UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

EPA-SAB-EHC-90-025

OFFICE OF
THE ADMINISTRATOR

August 24, 1990

Honorable William K. Reilly
Administrator
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

Subject: Science Advisory Board's review of the Office of Research and Development's biomarker research strategy

Dear Mr. Reilly,

The Science Advisory Board's Environmental Health Committee met in Miami Beach, Florida, on February 15-16, 1990, to review the Office of Research and Development's biomarker research strategy. The Committee was provided with a document describing the strategy.

Biomarkers, broadly defined, are indicators of variation in cellular or biochemical components or processes, structure, or function that are measurable in biologic systems or samples. They can, in the limited number of instances validated thus far, provide evidence of exposure to pollutants, early indicators of disease, and/or indication of the susceptibility of individuals to a pollutant or disorder. The Agency is to be commended for taking steps to develop a program in this emerging scientific area, which holds the promise of enabling environmental questions to be examined in a more rigorous and cost-effective way.

The charge to the Committee included the following questions:

a. Does the Committee agree with the Office of Research and Development's concepts, definitions, and priorities?

b. Does the Committee agree with EPA's tiered approach for application of effects biomarkers?

c. Does the Committee agree with EPA's recommendations for research?

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d. Does the Committee think that the priority areas for application of biomarkers should be different in the near and far terms?

e. What does the Committee think EPA's obligations should be in the interpretation and reporting of the health significance of exposure biomarkers?

f. What is the utility/validity of biologic markers like sister chromatid exchange and gene mutations for exposure assessment?

The major recommendations of the Committee concerning the document and strategy were: a) the specific aims of the strategy should be stated clearly; b) a rationale for setting priorities should be included; c) the program should be coordinated with similar programs in other Federal agencies; and d) the program should distinguish between exposure and effects biomarkers.

We appreciate having been given the opportunity to conduct this particular scientific review. We request that the Agency respond formally to the scientific advice provided herein.

Sincerely,

Raymond C. Loehr
Chairman
Executive Committee

Arthur Upton
Chairman
Environmental Health Committee

REPORT BY THE SCIENCE ADVISORY BOARD'S ENVIRONMENTAL HEALTH COMMITTEE ON THE OFFICE OF RESEARCH AND DEVELOPMENT'S BIOMARKERS RESEARCH STRATEGY

1.0 Executive Summary

The Science Advisory Board's Environmental Health Committee met in Miami Beach, Florida, on February 15-16, 1990, to review the Office of Research and Development's biomarker research strategy. The Committee was provided with a detailed document describing the strategy (ORD Health Biomarker Research Program, A Strategy For The Future, Briefing Document for the EPA Science Advisory Board).

Biomarkers, broadly defined, are indicators of variation in cellular or biochemical components or processes, structure, or function that are measurable in biologic systems or samples. They can, in some instances, provide evidence of exposure to pollutants, early indicators of disease, and/or indication of the susceptibility of individuals to a pollutant or disorder. The Agency is to be commended for taking steps to develop a program in this emerging scientific area, which holds the promise of examining environmental questions in a more rigorous and cost-effective way.

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e. What does the Committee think EPA's obligations should be in the interpretation and reporting of the health significance of exposure biomarkers?

f. What is the utility/validity of biomarkers like sister chromatid exchange and gene mutations for exposure assessment?

The biomarker research strategy document presented to the

Science Advisory Board's Environmental Health Committee was basically a plan for a plan. It contained much useful and generally accurate information about biomarkers, but it could benefit from additions, clarifications, and other changes, as suggested below. The major recommendations of the Committee concerning the document and strategy were: a) the specific aims of the strategy should be stated clearly; b) a rationale for setting priorities should be included; c) the program should be coordinated with similar programs in other Federal agencies; and d) exposure biomarkers should be distinguished from effects biomarkers.

2.0 Introduction

The briefing document "ORD Health Biomarker Research Program- A Strategy for the Future", presented for review to the Environmental Health Committee, was what EPA representatives called a "plan for a plan". This strategy was presented to the Committee early in the developmental planning of the Office of Research and Development, to get input and ideas from the Science Advisory Board. This "brainstorming" kind of activity is useful to the Agency and is occasionally a part of the activity of the Science Advisory Board.

