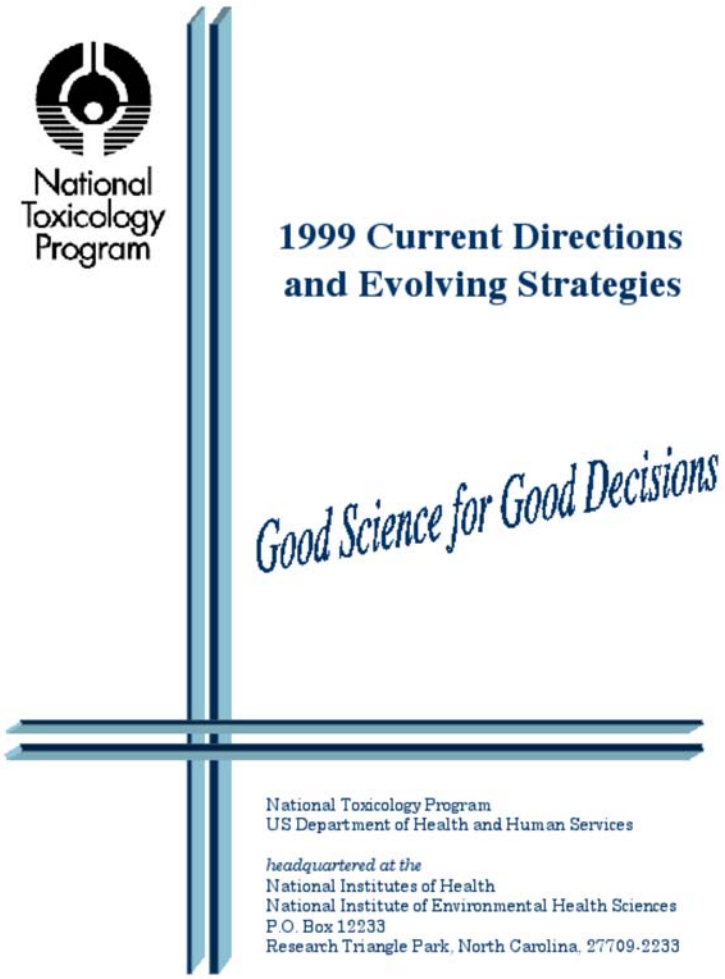

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Table of Contents

Overview of the National Toxicology Program

Mission and Goals

Today more than 80,000 chemicals are used in the United States and an estimated 2,000 new ones are introduced annually to be used in products we encounter in our daily lives such as foods, personal care products, prescription drugs, household cleaners, and lawn care products. The effects of many of these chemicals on human health are unknown, yet people and our environment may be exposed to them during their manufacture, distribution, use, and disposal or as pollutants in our air, water, or soil. While relatively few such chemicals are thought to pose a significant risk to human health, the safeguarding of public health depends upon identifying the effects of these chemicals and the levels of exposure at which they may become potentially hazardous to humans.

The National Toxicology Program (NTP) was established by the Department of Health and Human Services (DHHS) in 1978 and charged with coordinating toxicological testing programs within the Public Health Service of the Department; strengthening the science base in toxicology; and providing information about potentially toxic chemicals to health regulatory and research agencies, scientific and medical communities, and the public. The NTP is an interagency program whose mission is to evaluate agents of public health concern by developing and applying the tools of modern toxicology and molecular biology. In carrying out its mission, the NTP has several goals:

- to provide toxicological evaluations of substances of public health concern,
- to develop and validate improved (sensitive, specific, rapid) testing methods,
- to develop approaches and generate data to strengthen the science base for risk assessment, and
- to communicate with all stakeholders including government, industry, academia, the environmental community, and the public.

