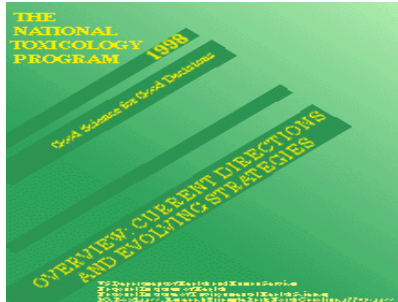




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**The National Toxicology Program  
1998 -- Good Science for Good Decisions**

**OVERVIEW:  
CURRENT DIRECTIONS  
AND  
EVOLVING STRATEGIES**

The National Toxicology Program (NTP) was established as a cooperative effort within the Public Health Service (PHS) of the Department of Health and Human Services 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 which 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.

With over 80,000 chemicals in commerce, the people of the United States are exposed to chemicals through their use in a wide variety of industrial and consumer products as well as those naturally occurring in food, drinking water and the air they breathe. While it is generally assumed that relatively few of these chemicals are likely to pose a significant risk to human health at the levels of exposure that exist, the health effects of most of these chemicals are generally unknown. Thus, the NTP's role in research and testing of chemicals and other agents is a logical extension of the Public Health Service's responsibility for safeguarding the public's health, and fulfilling the fundamental public health precept of preventing unnecessary exposure to hazards.

#### Goals of the National Toxicology Program

- Provide toxicological evaluation on substances of public health concern
- Develop and validate improved methods (sensitive-specific-faster)
- Develop approaches and generate data to strengthen the science base for risk assessments
- Communicate with all stakeholders

#### Current Directions and Evolving Strategies

In order to meet these 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 strengthens 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 in 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. For example, a major interagency initiative is being developed in exposure assessment which is frequently the weakest link in risk assessments. This initiative, in collaboration with the membership agencies, 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 document. NTP studies aimed at understanding gene/environment interactions will benefit tremendously by the National Institute of Environmental Health Science's (NIEHS) Environmental Genome Project which will characterize the human variability of hundreds of environmentally-relevant genes. 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.

During 1997 and 1998 the NTP has been working on a broad range of high priority agents and issues. These include the Congressionally-mandated evaluation of human-health risks from exposure to electric and magnetic fields, toxicological evaluations of pharmaceutical agents such as phenolphthalein (the active ingredient in some over-the-counter laxatives), and natural products such as fumonisin and a series of phytol and fungal estrogens. We are collaborating with EPA in a series of studies designed to assess the risks of exposure to the major drinking water disinfection byproducts. These studies,

which include the use of transgenic animals and mechanistic studies, will determine which of the byproducts are safe and which are dangerous so that strategies can be developed to maximize the benefits of water disinfection and minimize the risks. The NTP is working to determine the relationships between ecological/wildlife effects and human health; for example, we are attempting to determine if the high incidence of malformed frogs in several states in the U.S. and in other countries is associated with increases in human disease. This is a collaborative effort with the State of Minnesota and other State and Federal agencies. Moreover, we are investigating public health questions involving exposure to pfiesteria and fish-kill waters.

The NTP continues to be recognized as objective and science-based in several other highly controversial issues such as the endocrine disrupting chemicals, mercury in seafood, and dietary supplements. Its goals are achieved through a combination of basic and applied research coupled with a commitment to two-way communications as evidenced by numerous partnership activities and conference/workshop approaches for enhancing input into NTP priorities and programs.

### Organizational and Oversight Structure of the NTP

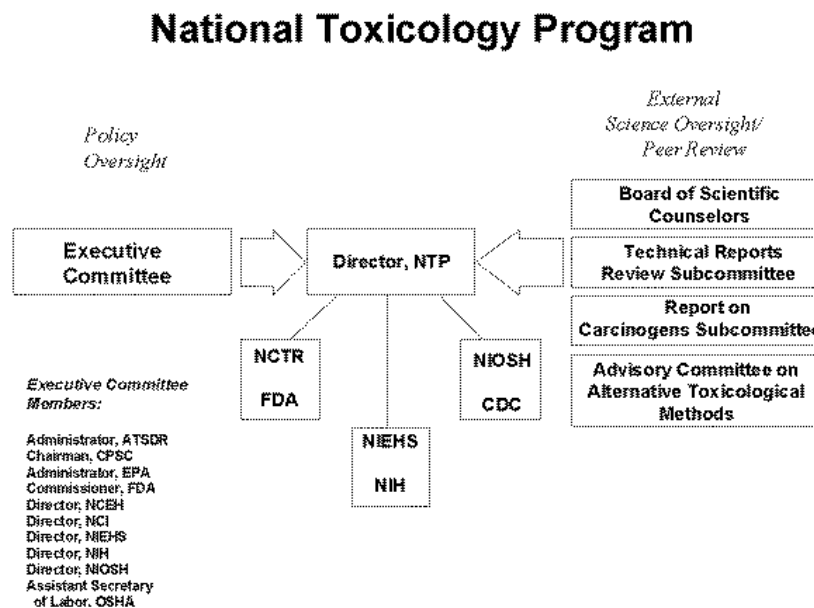
The Program consists of relevant toxicology activities of its three component agencies:

- National Institutes of Health's National Institute of Environmental Health Sciences (NIH/NIEHS);
- Centers for Disease Control and Prevention's National Institute for Occupational Safety and Health (CDC/NIOSH); and
- Food and Drug Administration's National Center for Toxicological Research (FDA/NCTR).

The NIH's National Cancer Institute (NIH/NCI) was also a charter agency. The NCI carcinogenesis bioassay program was transferred to the NIEHS in July 1981. The NCI remains active in the Program through membership on the Executive Committee and by providing a large number of nominations for study.

Primary program oversight is provided by the NTP Executive Committee composed of the heads of the participating DHHS agencies (including NIH's NIEHS and NCI, Agency for Toxic Substances and Disease Registry [ATSDR], the CDC's National Center for Environmental Health [NCEH] and NIOSH, and the FDA) as well as the heads of the major non-DHHS regulatory agencies concerned with human health. These agencies are the Occupational Safety and Health Administration (OSHA) of the Department of Labor, the Environmental Protection Agency (EPA), and the Consumer Product Safety Commission (CPSC). Primary scientific oversight is provided by the NTP Board of Scientific Counselors, composed of scientists from the public and private sectors. Activities of the NTP are coordinated under the leadership of the Program Director, who is also the Director of the NIEHS. For purposes of the NTP, the Director reports to the Assistant Secretary for Health, DHHS.

The organizational and oversight structure of the NTP is depicted in the following figure.



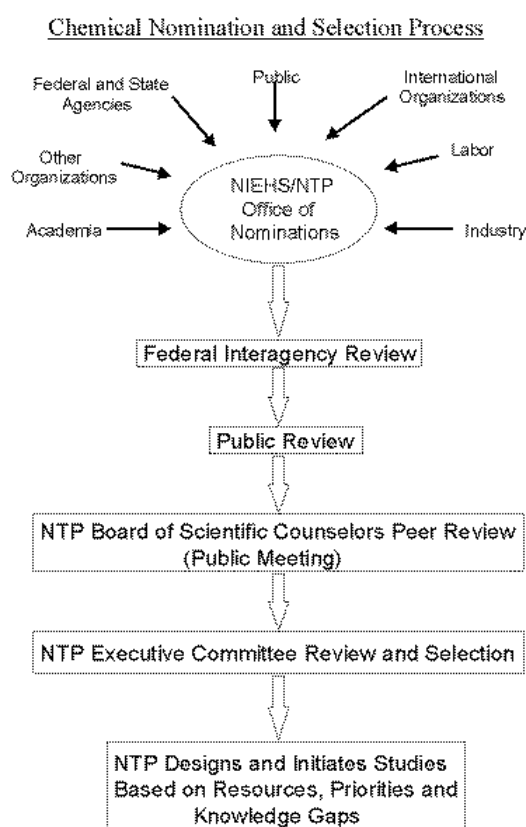
### Priority Setting and Chemical Nomination and Selection

The nomination and selection for study of chemicals and agents with the highest potential for adversely impacting public health are essential to the success of the Program. Nominations are solicited from a variety of sources in academia, Federal and State regulatory and health agencies, industry, and unions, as well as from environmental groups and the general public. Particular assistance is sought with the selection of studies that permit testing of hypotheses to enhance the predictive ability of NTP studies, address mechanisms of toxicity, or identify significant gaps in knowledge of the toxicity of chemicals or classes of chemicals.

Chemicals may be studied for a variety of health-related effects, including but not limited to, reproductive and developmental toxicity, genotoxicity, immunotoxicity, neurotoxicity, metabolism and disposition, and carcinogenicity. The possible public health consequences of exposure remain the over-riding factor in the decision to study a particular chemical or agent. Selections for government testing are based on the principle that responsible industries will evaluate their own chemicals or agents for health and environmental effects as mandated by Congress under legislative authorities. Nominations to the NTP should be based on the following principles:

1. Chemicals found in the environment not closely associated with commercial operations: (Responsible industries can often be required to study chemicals they produce or are known to have released.)
2. Biological or physical agents that might not be tested without Federal involvement: (This includes naturally occurring compounds, chemicals formed in the environment, and agents such as electromagnetic frequencies.)
3. Commercial agents first marketed prior to current testing requirements: (e.g., Chemicals marketed prior to implementation of TSCA in 1977.)
4. Orphan drugs or chemicals that might not be developed without Federal involvement: (Some drugs without a large potential market would not be commercially feasible if industry was required to pay all developmental costs. In such cases the NTP may conduct toxicity and/or carcinogenicity studies.)
5. Mixtures of chemicals for which evaluations cannot be required of industry.
6. Chemicals or agents that will aid our understanding of toxicities or test systems to evaluate potential toxicities. (Information from these studies is used to help predict the toxic effects of chemicals that have not been studied.)
7. Chemicals involved in emergencies that require immediate government evaluation.

A description of the chemical nomination and selection process is shown on the following figure.



### Mechanism-Based Toxicology

The emerging tools of molecular biology, which can be used to characterize interactions of chemicals with critical target genes, are offering tractable approaches for the development of more accurate and inexpensive methods to perform the hazard identification step in risk assessment. Examples include employing methods for identifying receptor-mediated toxicants, molecular screening strategies, use of transgenic animals, and developing alternative/complementary *in vivo* tests to the rodent bioassay. Additionally, the use of predictive toxicology is evolving rapidly and should help considerably in hazard identification. Appropriate mechanistic and predictive methods to identify environmental health risks must be developed, validated, and accepted by regulatory agencies. It is clear that agencies such as EPA are committed to using all relevant information in their assessments so it is critical that the NTP play a leadership role in providing the necessary science base. These approaches could increase by several-fold the number of environmental agents evaluated. Although mechanistic approaches should and are being more frequently incorporated into toxicity testing, the chronic bioassay in rodents must be used in many cases including those where mechanistic data are not available and for the purpose of validating new methods. Thus, it must be emphasized that there is a strong and continuing commitment by the NTP to increase the number of agents entered into toxicology and carcinogenesis studies. To ensure that the agents selected for study represent the best choices from a standpoint of public or occupational health importance and/or scientific importance, the Program has broadened its call for nominations to include more nominations from non-government organizations and the general public, and to continue to give more emphasis to non-cancer endpoints. Reproductive, developmental, neurotoxicology and immunotoxicity studies incorporate mechanistic approaches so that the data generated will be as relevant as possible for evaluating human risks.

Supporting and underpinning new directions and evolving approaches over the past two fiscal years have been major scientific and public reviews of the NTP, a major reorganization of the NIEHS intramural research program to bring a broader science base to the NIEHS and NTP while enabling better use of limited resources, and legislative action in the form of the National Institutes of Health Revitalization Act of 1993 which directed the NIH and NIEHS to take specific actions to develop and validate alternative methods to the use of animals in research and testing.

### **Experimental Design Strategy, Study Performance and Peer Review**

Most chemicals recommended to the NTP come with a request for studies in a particular area of concern, such as neurotoxicity or immunotoxicity. However NIEHS staff review the toxicology literature for each chemical and attempt to design a comprehensive testing strategy. The Study Scientist for an individual chemical or class of chemicals has available several standing NIEHS Faculties willing to provide expert guidance in given areas. The Study Scientist also consults with the scientific and regulatory communities, NIEHS intramural research staff and other interested parties while formulating study plans. Each study design is developed by a Study Design Team, and approval sought is from the Project Review Committee prior to study conduct.

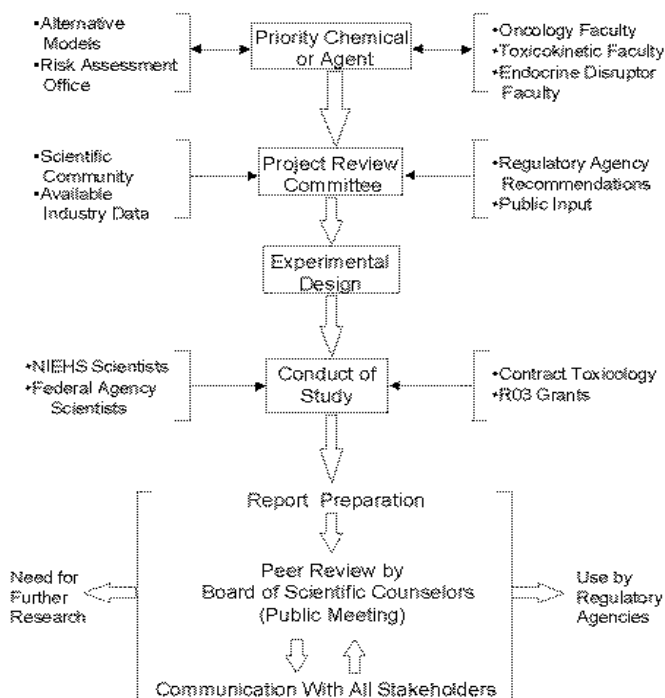
Cancer bioassays and other standard toxicological evaluations are carried out at contracted commercial laboratories. The academic community can participate in these studies through a small grants program designed to support special toxicity assessments on tissues or animals from the main studies. Frequently initial studies will include a mutagenicity evaluation and short-term-toxicity studies in animals. These short-term studies include a number of endpoints that, if positive, would lead to a more comprehensive evaluation in a particular area. For example, abnormalities in behavior in a functional observational battery may lead to formal neurobehavioral testing, or changes in hematologic indices may lead to an immunotoxicity study. Chemicals that undergo a chronic toxicity assessment are also considered by the Toxicokinetics Faculty, the purpose being to ensure that needed information is provided in the areas of chemical metabolism and the kinetics of the handling of the chemical by the body. In selected cases a formal physiologically-based pharmacokinetic model (PBPK) will be derived to provide the most comprehensive dataset for further risk assessment activities by regulatory agencies.