The biomarker research strategy document outlining EPA's strategy for research on health-related biomarkers appropriately labels such research as relevant, timely, and promising. Insofar as the report is intended to constitute no more than a preliminary planning document (i.e.. a "plan for a plan"), it is reasonably effective when considered in its totality, including its appendices. In several respects, however, the report and the strategic plan it describes could benefit from additions, clarifications, and other changes. These are suggested in the following sections of this report.

Biomarkers are not and should not be an objective of and by themselves. Biomarkers are a desirable and useful tool in the design, execution and interpretation of research in the program areas of EPA. We agree that biomarkers should be used whenever they can advance our understanding of exposure, mechanisms of action, adverse health outcomes, and their interrelations. In general, investigators are already using biomarkers in those instances where they are available and are of clear benefit. It is possible, and even likely, that the biomarkers being used in some of EPA's research could be useful in other areas; for example, biomarkers from health effects research could be used for population exposure assessment or in the evaluation of exposure reduction strategies, and a high priority should be given to this form of cross-fertilization. Sometimes this will require further development, simplification or validation of biomarker techniques.

A large part of the biomarker research strategy document was devoted to discussion of biomarkers which perhaps are best characterized as diagnostic techniques developed for medical applications. These are often invasive, expensive and designed to be helpful in the treatment of individual patients. Because patients expect benefits from such treatments they will tolerate being examined for such biomarkers. In field settings, or even in experimental settings in the laboratory where the individuals are not likely to benefit personally from application of biomarkers, very different criteria of acceptability and utility apply, with psychological, ethical, and legal ramifications

relating to privacy and well being of the individuals examined. The biomarker research strategy document does not address this difference in great detail, although it is presumably important.

2.1 Aims of the Document

The concept of biomarkers encompasses many stages ranging from contact with an environmental toxicant to the resulting ultimate health outcome. Unfortunately, however, the specific aims of EPA's proposed research on biomarkers with respect to these stages are not clear. For example, two reasons for having a biomarkers research program at EPA are listed in page 1-5 of the strategy document as: "(1) scientific and (2) assessment", but the rationale for the first, as distinct and separate from the second, is not explained. The aims need to be clarified.

2.2 Relationship to programs of other agencies

The extent to which EPA's program is intended to complement, rather than to duplicate, the programs of other agencies needs to be brought out more clearly. The breadth of the Federal effort in the area of biomarkers can, in part, be seen in two recent publications from the National Academy of Sciences in the area of pulmonary and reproductive toxicology.[1]

2.3 Information gaps

The usefulness of biomarkers deserves further comment, with additional cogent examples. In the first sections of the report, for instance, few good examples are illustrated. Blood lead levels are mentioned only parenthetically on pages 1-5, and the discussion of bronchoconstriction in asthmatics on pages 3-9 and 5-10 is simplistic at best. Also, as Horstman and others at HERL have demonstrated, the response of exercising asthmatics to SO_2 exposure is highly variable, even in a given individual.[2] Similarly, the change in spirometry on exposure to ozone varies among individuals in ways that cannot as yet be related to health outcomes.[3]

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[1] National Academy of Sciences, Biologic Markers in Pulmonary Toxicology and Biologic Markers in Reproductive Toxicology, National Academy Press, Washington, D.C., 1989.

[2] Horstman, D.H., Seal, E. Jr., Folinsbee, L.J., Ives, P. and Roger, L.J., The relationship between exposure duration and sulfur dioxide-induced bronchoconstriction in asthmatic subjects, Am. Ind. Hyg. Assoc. J., 49:38-47, 1988

[3] Lippmann, M., Health effects of ozone: A critical review, JAPCA 39:672-695, 1989.

2.4 Validation

The sections on research issues and research strategy should give further emphasis to the need for validation of the methods proposed and should delineate more clearly the rationale for setting program priorities and the approaches to be taken for further program planning and implementation. In this connection, Section 4 in the strategy document should be linked more clearly to the preceding sections of the report.

3.0 Response to the Charge

3.1 Does the Committee agree with the Office of Research and Development's biomarker concepts, definitions, and priorities?

