The National Toxicology Program (NTP) was established as a cooperative effort within the Public Health Service of the Department of Health and Human Services (DHHS) to coordinate toxicology research and testing activities within the department; to provide information about potentially toxic chemicals to health regulatory and research agencies, scientific and medical communities, and the public; and to strengthen the science base in toxicology. In its 20 years, the NTP has become the world’s leader in designing, conducting, and interpreting various types of assays for toxicity. Through its activities, the NTP provides, directly or indirectly, a large component of the basic scientific data that other federal and state scientific and regulatory agencies, as well as private sector organizations, find useful in responding to issues relevant to the effects of chemical substances on human health and the environment.

In order to meet the responsibilities, NTP strategies and approaches are evolving along a number of fronts. The overall goal of these initiatives is to more efficiently evaluate chemicals for toxic effects using a broad array of test systems and to generate data that strengthen the scientific foundation on which risk assessments are based. The overarching motivation of the program is to use the best science possible in setting priorities, designing and conducting studies, and reporting results in an objective way that best meets the needs of the public and federal and state health and regulatory agencies. We believe that studies which address critical knowledge gaps that create uncertainty in toxicological evaluations offer the best opportunities for preventing environmentally mediated diseases.

Human studies are an increasingly important factor in NTP studies, and opportunities in molecular epidemiology and exposure assessment have produced significant changes in the NTP (1). The human exposure work builds on the National Health and Nutrition Examination Surveys (NHANES), a pioneering federal interagency program in which the Centers for Disease Control and Prevention (CDC) laboratories developed new analytic methods and generated considerable human blood and urine data for exposure estimation of the U.S. population (2). The work also builds on another interagency pilot study lead by the EPA, the National Human Exposure Assessment Survey (NHEAS), which is designing an exposure surveillance system for the U.S. population. This will obtain periodic and systematic measurements of human exposures to multiple chemicals (3). For example, a major interagency initiative is being developed in exposure assessment, which is frequently the weakest link in risk assessments (4). This initiative, in collaboration with the CDC National Center for Environmental Health (CDC-NCEH), the National Institute for Occupational Safety and Health (NIOSH), and the EPA, will quantify the body burdens of chemicals released into the environment and workplace and will address a number of public health issues, as discussed later in this commentary. NTP studies aimed at understanding gene/environment interactions will benefit tremendously from the NIEHS’s Environmental Genome Project, which will characterize the human variability of hundreds of environmentally relevant genes (5,6). This information, taken together with the exposure initiative, will create new directions in risk assessment methodologies for the NTP and should lead to methods for reducing reliance on default assumptions in risk assessment. The following sections address the benefits and opportunities to the NTP that should result from this human exposure assessment initiative (Fig. 1).

**Priority Setting**

With limited resources it is necessary to set priorities for studying the approximately 70,000 chemicals currently in use (7). For example, the NTP, which is the nation’s largest toxicology program, can initiate approximately 10 long-term cancer studies and 10 reproductive studies per year. These studies are lengthy—each study can take several years to complete—and cost millions of dollars. In order to know where to set priorities for use of limited resources, we need to know not only which chemicals are found in the environment, and in occupational exposure circumstances, but what mixtures of toxic compounds are in humans and what...
levels. In addition, trends over time must be determined. We need to know whether body burdens of lead, polychlorinated biphenyls (PCBs), dioxins, volatile organics, and other air and water pollutants are increasing, remaining at the same levels, or decreasing as regulations meant to decrease the levels of these chemicals in the environment are designed and implemented. Workers are frequently exposed to higher levels of many of the 85,000 chemicals in use in the United States than the general public. These chemicals include benzene, methylene chloride, jet fuel, herbicides, and pesticides. Frequently, the only way to determine actual increase in human body burden is to take blood measurements before and after exposure. Improving the specificity and sensitivity of the chemical tests now available for this purpose will allow small blood samples to be used to generate data of high quality on the relationship between workplace exposure circumstances and worker exposure. This information is critical in priority setting. Chemicals found in a high proportion of the population or in high amounts in certain segments of the population would be given a high priority for toxicological and epidemiological studies. Furthermore, the design of studies will benefit from knowledge of chemical levels in the general population being used to select low doses for NTP studies that will be relevant to the real world. Another example of the benefits of our exposure assessment initiative is popular dietary supplements. Over 1,000 are currently in use. It is important to determine which are harmful and which are safe. They are not subject to the Food and Drug Administration (FDA) premarket regulatory authority, so toxicological and exposure information is frequently not available. The NTP and the NIH Office of Dietary Supplements is organizing a workshop in September 1998 to set priorities for research on dietary supplements and to determine which ones should be studied first. Blood measurements of those dietary supplements in heavy users will provide valuable body burden data relative to the general population. Comparisons of levels causing adverse health effects in experimental animals can be compared to body burdens in people to determine if there is or is not an adequate margin of safety.