Each chronic bioassay for carcinogenicity costs 2-4 million dollars and takes several years to complete. Therefore, chronic bioassays can be conducted only on a small fraction of the thousands of chemicals for which there is little or no toxicologic information. In order to best meet our public health responsibilities, the NTP is developing improved strategies for selecting those chemicals examined in long-term bioassays. Also being evaluated are several genetically altered mouse strains for their potential to respond to carcinogens more quickly (and at less cost) than conventional rodent strains. These strains carry activated oncogenes or inactivated tumor suppressor genes, and appear to detect chemical carcinogens acting through pathways likely to operate in human cancers. Scientific information on mechanisms (see section on Mechanism-based Toxicology), existing toxicological data, predictive toxicology, computational graphics, and structure-activity relationships may also help to identify those agents which have a high likelihood of being carcinogens. One approach would be to use the long-term bioassay resources to test chemicals for which the outcome is uncertain; and where available data strongly suggest a chemical to be carcinogenic, design specific studies that would address uncertainties in risk assessment, such as dose response relationships, species extrapolation, and inter-individual variation in response. This strategy would require that regulatory agencies could make decisions on this kind of data; however this is becoming increasingly likely because of changes in regulatory practices; e.g. EPA's revised risk assessment guidelines specify use of all changes in testing strategies or standard protocols to facilitate such acceptance.

The results of all NTP studies undergo a rigorous public peer review. Technical Reports from toxicity or carcinogenicity studies are evaluated by a standing subcommittee of the NTP Board of Scientific Counselors. These activities are essential in involving the public in NTP activities, but public input is sought during all phases of study design, performance and review, and the program is committed to working with interested parties in every way possible.

An outline of experimental design strategies is depicted in the following figure.

### Experimental Design Strategies for Priority Chemicals



### Body Burden 2000 - Exposure Assessment

The NIEHS/NTP is leading the development of an interagency initiative in exposure assessment which addresses several critical public health issues such as uncertainty in risk assessment, priority setting by government agencies, worker safety, special exposures such as the Gulf War, chemical mixtures, and children's health. This initiative will measure the amount of chemicals of public health interest present in people's bodies as a consequence of exposures encountered in the general environment, home and workplace. This is now feasible because of recent advances in analytical methodology which permit detection of environmental and occupational chemicals in small samples of blood and urine. This effort is truly multidisciplinary and will significantly enhance the ability of several Federal agencies and institutes to better fulfill their respective missions including CDC and EPA.

Exposure assessment is frequently a weak link in risk assessment. This weakness limits the effective utilization of experimental data for reducing uncertainty in human risk assessments arising from exposure to environmental agents. The NIEHS and CDC currently are collaborating on a pilot project for improving the exposure assessment of a particular group of environmental exposures—the environmental endocrine disruptors. 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 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 or other 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 or other actions have reduced exposure. If there is an adequate margin, then 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 byproducts, health care products and those arising from the manufacture and use of plastics and detergents. 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, very little is known about the human body burden of these chemicals, and this lack of knowledge creates much of the controversy over their impact on human health.