3.1.1 Concepts and Definitions

Definitions are clearly important to establishing a multidisciplinary research program focused on biomarkers. Unfortunately, the briefing document itself is inconsistent in the use of several terms, including "biomarker". For example, on page 1-1, paragraph 5 of the strategy document, it is stated that:

> " ... a biomarker must be taken from material from an intact organism or involve a functional evaluation of the organism itself, and it must be possible to interpret the measurement in some way as an indicator of susceptibility, exposure and/or adverse effect."

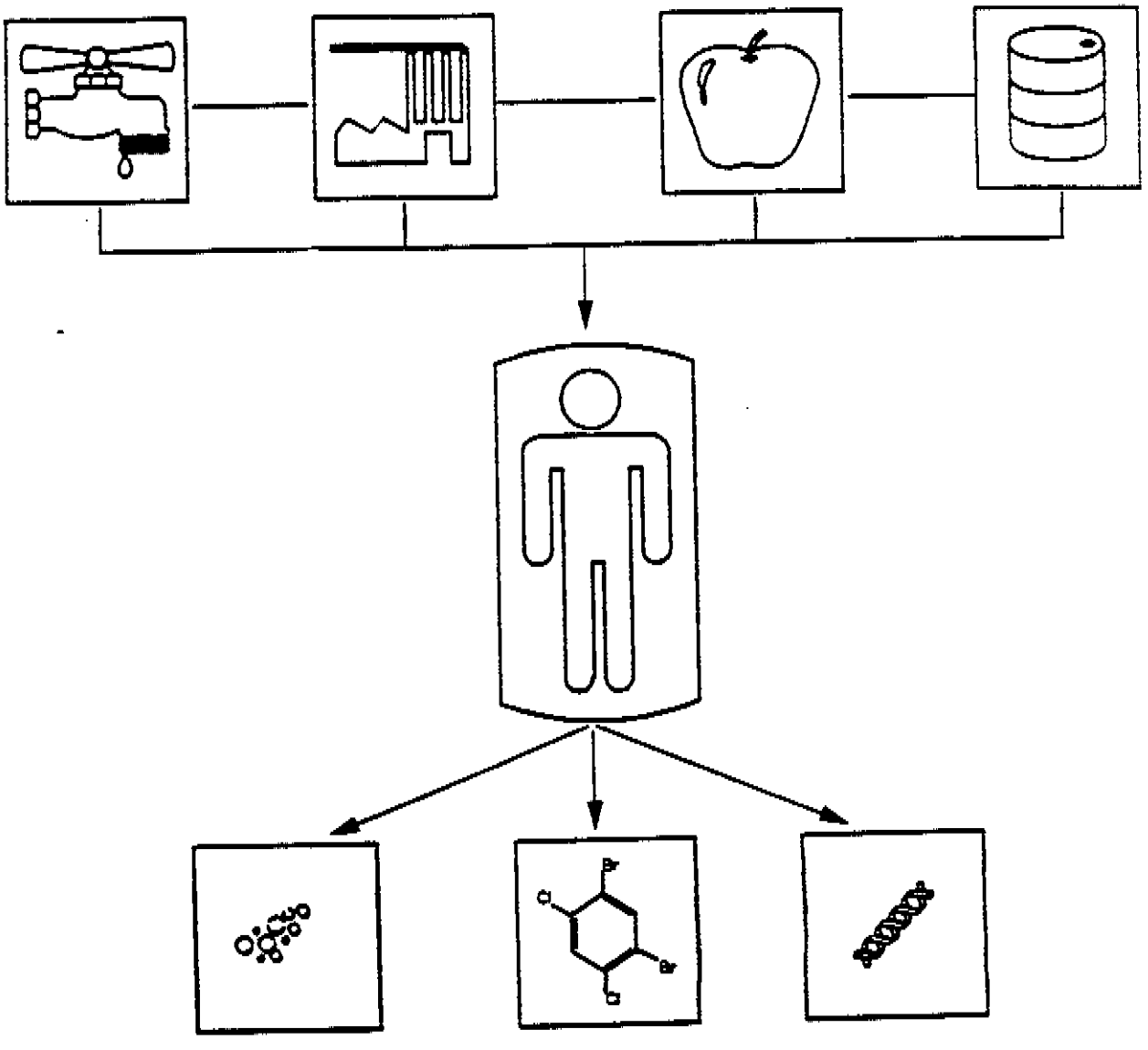
Yet, on page 1-4, paragraph 1, the document describes features of a biomarker which pertain exclusively to humans. This effectively redefines a biomarker as a measure of human "susceptibility, exposure and/or effect". The statement also changes without comment the earlier definition from one which pertains to "adverse effect" to one which includes any "effect". Further inconsistencies crop up from time to time in the document. The Committee recommends that EPA adopt and consistently use a definition for the term "biomarker" that is sufficiently general to include both non-human samples or tests and non-adverse effects and be consistent with the definition of the National Academy of Sciences.

