPLICATIONS TO AIR POLLUTANT EXPOSURE ASSESSMENT

Ultrasonic Flexural Plate Wave (FPW) Devices for Chemical Multi-Array Microsensors. Highly sensitive flexural plate wave devices are being developed for *in situ*, real-time analyses of particles and volatile organic compounds in indoor and outdoor air and clean rooms, and in emissions sources. FPW sensors can be batch fabricated using well-developed and inexpensive silicon technology and interfaced with microprocessors that record and analyze the sensed measurements.

Excimer Laser Fragmentation/Fluorescence Spectroscopy (ELFFS). Detection of metals and organics in the ppb range is possible using ELFFS. The method is non-intrusive, fast, and can selectively detect and quantify many metals, metal species, and organics. Major applications are likely to be for monitoring emissions from sources; such information will be of value as input to transport and transformation models to estimate concentrations of pollutants likely to reach human receptors. Although ELFFS is unlikely to have the full selectivity and specificity of grab samples analyzed by gas chromatography and mass spectrometry, such continuously collected source emissions data would capture the variability in emissions from sources that cannot be obtained from current grab-sampling techniques.

Computer Tomography/Fourier-Transform Infrared Spectrometry. This emerging technology will provide the means to characterize spatial distributions and movements of air pollutants in three-dimensions in indoor and outdoor environments. Recent breakthroughs in computer algorithms for the computer tomography have made it possible for this technology to be commercially available within three to five years.

Advances in technology should not blind us to the potential for developing and deploying very inexpensive, passive monitors that can be used to survey population exposures at relatively small costs. The California Department of Health Services, for example, has used passive monitors for radon and for formaldehyde to provide information on exposures of California populations. The development of microsensors for other media, however, needs significantly more research to approach the level of those now available and used for air quality analysis.

Many different kinds of exposure-related models, which take advantage of computer capabilities and large databases of information, have already been developed and are currently available. These include the many multimedia transport and transformation models that provide estimates of pollutant concentrations in exposure media (See Section 3.3), exposure models that combine concentration data with time-activity patterns to estimate exposures, physiologically-based pharmacokinetic models that describe the distribution and metabolism of toxic chemicals (including biomarkers) in the body, and health effects models (e.g., cancer risk models). Such models are typically developed as single models, without consideration of linkages to other models, and are often written in different computer languages and have system designs that are not readily compatible with other models. For more fully integrated exposure analysis, from sources to health effects, integrating frameworks must be developed that more readily allow the output from one model to easily serve as input into other models.

A significant problem in exposure analysis has been the lack of communication and cooperation between modelers and the experimentalists. The consequences have been that models did not get tested, modified, and validated in a systematic way, and measurements are often made without reference to a conceptual framework or hypothesis that could make them useful for producing generalizable results. If we are to identify and effectively reduce the most significant human exposures and risks, we must understand the relationship between exposure and adverse health effects, as well as the cause of such exposures and the control technologies that can reduce the exposures. This can be accomplished only through more integrated and multidisciplinary research on total exposure. Measurements and modeling must be integrated to provide a single exposure analysis discipline, not many. New ways of organizing our research and research institutions and rewarding multi-investigator research will also be needed to foster interdisciplinary research.

Advances in computer and communications networks have already provided greater access to existing databases useful for exposure assessment. Present shortcomings in existing databases, (as discussed in Section 3.1) often reduce their usefulness in efforts to elucidate cause and effect or to plan effective risk management steps. The advanced communications networks that are being rapidly deployed could provide access to information collected for other purposes that would be of value in assessing human exposure. For example, access to computer databases of market information on food, consumer products, and time spent on various activities such as hobbies or commuter travel, could be extremely valuable for inferences about exposures when combined with measurements of pollutants in food, water, consumer products, building materials, etc. Gaining access to such information while ensuring privacy of individuals could, however, be a challenge.

With the rapid interconnection of our society through the "Communications Superhighway," databases, computer models and environmental health information, and in some cases, misinformation, will become more easily accessible to scientists, to regulators, and to the public. On the positive side, rapid and widespread communications could enable EPA to influence changes in exposure-related behaviors of the public through information dissemination. To fulfill its mission of protecting the environment and human health, EPA may have to develop new (non-regulatory) ways of thinking about and communicating risks and control strategies to the public. On the negative side, mis-information can also be easily and rapidly disseminated. An increasingly important need in this emerging era is to ensure the validity and security of databases and information.

In the near future, new insights will inevitably come from combining measurements of the personal environment with measurements of the individual's capacity to interact with that environment. For example, it is technically possible to record simultaneous real-time measurements of specific airborne compounds in an individual's breathing zone, an individual's breathing and exercise rates, and his or her geographic location. As these technologies advance, it will become easier to make these measurements over increasingly larger and more diverse populations. In addition, advances in the analysis of small solid samples (such as food or soil) make it feasible to collect and analyze food, water and soil samples from a given individual on a day-to-day basis. As these analytical technologies advance and the costs are lowered, routine monitoring of these environments will be possible.

2.7 Anticipation of Longer-Term Developments

In the longer term, the science of personal monitoring will provide important tools that could be used for assessing health risks of the population. In addition, the technology of personal monitoring could also provide on-line important information to a given individual. Equipped with advanced sensor technology, the individual will want to interact with it. As personal monitoring technology develops, it will undoubtedly be combined with risk information systems. These systems could be in the form of summary statements, warning alarms, or access to guidance on actions to reduce personal risks. Whatever the case, it is certain that individual risk avoidance behavior will occur. The extent to which behavioral decisions will be informed and useful will depend in part on the additional information provided with this sensor technology. EPA should be involved in the development of these information systems, and provide the public with useful information needed to make rational behavioral decisions affecting personal exposures.

3. CONSTRAINTS AFFECTING CURRENT HUMAN EXPOSURE ASSESSMENT

3.1 Constraints in Current Data Resources and Data Management Practices

There are multiple needs for exposure data throughout the risk assessment and risk management continuum. Exposure data are needed to: 1) establish baseline exposure levels for populations and to observe trends in those levels as a measure of the success or failure of risk management efforts (e.g., regulations); 2) perform surveillance functions, using the data to identify high exposure/high risk groups where public health interventions might be appropriate and effective before harmful effects occur; 3) investigate exposure-response relationships for environmental health hazards (e.g., epidemiologic research); and 4) better inform regulatory decisions by supporting population exposure assessments, cost estimates and other aspects of regulatory analyses.

The bottom line for these applications is the protection of public health. Each requires direct measures of exposure or the monitoring of environmental factors that will permit an estimation of those exposures. To be useful, repositories of exposure data should contain not only measurements of contaminant concentrations in relevant media, but also information about the circumstances that give rise to the concentrations and to potential exposures to those media, i.e., simultaneous measurements of the activities of populations of interest. This section discusses some salient aspects of current exposure databases and the manner in which current assumptions and practices in exposure monitoring affect the nature and usefulness of such data.

The last two decades have seen a sea-change in the availability of methods for sampling and analysis of environmental exposures, as well as in the means to store and manipulate data through ever cheaper and more efficient computers. Coupled with the regulatory legislation of the same period, these changes have triggered an explosion in the volume of quasi exposure-related data collected and stored. Substantial financial, human and technological resources are devoted to this task throughout the nation. However, the quality, availability and usefulness of the resulting data resources leave much to be desired for their application to long-term assessment of exposure and changes in exposure. Present data collection approaches are neither comprehensive nor cost-effective, and the collected data have not been optimally utilized.

Government agencies, particularly the EPA and FDA, are the major collectors of human exposure data, with the notable exception of the occupational environment, where OSHA, NIOSH and MSHA have primary domain. EPA typically monitors contaminants in source emissions (i.e., industrial stacks or discharge pipes), in the environment (i.e., air and drinking water) and, much less frequently, in human tissue or blood (i.e., the former National Human Adipose Tissue Survey). The data, however, are frequently inadequate for estimating exposure in various exposure assessment applications. The monitoring is largely driven by regulatory or legal mandates related to compliance with source emission or environmental standards. Environmental monitoring focused on measuring contaminants in the air, water, food and soil, does not provide actual measures of human exposure.

In addition to meeting regulatory mandates,, government agencies are frequently forced to deal with crises (i.e., "contaminant of the day") forcing them to expend a considerable amount of their time, effort and resources on programs that are re-active rather than pro-active. Furthermore, as a result of the current regulatory structure, the measurement of environmental contaminants is highly compartmentalized among and within various government agencies (OSHA, EPA, FDA, etc.). This compartmentalization frequently results in artificial barriers that limit the ability of any one Agency or industry to assess total human exposure and develop effective mitigation strategies.

Assessing exposures to air contaminants provides a good example of the problems posed by the current regulatory structure. EPA has regulatory responsibility for monitoring community air quality, and OSHA and the regulated industry have responsibilities for monitoring air in the work place. Indoor residential sources, despite their importance (particularly for the susceptible segments of the population), are not assessed on any routine basis by any agency, and are not considered in establishing exposure standards. The ability to foresee and effectively address emerging environmental issues will require such regulatory barriers to be removed, minimized, or adapted in ways that promote multiple uses of the data.