This initiative will benefit public health and priority setting in a number of other ways. First, it will provide the kind of information necessary for deciding which chemicals should be studied with the limited resources available for toxicological testing. For example, of the 80,000 chemicals in commerce today many lack adequate health effects data, and the NTP can only provide toxicological evaluations on 10-20 per year. Second, the nature of special exposures can be more precisely determined such as those which occurred for American military personnel in the Gulf War. If blood samples had been taken from some individuals before, during and after the war, we would be in a much better position to evaluate health effects, and the current acrimony and controversy on this issue might have been avoided. Third, information obtained from the exposure initiative would be used to focus our research on mixtures which are environmentally relevant. Fourth, we would obtain information on the kinds and amounts of chemicals in children so that, when necessary, appropriate actions could be taken to protect the health of our children. Fifth, this initiative, taken together with the NIEHS Environmental Genome Initiative, will provide the science base essential for meaningful studies on gene/environment interactions. Without good information on the kinds and amounts of chemicals in people's bodies, applications of information from the genome project to prevention strategies will not reach their full potential.

### Human Studies

From its origins as a rodent cancer testing program, NTP activities have expanded to encompass broad chemical toxicity characterizations, and increasing emphasis is placed on determining mechanisms responsible for adverse health effects. Similarly, the direct study of human tissues has become an important

part of the determination of the relevance of animal toxicology findings to human health, and knowledge of comparative human and animal physiology is allowing for the refinement of human risk assessments through construction of physiologically-based pharmacokinetic models. While efforts in these areas continue, new initiatives are underway in exposure assessments (described in the preceding section), in comparative metabolism and kinetics, and in the use of rodent or other tissues genetically altered to include human genes.

The NIEHS has recently established an interagency agreement (IAG) with CDC's National Center for Environmental Health (NCEH) to determine quantities of approximately 50 endocrine disrupting agents in human blood. These data will help identify which endocrine disrupting agents are of greatest public health concern thereby helping to prioritize which chemicals should be studied by the NTP. It will also help in the development of biologically-based models for estimating human risks.

*1) Comparative Metabolism/Kinetics:* The recent commercial availability of human liver coupled with methods for assessing comparative metabolism in liver slices from rodents and humans has allowed the development of information useful in risk characterization. However, a number of factors, e.g. individual variability, prior exposures, conditions under which tissues are collected and time between collection and use make data obtained with human tissues quite variable. Further efforts toward refining these techniques to yield quantitative data useful for PBPK modeling are underway.

*2) Application of Biomarkers to Human Field Studies:* Epidemiological studies that assess potential health risk are compromised by the lack of quantitative exposure data for the worker. Air concentrations, while useful as an indicator of exposure, are not sufficient to determine the biologically-relevant internal dose. The biological monitoring methods used in this study can accurately and sensitively determine an individual's internal dose and can be predictive of the putative effects produced by chemical exposure. Additionally, host susceptibility factors such as metabolic capability and DNA repair are utilized to assist in evaluating variations in an individual's response to comparable environmental exposures.

*3) Human/rodent parallel endpoints:* Other opportunities to better understand the human relevance of laboratory animal test results are presented by the development of new methods to assess the same toxicity endpoints in both rodents and humans. By this means, effects observed in humans can be replicated in rodents and a deeper understanding of mechanisms and risks can be gained by extending the dose range, dose rates, routes of exposure, and other variables in controlled laboratory experiments. Recent progress in this area has been achieved through a) the development of parallel endpoints for immunotoxicity in rodents and immune effects in exposed worker populations, b) development of chromosome specific probes that permit the detection of chromosomal abnormalities in the sperm of rodents, primates and humans, and c) assessment of male reproductive toxicity in *ex vivo* studies employing seminiferous tubules from rodents and humans.

Another approach used to enhance the human relevance of experimental studies is through the insertion of human genes into animal or bacterial genomes. Examples of this include the augmentation of cells used in *in vitro* genetic toxicity screens with the ability to metabolically activate chemicals using human cytochrome P450s. Another example is the transgenic mouse model *ras* H2. Developed by a Japanese group, the mouse carries five or six copies of the human c-Ha-*ras* gene integrated into the genome in a tandem array. Hemizygous mice are being evaluated for possible use as a short-term cancer bioassay model. The manipulation of animal models to provide human targets, or to better mimic particular characteristics of sensitive human subpopulations would seem to be desirable, and further development of these approaches is warranted.