Concerning other concepts and definitions, the Committee believes that additional clarification is needed. This is best illustrated by referring to Figure 1-1 in the briefing document described on page one of this report. The figure indicates that there is a sharp line between biomarkers of exposure and effect. This is not really true. A presentation would be clearer if the vertical line between exposure and effect were removed to indicate that a continuum exists. The Committee recommends that the figure be amended by simply removing the line between exposure and effect. The Committee also recommends that the term "applied dose" be removed from the first box of Figure 1-1 since this term has no place in the discussion and is not equivalent to "exposure" as suggested in the figure.

Several changes should be made in Table 1-1. The term "concentration" is defined with reference to a "volume" of an "ambient" sample. The Committee recommends two changes in this

ORD Health Biomarker Research Program

A Strategy For The Future



Briefing Document for the EPA Science Advisory Board Review February 15 & 16 1990

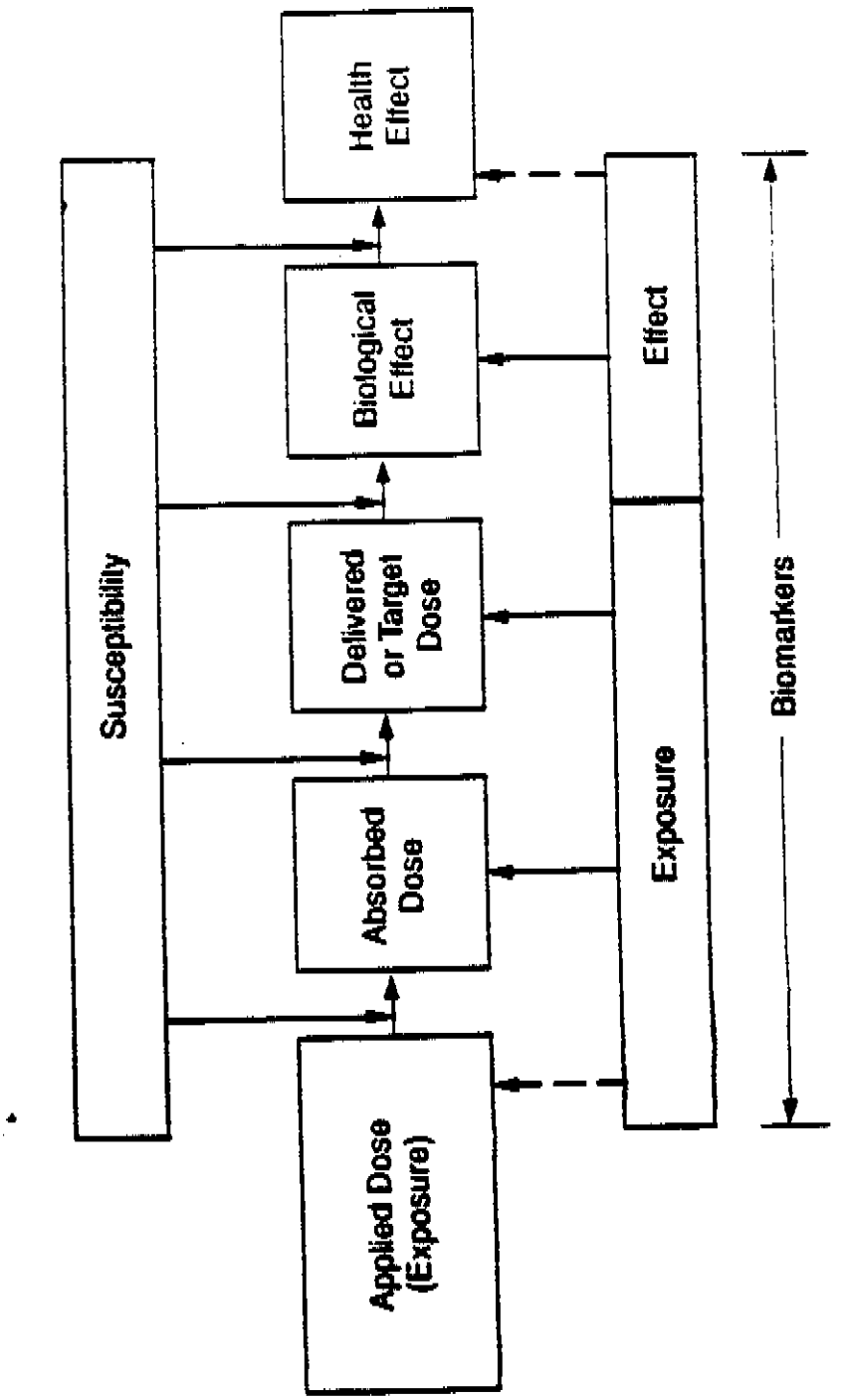


FIGURE 1-1 RELATIONSHIP BETWEEN BIOMARKERS OF SUSCEPTILITY EXPOSURE AND EFFECT

TABLE 1-1 STRUCTURAL DEFINITIONS OF BIOMARKERS AND RELATED TERMS

Term	Definition
Concentration	Amount of material (contaminant) per unit volume in an environmental (ambient) sample
Exposure (Applied Dose)	Contact between an environmental contaminant and a living organism(s) (e.g., human, indicator organism, ecosystem)
Absorbed Dose (Internal Dose)	Amount of material that crosses one or more of the body's boundaries
Delivered Dose (Target Dose)	Amount of the absorbed dose and/or its metabolites that reach the target (e.g., tissue, cell)
Body Burden	Amount and distribution of material and/or its metabolites in the body
Biological Effect	A measurable response in a molecule, cell, tissue or fluid
Health Effect	A biological effect that causes dysfunction, injury, illness or death

definition. First, "volume" should be changed to "volume or mass" so that relative concentrations of mass/mass (e.g. ppm in tissue) can be included. Second, the term "ambient" should be dropped since some samples will be derived from occupational or other environments not generally considered "ambient".