Another example relates to Europe’s ban on import of meats from the United States because of the use of growth-promoting hormones. Data showing increased levels of growth-promoting hormones in human blood, if an increase actually occurs, would be of critical importance for health and economic reasons. If there is little or no increase in these compounds in the human body burden as determined by blood or urine measurements, then it would be unlikely that eating meat from growth-promoted animals could cause deleterious health consequences. If there are elevations of these compounds in blood or urine, the biological meaning of the increases would then have to be determined by toxicology and epidemiology studies.

The NTP has published nearly 500 peer-reviewed technical reports on lifetime bioassays for cancer. These reports are used to alert the public to carcinogenic risks posed by chemical agents in the environment, home, and workplace and in drugs and pharmaceuticals. NTP technical reports often provide the scientific information for regulatory decision making by the EPA, the Occupational Safety and Health Association (OSHA), the FDA, the Consumer Product Safety Commission, and many states. Human exposure data are needed to interpret NTP toxicology data. For example, current NTP studies quantify the amount of chemical and/or active metabolites in blood and target tissues associated with a given incidence of cancer in rodents. In future technical reports, we intend to quantify the amount of that chemical in human blood as a consequence of exposure circumstances encountered in the home, general environment, or workplace, or through the prescribed use of a pharmaceutical. This information will help determine more accurately the level of public health concern as a consequence of NTP toxicology studies.

The Center for the Evaluation of Risks to Human Reproduction, a center for the assessment of human reproductive health risks, will soon be established at the NIEHS. The health issues addressed will include adverse effects of human exposures on all aspects of reproduction including genetics, fertility, and development. This activity is considered a priority because of the need for timely, expert, and balanced assessments of reproductive health hazards associated with human exposures to environmental agents. Cases in the recent past, such as the controversies surrounding the reproductive effects of Agent Orange, the effects of pesticide exposures in children, and current concerns regarding the Gulf War Syndrome and endocrine disruptors in the environment emphasize the public interest in such an activity. The assessments produced by the center will have limited value without the inclusion of reliable exposure information.

The NTP also prepares the Report on Carcinogens in response to section 301(b)(4) of the Public Health Service Act as amended, which stipulates that the Secretary of DHHS shall publish a report that contains a list of all substances 1) which either are known to be human carcinogens, or may reasonably be anticipated to be human carcinogens, and 2) to which a significant number of persons residing in the United States are exposed. The Secretary of DHHS has delegated responsibility for preparation of the report to the director of NTP. This document is used by regulatory agencies in priority setting and risk assessment. To maximize use of the report in regulatory decision making, exposure information should accompany each chemical or substance listed. Such information would be provided by this exposure initiative.

Sensitive Subpopulations

Our current exposure database provides strong evidence that body burdens of individual chemicals vary tremendously across
The recent flurry of activity and intense controversy associated with health risk assessment and its use in regulatory decisions is generated by a number of forces, including concerns of industry that costs of complying with environmental regulations are excessive, concerns of environmentalists that risk assessment practices and policies do not adequately protect human and environmental health, the public's lack of confidence in regulatory decision making, and increasing awareness that the scientific foundation for many risk assessments is weak (17).