The Program uses these goals to set priorities as it moves forward to improve the nations ability to evaluate human health effects from chemical exposures. Its vision, leadership, and commitment to the concept of good science for good decisions have created an atmosphere that allows the NTP to be flexible and innovative in its approach toward addressing public health concerns related to chemical exposures at home and work and in our environment. Nationally, the NTP rodent bioassay is recognized as the standard for identification of carcinogenic agents. However, the NTP has expanded its scope beyond cancer to include examining the impact of chemicals on non-cancer toxicities such as those affecting reproduction and development, inhalation, and the immune, respiratory, and nervous systems. In this effort, The Center for Evaluation of Risks to Human Reproduction was created (see page 18). The NTP has also worked to reduce the use of experimental animals and to develop and validate alternative testing methods leading to creation of The Center for the Evaluation of Alternative Toxicological Methods (see page 16).

The strengthening of existing partnerships and the forging of new ones are important to the NTPs achievement of its goals. Partnerships with sister Federal agencies are increasing and the NTP continues to seek ones with the private sector. Examples include co-sponsorship of numerous workshops, an interagency initiative in exposure assessment, and establishment of an interagency committee to oversee validation of alternative testing methods. The NTP recognizes that initiatives, which address critical knowledge gaps in toxicological evaluation, offer the best opportunities for preventing environmentally mediated diseases. Therefore, the Programs testing of chemicals is evolving to include more mechanism-based toxicology studies (see page 11) that focus on understanding the mechanistic actions of chemical agents. The NTP also recognizes that the use of human data in toxicological evaluations is imperative in order to be at the forefront in studying and developing risk assessment methodologies for quantifying the sequence of events that starts with chemical exposure and ends with toxicity. A new initiative in human exposure assessment (see page 13) contributes to this effort. During the next year, the NTP is embarking on a process aimed at defining how the NTP can best meet critical issues in public health as we begin the new millennium. This process will involve our partners in the scientific community, industry, and the public sector and will lead to a White Paper on NTP priorities and initiatives. Looking forward, the NTP is evolving to remain at the cutting edge of science as a means to meet its commitment to good science for good decisions.

Organizational Structure and Oversight

Three agencies, the National Institute of Environmental Health Sciences of the National Institutes of Health (NIEHS/NIH), the National Institute for Occupational Safety and Health of the Centers for Disease Control and Prevention (NIOSH/CDC), and the National Center for Toxicological Research of the Food and Drug Administration (NCTR/FDA) form the core for this program (Figure 1). The NTP is located administratively at the NIEHS/NIH and the Director of the NIEHS/NIH, Dr. Kenneth Olden, serves as Director of the NTP and as such reports to the Secretary, DHHS. The National Cancer Institute of the National Institutes of Health (NCI/NIH) was a charter agency and continues to serve on the NTP Executive Committee.

The NTP Executive Committee provides oversight to the NTP for policy issues. This committee is composed of the heads of participating DHHS agencies including the Agency for Toxic Substances and Disease Registry (ATSDR), the Food and Drug Administration (FDA), National Center for Environmental Health of the CDC (NCEH/CDC), NCI/NIH, NIEHS/NIH, NIH, and NIOSH/CDC as well as the heads of several non-DHHS agencies that are concerned with human health including the Consumer Product Safety Commission (CPCS), the Environmental Protection Agency (EPA), and the Occupational Safety and Health Administration of the Department of Labor (OSHA).

The NTP Board of Scientific Counselors, which is composed of scientists from the public and private sectors, provides primary scientific oversight. The Boards Technical Reports Review Subcommittee provides peer review of NTP long-term toxicity, carcinogenesis, and short-term toxicity study reports. The Report on Carcinogens Subcommittee provides external scientific evaluation of substances nominated for listing in or delisting from the *Report on Carcinogens.* The Advisory Committee on Alternative Toxicological Methods provides oversight to The Center for the Evaluation of Alternative Toxicological Methods.