The Committee recommends that the following terms be defined as shown.

a. The term "exposure" neglects the important element of time. The Committee recommends that the term be defined to reflect contact between an environmental contaminant, at a given concentration, and a living organism for a specified period of time.

b. The term "absorbed dose" should embrace the notion of time integration of exposure. The Committee recommends that the term be defined as the amount of contaminant, at a given concentration, that crosses one or more of the body's boundaries in a specified period of time.

The Committee also recommends that the Agency consider changing the term "delivered dose" to "biologically-effective dose", to be consistent with the National Academy of Sciences report.[4]

c. The term "delivered dose or biologically effective dose" should be defined as the amount of the contaminant or its products which reach the target tissue in a specified period of time.

d. The term "internal dose" should be defined as the amount of the contaminant or its products absorbed in body tissue on interacting with an organic membrane surface over a specified period of time.

Finally, in the first paragraph in section 1.3, "susceptibility" is defined as whether an organism is more or less sensitive to future exposure via lessened or increased uptake or biological response. This definition tends to limit biomarkers of susceptibility to only those which were caused by prior exposure. Susceptibility can also be related to a variety of host factors, including genetics, age, and disease status. The Committee recommends that the definition be changed to include susceptibilities that are either caused by prior exposure or preexisting host factors.

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[4] Committee on Biological Markers of the National Research Council, "Biological markers in environmental health research", Environ. Health Perspect. 74:3-9, 1987.

3.1.2 Priorities

Does the Committee agree with EPA's priority areas for biomarkers research?