### Risk Assessment Models

The development and application of mathematical risk assessment models are often criticized for inadequate linkage to real biological systems. However, these models are necessary for quantifying the sequence of events which start with chemical exposure and end with overt toxicity. Biologically-based models allow researchers to link a broad array of experimental findings in a way which is biologically logical and eventually useful for risk assessment including dose-response relationships, species comparisons, and interindividual variation. Several analyses have already been completed which bear noting. Complete models were developed for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, dioxin) and 1,3-butadiene which include the best characterizations available of the pharmacological and biochemical effects of these compounds. The model for TCDD is being used as part of the basis for the mechanistically-based risk assessment done by the EPA. Mechanistically-based cancer models are being developed for and applied to NTP data, while predictive toxicology is a new area under study and refers to the use of physico-chemical parameters in concert with biological data to predict human toxicity and quantify dose-response relationships for that toxicity. Formal inclusion of PBPK models in NTP technical reports is being studied and should provide guidance for regulatory agencies interested in extrapolation across species using these data. These, along with other activities aimed at providing improved statistical and mathematical procedures for estimating risks, will hopefully provide a stronger basis for comparative risk analyses. Each chemical to be tested by the NTP is evaluated by its toxicokinetics faculty as a candidate for a biologically-based model. If a credible and potentially useful model could be constructed, then the study is designed to generate the appropriate data. In addition, the NTP is developing alliances with several agencies in the generation of similar data following human exposure to many environmental agents. Our efforts in risk assessment methodology are strongly linked to mechanism-based toxicology. This linkage offers opportunities to: (1) improve priority setting, (2) use mechanistic information to establish safety or risk, (3) clarify dose response relationships in the low dose region, (4) select the most appropriate experimental systems for estimating risks and (5) develop science-based models for sensitive subpopulations based on age, gender and genetic predisposition. The NIEHS world-wide web site identifies models and projects related to risk assessment (<http://www.niehs.nih.gov>).

### Center for the Evaluation of Risks to Human Reproduction

A center for the assessment of human reproductive health risks is to be established. The health issues addressed would 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. Recent development and broad acceptance of a process for assessing reproductive and developmental toxicity (*Reproductive Toxicology* 9:61-95, 1995) provides the cornerstone for establishment of such a Center at this time. 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 Gulf War Syndrome and endocrine disruptors in the environment emphasize the public need for such an activity.

The general strategy is to provide funding and oversight for a Center office that would be staffed by toxicologists and support personnel. This office would

be responsible for organizing and coordinating the activities of the Center, to include establishing and maintaining a registry of experts, arranging meetings of expert committees, and preparation, publication, and distribution of reports. The evaluation process itself would involve collection of literature, identification of panels of appropriate experts, meetings of the experts, and preparation of reports.

The product of the process would be published reports that present a comprehensive evaluation of all relevant data on a selected agent or exposure situation and a consensus judgment on the potential for reproductive or developmental toxicity in humans. Wherever possible, the mechanism(s) of toxicity would be presented and discussed, as would the relationship between exposure and effect. Of particular importance would be the identification of specific needs for additional testing and/or research. The reports of the Center would be of benefit to the public, industry, regulatory bodies, and the scientific community.

Progress to date includes approval of the concept by the NTP Board of Scientific Counselors, identification of initial funding, and the review of contract proposals. It is anticipated that the award will be made in the second quarter of Fiscal Year 1998. Although the Center would, ideally, be co-funded by Federal environmental health agencies, industrial and other private sector organizations, and international groups concerned with environmental health, the establishment and initial activities of the Center will be funded by NIEHS. Enhancing the Center's operations and activities through such partnerships is being explored.

### Development and Validation of Alternative Testing Methods

One of the major responsibilities of the NIEHS is the development, validation, and regulatory acceptance of improved alternative methods for toxicological research and testing. The Program seeks innovative methodologies that incorporate advances in technology and understanding of toxic mechanisms at the molecular and cellular level. Testing methods and strategies are sought that will be more predictive of toxic effects than currently available methods, and that can evaluate toxicity endpoints not previously assessed. Additional emphasis is placed on methods that provide for improved efficiency in terms of time and expense, and that provide for the replacement, reduction, and refinement of animal use. Scientists at NIEHS, NCTR, and NIOSH are involved in the development and validation of a wide range of testing methods, including transgenic mice for carcinogenicity testing and genetically engineered cell systems to measure endocrine disruptor activity. University-based scientists are also involved in developing models for toxicological research and testing through the extramural grants program. Model systems in development include non-mammalian species, transgenic species, genetically engineered *in vitro* cell systems, and computer-based predictive toxicology.

A major accomplishment in 1997 was the publication of a report describing criteria and processes for the validation and regulatory acceptance of toxicological test methods. This publication, *Validation and Regulatory Acceptance of Toxicological Test Methods, a Report of the ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods* (NIH Publication 97-3981), was prepared in response to directives in the National Institutes of Health Revitalization Act of 1993 (P.L. 103-43). Broad stakeholder input was sought throughout development of the report, which was prepared by an interagency committee composed of representatives from 15 Federal regulatory and research agencies and programs. Contributions and comments were provided by stakeholders from industry, academia, government, animal welfare and other public interest groups, and the international community.