Regulatory efforts frequently separate contaminants by whether they are found in these different media, whether they are ingested, inhaled or absorbed through the skin, and by the environment in which the exposure occurs (e.g., work place, home). Contaminants in multi-environmental media and multi-human exposure pathways, such as pesticides, automotive fuels, polycyclic aromatic hydrocarbons, and heavy metals, are not monitored in a systematic way such that the media and pathway of exposures can be assessed or the actual exposures quantified. A 1992 survey of the availability and utility of existing federally sponsored databases (Sexton et al. 1992), with excluded occupational exposure databases, identified 67 such databases. Of these, 41 collected data in one media and 9 in two media. Databases with data collected in more than one media or pathway are typically associated with special studies rather than ongoing programs. The focus of environmental monitoring needs to shift to an integrated approach. Exposures need to be considered across sources, media, pathways and environments, then tied to population activity patterns. The ongoing National Human Exposure Assessment Survey (NHEXAS) will eventually develop into the first national study to provide estimates of exposures across different media for a variety of environmental contaminants. This integrated approach needs to be further developed as a tool for EPA risk assessments. The results will provide baseline and trend data for incorporation into the process of developing policy and regulatory strategies.

A primary justification for human exposure assessment is to support actions that protect public health and welfare. Seldom, however, are environmental exposure data gathered in combination with measures of dose or effects. The National Health and Nutrition Examination Surveys (NHANES) of the National Center for Health Statistics are some of the few national health surveys that have gathered biomarker indicators of exposure in combination with health outcome data. These studies, however, have relied mostly on questionnaires to assess exposures, with some utilization of environmental monitoring data that were collected independently. Exposure monitoring needs to be linked to indicators of dose (i.e. ,biomarkers) and health or comfort outcomes, as well as to information about the sources and circumstances that gave rise to the exposures. In many ways NHEXAS is being developed in a fashion that parallels, and significantly improves on, the limited exposure metrics that can reasonably be employed in NHANES.

Since environmental contaminants, whether found in the air, water, food or soil, are generally found as part of a complex mix, current efforts to monitor environmental contaminants that focus on single compounds (specific pesticides, individual air contaminants, specific heavy metals, etc.), may not reflect the complex nature of the mix or the toxicity from synergistic interactions among the components. If monitoring efforts are to be tied to effects they must take into account the complex nature of contaminant mixtures

Environmental monitoring networks are designed to assess environmental concentrations of regulated contaminants in areas of suspected high concentrations and media where the potential for large scale exposure exists (i.e., ambient air, soil, and water quality monitoring networks). While these monitoring networks may meet the mandated regulatory needs, they usually do not provide data for the direct measurement of human exposure, or data necessary to estimate human exposure, characterize exposure distributions, or identify high-risk groups. Monitoring locations are rarely selected to be statistically representative of populations or geographic areas. Population time-activity patterns are not measured or considered in site selections, or in the interpretation of data.

Numerous environmental monitoring databases have been established by a variety of federal and state agencies to serve an assortment of needs. Each database has associated with it potential sources of bias, error and inconsistencies resulting from all aspects of the data gathering effort (site selection, frequency of sampling, sampling and analytical methods utilized, etc.). Quality control and quality assurance procedures vary greatly among these databases. Seldom is the documentation for the data presented and the limitations and inconsistencies identified. No standardized procedures exist for the collection or reporting of environmental data. The lack of such procedures introduces considerable difficulties in combining existing monitoring data for the estimation of human exposures.

Furthermore, much of the available environmental data are maintained in formats that are not easily accessible. The systems through which these data are stored, retrieved, analyzed and reported are not designed to be easily accessible and useable by government or nongovernment groups interested in assessing human exposures. Those databases that are more easily accessible frequently do not contain the necessary documentation.

3.2 Constraints in Current EPA Practices

Although EPA's research has pioneered and helped to establish much of the framework and methodology of environmental exposure assessment, these concepts and principles have only very slowly permeated the practice of exposure and risk assessment by the Agency as a whole. To a large extent, exposure assessment for application in risks assessments is still performed under a number of assumptions which have been proven incorrect, or are not supported by common experience and systematic verification by direct observation. These assumptions and their shortcomings are summarized in Sections 3.2.1 to 3.2.9 below.

3.2.1 Time-Activity Patterns

Consideration of the time spent by individuals in different locations and their activities have been incorporated to a very limited extent in exposure assessments conducted for risk assessment purposes. Current practice is generally based on the following questionable assumptions:

1. time-activity patterns are invariant during an individual's lifetime,

2. there are no significant differences in time-activity patterns of the population as a function of age, gender, socioeconomic status, or ethnic origin which may affect exposures, and

3. there are no significant differences in time-activity patterns of the population in relation to regional variability, as well as urban, suburban, or rural place of residence.

In actuality, the amount of time spent in different microenvironments often varies significantly over an individual's lifetime. Young children are likely to spend more time outdoors and to be engaged in physically demanding (play) activities than adults. As the individual ages, the place of activities shifts towards school and work, largely indoors. After retirement, a shift may occur again towards spending more time outdoors, but in leisure activities.

Time-activity patterns at any given age can also change significantly over time due to societal trends. For example, children used to remain at home until school age. With more women working outside the home, however, more infants and preschoolers spend most of their day in child care settings. There is also a trend towards lengthening the school year, which could result in children spending less time in the home or outdoors, or in changed times of the year for school vacations. Children and adolescents are also increasingly involved in structured, competitive sports activities, either indoors or outdoors, for significant amounts of time. The duration and place where these activities are undertaken could impact children's exposures and their inhalation doses associated with elevated ventilation rates. The trend towards telecommuting and the increased number of home-based businesses increases the amount of time spent at home, as compared to a separate work place, for at least some fraction of the adult population. A large segment of the adult population also engages in sports or exercise activities, both indoors and outdoors, during significant amounts of time, for health maintenance or cosmetic reasons. As such adults age, and have more free time, they are likely to engage in less strenuous, longer duration exercise and leisure activities (e.g., daily walks, golf) performed outdoors, resulting in less time spent indoors. Consideration of these societal trends means that activity patterns cannot be considered fixed in time.

Although research in the U.S. and abroad has indicated that time-location budgets are rather consistent (i.e., approximately 90% of the time is spent indoors), there has been inadequate consideration of time-activity pattern variability as a function of socioeconomic status, gender, ethnic origin, or location of residence. For example, population subgroups in lower socioeconomic strata with significant levels of unemployment would be expected to have very different time-activity patterns than those in the middle or upper socioeconomic strata. They are also less likely to engage in the health maintenance and leisure activities previously described. The type of employment also can influence the outdoors vs. indoors time budget (e.g., construction, lawn maintenance). Gender also affects individual time-activity patterns. Even when over half the women with school age children work away from the home, a significant number still remain within the home environment most of the day. There is also limited information on differences in activity patterns which may affect exposures as a function of the region of the country, or urban vs. suburban vs. rural populations, due at least in part, to the lack of activity in behavioral science research. This is a critical gap in exposure analysis.

3.2.2 Exposure Pathways

Although EPA exposure assessments, as applied to risk assessment, have incorporated the consideration that certain exposure sources and pathways may be more important for some population subgroups (e.g., ingestion of contaminated soil by children), current practice is, by and large, based on the following questionable assumptions:

1. source emissions and concentrations of contaminants in media, foodstuffs, and consumer products to which an individual may be exposed are invariant during an average lifetime of 70 years, and

2. the relative importance of different exposure pathways does not change over an individual's lifetime (exception: soil ingestion by children).

3. there are no significant differences in relevant exposure pathways as a function of gender, socioeconomic status, or ethnic origin.

Reformulation of consumer products, e.g., cosmetics, cleansing agents, personal care products, occurs continuously, both in terms of the types and relative concentrations of the chemical constituents of such products. Emissions from mobile sources in particular, but those from industrial point sources as well, have shown a consistent trend of reductions during the last four decades, largely as a result of improvements in technology and regulatory pressures. The types of emissions have also changed in many cases. For example, benzene and other aromatic compounds have replaced tetraethyl lead as engine antiknock additives, with the consequent changes in airborne lead and benzene concentrations, as well as the exposures associated with mobile sources. Changes in the types and relative consumption of different fuels as well as improvements in combustion technology have also resulted in reductions of airborne concentrations of some pollutants such as sulfur oxides and particulate matter. As a result, exposures have changed both qualitatively and quantitatively well within the generally assumed 70-year life span, and current models do not account for increasing life expectancy.

The types and relative proportions of different foodstuffs in the diet and, consequently, food consumption-related exposures are generally assumed to be constant over a lifetime after infancy. However, food preferences can vary significantly with the age of the individual, as well as with societal trends. Young children may consume proportionally larger amounts of fruits and milk in their diet as compared to adults. Adolescents may consume significantly larger amounts of "fast" or "junk" foods. As adults, they may become more aware of the importance of a healthy diet and reduce their intakes of such foods, fat, and meat, and revert to an increased consumption of fruits and vegetables. Advice regarding what constitutes a healthy diet also changes over time, therefore affecting exposures as well. In addition, a significant fraction of the population at any given time may be on special diets (e.g.; weight reduction diets).

Dietary sources of exposure also vary over time as a result of changes in agriculture and food production practices. For example, pesticides, herbicides, and other chemicals used in the production, preservation and processing of foods vary as a result of regulatory and market pressures. New food products are introduced into the market place constantly, affecting dietary exposures. The levels of contaminants present in locally grown foods may not be a good indicator of dietary exposures for a particular population. Foods grown in one area of the country are distributed nationally; food imports have also increased significantly as a result of increased trade. The types and relative amounts of foods consumed also vary according to socioeconomic status, ethnic origin, and gender.