The Committee had difficulty agreeing or disagreeing with priorities since the document does not establish criteria for setting priorities, and the research recommendations are usually too vague and all-encompassing to be judged on individual merit. The strategy (in section 3.1 of the ORD report) does recognize several factors to be included in selecting chemicals for study such as: frequency of occurrence, uniqueness of occurrence, and quantifiable human exposure. Though this criteria list has merit, it is of limited use for setting biomarkers research priorities, since such general criteria could be applied to many environmental and public health endeavors, such as the development of individual measures of exposure. The report is not structured in a way that allows the reader to list easily the research areas according to priority. For example, there are no priorities set among research areas for cancer effects biomarkers, pulmonary effects biomarkers, etc. Also the report is vague in some parts such as the all-encompassing research, and the inappropriateness of the highest priority research recommendation "Develop pulmonary exposure biomarkers" in the section Effects Biomarkers.

The biomarkers research strategy document paints with too broad a brush in an apparent attempt to include all aspects of biomarkers research, thus losing the well intentioned focus of the document. The Committee appreciates that this may be due to the fact that there is no biomarker research program per se in EPA and thus the authors were attempting to integrate the efforts of many EPA biomarkers researchers in different EPA programs.

The Committee recommends that the next draft of the strategy document include a list of specific criteria for setting research priorities. The criteria should include the needs of EPA's various programs, the need for competency building, and anticipatory research needs. For example, no mention was made of exposure, effect, or susceptibility biomarkers needs in the Indoor Air Quality program of EPA. This should be included as well as an explanation of which of these needs will be met by research programs of other Agencies. Staff should then make the difficult recommendation of the approximate percentage of the EPA's biomarker research budget which should go to the three categories of markers: exposure, effects, and susceptibility (the use of pie charts would be useful). The Committee agrees with the strategy document's implied recommendation that emphasis be placed on exposure biomarkers, since EPA's control and mitigation effort focuses, at least in practical terms, on the direct reduction of exposure as opposed to outcome.

The overwhelming majority of the biomarker program objectives are directed toward cancer. All but a small handful of literature cited provides support for this orientation. Right now there are not many useful or innovative markers for developmental toxicity. The markers in female reproductive toxicity are few in number and inadequate. Those for male reproductive toxicity are good and useful within carefully stated limits, but even they are not highly viable (see footnote 1). These gaps either merit careful examination to suggest possibly useful research or at least a candid statement that they exist as significant gaps in the biomarker program.

Effect and susceptibility biomarker research is justified for those pollutants where health effects data are insufficient for carrying out specific EPA missions, such as standard-setting or risk assessment. Each of these categories can be further subdivided as was done in the document (cancer, pulmonary, etc.), and more pie charts generated, recommending the percentage of the budget to be used for the subcategories. Then a specific list of projects for each subcategory according to priority can be accommodated by the anticipated budget. Although the strategy document considered here is only a "plan for a plan", the research projects should be outlined and more explicitly described than they are in the present draft of the document.

The Committee does not agree that research should be done simply because the expertise already exists. For example, just because one has a "large pulmonary program" is not a sufficient rationale for setting it as a first priority status for biomarker research. Similarly, because "many advances have been made in (cancer research) ... " does not give it first priority status.

Biomarkers competency building can and should be structured around pressing Agency biomarker needs.

3.2 Does the Committee agree with EPA's tiered approach for application of effects biomarkers?

In general, the Committee agrees with a tiered approach for application of both effects and exposure markers. It would be better if this tier concept and proposed tier method were moved to the very beginning of the document to serve as a basis for the research sections that follow. The criteria and prioritization of specific research could then grow as direct responses to needs, establishing the relevance, utility and practicality of the tier stages.

Exposure biomarkers of several types are available now and could be the focus of a priority research effort. For example, lead is a potent postnatal development toxicant and methylmercury is a potent in utero developmental toxicant.