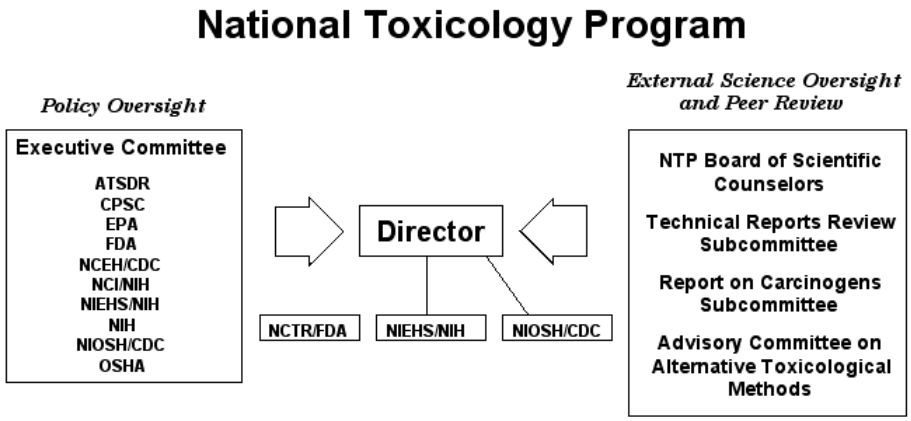

Figure 1. The National Toxicology Program, (NTP) is comprised of the relevant toxicology activities from three federal agencies - the National Center for Toxicological Research of the Food and Drug Administration (NCTR/FDA), the National Institute of Environmental Health Sciences of the National Institutes of Health (NIEHS/NIH), and the National Institute for Occupational Safety and Health of the Centers for Disease Control and Prevention (NIOSH/CDC). The NTP is headquartered at the NIEHS/NIH and its director serves as director of the NTP. Oversight for policy issues is provided by the Executive Committee composed of the heads of key research and regulatory Federal agencies. Science oversight and peer review are provided through a mix of Federal, academic, industrial, and public interest science experts.

Role in Shaping Public Health Policy

Scientific information from multiple sources forms a core upon which regulatory agencies make decisions regarding public health (Figure 2). Over the past 20 years the NTP has maintained an interactive relationship with regulatory agencies and indirectly played a role in setting public health policy. The Program maintains an objective, science-based approach for dealing with critical issues in toxicology that has had a profound impact on building a strong link between use of scientific data and establishment of regulatory guidelines and public health decisions. 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 regulatory agencies. Effective and timely communication with regulatory agencies, the scientific community, and the public is also an integral part of these efforts.

The American people and government agencies at the State and Federal levels rely on the science base provided by the NTP in making credible decisions that will protect public health without necessarily increasing the regulatory burden on American industry. The NTP contributes to this process through the generation of scientific data from the conduct of toxicological studies and through its interactive role with regulatory agencies in interpretation of those data. A significant contribution to public health policy is publication of the *Report on Carcinogens* (see page 14), a hazard identification document that lists potentially carcinogenic substances to which the public is exposed.

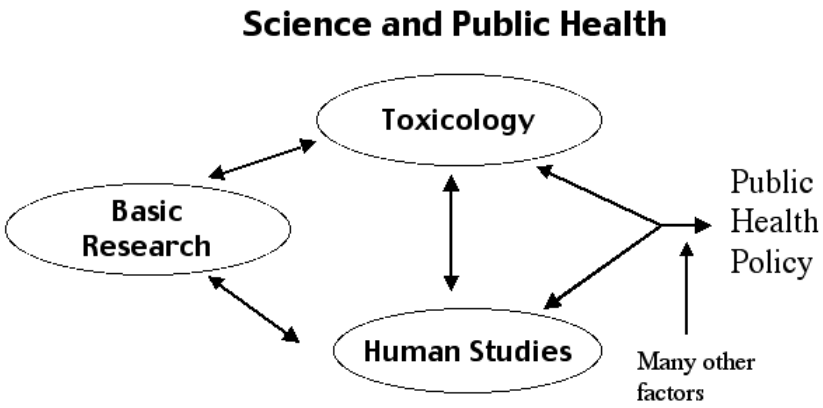

Figure 2: Scientific information comes from multiple sources and types of investigations: basic research, toxicology studies, and human studies. Each of these contributions to the science base upon which further study can be conducted. Regulatory agencies rely upon the availability of scientific data and its iinterpretation as well as other factors in making decisions about public health.

Selected reading

1. Lucier, GW, Barrett JC. Public health policy and the National Toxicology Program (editorial). *Environmental Health Perspectives* 106(10):A470-471 (1998).
2. Fisher BE. Twenty years of toxicology. *Environmental Health Perspectives* 106(10):A480-487 (1998).