Resolution of the controversy, development of effective prevention strategies, and rational priority setting can only be achieved by strengthening the database used to make regulatory decisions. A recent estimate of federal expenditures for health risk assessment-related research is $600 million/year (18); however, this figure is probably greater than the actual dollars spent. Although this seems to be a huge sum, it is negligible in comparison to the costs of the consequences of regulatory decisions. The NIEHS and the CDC currently are collaborating on a pilot project for quantifying approximately 70 chemicals that are considered to be endocrine disruptors in either human blood and urine (4). This collaboration will strengthen the science base for risk assessments in a number of ways. For example, it will quantify the amount of a given chemical or a chemical structural class in the human body as a consequence of exposure from daily living. Thus, this measurement can be considered background exposure and directly compared to the amount of chemical needed to produce adverse effects in experimental

Risk Assessment

The tools of molecular genetics provide new opportunities to understand the genetic basis for individual differences in susceptibility to environmental exposure. The NIEHS plans to expand its research program on genetic susceptibility to environmentally associated diseases through a new Environmental Genome Project. This project, which makes use of technology developed in the Human Genome Project, will systematically identify the allelic variants of environmental disease susceptibility genes in the U.S. population, develop a central database of known polymorphisms for these genes, and foster population-based studies of gene/environment interaction in disease etiology. By identifying those genes and allelic variants that affect individual response to environmental toxins, we can better predict health risks and develop environmental policies to protect the most vulnerable subgroups of the population. To meet this objective, accurate exposure indices must accompany the genetic information (Fig. 2).

The NIEHS Environmental Genome Project will be a broad, multicenter effort to identify systematically in the U.S. population the alleles of 200 or more environmental disease susceptibility genes (3). A central database of the polymorphisms will be made available. This database will in turn support both functional studies of alleles and population-based studies of disease risk. Such population-based epidemiologic studies are central to the identification of both the allelic differences and the environmental exposures that cause disease, and represent an integral application of the Environmental Genome Project.

Working with genetically susceptible subgroups will allow us to identify more precisely the environmental agents that cause disease and the true risks of exposure. Results from the Environmental Genome Project will lead to public health programs 1) for protecting susceptible populations, 2) for targeted screening of groups at higher risk of disease, and 3) for more definitive epidemiology studies including evaluation in sensitive populations, provided that credible exposure indices are available.

After all, if we wish to improve our understanding of exposure/response relationships in sensitive subpopulations, we must have credible exposure data.
models such as rats and mice. If there is not an adequate margin of safety, then public health or worker protection could be achieved by appropriate regulatory action. The efficacy of those actions in reducing human body burdens of hazardous agents could be evaluated by continuing to monitor human body burdens after new regulations are put into place. If there is an adequate margin, additional regulatory actions may be unnecessary. In the case of environmental endocrine disruptors, we know that there are scores of environmental chemicals that possess hormonal activity, including pesticides, industrial by-products, health care products, and those arising from the manufacture and use of plastics and detergents (19). In addition, there are numerous plant and fungal products that also possess hormonal activity and are known to produce health effects when people are exposed to them in sufficient quantities. Unfortunately, we know very little about the human body burden of these chemicals, and this lack of knowledge creates much of the controversy over their impact on human health.

Human exposure assessment can also be used in dose–response assessment and extrapolation methodology. For example, because the toxicity of a given xenobiotic can differ substantially between species, investigators relying on animal data in risk assessment are forced to assume that humans are at least as susceptible as the most sensitive animal species tested and to then use uncertainty factors. However, interspecies differences are often mediated by differences in metabolism, physiologic and anatomic differences, and molecular receptor structure. Use of the internal dose, or better yet the biologically effective dose, accounts for the toxicokinetic differences and thus allows for better interspecies comparisons. This decreases the need for uncertainty factors.

Accuracy of risk estimates can only be improved by better scientific data and better methods for incorporating such data into the risk assessment process. Better exposure assessment with body burden data for general and exposed U.S. populations will greatly improve the process.