3.2.3 Lifestyle and Other Personal Factors

Current EPA practice in exposure assessment assumes that:

1. in general, lifestyle and/or other personal factors do not impact exposures significantly.

2. lifestyle and/or other personal factors which might impact exposures do not vary significantly throughout an individual's lifetime or across the population.

Lifestyle factors will significantly affect exposures. The most notorious behavioral factor with a strong influence on exposures to a wide range of contaminants is, obviously, smoking. But other lifestyle factors are also potentially important. Dietary intakes of benzo(a)pyrene may not only be strongly affected by food preferences, but can also be strongly affected by the method used to cook the food. Any lifestyle factor affecting time-activity patterns will also affect exposures. For example, the choice of using a personal motor vehicle or public rail for work-related commuting to and from the suburbs could significantly impact the motor-vehicle related exposure of commuters, or the use of pesticides or herbicides at home can lead to significant personal exposures to children by dermal contact, ingestion, and inhalation.

3.2.4 Residential Mobility

The typical current assumption by EPA is that *individuals reside in the same location throughout their lifetime*.

The reality is, however, that the U.S. population is highly mobile, with the average family changing residences every 5 to 7 years on average. There may also be differences in mobility associated with socioeconomic status.

3.2.5 Reliability of Predictive Models Based on Sources and Transport

Current EPA practice in exposure assessment is based on the assumption that:

exposures can be adequately assessed by using source emissions or concentrations of contaminants in media and environmental transport models, and a limited number of exposure situations (i.e., scenarios).

The sophistication and complexity of models used for exposure assessment have increased notably over the last decade and has also led to the development of new models that attempt to link exposure to the internal dose of a chemical at a critical target site. However, there is a significant lack of validation of such models with actual data.

All models are based on explicit and implicit assumptions about how contaminants move into, through, and across environmental compartments, as well as on some conceptual framework about the most significant routes of exposure. The weakness of this approach is that, frequently, neither the assumptions nor the model results are validated with actual exposure data. The TEAM results are an excellent example in which measurements of volatile organic compounds in outdoor, indoor, and personal air demonstrated that the long-held assumption that populations living near industrial sources experience higher exposures to these compounds than those living in less industrialized areas was incorrect. The study showed, in fact, that indoor sources dominate exposures to many volatile organic compounds, and that exposures to the study populations were similar and not dominated by the presence of nearby sources. Another example is the assumption that ingestion is the dominant route of exposure for chemicals in potable water. In many cases, major contributions to internal dose derive from dermal contact in bathing or inhalation of vapors and aerosols released in showers and sprays.

Another limitation in exposure model development, as currently done, is that available information on parameters or variables necessary to estimate concentrations and transport through compartments may be lacking, very limited, or even inappropriate for the specific application, adding further uncertainty to the reliability of model outcomes. In these cases, efforts should be made to obtain the appropriate data. By limiting assessment of exposures to specific scenarios and pathways of exposure without validating their importance, these models may fail to recognize important exposure pathways as well as variability across the diverse U.S. population. They do not take in consideration factors such as time-activity patterns which can directly and significantly influence exposures.

3.2.6 Temporal Variability at Specific Locations

Although EPA occasionally includes consideration of long-term accumulation of contaminants in environmental compartments, the Agency often assumes that: *the concentration of contaminants in media remains constant over time.*

As a result of this very questionable assumption, exposures associated with those contaminants and compartments are also assumed to be invariant over time. To a large extent, this assumption is related to the heavy reliance on environmental transport and fate models which are generally based on steady state condition assumptions. Each source has its own attributable effects, independent of other sources. In reality for agents with the threshold-type responses, the responses may differ substantially when multiple sources impact a receptor. Furthermore, concentrations of contaminants in media can either increase or decrease over time due to changes in environmental conditions or human activities which may result in either enhancing or diminishing the release and bioavailability of the contaminant in specific compartments.

3.2.7 Independence of Exposures to Multiple Individual Agents and Sources

Current EPA practice is based on the assumption that: *exposures can be assessed on a chemical by chemical basis, or, conversely, that there are no significant interactions between simultaneous exposures to more than one agent*.

There is, however, significant evidence that suggests that this assumption is not appropriate, since effects from a combination of agents may be more or less than additive. More information is needed on multiple chemical exposures and their effects. For those cases in which such interactions are known to be important, the implications for public policy can be substantial. For example, in the case of the risk from radon exposure for smokers, which are almost one order of magnitude higher than for non-smokers, a more cost-effective means of reducing lung cancer, as compared to reducing average population exposures to radon through radon control in all homes with radon >$4_pC/L$ might be to reduce the number of smokers. This would have the added benefit of reducing other health risks associated with smoking, e.g., heart and non-malignant lung disease. The ability to undertake other than chemical-by-chemical exposure assessment is highly dependent upon the state of knowledge of such interactions. Although possible, it is obviously not practical to measure exposures to all potential chemicals simultaneously. However, determination of simultaneous exposures to more than one chemical could be done and would be useful when there is toxicologic information on their combined effects and to guide toxicologic research.

3.2.8 Infiltration of Outdoor Air into Indoor Spaces

Although there has been some recognition that indoor environments are more significant contributors to solvent and NO_2 exposures that outdoor air, current EPA exposure assessment practice is still largely based on the following questionable assumptions:

1. buildings do not significantly affect exposures to outdoor airborne pollutants, and

2. buildings are static and indoor concentrations of airborne contaminants can be modeled using steady state assumptions.

As previously indicated, most of the population spends about 90% of their time indoors. As a result, indoor environments are typically more important in determining exposures to some airborne contaminants than ambient air. Indoor exposures to airborne pollutants are the sum of the fraction of the outdoor concentration which penetrates into a building plus the contribution from indoor sources. The extent of infiltration of outdoor air and contaminants into a structure depends on a number of variables related to the building itself (e.g, type of construction, type of ventilation system and its maintenance), environmental conditions (e.g., season of the year, temperature differences between outdoors and indoors), the type of contaminant (e.g., reactive or non-reactive, small or large particles), and human factors (e.g., opening of windows, obstruction of air intakes to maintain higher temperatures indoors, use of the space for purposes other than the original design). As a result, infiltration of outdoor contaminants can vary significantly from building to building as well as over time for the same building. Steady state conditions are, therefore, unlikely to occur.

3.2.9 Population Distributions of Exposure

Inherent in current EPA practice on exposure assessment are the assumptions that:

1. the population exposure to any contaminant can be described by one of the well characterized statistical distributions (e.g., log-normal).

2. the distribution of exposures in the population is not affected by factors such as socioeconomic status, gender, ethnicity, and lifestyle factors.

EPA generally assumes that population exposure distributions behave similarly because concentrations of contaminants in media generally approach one of the simpler statistical distributions (i.e.,typically a unimodal, log-normal distribution). The idea that, for risk assessment purposes, an acceptable exposure can be established at a certain percentile in the upper tail of such distribution is also based on the assumption of a "well behaved" statistical distribution of exposures.

Figure 1, from EPA's Guidelines for Exposure Assessment (FR 57(104) 5/29/94, 22888-22938) shows the current terminology for describing exposures at the upper end of the population distribution. This guidance replaced armchair and uninterpretable terminology, such as a maximally exposed individual. When total exposures occur via multiple media, and especially when indirect exposures to contaminants emitted into and transported through the atmosphere are involved, the situation can become quite complex. In its recent review of EPA's Draft "Addendum to the Methodology for Assessing Health Risks Associated with Indirect Exposure to Combustion Emissions," the SAB advised the Administrator that Addendum was not ready for release as an "EPA Methodology" for routine regulatory assessments. At this stage of its development it can be useful as an analytical tool to identify the chemicals most likely to accumulate in the environment, the environmental compartments most at risk of excessive accumulations, and the exposure pathways most likely to lead to aggregate risks of concern. The SAB report (EPA-SAB-IAQC-94-0096) also recommended that EPA: 1) develop and implement a strategic plan to collect critical input data for the models and to validate the methodology; and 2) establish a framework to ensure that the entire range of potential risks from stationary combustors are addressed holistically. Implementation of these recommendations would make it possible to validate and use reliable total human exposure analysis models.

Figure 1

Recommended Alternative to Figure 5.1 of the Draft EPA Document

Primary features of Figure 1 are the following:

a. Separation of the semi-quantitative measures of exposure from the quantitative estimators of exposures depicted in the figure.

b. Emphasis on determining or estimating a distribution of population exposure (not concentration) and selection of a default distribution when the actual distribution is not available or too little information can be obtained to estimate the distribution.

c. Identification of several statistical estimators of exposure: 1) 50th percentile; 2) 90th percentile, the "High End", 3) 95th percentile, 4) 98th percentile and a range for bounding estimates.

d. The Bounding Estimate is an estimate of individual exposure or dose where the estimate is intentionally constructed to be higher than the individual in the distribution having the 99.9th percentile exposure. A bounding estimate can be useful in constructing statements that the exposure is "not greater than .....".

* Measured Distribution of Exposure.