Toxicological Evaluations

In keeping with its goal of providing up-to-date information about chemicals and potential toxicities, the NTP can initiate chronic bioassays (approximately 10 per year) on only a small fraction of the thousands of chemicals for which there is little or no toxicological information. The cancer studies are lengthy, can cost approximately $2-4 million each, and may take up to five years from initiation through completion and review. Many more chemicals are also studied to assess a variety of health-related effects, including but not limited to reproduction and development, immunotoxicity, neurotoxicity, genotoxicity, metabolism, toxicity to various organs, and carcinogenesis. The possible public health consequences of exposure remain the overriding factor in the decision to study a particular chemical or agent.

The NTP strives to balance the selection of chemicals for study (e.g. occupational, environmental, food additives, agricultural chemicals, pharmaceuticals). In selecting chemicals for study, the NTP Executive Committee operates under the principle that industry will evaluate chemicals or other agents for health and environmental impacts as intended and mandated by Congress under legislative authorities. Chemicals are selected based upon two broad criteria: 1) those chemicals of greatest concern for public or occupational health and 2) chemicals for which toxicologic data is needed to fill major knowledge gaps, address mechanisms of toxicity, and reduce uncertainty in risk assessment. The specific categories for which the NTP solicits nominations are given in Table 1. Nominations are sought from academia, Federal and State regulatory agencies, industry, unions, environmental groups, and the public. Toxic release inventories and exposure surveys (e.g. National Health and Nutrition Examination Surveys (NHANES) and National Human Exposure Assessment Survey (NHEXAS) are also reviewed to identify chemicals of concern based upon the opportunity for identifying human exposure and body burden data.

Table 1
Categories for NTP Solicitations

- Chemicals found in the environment not closely associated with a single commercial organization
- Biological or physical agents that may not be adequately evaluated without Federal involvement
- Orphan drugs or chemicals with significant exposure that generate too little revenue to support further evaluations
- Chemical agents first marketed prior to current testing requirements (e.g. 1977 Toxic Substances Control Act)
- Substances that occur as mixtures for which evaluations cannot be required of industry
- Chemicals or agents that will aid the understanding of chemical toxicities or an understanding of the use of test systems to evaluate potential toxicities
- Emergencies or other events that warrant immediate government evaluation of a chemical or agent

A schematic of the chemical nomination process is given in Figure 3. An interagency working group drawn from the NTP Executive Committee member agencies reviews the chemical nominations. Public comment is solicited on the list of nominees throughout the process. At a public meeting, the NTP Board of Scientific Counselors reviews the recommendations from the working group and accepts public comments. The NTP Executive Committee then reviews and and votes on the chemicals recommended for study, deferral, or withdrawal. The selection of a chemical or agent by the Executive Committee does not

automatically commit the NTP to its evaluation. The priority of the chemicals and the proposed studies are assessed during the nomination process and reassessed during the study design process. During any of these stages, a chemical or study may be withdrawn if applicable research data is identified, higher priority studies are identified, or if a study proves impractical.