**Evaluation of Intervention Strategies**

The EPA and various state environmental agencies are mandated to establish regulations involving air and water standards and cleanup of contaminated sites including Superfund sites. Without body burden measurements, it is not possible to determine how effective these regulations are. The lower blood lead levels measured in children by the CDC-NCEH following EPA regulations mandating removal of lead from gasoline was the most convincing demonstration of the efficacy of this regulation (20). In fact, the decreased blood lead levels far exceeded expectations. Similar measurement of body burden in children playing in a Superfund site can demonstrate whether or not elevated body burdens of the chemical contaminants, such as lead or volatile organics, exist. If they do, appropriate public health measures may be indicated, and follow-up blood measurements will be able to determine efficacy of action taken. If elevated body burdens do not exist at sites where there is potential for exposure, costly remediation measures may not be necessary. Likewise, strategies for minimizing exposure to chemicals in the workplace can be evaluated and changes made when necessary.

Little if any data exist on body burdens for most chemicals of interest in the U.S. general population and in groups potentially exposed over time (21). Recent substantial declines in dioxin body burden of Europeans have been reported. These decreases have been attributed to new inactivator emission regulations. It is not known whether the same is true for the U.S. general population. Other exposure circumstances of concern include exposures that occur in the vicinity of Superfund sites or in the workplace, or those that arise from exposure to household chemicals. Measurements of toxic chemicals in workers' blood before and after actual or potential exposure are essential to determine whether there are increases in body burden of specific chemicals such as perchloroethylene, benzene, or chloroform. Outdated body burden measurements can lead to misleading interpretations of risks. For example, blood PCB levels in the general U.S. adult population are currently lower than in the recent past (22). Without this kind of knowledge, risk assessments, epidemiology studies, and individual medical decisions would be based on outdated information.

**Mixtures**

Credible experimental strategies on mixtures are either limited or nonexistent, yet mixture studies are the most relevant because people are exposed to chemicals as mixtures in the environment and in the workplace, not as single chemicals. The problem in designing mixture studies stems, in part, from our lack of knowledge concerning the characterization of real-life mixtures based on human exposure or human body burden. The exposure initiative will provide the kind of information necessary for constructing real-life mixtures. These mixtures will then be used in a variety of experimental situations: *in vitro*, rodent toxicology, and computational analysis (i.e., predictions of chemical interactions with cellular macromolecules such as receptors). In the case of environmental estrogens, we will have the information necessary to develop approaches for determining if interactions result in synergy or antagonism, or neither, and thereby resolve much of the controversy over whether or not weak environmental estrogens act synergistically and pose a serious human health threat. Of course, the problem with mixtures extends far beyond the endocrine disruptor issue. We know that particulates and volatile air toxics can interact to substantially increase lung cancer risks. Likewise, risk of radon-induced lung cancer is increased in cigarette smokers, and hepatitis B infection increases chemically-induced liver cancer (23,24).

Broad-based knowledge on the quantities of different chemicals in people's bodies will facilitate the evolution of mixture research to take advantage of the tools of molecular toxicology. For example, a first step in using real-life mixtures could be to test them in high-throughput molecular screens to determine if mixtures are causing changes in gene expression or other early critical events in toxicity. It will also be possible, using such approaches, to evaluate whether the mixture is modifying the toxicity of individual components of that mixture (i.e., increased DNA damage from polycyclic aromatic hydrocarbons). Results from the molecular screens would be used to set priorities for further research including more time-consuming animal toxicology and/or molecular epidemiologic studies. This approach ensures that valuable resources are not wasted on the study of low priority mixtures.

In summary, the exposure assessment initiative is needed to address public health issues and to enhance the NTP's ability to meet its public health goals. It is feasible because of recent advances in analytical technology and molecular biology, and it is an example of how different agencies can work together to address environmental health concerns.