However, great caution is warranted, especially at the outset, to address possible public concern. The issue of public concern pertains to unfamiliarity of the public with the limits of biological tests and their specificity in terms of groups but not necessarily individuals. There is no societal consensus as to the ways these indices should be used. One kind of concern is exemplified by "dioxin", which some feel is a developmental toxicant and even may have adverse effect on spermatogenesis. The concern that happens with women who think they have been exposed to a "teratogen" is to consider elective abortion, because they don't realize that developmental toxicity is considered a threshold phenomenon.[5]

Laboratory animals are essential for research, not only in testing exposure-marker relevance to specific effects, but also may serve as useful human predictors. Revision and updating of markers will be needed as the knowledge and database improve, and animal data could prove useful in this process.

3.3 Does the Committee agree with EPA's recommendations for research both in the near term and for longer range efforts?

EPA's recommendations would be quite reasonable if examined in isolation, and if there were substantially greater resources to implement them. However, even if all the projected resources were available for the development of new, more sensitive biomarkers, they would only permit modest incremental contributions to those already being developed in the Health Effects Research Laboratory of EPA (HERL), the National Institute for Occupational Safety and Health (NIOSH), the Agency for Toxic Substances and Disease Registry (ATSDR) the National Institute of Environmental Health Sciences (NIEHS) and the NIEHS Superfund program project grants at academic centers.

The Committee recommends that EPA focus its limited additional resources on aspects of biomarkers that would represent unique and essential contributions to the application of biomarker techniques for exposure and effects assessments. It could then leverage the results of the very substantial research laboratory developments in biomarker assays already in progress in HERL, NIOSH, ATSDR, NIEHS and their existing extramural grants programs, bringing the more promising of them rapidly into field validations and applications. Early demonstrations of the utility and power of the emerging biomarker technologies will further stimulate additional research and applications in EPA

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[5] See The Way Women Perceive Teratogenic: A Decision to Terminate Pregnancy, Gideon Koren, M. Bologa and A. Pastuszak on pages 373 to 382 of Maternal Fetal Toxicology, A Clinician's Guide, edited by G. Koren, Marcel Dekker, Inc., New York, 1990.

programs and the field in general.

The Committee specifically recommends that a portion of the new EPA biomarkers initiative be devoted to exploitation of opportunities in the substantial and grossly underutilized data bases from the National Health Assessment and Nutrition Surveys (NHANES) and Health Interview Surveys (HIS). NHANES, for example, has large quality-assured data bases on national population samples, including trace metals in blood, serum chemistry, tap water concentration, pulmonary function, clinical data, household characteristics, audiometry, etc. The published work of Joel Schwartz (OPPE) and colleagues of EPA demonstrating highly significant associations between low blood lead levels and elevated blood pressure in adults and reduced stature and hearing acuity in children illustrates the ways in which NHANES data sets can be used to demonstrate the power of biomarkers in EPA epidemiologic research.[6] In addition, during the 1976-1982 NHANES II data collection interval, blood lead levels dropped precipitously, in parallel with the decline in lead content in motor vehicles fuel, showing the utility of blood lead as an exposure marker as well as an effects marker.[7]

Further utilization of the existing NHANES I and NHANES II data bases could yield additional linkages between environmental factors and human disease. EPA could also devote additional resources to permit utilization of the current NHANES III survey data. Finally, EPA should begin anticipating scientific and financial planning for future NHANES surveys, so that additional opportunities for biomarkers can be built into the survey plan.

The biomarkers program should plan to be flexible and opportunistic. Program managers should maintain close liaison with scientists within HERL, other Federal laboratories, and academic laboratories, so that they can facilitate the application of newly developed biomarkers appropriate to EPA concerns directly into field trials being conducted by environmental epidemiologists. The lessons learned in the field trials should, in turn, be used to help guide the laboratory research to extend and improve the capabilities of the biomarkers techniques.

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[6] Schwartz, J., The relationship between blood lead and blood pressure in the NHANES II survey, Environ. Health Perspect. 78:15-22, 1988, Schwartz, J. Angle, C., and Pitcher, H., Relationship between childhood blood lead levels and stature, Pediatrics, 77:281-188, 1986 and Schwartz, J. and Otto, D., Blood lead, hearing thresholds, and neuorobehavioral development in children and youth, Arch. Environ. Health, 42:153-160, 1987.

[7] Lippmann, M., Lead and human health, Background and recent findings, Environ. Res., 51:1-24, 1990

Close associations between the biomarkers program and any newly constituted in-house EPA program in environmental epidemiology will be of mutual benefit to both programs, and provide new kinds of research opportunities.