As part of the implementation activities outlined in the report, fourteen Federal regulatory and research agencies and programs are participating in the newly formed permanent Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). The Committee functions to facilitate cross-agency communication and coordination on issues relating to validation, acceptance, and national/international harmonization of toxicological test methods. This includes coordinating reviews of proposed methods of multi-agency interest and providing recommendations regarding their usefulness to appropriate agencies. The Committee seeks to promote the scientific validation and regulatory acceptance of toxicological test methods that will enhance agencies' ability to assess risks and make decisions, and that will refine, reduce, and replace animal use whenever possible.

An NTP Center for the Evaluation of Alternative Toxicological Methods is being established that will provide operational support for the ICCVAM, and function to carry out committee-related activities, including peer review panels and workshops. Peer review panels will develop scientific consensus on the usefulness of test methods to generate information for specific human health and/or ecological risk assessment purposes. Expert workshops will be convened as needed to evaluate the adequacy of current methods for assessing specific toxicities, to identify areas in need of improved or new methods, to evaluate proposed validation studies, and to evaluate the validation status of methods. The Center will provide an opportunity for partnerships with other agencies and organizations to facilitate the development, validation, and review of alternative testing methods. The Center Office, located at NIEHS, is expected to become operational in 1998.

A Federal Advisory Committee on Alternative Toxicological Methods is being established to provide advice on the activities and priorities of the Center and ICCVAM, and to provide advice on ways to foster partnership activities and productive interactions among all stakeholders. The Advisory Committee will be composed of knowledgeable representatives drawn from academia, industry, public interest and animal welfare organizations, other agencies, and the international community. The first meeting of the Advisory Committee will be convened in 1998.

The publication *Validation and Regulatory Acceptance of Toxicological Test Methods, a Report of the ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods* (NIH Publication 97-3981) can be located on the Internet at: [/index.cfm?objectid=03E72D52-98A3-CB4B-C0564CDA5EA4096D](http://index.cfm?objectid=03E72D52-98A3-CB4B-C0564CDA5EA4096D).

For further information about ICCVAM and the Center, please contact one of the ICCVAM co-chairs: Dr. William Stokes, NIEHS, P.O. Box 12233, MD EC-17, Research Triangle Park, NC 27709, tel (919) 541-7997, e-mail: [stokes@niehs.nih.gov](mailto:stokes@niehs.nih.gov), or Dr. Richard Hill, US EPA, Mail Code: 7101, 401 M Street, SW, Washington, DC 20460, fax: (202) 260-1847, e-mail: [hill.richard@epamail.epa.gov](mailto:hill.richard@epamail.epa.gov).

### Report on Carcinogens (RoC)

The *Report on Carcinogens* (RoC), previously called the *Annual Report on Carcinogens*, is prepared in response to section 301 (b) (4) of the Public Health Service Act, as amended, which stipulates that the Secretary of the Department of Health and Human Services (DHHS) shall publish a report which contains a list of all substances (i) which either are known to be human carcinogens or may reasonably be anticipated to be human carcinogens; and (ii) 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 the NTP. The *Report on Carcinogens* is prepared by the NTP with the assistance of other Federal health research and regulatory agencies and non-government institutions. The listing of a substance in the RoC is descriptive in nature and represents an initial step in hazard identification, which is generally considered the first step in the analytical process known as risk assessment. The Report is not intended to constitute a risk assessment; it is a hazard identification document only.

The review of the substances, mixtures or exposure circumstances for listing in, or delisting from the RoC involves a multiphased, peer review process involving two Federal scientific review groups and one non-government, scientific peer review body (a subcommittee of the NTP Board of Scientific Counselors) which meets in an open, public meeting that also provides an opportunity for public comments. All available data relevant to the criteria for inclusion or removal of candidate agents, substances, mixtures or exposure circumstances in the RoC are evaluated by the three scientific review committees. The criteria used in the review process and a detailed description of the review procedures, including the steps in the formal review process, can be obtained by contacting: Dr. C. W. Jameson, National Toxicology Program, Report on Carcinogens, MD EC-14, P.O. Box 12233, Research Triangle Park, NC 27709; phone: (919) 541-4096, fax: (919) 541-2242, e-mail: [jameson@niehs.nih.gov](mailto:jameson@niehs.nih.gov).

The NTP solicits and encourages the broadest participation from interested individuals or parties in nominating agents, substances, or mixtures for listing in or delisting from the *Report on Carcinogens*. Petitions should contain a rationale for listing or delisting. Appropriate background information and relevant data (e.g. journal articles, NTP Technical Reports, IARC listings, exposure surveys, release inventories, etc.) which support a petition should be provided or referenced when possible. Anyone may nominate a substance to be considered for listing in or delisting from the RoC. Petitions for listing or delisting may be submitted by any interested party and should be sent to Dr. Jameson at the address provided above.