** The Default Distribution - in the absence of sufficient data to establish the form of the distribution of exposure (not concentrations) for the population of interest, a default distribution using a log-normal format should be employed. It should be defined on the basis of median and geometric standard deviation values established using the best information available on the concentrations and the human activity patterns that lead to exposure.

presented in Chapter 6 correctly recognizes that uncertainty analysis cannot be done by following a formula, that such a process can range from a very simple to a quite complex process, and that the process requires scientific judgment. Both qualitative (choice of model or measurement method, underlying assumptions, etc.) and quantitative aspects of uncertainty are recognized and clearly presented. The types of uncertainties that must be considered have been clearly identified and the various approaches which may be taken to evaluate and/or estimate uncertainty are scientifically correct and adequate.

While data on population exposures and their distributions are very limited, there is some evidence that population exposure distributions are often skewed, i.e., they may be multimodal because the overall distribution of population exposures is a juxtaposition of different population subgroups exposures). A major reason for this is the influence of societal factors and sex in determining exposures, as previously described. Socioeconomic status (which is also linked to ethnicity, education, gender, and age in the U.S.), for example, is a powerful determinant of where people live, the food they consume, their activities, and their personal habits, all variables that affect exposures. The population subgroups that experience higher exposures as a result of their living conditions and lifestyles may also be more prone to experience the negative health outcomes from such exposures, either because of genetic susceptibility, or as a result of poor health status. Current approaches to exposure and risk assessment cannot either identify or adequately protect these subpopulations.

3.3 Currently Available Models

Up to now, the most thoroughly developed and validated models used by EPA are the recent versions of the NEM models used in support of the National Ambient Air Quality Standards (McCurdy, ISEA, ISEE, 1994). They are also the most data intensive models, and the resources that have gone into the development and validation are not likely to be available for exposure assessment of other environmental exposures.

The NEM models have used measurements of personal exposure as indicators of the potential for the development of future chronic disease. In their absence, environmental fate and transport models can be used to estimate future personal exposures. A comprehensive suite of models that could credibly predict movement, degradation, and accumulation of chemicals in the environment could serve as the common metric for regulatory decisions in the areas of standard development, permitting, site specific risk assessments, site ranking, and cleanup. Unfortunately, there are, as yet, no validated models that meet these goals.

Current models for human exposure assessment provide estimates of chemical concentrations in environmental media, as well as mass flux from sources, through environmental compartments, to human receptor target organs, tissues or cells. Most of the modeling effort has been focussed on the solution of chemical fate and transport equations for the prediction of concentrations in air, food, water and soil. Common pathways of concern include: drinking water, incidental ingestion of soil, inhalation of vapors and particulate matter, and ingestion of fish and garden vegetables.

The following is a brief summary of some of the current applications of fate and transport modeling:[2]

Non-Governmental Models

A recent review article compared the output of ten soil standard models when applied to one site in Vancouver. The authors observed that the models fell into two categories; those with one cleanup number for each chemical regardless of site conditions (absolute approach) and those which would accept site specific conditions as determinants of the chemical specific cleanup number (relative approach). [Jessiman, 1992].

In a summary table comparing significant pathways of exposure across all models, ingestion accounted for 99% of all exposure to inorganics. The other tabulated pathways were dust inhalation, vapor inhalation, and dermal uptake from soil and water. In contrast for organics, dermal contact with soil and water accounted for about 50% of the dose, with ingestion making up most of the remainder. Crop exposure was most often the largest contribution to ingestion for the 23 chemicals examined.

A multimedia chemical transport and transformation model, GEOTOX, was used by McKone (1991) to estimate concentrations of contaminants in air (particulate and gas phase), soil, drinking water and surface water. The model has different exposure pathways pertaining to each of the media when they are considered as sources. Test simulations found that the ingestion pathways of fruit, vegetables, and grains were important contributors to total exposure and dose.

Risk Assistant, developed by Hampshire Research Institute Inc. (Hampshire 1991) with EPA support, is a microcomputer-based software system that contains formulas for 14 pathways of exposure. This software development was funded by U.S. EPA with contributions and reviews by the New Jersey Department of Environmental Protection and the California Environmental

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[2] This summary is abstracted from material presented by the New Jersey Department of Environmental Protection and Energy to the Environmental Risk Assessment and Risk Management Study Commission in March 1994.

Protection Agency. Numerous pathways are considered (drinking water, showering, ingestion of fish and shellfish and homegrown food products, inhalation of vapors and particulates inside and outside the residence, and others), along with numerous media (groundwater, surface water, biota, soil, air, and sediment).

State Models

The State of New Jersey proposed rules for the cleanup of contaminated sites in 1992 (NJR 1992). Numerical soil standards were proposed for over 100 contaminants. The pathways considered were soil ingestion, contamination of ground water, inhalation, and contamination of surface water bodies and the food chain due to erosion of soil. Vapor migration into structures was approached with a trigger level soil gas concentration which would require further investigation.

The State of California model (CalTOX 1993), which is in the Beta-test stage, is potentially the most advanced of all of the models reviewed with respect to exposure, although the transport components are simplified for ease of handling. Intake equations are the same as those used by the USEPA with two modifications. First, there is a multimedia total exposure model. Second, it is used stochastically (instead of a single risk level, a Monte Carlo derived distribution of risk is presented). CalTOX contains fugacity based multimedia fate and transport equations.

USEPA Models (Superfund)

The Risk Assessment Guidance for Superfund, Part B (USEPA 1991), reflects current EPA guidance for developing soil cleanup levels. Pathways of exposure are suggested for two land-use scenarios, residential and commercial/industrial. Default equations are only provided for some of the pathways. It is the responsibility of the risk assessor to find appropriate equations for the other pathways in these two generic exposure scenarios.

Draft Soil Screening Level Guidance, (USEPA 1993) is a response to the Administrator's request for a 30-day study to outline options for accelerating the rate of cleanups at Superfund sites. There are changes in this guidance from the pre-existing guidance (USEPA 1991), such as those involving soil saturation by a chemical as a trigger level for cleanup, and different integration of childhood soil ingestion. A quantitative approach for the soil to groundwater pathway is given. Monte Carlo analysis is suggested for use in this guidance, but only for the groundwater pathway.

Assessing Potential Indoor Air Impacts for Superfund sites, September 1992 (USEPA 1992) was developed to assess the risk for occupants of buildings near Superfund sites. The model accounts for contaminated water or soil leading to volatilization of chemicals and movement through the soil to building interiors because of withdrawal of soil gas to interior living spaces. Several tiers of screening equations lead to quantitative estimates of the relationship between soil and or groundwater contamination to soil gas and, thereby, interior concentrations of contaminants. The only pathway considered in this document is soil gas to building interiors.

USEPA Models (Non-Superfund)

Methodology for Assessing Health Risks Associated with Indirect Exposure to Combustor Emissions, January 1990 (USEPA 1990) is an Interim Final EPA report with quantitative models sufficient for a multi-pollutant, multimedia human exposure assessment. The focus of this document is risk assessment of several pathways arising from of stationary source combustion facilities. as noted earlier, a revised version of this model was reviewed by IAQC/SAB and judged to be inadequate for quantitative exposure assessment.

The Sludge Risk Assessment Branch of the Office of Science and Technology of the Office of Water developed the Standards for the Use or Disposal of Sewage Sludge (40 CFR Part 503) (USEPA 1992a). In these regulations there is a basis and background which describes 5 pathways of human exposure to land applied sewage sludge, including a quantitative approach and the data requirements for the pollutant fate and transport analysis.

4. DEVELOPMENTS AND PROSPECTS FOR IMPROVEMENTS IN EXPOSURE ASSESSMENT

EPA has: 1) conducted many field studies which have contributed to our understanding of human exposure; and 2) has developed many models for human exposure assessment. Under the current organization of scientific research at EPA, however, modeling and field measurement activities are often compartmentalized and there is little or no interaction between scientists involved in these two activities. The consequences are that models do not get tested, modified, and validated in a systematic way and measurements are often done without some conceptual framework or hypothesis that would allow generation of more generalizable results.

Development of effective policies for the protection of human health requires a sound scientific understanding of complex systems. The scientific process of hypothesis generation and testing requires *integrated* use of exposure models and field measurements to develop such understanding. Well-developed and validated models clearly have predictive powers that are useful for evaluating the outcome of alternative proposed policies. However, they also provide the means to integrate field measurement data into coherent theoretical frameworks that allow us to quantitatively link the sources and dynamics of exposure to exposure, dose, and health effect, and to develop control policies that are targeted to the largest sources of exposure and the most significant environmental factors controlling exposure. Models also provide the means to design more strategic and cost-effective field studies for hypothesis testing. Field measurements, in turn, are *absolutely essential* to the validation of models. Comparison of field measurements to model predictions often reveals a lack of understanding of a given exposure pathway and the need to modify the model. Furthermore, well-designed and conducted field measurements provide the "ground truth" for exposure analysis.

In an era of constrained budgets and increased demand for sound environmental policies, it will be essential to integrate the measurement and modeling activities to provide a single integrated science of exposure analysis.

4.1 Framework for the Science of Exposure Analysis

The development, in this report, of a fundamental framework for conducting exposure analyses to be applied in exposure assessments for epidemiology, risk assessment, or risk management purposes has identified two basic approaches for obtaining data on human contact with environmental chemicals: i.e., direct and indirect. An overall schematic diagram of the categories which are included within each approach are shown in Figure 2. Present techniques can reliably obtain information for one or more categories associated with each route of exposure. However, there are numerous gaps, and improvements are needed, especially for indirect approaches, such as biological markers for all media and routes of entry to the body. As discussed in the following, identification of exposures of significance to human health above natural or baseline levels and norms necessitates the collection of data on general population norms.