3.4 Does the Committee think that the priority areas for application of biomarkers should be different in the near and far terms?

The Committee recommends that the priority areas for application of biomarkers be based on the main mission objectives of EPA, in coordination with other programs with responsibilities for exposure assessment and risk assessment. Application of available biomarkers to the assessment of population exposures (status and trends) should have a high priority, especially if this can be accomplished with already ongoing surveillance surveys such as NHANES and HIS.

Exposure over long time periods and many exposure routes, is valuable in understanding disease endpoints in the population. However, many short-term exposures can also have significant effects. Short-term exposures to a pregnant woman and the fetus can be disastrous. Short-term exposures to chemicals such as isocyanates can lead to delayed health effects or permanent lung damage. A biomarker research program to understand chronic exposure and health effects is invaluable. Thus, the Committee recommends that the biomarker research program include a component on potential short-term, as well as long-term, exposure biomarkers.

3.5 What does the Committee think EPA's obligations should be in the interpretation and reporting of the health significance of exposure biomarkers?

The Committee recommends that EPA develop a comprehensive plan for informing all participants of biological monitoring of the results. This pertains to markers of exposure, effect and susceptibility. The Committee recognizes that it is important to provide an interpretation of findings, as well as the findings themselves, and to anticipate the need for follow-up or other ways to remediate the impact of notifying subjects. Care should be taken in the EPA plan to consider the issues of the results of confidentiality and privacy. EPA should be cognizant of other governmental efforts with regard to notifying subjects of biological monitoring.

Additionally, the Committee recommends that EPA develop guidelines to anticipate ethical, legal and social impacts of biological monitoring. This has been recently described by

Ashford et al[8].

3.6 What is the utility/validity of biomarkers like sister chromatid exchanges and gene mutations for exposure assessment?

Bioindicators such as sister chromatid exchanges and gene mutations are not contaminant-specific and thus will not provide precise information on exposure to, or effects of a given contaminant. With proper background data these biomarkers may, however, be useful as indicators of genetic damage due to exposure to complex mixtures of compounds. These types of biomarkers, if sufficiently sensitive, could be useful as tier one screening tools to determine if individuals or populations are exposed to genotoxic compounds. If positive results are obtained, second tier bioassays which are more contaminant specific, could be employed to define the cause of the observed genotoxicity. This multitiered approach with increasing chemical specificity in the higher tiers would provide a useful framework for applying biomarkers.

The Committee recommends the development of a broader data base as to the threshold concentrations at which various compounds make significant increases in these parameters relative to background. This is particularly true of sister chromatid exchanges which have a relatively high background level. The dose-response relationships for various compounds also need to be better established.

The utility of these biomarkers in assessing effects is less well defined. The Committee recommends that longitudinal animal studies be conducted to define more clearly the relationship between these biomarkers and the subsequent onset of well defined health effects. It would also be particularly useful for the Agency to examine the sister chromatid exchange literature with regard to the utility of sister chromatid exchanges as a predictor of carcinogenicity such as the National Toxicology Program (NTP) data base.

3.7 Other Questions: How can multidisciplinary coordination be achieved?

Biomarkers can be used to evaluate exposure, effect, or susceptibility and can be related to the sequence of steps occurring between initial exposure and ultimate effect. Many scientific disciplines are needed to understand how an initial exposure leads to a health effect in individuals or in the

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[8] Ashford et al, Monitoring the worker for exposure and disease; scientific, legal and ethical considerations in the use of biomarkers, Johns Hopkins University Press, 1990.

general population. Many disciplines are also needed to observe health effects in a population, identify the causes of the effects, and understand the mechanisms of action of specific chemicals. The strength of the biomarker research program will be enhanced greatly by the continual exchange of ideas among the professional disciplines involved in biomarker research. The Committee recommends that the biomarker research activities be placed in a structure which will ensure interaction among toxicologists, particularly those with pharmacodynamic and pharmacokinetic backgrounds, chemists, statisticians, exposure assessors and epidemiologists. Each of these disciplines can contribute valuable insights about the utility and validity of biomarkers.

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