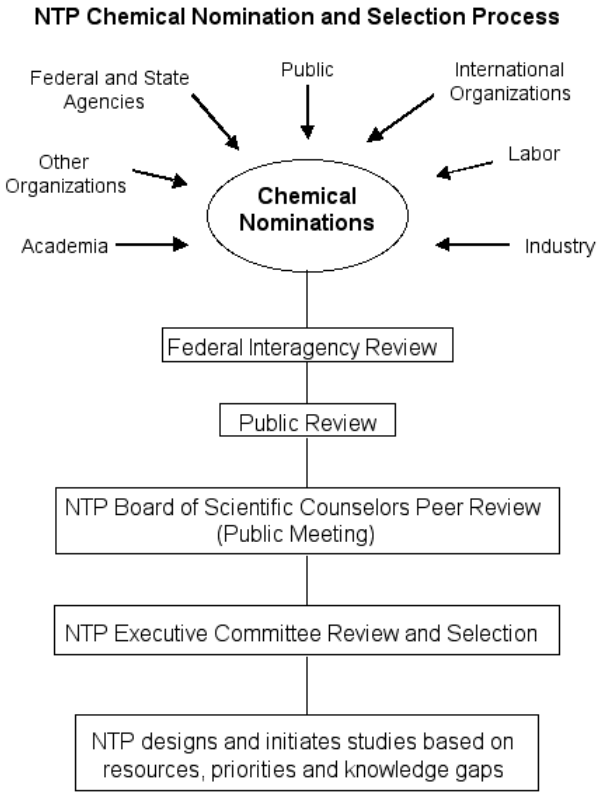

Figure 3. Schematic representation of the steps in nomination and selection of chemicals for study by the National Toxicology Program.

For all selected chemicals, studies are initiated as time and resources permit. Prechronic, short-term studies generally are performed for two or 13 weeks. Long-term, chronic bioassays last up to two years. The NIEHS/NTP staff reviews the toxicology literature for each chemical and designs a comprehensive testing strategy. Project plans are reviewed by a NIEHS/NTP project review committee that evaluates the project plan (e.g. design, methods, hypothesis, etc.) and proposed the vehicle for execution (e.g. grant, contract, etc). The NIEHS/NIH toxicokinetics faculty examines all chemicals under study and delineates any areas of chemical metabolism and kinetics for which sufficient data are lacking; studies are designed to address these deficiencies. The results of toxicological studies undergo rigorous peer review. These findings are published in NTP Technical Reports and may also be published in peer reviewed scientific journals. The NTP Technical Reports Review Subcommittee, a standing subcommittee of the NTP Board of Scientific Counselors, evaluates the technical reports from carcinogenicity and toxicity studies. Studies peer reviewed in fiscal year 1999 are listed in Table 2.

Table 2
Chemicals Peer Reviewed by the
NTP Board Technical Reports Review Subcommittee

Peer Reviewed on October 30, 1998	**Peer Reviewed on May 21, 1999**
Triethanolamine	*Anthraquinone*
Methyleugenol	*Emodin*
Ethylene Glycol Monobutyl Ether	*Fumonisin B_1*
Oxymetholone	*Gallium Arsenide*
Glutaraldehyde	

Public input at these meetings is very important as it is at all phases of study design, performance, and review. NTP Technical Reports are available to the public and other interested parties (see page 20).

The NTP has a broad mandate to provide toxicological characterizations for chemicals and agents of public health concern. The chemicals recommended for study most recently by the NTP Executive Committee are given in Table 3. The NTP works on a broad range of high priority agents and issues. During the past six years, the NTP has been involved in the Congressionally-mandated evaluation of possible human health effects resulting from exposure to electric and magnetic fields that are associated with the generation, distribution, and use of electric power. In 1998, the NTP completed and reviewed the results from a two-year bioassay of whole body exposure to magnetic fields in rodents (1-2). The NTP has performed or is performing 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. The NTP is working to determine the relationships between ecological/wildlife effects and human health. Specifically, the NTP is collaborating with the State of Minnesota and other State and Federal agencies to determine if the high incidence of malformed frogs found in several states is associated with increases in human disease. Examples of two new initiatives, the characterization of potential adverse health effects from dietary supplements and herbal medicines and an assessment of the risk of exposure to the major drinking water disinfection by-products, are described below.

Table 3
Chemicals Approved for Study by the NTP Executive Committee

Approved December 16, 1998	*Approved February 24, 1999*
Annatto	Androstenedione
Bixin	Bentonite
Diethylamine	Bis (2-chloromethoxy) methane
Dihydroxyacetone	Chromium picolinate
Fenchone	Cumene hydroperoxide
Isopropylamine	Echinacea
Pulegone	Fluasterone
a-Solanine	Ginkgo
Thujone	Pyrogallol
Triethylamine	
Trigonelline	

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1. McCormick DL, Ryan BM, Findlay JC, Gauger JR, Johnson TR, Morrissey RL, Boorman GA. Exposure to 60 Hz magnetic fields and risk of lymphoma in PIM transgenic and TSG-p53 (p53 knockout) mice. *Carcinogenesis*19(9):1649-1653 (1998).
2. NTP. Toxicology and Carcinogenesis Studies of 60-Hz Magnetic Fields in F344/N Rats and B6C3F1 Mice (Whole Body Exposure Studies). Technical Report Series No. 488 NIH Publication No. 98-3978. Research Triangle Park: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program, 1998.