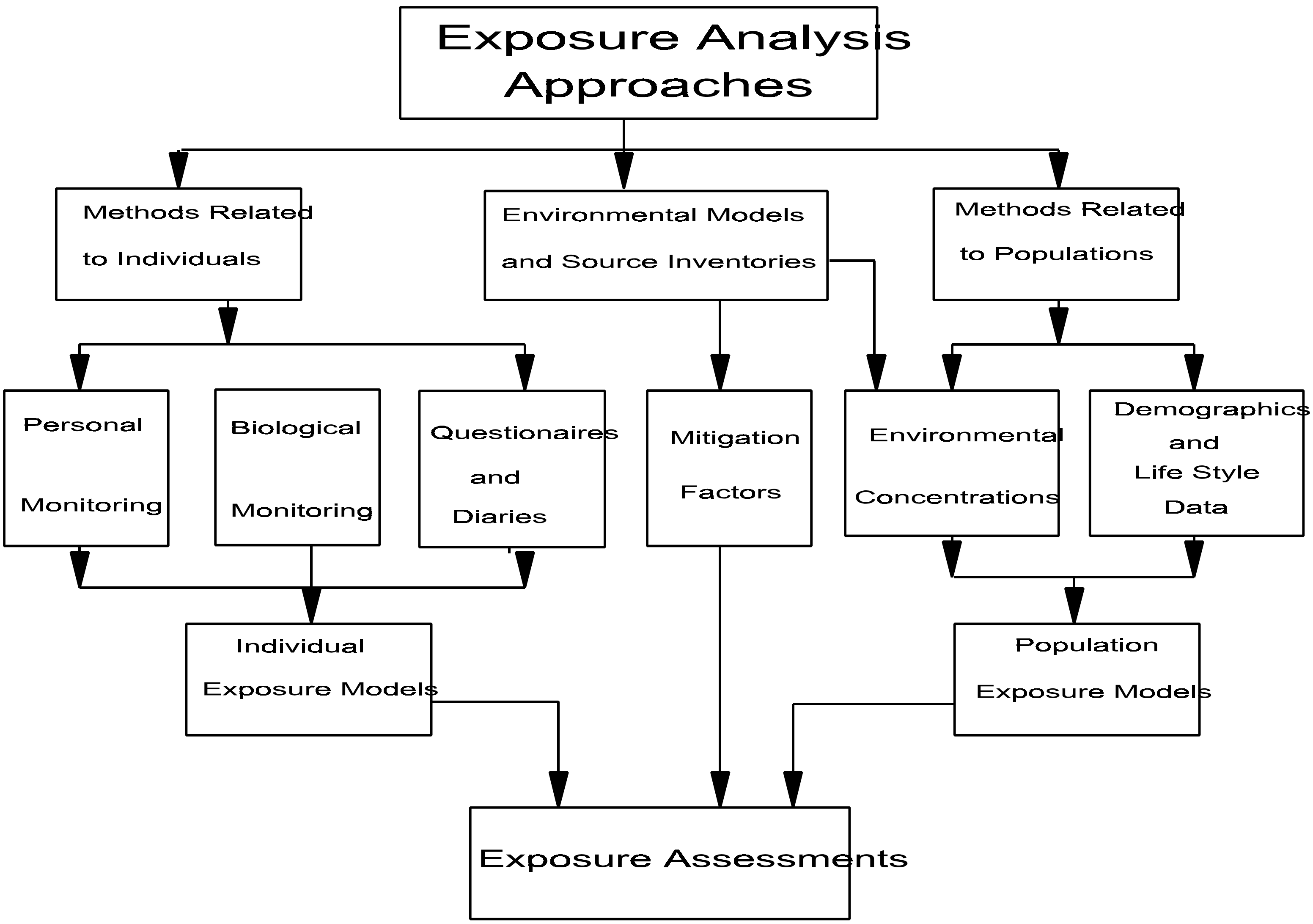

Figure 2. Possible Approaches for Analysis of Contaminant Exposures.

For the indirect approaches, needs have been identified for validation of exposure/dose and microenvironmental models, biomarkers survey instruments, and microenvironmental measurement techniques. The technological needs are quite varied with respect to both sophistication and reliability for each route of exposure. Some devices are relatively well developed for measurements of environmental quality. Unfortunately, there are still some significant problems with the interpretation of measurements made for assessing exposure, since little information is collected on the potential for actual human contact. This discussion will focus on some serious issues related to achieving better techniques for both environmental quality and exposure related problems and how to access and store such data.

The fundamental framework evolving for exposure analysis is also challenging the field to validate models, integrate across routes of exposure, and use pharmacokinetics in quantitative attempts to determine dose from single and multiroute exposure. These types of information are essential for the continued evolution of the measurement technology that can feed back information on the gaps in data indicated by the models, and help reduce uncertainty. Microsensors for all media can be used in such applications.

4.1.1 Databases

Changes in a broad range of domains affecting environmental exposures (fuel usage, consumer products, population demographics, source and type of foods, transportation, type and location of work, population time-activity patterns, environmental monitoring technology, etc.) will greatly influence the nature and extent of effects of environmental contaminants on human health and environmental quality over the next several decades . The ability to anticipate and assess population exposures will be critical in EPA's effort to assess potential risks associated with emerging problems and to develop effective mitigation strategies to reduce or eliminate those risks. The EPA and other federal and local agencies will have to make fundamental changes in their current rationales for environmental monitoring if they are to meet the challenges of the future. The widely accepted approach of highly compartmentalized sampling efforts that are single contaminant, single media, and single pathway based with no clear relationship to the time-activities of individuals, to other exposure determinants, or to at risk populations will not be adequate for addressing future needs. This is especially true for chemicals in consumer products, such as those in motor vehicles, fuels, solvents, and pesticides.

The lack of a comprehensive system for the collection, storage and use of exposure data, as outlined in Section 3.1, should come as no surprise. The patchwork character of our environmental legislation and regulation, and the resulting exposure monitoring and data systems, are a natural consequence of current Agency mandates and organization. The challenge today is to re-orient our environmental protection infrastructure so that it can become more coherent and cost-efficient. The improved collection and use of exposure data, as key elements in risk assessment and management, are integral parts of this overall goal. The focus will always remain on protecting the public health and welfare, but a greater emphasis should be placed on establishing links between total exposure and its determinants, doses and effects. The capability of EPA to assess exposures will in large part be determined by the framework within which it approaches to exposure assessment. Among some of the steps that should be taken to position the Agency to meet the future challenges in human exposure assessment posed by emerging issue are the following:

1. BROADEN THE RATIONALE FOR ENVIRONMENTAL MONITORING TO INCLUDE EXPOSURE ANALYSIS: Environmental monitoring efforts currently underway are generally for regulatory purposes and not guided by an exposure assessment framework. Efforts should be made to restructure or augment the data collection process to assess exposures to complex contaminant mixtures and relate those exposures to dose and ultimately the health, comfort, or ecological endpoint. Limitations or gaps in information should be identified and methods of supplementing current data gathering protocols to make them more relevant to exposure assessment should be identified and incorporated into ongoing monitoring efforts.

2. ESTABLISH AN ONGOING PROGRAM OF TREND MONITORING: Monitoring programs that are explicitly directed toward assessing time trends in micro-environmental concentrations, factors impacting concentrations, receptor time-activity patterns, and time trends in exposures should be established, using both existing data resources and new programs to fill critical data gaps. For human health effects, an objective should be to obtain representative U.S. population distributions of exposure, with emphasis on populations at high risk groups (young, low socio-economic status, minorities, etc.). A stable, long-term monitoring system (production volumes, concentrations, emissions, time-activity patterns, personal exposures, etc.) is crucial for identifying emerging trends (identifying new contaminants, determining the factors impacting transport through the environment, identifying high exposure populations, determining exposures of sensitive populations, etc.), following the time course of current and past environmental contaminants, providing exposure data for risk based priority setting, developing and validating exposure models, developing effective mitigation policies, and tracking progress toward meeting exposure reduction goals.

3. ORGANIZE EXPOSURE RESEARCH TO INTEGRATE MODELING AND MEASUREMENTS. EPA has numerous opportunities to utilize large data sets containing information on concentrations of chemicals in environmental media collected for specific research studies and enforcement efforts, for dispersion model evaluation and/or validation. The exposure assessment group in EPA should be directed to identify and utilize existing environmental data resources for testing EPA dispersion and exposure models, and to look for opportunities to "boot-strap" some additional data collection onto forthcoming monitoring activities in order to provide unique opportunities for model evaluation. These efforts could lead to new models and modifications of existing models that would enhance the credibility and utility of risk assessment and risk management decisions.

4. IMPROVE COORDINATION BETWEEN FEDERAL AGENCIES: Numerous federal agencies are responsible for a variety of environmental monitoring efforts. These efforts are typically conducted independently. Approaches to fostering a greater level of cooperation between these agencies in the design and conduct of their monitoring programs is needed. Cooperation should be sought in standardizing procedures for collecting, storing, analyzing, reporting and providing access to databases for all relevant exposure data. This standardization should include the establishment of a common set of criteria under which environmental monitoring should be conducted and evaluated. Cooperation should also extend to exploring the establishment of integrated data bases where data collected by various agencies is presented in a format suitable for use in a wide range of exposure assessment applications. Such data bases will enhance efforts in risk assessment, risk-management and environmental epidemiology and in determining trends and result in the formulation of more cost effective environmental and health policy. For example, geographical mapping of measured or estimated exposure could be used in combination with effects data to identify potential environmental and health risks and develop testable hypotheses.