**References and Notes**

1. Lucier G. NTP's evolving strategies: the role of human studies. Risk Policy Report 4(4):27–31 (1997).
2. Needham LL, Hill RH Jr, Ashley DL, Pirkle JL, Sampson ES. The priority toxicant reference range study: interim report. Environ Health Perspect 103(suppl 3):89–94 (1995).
3. Sexton K, Kellman DE, Calahan MA. An introduction to the National Human Exposure Assessment Survey (NHEAS) and related Phase I field studies. J Expo Anal Environ Epidemiol 5:229–232 (1995).
4. Lucier G, Needham L, NIEHS, CDC collaborate to improve human exposure assessment. Environ Health Lett 37:127–128 (1998).
5. Kaiser J. Environment Institute lays plans for gene hunt. Science 278:569–570 (1997).
6. Guennerich FP. The Environmental Genome Project: functional analysis of polymorphisms. Environ Health Perspect 106:365–368 (1998).
7. EPA’s Office of Pollution Prevention and Toxics Website. Washington, DC; U.S. Environmental Protection Agency, 1998. Available: http://www.epa.gov/opptintr/chemtest/ (cited 3 August 1998).
8. Commission on Dietary Supplement Labels Report to the President, Congress, and The Secretary of the Department of Health and Human Services. Prepared by the Commission on Dietary Supplement Labels, 1997. Research Triangle Park:National Toxicology Program, 1998.
9. NTP Home Page. Research Triangle Park, NC: National Toxicology Program, 1998. Available: http://ntp-server.niehs.nih.gov (cited 3 August 1998).
10. NTP Technical Reports. Research Triangle Park, NC: National Toxicology Program, 1998. Available: http://ntp-server.niehs.nih.gov/docs/pub.html (cited 3 August 1998).
11. NIEHS News: New center to study environmental impacts on reproductive risk. Environ Health Perspect 104:376-377 (1996).
12. NTP. Report on Carcinogens. 8th edition. Research Triangle Park, NC: National Toxicology Program, 1998.
13. Schreiber JS, House S, Prohonic E, Smead G, Hudson C, Styk M, Lauber J. An investigation of indoor air contamination in residences above dry cleaners. Risk Anal 13(3):335-344 (1993).
14. Popp W, Muller G, Bailes-Schmitz B, Wehner B, Vahrenholz C, Schmieding W, Benninghof M, Norpoth K. Concentrations of tetrachloroethene in blood and trichloroacetic acid in urine in workers and neighbours of dry-cleaning shops. Int Arch Occup Environ Health 63(6):333-335 (1992).
15. Patterson DG Jr, Holler JS, Smith FJ, Liddle JA, Sampson EJ, Needham LL. Human adipose data for 2,3,7,8-TCDD in certain US samples. Chemosphere 15:2055-2066 (1986).
16. Schecter A. Exposure Assessment: Measurement of Dioxins and Related Chemicals in Human Tissues. Dioxins and Health. New York:Plenum Press, 1994.
17. Lucier G. Risk assessment: good science for good decisions? Editorial. Environ Health Perspect 110:386 (1993).
18. Wiener JD. Spheres of Influence: Risk assessment and cost-benefit analyses: in the public interest? Environ Health Perspect 101:408-409 (1993).
19. Colborn T, vom Saal FS, Soto AM. Developmental effects of endocrine-disrupting chemicals in wildlife and humans. Environ Health Perspect 101:378-384 (1993).
20. Priddle JL, Brody DJ, Gunter EW, Kramer RA, Paschal DC, Regal KM, Matte TD. The decline in blood lead levels in the United States. JAMA 272:284-291 (1994).
21. Schecter A, Pølke Ø, Fürst P, Ryan JJ. Temporal changes in dioxin and dibenzo furan levels in general population human blood and milk from Germany and the United States. Organohalogen Compounds 32:473-478 (1997).
22. Robinson PE, Mack GA, Remmers J, Levy R, Mohadjer L. Trends of PCB, hexachlorobenzene, and B-benzene hexachloride levels in the adipose tissue of the US population. Environ Res 53:175-192 (1990).
23. Bucher JR, Lucier G. Current Approaches Towards Chemical Mixture Studies at the National Institute of Environmental Health Sciences and National Toxicology Program. Environ Health Perspect 106:615-621 (1998).
24. Current Issues on Chemical Mixtures. Environ Health Perspect (suppl, in press).