Herbal Medicines

Medicinal herbs are some of our oldest medicines and their increasing use in recent years is evidence of a public interest in having alternatives to conventional medicine. Herbal medicines currently account for one of the fastest growing markets in U.S. pharmacies and constitute a multi-billion dollar industry. Although approximately 1500 botanicals are sold as dietary supplements or ethnic traditional medicines, herbal formulations are not subject to FDA premarket toxicity testing to assure their safety or efficacy.

In response to concerns regarding the use and efficacy of medicinal herbs and to recent nominations of these products for study by the NTP, a workshop on herbal medicines was organized to address research needs. This workshop was sponsored by the NTP in conjunction with the NIH Office of Dietary Supplements, the DHHS Office of Disease Prevention and Health Promotion, the FDA Office of Special Nutrition, and the Society for the Advancement of Womens Health Research and held 23-24 September 1998 in Raleigh, NC. Its objectives were to discuss the use, safety, and possible health-related problems of medicinal herbs; identify how other countries evaluate and regulate medicinal herbs; establish the NTPs role in determining their long-term safety; and recommend areas for research. A broader objective of the meeting was the focus and coordination of U.S./international research efforts. Recommendations from the workshop include a call for more research, identification and standardization of product ingredients by industry, and increased consumer education through package inserts (1).

In follow-up to this workshop, the NTP staff is working with the NIH Office of Dietary Supplements, the FDA, the academic community, and others to further define and implement research that addresses deficiencies in our knowledge about herbal medicines and their potential toxicities. Several herbs and active or toxic ingredients found in some herbs have been nominated and selected for study by the NTP (Table 4). These studies will focus on characterization of potential adverse health effects including reproductive toxicity, neurotoxicity, and immunotoxicity as well as those associated with acute high dose exposure and chronic exposure to lower doses. In addition, special attention will be given to the potential for herb/herb and herb/drug interactions and the responses of sensitive subpopulations (e.g. pregnant women, the young, the developing fetus, the elderly, etc). Comments from the public and others regarding NTP research in this area are welcome and should be forwarded to the NTP Liaison and Scientific Review Office (see page 19).

Table 4
Herbs and Active or Toxic Ingredients for Study by the NTP

Herb or Ingredient	*Information*
Golden Seal	Second or third most popular medicinal herb used in this country
Comfrey	Herb consumed in teas and as fresh leaves for salads; contains pyrrolizidine alkaloids, which are known to be toxic
Ginkgo	Among the five or six most frequently used medicinal herbs
Echinacea	Most commonly used medicinal herb in the United States
Berberine	An active ingredient in golden seal
Thujone	A toxic compound of worm wood
Pulegone	A toxic compound found in pennyroyal

Reference

1. Herbal Health. *Environmental Health Perspectives* 106(12): A590-592 (1998).

Safe Drinking Water

The availability of safe drinking water is a substantive health concern. Chlorination of our water supply is a standard treatment technique and is considered as one of the major public health advances in this century. Despite almost two decades of research, questions remain about the potential hazards of disinfection by-products (DBP) that are produced during this treatment process and found in our water supply. The NTPs studies, which include the use of transgenic animals and mechanistic studies, will determine which of the by-products are safe and which are dangerous. This information will facilitate development of strategies to maximize the benefits of disinfection and minimize the risks.

The Safe Water Drinking Program is of enormous public health significance since it is estimated that more than 200 million Americans use treated drinking water. The NTP in collaboration with the EPA has established a research program to assess the potential risks from human exposure to the major DBPs. The research program includes a systematic, mechanistic-based, toxicologic evaluation of DBPs that can help policy makers in setting drinking water standards. Research efforts are also underway with the Department of Defense (DOD), and the NIEHS/NTP is interested in involving the extramural research community in this effort through support of hypothesis-based mechanistic studies.