Two complementary approaches to accomplish many of these objectives have emerged in the recent scientific literature. One approach seeks to implement schemes that collect, *de novo*, information about total human exposures from the nation as a whole or from particular subpopulations. Naturally, any such project must limit the number of contaminants, populations and exposure routes that are examined, or it becomes unmanageable. The EPA is now in the pilot stages of the National Human Exposure Assessment Survey (NHEXAS). The results of this program should shed much light on the viability and utility of this approach to provide the long-term multi-pollutant and multiple data route needed to assess exposures in coming decades.

A complementary approach seeks to maximize the usefulness of the very large volume of compliance data that are already collected under the mandates of the various statutes and programs. This represents a substantial target of opportunity, given the vast resources that are already being spent on the collection of such data, and because compliance data will continue to make up the bulk of the exposure-related data that will be collected in any systematic way in the future.

It will not, however, be easy to modify routine compliance protocols to enable such data to serve both the practical and short-term needs of fulfilling multiple legal requirements, as well as the longer-term needs of risk assessors and managers to consider exposures. There are challenges at many levels. At the simplest level, it will be necessary to collect more and different information about the circumstances that influence the raw exposure measurements than is now the case. Those who collect the data, but have no immediate need for such additional information, may tend to resist the collection of the critical accessory data. On the other hand, temptations will also exist for excessive data collection, with consequent drain on resources. Also, if multiple compliance data resources are to achieve the coherence necessary to help evaluate total human and ecological exposures, they must be sufficiently compatible and standardized, which is no trivial task. Finally, there are major scientific questions about precisely what additional information is needed, along with raw measurements, to establish closer links between exposure data that are routinely collected and those needed for effects evaluations, dose estimations (e.g., biomarkers), exposure estimates for specific populations or targets of interest, or surveillance, as well as links to sources and pathways of exposure.

Efforts have already begun in EPA and elsewhere to improve the character of the exposure data to be collected in the future, so that it can contribute more fully to the resolution of environmental dilemmas. Two landmark conferences focussed attention on these challenges and produced recommendations to develop mechanisms to tackle them. A workshop designed to examine exposure-related databases in the traditional EPA media--air, water, soil--was held in 1992[3], and an International Conference on Occupational

[3] The proceedings were published in the November/December 1992 issue of Archives of Environmental Health Vol. 47 (6).

Exposure Databases was held in 1993[4]. Both gatherings resulted in important recommendations for the improvement of data resources to meet the broader needs of the future. The ability of the sponsoring organizations and others in the field to form a critical mass and implement these recommendations will have important implications for the 5-30 year time frame covered in the reports on Environmental Futures.

While a danger exists that the current scenario of uncoordinated collection of data will become even more entrenched, the almost certain advances in the technologies used to monitor exposures and the technical abilities to manage vast amounts of data, discussed elsewhere in this report, set the stage for qualitative advances in the exposure data resources that will be available to support environmental and health protection needs.

4.1.2 Personal Samplers and Monitors

The historical development of personal inhalation exposure monitoring has focused on measurements of the environment surrounding the individual. This is still true in most cases. For example, personal monitors of airborne contaminants provide information on concentrations of a variety of compounds near the individual's breathing zone. However these measurements are rarely accompanied by concurrent measures of breathing rates or exercise patterns, even though these measurements are technically feasible. Finally, we know of no commercially available personal air sampler that measures the accompanying composition of an individual's exhaled air - information relevant to the respiratory uptake of the compound(s) of interest.

An analogous, if less characterized, human exposure pathway is dermal exposure. Measurements of the surface composition of skin or of devices attached to the skin can provide useful information on the time-averaged concentrations of compounds of interest. However there is currently no routine personal monitoring of the adhesion to or uptake of compounds through the skin. Further, the lack of time-activity data precludes identifying the factors that reduce adhesion of particles or compounds on the skin.

Whereas inhalation and dermal exposure assessment lacks information on the individual compared with the environment, ingestion exposure assessment historically lacks information on the environment compared with the individual. Instead of a physical sampling device, the instrument of choice is the questionnaire. In many cases, questionnaire surveys can adequately estimate what and how much food and water an individual has ingested (but not how

4 The proceedings of this conference will be published in the April 1995 issue of the Journal of App Occupational and Environmental Hygiene 10(4).

much soil). However information on the specific chemical composition of this ingested material is lacking. We do not have a personal monitor that senses the time averaged composition of ingested food, water or soil. Duplicate diet techniques hold some promise for obtaining information on contaminant ingestion, but the lack of well-designed and non-intrusive protocols precludes implementation within large populations at this time.

4.1.3 Biomarkers

The term "biomarkers" is now widely used to refer to measurements that can be made in biological materials; the quantities measured may be indicators of exposure, dose, susceptibility, pre-clinical disease, and biological injury and disease processes. Biomarkers offer the promise of serving as indicators for these endpoints that can be more biologically appropriate than those utilized in present research approaches. While validated biomarkers have already proven valuable as research tools, their promise as practical indicators of population susceptibility, exposure, or response has not yet been fulfilled. This failure, in spite of intensive research in the last decade, reflects the unanticipated complexity of validating biomarkers; we also lack strategies for efficiently and quickly moving new biomarkers through the sequence that begins with development, continues with validation, and ends with applications in populations. These limitations apply to both biomarkers of exposure and of response.

4.1.3.1 Biomarkers of Exposure

Biomarkers of exposure are indicators of prior contact with an environmental agent, including the agent itself or its metabolites, markers of immune response to the agent or metabolites, or other changes indicative of exposure. Exposure biomarkers are considered complementary to, and more biologically informative than, indirect and qualitative measures of exposure, such as questionnaires. There are diverse types of biomarkers, ranging from simple to complex in measurement requirements and indexing remote to recent exposures. There is also a range of biological relevance among exposure biomarkers: some provide indices that are directly biologically relevant, e.g., level of carbon monoxide in end-tidal air samples and risk of myocardial ischemia, whereas others may not cover the temporally appropriate exposure window, e.g., nicotine levels in biological fluids and lung cancer risk from smoke exposure.

What is the potential of exposure biomarkers for future research and assessment and control of environmental risks? For the near-term, extensive development of new biomarkers relevant to malignant and non-malignant diseases can be anticipated. However, these new exposure biomarkers remain to be validated, and few will be ready for translation to the population over the short-term. Their most immediate application will be in the context of epidemiologic studies of environmental agents. Biomarkers will increasingly become components of the exposure assessment strategies used in environmental epidemiology; efficient research strategies will apply biomarkers to samples of subjects to validate more broadly used exposure assessment methods, and to provide better estimates of dose.

For the longer term, biomarker measurements should become one of the approaches used for monitoring the exposures and health risks of population groups. Exposure biomarkers may be applied to groups with unique exposure or susceptibility patterns, to monitor the population in general, and to document the consequences of exposure assessment strategies designed to reduce population exposures. Exposure biomarkers validated against the endpoint of disease risk, and used in conjunction with other measurements and metrics of exposure, should prove particularly effective in risk assessment.

4.1.3.1 Biomarkers of Response

Biomarkers of response are indicators of injury induced by environmental agents. They may be reflective of the earliest stages of the process initiated by exposure, even at the molecular level, or markers of changes that presage disease at its earliest phases. As for biomarkers of exposure, the near-term need is for basic developmental research. For chronic diseases, such as cancer, only lengthy studies can provide the needed validation against the occurrence of disease as the most relevant "gold standard." For the longer-term, biomarkers of response may serve the same population monitoring purposes listed above for exposure biomarkers. However, the validation process may not be completed for many biomarkers of response over the 30-year time frame considered in this report.

4.1.3.3 Ethical Issues

The ethical issues inherent in applying biomarkers are already a subject of considerable research and discussion, largely centered around use of genetic markers of susceptibility (such ethical issues have been considered in a rapidly enlarging literature; see for example, Kevies and Hood, 1992). However, biomarkers of exposure and response may also pose complex ethical challenges and new and unanticipated ethical dilemmas. Information gained from biomarkers of exposure, response and susceptibility may provide an early warning of high risk or pre-clinical disease; capability for early warning will require a high level of, and an accepted social-regulatory framework for follow-up actions. They may also cause false alarms and needless stress for individuals warned about the presence of uncertain signals.

As biomarkers of exposure are developed over the short-term, a parallel research program is needed on the ethical issues that will inevitably follow application of the markers. Anticipating the longer term is more difficult, but it seems likely that increasingly sensitive exposure markers and increasingly comprehensive understanding of genetic determinants of response will lead to increasingly difficult ethical issues.

4.1.4 Questionnaires

Questionnaires have been a central tool in environmental epidemiology, used to assess exposure, susceptibility, and response. This central role led to an early recognition of the need for standardization and validation. As a result, many of the questionnaires currently used in environmental epidemiology have been characterized as to their accuracy. Major advances in questionnaire technology would require substantial advances in applications of behavioral science, although increasingly automated methods of administration involving computer and video administration can be anticipated for collecting useful data on personal activities. Biomarkers will prove to be a useful tool for validating questionnaires, and vice versa.