The 8th Edition of the *Report on Carcinogens* will be published in 1998 and may be obtained by contacting the NIEHS Environmental Health Information Service (EHIS) at 919-541-3841, Fax 919-541-0273, e-mail at [ehis@niehs.nih.gov](mailto:ehis@niehs.nih.gov), or subscribe on-line at <http://ehis.niehs.nih.gov/>. The 9th Report is scheduled for publication in 1999. A list of the nominations under consideration for listing in or delisting from the 9th RoC can be obtained by accessing the NTP Home Page on the Web at <http://ntp.niehs.nih.gov/ntp/> or by contacting Dr. Jameson at the address provided above. Nominations received in 1998 will receive consideration and review in 1999, and any new listings or delistings will be included in the 10th RoC to be published in 2001.

### Communications and Partnerships

The evolving and new directions of the NTP continue to be greatly influenced and shaped by input received from the public and scientific communities. The NTP Board of Scientific Counselors, its subcommittees for review of Technical Reports and the *Report on Carcinogens*, and the newly established Advisory Committee on Alternative Toxicological Methods, assure regular scientific and public peer review and input. NTP workshops and conferences designed to bring researchers, regulators, policy makers, and the public together to examine issues and to achieve consensus on future directions in toxicology and risk assessment have proven to be very important and will continue as a priority area. Partnerships with sister Federal agencies are increasing and a number of these new efforts are described within the overview. We continue to explore the utilization of private sector partnerships to develop stronger and more efficient links between toxicology, risk assessment, and regulatory decision-making. Partnership discussions at this time are focused in the areas of: the evaluation and validation of transgenic carcinogenicity models, the evaluation of risks to human reproduction, and the evaluation of alternative toxicological methods, and the developing initiative on exposure assessment.

Increased emphasis continues on ensuring broader dissemination of the results of NTP research and testing; broader solicitation of nominations for chemicals and chemical issues for toxicological evaluation and listing/delisting in the *Report on Carcinogens*; and broader communication of evolving programs and priorities. Updates are mailed from the NTP Liaison and Scientific Review Office throughout the year, and posted continually through the NTP world-wide web site: <http://ntp.niehs.nih.gov/ntp/>.

### Requests for Information, Mailing Lists and Documents

The NTP Liaison and Scientific Review Office serves as the focal point within the NTP for receiving general comments and input to the Program and for regularly distributing announcements and updates regarding upcoming reviews, meetings, conferences, NTP initiatives, reports, etc. Comments and input as well as requests to be added to the NTP mailing list should be directed to:

NTP Liaison and Scientific Review  
Office  
National Institute of Environmental  
Health Sciences  
MD A3-01  
P.O. Box 12233  
Research Triangle Park, North Carolina  
27709  
FAX number: (919) 541-0295  
Telephone number: (919) 541-0530  
Internet e-mail address:  
[britton@niehs.nih.gov](mailto:britton@niehs.nih.gov)

Central Data Management distributes, upon request, specific chemical study information and NTP documents such as the following:

- NTP Annual Plan (including Review of Current DHHS, DOE, and EPA Research Related to Toxicology) and Annual Plan Summary;
- NTP Study Status Report, produced from the NTP CHEMTRACK system;
- Summary minutes of the NTP Board of Scientific Counselors' and its Technical Reports
- Review Subcommittee and Report on Carcinogens Subcommittee meetings;
- Suggested background reading relevant to National Toxicology Program Studies;
- Background documents from nominations to the National Toxicology Program.



Requests for these documents and requests to be added to the NTP Study Status Report mailing list should be directed to:

Central Data Management  
National Institute of Environmental Health Sciences  
P.O. Box 12233  
Mail-Drop E1-02  
Research Triangle Park, NC 27709  
FAX number: (919) 541-3687  
Telephone number: (919) 541-3419  
Internet e-mail Address: [CDM@NIEHS.NIH.GOV](mailto:CDM@NIEHS.NIH.GOV)

### Environmental Health Information Service

All major NTP data and published reports are now available as part of the Environmental Health Information Service, located on the Internet at <http://ehis.niehs.nih.gov>. The EHIS provides online, searchable access and hard copies of NTP Technical Reports, Toxicology Reports, the Report on Carcinogens, NTP databases, Environmental Health Perspectives and Supplements, and more.

Contact the EHIS for your online subscription. Call 919-541-3841, Fax 919-541-0273, e-mail [ehis@niehs.nih.gov](mailto:ehis@niehs.nih.gov), or subscribe online at <http://ehis.niehs.nih.gov>.



Visit the NTP Home Page at <http://ntp.niehs.nih.gov/ntp>

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