The selection of DBPs for study is based upon their presence in drinking water, their occurrence with different disinfection processes, their chemical structure, and representation from among the different DPB families. Research will focus on reproductive toxicity, immunotoxicity, and neurotoxicity as well as carcinogenesis. Many of the reproductive studies include toxicity and cell proliferation end-points. Traditional animal models, such as the F344 rats and B6C3F1 mice, are being used as well as transgenic strains (Tg.AC and $p53^{def}$, see page 11). A brief description of the testing strategy is provided.

- Studies are underway with DOD to test chloroform, a member of the halomethane family, in the small fish model, Medaka. Information from this model may help to provide information on health effects at low concentrations in water, an area that is still unresolved despite numerous long-term and mechanistic study on this chemical. NTP drinking water studies are underway to characterize the intestinal, renal, and liver responses to low concentrations of bromodichloromethane, a trihalomethane, in male rats and female mice. A transgenic mouse sensitive to colon cancer is also being used. Studies in collaboration with NIEHS/NIH will also be conducted in transgenic models (Tg.AC and $p53^{def}$) and with DOD in Medaka fish.
- Another family formed after chlorination is the haloacetic acids. Members of this family are being evaluated by NIEHS/NIH in F344 rats and B6C3F1 mice in short-term toxicity studies. Based upon these results, several haloacetic acids will be selected for long-term bioassays.
- Very little toxicity data is available on a third family of DBPs, the haloacetonitriles. Dibromoacetonitrile is selected as representative of this family; based upon the results, additional members may be evaluated.
- Preliminary studies at EPA and NIEHS/NIH show that chlorate, a by-product of chlorine dioxide, causes thyroid follicular cell hyperplasia in rats after short-term exposure. Mechanistic studies are underway at EPA to determine if chlorate interferes with iodine uptake by the thyroid. A two-year rodent bioassay is also underway at NIEHS/NIH, and DOD is evaluating chlorate in the Medaka fish model.
- Ozone use in water disinfection prevents the production of many DPBs, but a major by-product is bromate. EPAs testing of bromate in drinking water showed evidence of mesotheliomas in rats and kidney tumors in both rats and mice; potassium bromate feeding studies caused renal cancer in rats. Sodium bromate in drinking water is being evaluated in transgenic models (Tg.AC and $p53^{def}$); further mechanistic studies may be considered.

Emerging Research Strategies

A large number of chemicals (>80,000) are currently in use. The NTP continually faces the task of determining which ones should be studied with the limited resources available for toxicological testing. As a consequence, the NTP must set its priorities and develop strategies that best use its resources in ways that strengthen the science base used by regulatory agencies in making decisions for public health policy. It is clear that regulatory agencies, such as the EPA, are committed to using all relevant information in their assessments. Implementing new strategies, which provide additional information and/or are more accurate, can strengthen the science base on which regulatory decisions are made. The NTP has a strong and continuing commitment to increase the number of agents entered into toxicology and carcinogenesis studies. New methods, especially those that provide mechanistic data, may also allow for more rapid screening and decreased dependence on chronic two-year rodent bioassays.

Scientists at the NIEHS/NIH, NCTR/FDA, and NIOSH/CDC are involved in development and validation of a wide range of testing methods for toxicological research including transgenic animals for carcinogenicity testing and genetically engineered cell systems to measure endocrine disruptor activity. University-based researchers are also involved in this effort through the NIEHS/NIH extramural grants program. Model systems under development include non-mammalian species, transgenic species, genetically engineered *in vitro* cell systems, microchip array technology, and computer-based predictive toxicology models.