4.1.4.1 Source Characterization

For the purposes of exposure assessment, questionnaires have primarily obtained information on contact with sources, e.g., living in a home with a gas stove releasing invented combustion products. Some have incorporated items on activity patterns that may influence exposures, including source use and source avoidance. For the short-term, further advances in use of questionnaires for characterizing sources and exposures should be anticipated. Standardized instruments are likely to be developed that capture key sources and activities in a uniform manner. If applied in representative samples, data from such instruments could begin to better characterize population patterns of exposure. For the longer term, major advances in automated technology, such as activity loggers and factors affecting contaminant release from sources can be anticipated.

4.1.4.2 Diversity Pattern

We are increasingly recognizing the relevance of the population's heterogeneity in environmental epidemiology. Race, gender, ethnicity, education, and income are powerful determinants of both susceptibility and environmental exposures in the work place, at home, and in the neighborhood. Until recently, methods for capturing the population's diversity have received little attention in environmental health research. With the emergence of the concept of "environmental justice and equity" and the recognition of the substantial stratification of our society in the extent of environmental exposures, rapid advances can be anticipated in questionnaire-based methods for assessing racial, cultural, and socioeconomic factors that influence patterns of environmental exposure. For the short-term, application of these instruments should quickly provide new insights into previously overlooked determinants of exposure.

4.1.4.3 Health Status

We are gaining new insights of the need to assess a broad range of indicators of population response to environmental agents. While the focus of research and risk management approaches has largely been on medically relevant outcomes or on overt disease, increasingly sophisticated instruments are becoming available to assess quality of life and health status. Those more holistic data collection approaches have received limited application in regard to environmental exposures; on the other hand, the relevance of loss of well-being and comfort has been made clear by the emerging problem of indoor air pollution. Changing societal expectations in regard to the environment will also force wider application of questionnaires directed at quality of life and health status.

For the short-term, it is likely that environmental health researchers will increasingly incorporate existing instruments into research protocols. However, instruments appropriately tuned for investigating the environment are needed, and they will likely be developed over the short-term.

4.1.5 Improved and Validated Exposure Models

Over the past few years numerous state and federal agencies have proposed comprehensive exposure models for the purpose of regulating discharges to the environment and cleanup of hazardous waste sites. Most of these efforts have proceeded independently of each other. There is much to be gained by reviewing all the approaches for estimating exposure to contaminants for common pathways and reaching some consensus on the best approaches. This could provide a common logic and justification for regulating the many hundreds of chemicals in the environment. By testing the pathway analysis for many chemicals from many sources it would be expected that some chemicals by some pathways of exposure will be predicted to result in unacceptable doses to people. An effort could then be made to validate the critical pathway models. Most of the exposure models in current use have not been validated and also need to be linked within comprehensive models that attempt to characterize exposure and dose at target sites. Further, attempts should be made in the near-term to improve exposure models as tools for prioritizing the major routes and media of concern.

5. FINDINGS

5.1 The Near-Term (5-year) Perspective

5.1.1 Emerging Issues in Relation to Potentially Important Risks

There are numerous emerging issues confronting EPA and the nation for which much of the current uncertainty is related to the extent and nature of human and ecosystem exposures. Some examples are:

1. Environmental estrogens - There is considerable uncertainty concerning which of the numerous chemicals with estrogenic activities are most likely to produce adverse effects, and their time-constants for accumulation in environmental biota, food-chains, and human tissues. Thus, there is considerable uncertainty about what human contacts are, what environmental media to sample, how much to sample, over what sampling intervals, and what analytical protocols to employ to yield sufficient sensitivity and precision for meaningful analyses.

2. Electromagnetic fields (EMF) - A number of statistically significant associations between excesses in a variety of cancers and proximity to electrical power lines have been observed, causing serious public health concerns for people living near high-voltage power transmission lines and for people using powered appliances generating strong local fields (electric blankets, electric shavers, etc.). Unfortunately, the field properties most directly related to possible cancer causation are not known. Candidate factors include field intensity, specific frequency windows, local physical configurations leading to standing waves, etc. In view of the lack of knowledge of the basic biomedical mechanisms by which EMF can contribute to the expression of cancer, it is not yet possible to specify what aspects of EMFs should be measured in exposure assessments.

3. Particulate Matter (PM_{10}) - There is an ever-increasing array of epidemiological evidence linking daily ambient air particulate matter (PM) concentrations to daily mortality rates and indices of morbidity such as hospital admissions for respiratory diseases, emergency room visits for respiratory disease, exacerbation of asthma, and absences from school or work. Various metrics of PM have been used for such studies, including PM_{10} (particles < 10 m in aerodynamic diameter), $PM_{2.5}$ aka fine particles (particles < 2.5 m in aerodynamic diameter) and sulfate ion chemical equivalents

(sum of sulfuric acid, ammonium bisulfate, and ammonium sulfate - all particulates originating from the oxidation of sulfur dioxide vapor). The strongest correlations with health effects are generally with $PM_{2.5}$ and $SO_4^=$. It is important to identify the inorganic and/or organic constituents within ambient PM that drive the associations with health effects in order to guide control efforts by the most cost-effective means.

5.1.2 Capabilities

Market forces will be a major driver with respect to the demand for increasingly more powerful personal monitoring devices. This market will primarily be directed at characterizing work place exposures, as companies recognize the increasing importance of documenting workers' exposures. These monitoring capabilities can be broadly classified by route of exposure - inhalation, ingestion or dermal. As an example of the anticipated progress in exposure assessment, we discuss the inhalation route in some detail, although this does not mean that the other routes are of any less significance or concern.

As mentioned earlier, near-term progress is expected in our knowledge of inhalation exposures with the recognition that monitoring of airborne concentrations needs to be accompanied by monitoring of breathing characteristics. This will provide more accurate information on the extreme exposures within the population being studied and will help to improve models of exposure at the extremes.

In addition to this anticipated progress, there are currently a number of rapidly evolving technologies for monitoring the composition of air in an individual's breathing zone. These include active samplers that collect the entire air sample, or move air past a sensor or through a collection medium. They also include passive samplers that rely on collection of chemical vapors by diffusion onto a sampling substrate. EPA researchers have recently developed a prototype personal whole air sampler for collection of volatile organic compounds. This sampling approach, combined with modern GC/MS technology, will continue to expand our knowledge of the breathing zone concentrations of a large number of compounds. An increasing number of electrochemical sensors have been developed for real-time measurement of inorganic vapors in the work place. As this technology improves its sensitivity, either through improved sensors or development of pre-concentrating capabilities, we will be able to document short-term exposures variations in breathing zone concentrations of a number for gaseous compounds.

Measurement of particle levels in the breathing zone also shows promise of dramatic advancement with the development of personal optically based particle sensors that rely on miniature laser diodes. The requisite sensitivity currently exists to use these devices to measure particle size distribution in real-time. In fact, modern clean room counters are now employing such miniaturized laser diode technology. Coupled with advanced microprocessor capabilities, we will see real-time optical particle sizing for personal exposure assessment in the near future. There is also a serious need for improvement of data on the inorganic and organic constituents of the mass collected or detected by such devices.

In summary, immediate progress is expected in our knowledge of personal exposures with the recognition that monitoring of environmental concentrations needs to be accompanied by monitoring of individual characteristics relevant to the uptake of environmental chemicals. This is true for all routes of intake. Using the inhalation route as an example, it is easily seen that application of current technologies will dramatically enhance our knowledge of personal environments in the near future.

5.1.3 EPA's Recent Role and Activities

In Future Risk (1988), EPA's Science Advisory Board recommended the creation of a human exposure research program as one of ten strategic research priorities for the next decade. Noting the fundamental lack of total exposure research and measurements for virtually all microenvironments and pollutants, the SAB stressed the importance of the exposure paradigm in reducing uncertainty in risk assessments and in strengthening the scientific basis for regulatory decision-making.

EPA's Office of Research and Development responded to this recommendation later that same year by creating a human exposure research program with strong commitment to cooperative research with the extramural research community. This included the establishment of an Exposure Assessment Research Division within the ORD laboratory in North Carolina. Although exposure research funding has been modest, it has facilitated research:

1. to advance the state of the science in exposure measurement and associated statistical methods;

2. to develop activity pattern data as well as single-and multi- media exposure models; and

3. to characterize human exposures to: motor vehicle emissions; particles, aerosol acidity, and PAH (polycyclic aromatic hydrocarbons) in urban areas; lead in urban residential areas; etc.

In addition, EPA's ORD human exposure research community has begun a partnership with federal and academic research institutions to develop protocols that would permit national-scale assessments of total human exposure to be conducted. This program, called the National Human Exposure Assessment Survey (NHEXAS), is supporting pilot and scoping studies through competitive cooperative agreements. They will study exposure at both community and regional levels and will test the scientific validity of current protocols over a period of five years. This work is being done in conjunction with the Exposure Assessment Group in ORD Washington. This group in EPA has advanced data and modeling needs for EPA exposure assessments by publishing the Exposure Assessment Guidelines and an Exposure Factors Handbook.

EPA is poised to expand its exposure research commitment. On July 27, 1994, EPA Administrator Carol Browner presented a plan to Congress that would reorganize EPA's research program into four national laboratories. The specific mission of one of these four laboratories would be exposure analysis.

5.1.5 Five Year Goals

In a 5-year time frame, initiatives should be promoted to facilitate:

1. an increased recognition of the importance of the exposure paradigm as a fundamental approach for investigating environmental and human health problems;

2. creation of a growing body of exposure and dose data and peer reviewed literature for the scientific and regulatory communities;

3. development of an approach that links the health concerns to the research priorities established for pollutants that affect people as a result of exposures in both single and multiple media.

4. development of exposure models that can be used to prioritize single and multiple route exposures, and provide information for improvement of the exposure measurements for current and future chemicals.

5. a strengthening of the partnership with the academic and federal communities to conduct basic and applied research on exposure assessment. These include model validation, instrumentation development and study design issues;

6. the training and availability of increasing numbers of Ph.D. graduates with expertise in exposure principles; and

7. the completion of a scientifically credible design for implementing the National Human Exposure Assessment Survey (NHEXAS), to establish long-term trends in exposure to airborne and waterborne pollutants, pesticides, and household exposures.

8. increased linkages between human behavior, biomarkers and external exposure markers.

5.2 The Longer-Term (10-30 year) Perspective

5.2.1 Methods for Identifying Early Warning Signs of Significant Exposures

Looking beyond the horizon for characterizing exposures, and the resulting human health and ecological risks resulting from such exposures, is a daunting challenge. Issues clearly needing further study during the next five years, such as those identified in Section 5.1, i.e., environmental estrogens and reproductive health effects on wildlife and humans, electromagnetic fields and possible increases in cancer, and airborne fine particles and associated increases in human mortality and morbidity, were not anticipated five years ago.

The only realistic approach for anticipatory exposure assessment for emerging issues in the decades to come is to create and exploit a broad-based data resource of concentrations of contaminants and pathogenic agents in environmental media (air, drinking water, soil and sediments, foods, etc.); emissions data (e.g., toxic release inventories by industry, stack and tailpipe emissions for fossil fuel usage, etc.); time-activity patterns of populations of interest (because of the susceptibilities or likelihood of high-end exposures); concentrations of biomarkers in biological fluids and tissues (environmental chemicals, their metabolites, protein and DNA markers, etc.); species distributions and diversity (in ecosystems under environmental stresses); and health surveillance data (mortality and morbidity rates by cause).

Effective exploitation of the environmental data resources will require further development and validation of: fate and transport models; exposure assessment models; toxicokinetic models; and population dynamics models for ecosystems, as well as implementation and refinement of quality-assurance protocols for all essential data elements, and advances in techniques for pattern-recognition for analysis of significant data trends.

The EPA is the natural home for such an environmental data resource, and needs to take the lead in establishing it. In order to create the basis for the establishment, maintenance, and utilization of this resource, EPA should:

a. Create, within the ongoing Environmental Futures Office, a core group responsible for the planning and organization of the environmental data resource.

b. Establish a mechanism to facilitate coordination in environmental data collection and the distribution within and among the various EPA programs, other federal agencies, state agencies, foreign governments, international agencies, university researchers, and private companies and trade associations.

c. Establish a mechanism to support investigator-initiated research for the development, validation, and application of: sensitive and specific environmental microsensors and biomarkers; models for environmental fate and transport, exposure assessment, toxicokinetics, etc; techniques for pattern recognition, especially with regard to trends analysis for exposures and responses of target populations of concern.

d. Establish a mechanism for communicating, on a continuing basis, to all interested stakeholders, in EPA and elsewhere; the nature and extent of the environmental data resource; the results of analyses, by EPA and others, of the data from the resource; the results of the coordinated research program, in order to inform data generators and users of new opportunities for the collection of data that would extend technical capabilities to: new levels of sensitivity; new compounds; new populations of concern; etc. The communication channels should also describe new challenges for data analysis raised by the outlook panel affiliated with the ongoing Environmental Futures program in EPA.

5.2.2 Technical Capabilities

In this section we extend our assessment of the development of inhalation exposure capabilities to the 10 to 30 year time-frame (see Section 5.2 for discussion of the 5 to 10 year time-frame).

The development of miniaturized vapor sensors will continue to progress. The number of miniaturized GC columns and sensors will continue to expand, as will their detection and resolution capabilities. In addition, new adsorbent materials and coatings will allow better pre-separation of complex, reactive mixtures on the same sensor platform. This detector miniaturization will mean that smaller air volumes can be characterized which, in turn, means that air moving devices will be able to run unattended for longer periods of time. Pushing this latter trend is the rapid development of energy storage devices with increasing energy densities. There is a need to increase the research that can provide microsensors for the other routes of exposure.

Vapor detectors based upon laser spectroscopy are currently employed over relatively long path lengths (e.g. 100-1000 m). Within the next few decades, laser based gas sensor technologies will improve dramatically. Diode pumped lasers requiring neither dyes nor gases have already been developed primarily for military applications. The civilian conversion of this technology will constitute a technology driver. Solid state lasers now exist that are continuously tunable in the 0.2 to 12 m wavelength range with narrow bandwidths (resolving the finest rotational-vibrational features for light molecules). This high degree of spectral resolution allows for a differential absorption LIDAR technology in the mid-infrared spectrum. Within the next few decades, this laser technology will be miniaturized to the point where extremely powerful personal air samplers become feasible.

In addition, microprocessing and data storage capabilities continue to increase. In the future, we will be able to store short-term averages (e.g. one-minute) of hundreds of measured gaseous compounds over weeks or months. In addition, concurrent advances in microprocessor technology will allow real time compound analysis from on-line compound libraries. This could be extended to include on-line source signature libraries as well. Voice recognition technology will also allow the capability for personal interaction with these sensors. The development of personal data communication devices will provide the ability to not only link personal monitors to global positioning systems, but also to link a population of these devices to a central computing facility. This will mean that time-location patterns could accompany chemical sensor data, additional information that would be needed to assess the sources of exposure.

Looking ahead, the future will bring powerful personal monitors that will be able to sense hundreds of compounds in real-time. This information along with personal characteristics (e.g. breathing patterns, location) will be telemetered to central computing facilities for additional analyses. On-board computers will also process individual data and will communicate judgements about risk avoidance to the individual. The near-term prospects are most promising for the inhalation route of exposure. In the longer term, it is essential to promote comparable developments for monitoring dermal and ingestion exposures.

5.2.3 Thirty Year Goals

The attainment of the thirty-year goals outlined below will depend, at least in part, on the leadership and resource commitment provided by EPA. If EPA leadership can envision the technical and programmatic advances that opportunities in the art and science of exposure assessment can provide to environmental risk recognition and prevention, then the Agency can set a high standard for foresight and accomplishment in the federal government as well as serve the public interest.

In a thirty-year time frame and with the emphasis on the importance of the exposure paradigm that is recommended above, a more sophisticated program of exposure assessment should become well established within EPA and research should advance the state of science to the point of:

1. developing a robust data base on the status and trends in national exposure, to current and anticipated contaminants, and the relationship of exposures (and environmental regulations) to indicators of health effects; and

2. demonstrating technologies and approaches that can integrate measures of exposure and dose within a single biomonitoring device.

3. providing exposure and dose models which can anticipate potential problems associated with the introduction of new chemical and biological toxins.

4. establishing enhanced credibility with industry and the public that provides a firmer basis for maintaining and enhancing progress on cost-effective environmental risk reduction.

6. RECOMMENDATIONS

Recommendation One:

Establish a mechanism to develop, validate with field data, and iteratively improve models that *integrate*: 1) measurements of total exposure and their determinants; 2) exposure distributions across different populations; and 3) the most current understanding available of exposure-dose relationships, including full utilization of developments in the use of biomarkers of exposure and dose, which are expected to provide more significant capabilities in the next decades. The determinants of exposure may need to include, as appropriate, factors as diverse as building materials, food consumption, time-activity patterns, behavior and lifestyle.

Recommendation Two:

Establish a mechanism to validate with data and iteratively improve the available models for environmental fate and transport of substances that may pose environmental or health hazards when released to the environment.

Recommendation Three:

Develop a robust database that reflects the status and trends in national exposure, to current and anticipated environmental contaminants. The contents of this database must be designed to closely match the data needs for modeling environmental fate and transport, for conducting exposure-dose assessments, and for surveillance for signs of environmental and health effects in populations and ecosystems and evaluation of exposure control efficacy.

Recommendation Four:

Develop sustained mechanisms and incentives to ensure a greater degree of interdisciplinary collaboration in exposure assessment, and, by extension, in the resulting risk assessment and risk management activities.

Recommendation Five:

Develop a mechanism to support the research, validation and application of: 1) more sensitive and specific microsensors and other monitoring technologies and approaches to measure exposures; 2) the determinants of human exposures, including relevant demographic characteristics, time-activity patterns, location, behavioral and lifestyle factors, and others; 3) the determinants of susceptibility to adverse effects from environmental exposures, including poverty, genetic background, proximity to sources of exposure, etc.

Recommendation Six:

Take advantage of exploding capabilities in monitoring technology, electronic handling of data, and electronic communications, to establish early-warnings of developing environmental stresses, so that actions can be taken that minimize environmental and health impacts. Such mechanisms might, for example, act to better inform societal choices of fuels and transportation, behavioral patterns and lifestyles. They would rely on exposure databases, relevant models, and increased understanding of health and environmental effects for existing as well as new hazards.

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