Mechanism-Based Toxicology and Risk Assessment Methodologies

As a leader in the design, conduct, and evaluation of toxicological data for use in making public health decisions, the NTP's testing program is committed to the use of mechanism-based toxicology studies as an enhancement to the traditional approaches. This field uses molecular biology tools to characterize interactions of chemicals with critical target genes. Examples of mechanism-based toxicology include identification of receptor-mediated toxicants, molecular screening strategies, use of transgenic animal models (see below) and the development of alternative or complementary *in vivo* tests to use with rodent bioassays. Inclusion of such strategies can provide insight into the molecular and biological events associated with a chemical's toxic effect and provide mechanistic information that is useful in assessing human risk. Such information can also lead to the development of more specific and sensitive (and often less expensive) tests for use in risk assessment. There is a strong linkage between mechanism-based toxicology and the development of more biologically based risk assessment models. Such models are useful in clarifying dose-response relationships, making species comparisons, and identifying sources of inter-individual variability (see below).

Transgenic Animals
Genetically altered or "transgenic" mouse models carry activated oncogenes or inactivated tumor suppressor genes known to be involved in the neoplastic processes both in humans and rodents. This trait may allow them to respond to carcinogens more quickly than conventional rodent strains. The advantage provided by such an approach over standard rodent models is that in addition to chemicals undergoing metabolism, distribution, and relevant pharmacokinetics, the neoplastic effects of agents can be observed in the transgenic models within a time frame in which few if any spontaneous tumors would arise. The high incidences of spontaneous or background tumors, which occur most often late in the two-year rodent cancer studies, are among the most confounding factors for interpreting the findings of chemical carcinogenesis and their implications for human health. It is proposed that this problem would be reduced through the use of transgenic models, since the likely genetic targets for the effects of chemicals are highly conserved oncogenes or tumor suppressor genes as opposed to the many potentially unidentified genes that contribute to the carcinogenic response in conventional rodent lines (1). The use of target or reporter genes also allows for direct molecular and cellular analysis of a chemicals effects in these models and can provide additional mechanistic information about mode of action.

Over the past few years, the NIEHS/NTP has conducted an evaluation of transgenic strains in toxicological testing strategies. The response for 38 chemicals was compared in two genetically altered mouse strains ($p53^{def}$: *p53+/-*heterozygous and Tg.AC: *v-Ha-ras* transgene) with that of wild-type mice tested in chronic two-year bioassays. Findings from these studies (2) were evaluated by the NTP Board of Scientific Counselors on 5 February 1998 (3) for their suitability for use in NTP toxicological evaluations. Based upon the NIEHS/NTP review, the transgenic models performed largely according to predictions; they identified all known human carcinogens and most of the multi-site/multi-species rodent carcinogens, but failed to identify completely rodent carcinogens that produced tumors in selected organs in two-year studies.

The use of these genetically altered mouse models holds promise in carcinogenesis research and testing and clearly is more rapid and less expensive than traditional NTP two-year bioassay studies. The challenge still facing the NTP is to design studies that address remaining questions and concerns and to explore how these models can be used in risk assessment (4). One current NTP project is examining tumor dose-response relationships of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD, dioxin) and diethylstilbestrol in the Tg.AC mouse. Comparative toxicokinetic studies in transgenic models and parental wild type strains are also underway; some recent findings are reported (5). The NTP is looking into ways that transgenic mouse assays could be used to provide information about selection of doses for the two-year bioassays. One example is their use in a current initiative to evaluate the safety of disinfection by-products found in drinking water (described earlier). The International Life Sciences Institute, a non-profit foundation, is also coordinating a partnership between Federal agencies and the pharmaceutical industry to study the utility of transgenic models; the NTP is participating in this effort.

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Risk Assessment Methodology
Mathematical risk assessment models are used to quantify the sequence of events that start with chemical exposure and end with overt toxicity. Models, whose designs are biologically based, allow researchers to link a broad array of experimental findings in ways that are both biologically logical and useful in risk assessment for defining dose-response relationships, making species comparisons, and assessing inter-individual variability. NTP initiatives, such as the human exposure assessment (see below), are being undertaken to try and improve the availability of human data for use in development of such risk assessment models.

Several models are now complete and bear noting. EPA is using a model developed for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD, dioxin) as part of an ongoing mechanistically based risk assessment. This model and one developed for 1,3-butadiene include the best characterizations available for the pharmacological and biochemical effects of these compounds. Mechanistically based models are also being developed and applied to NTP data to provide a better means for analyzing and interpreting bioassay results. Inclusion of physiologically based pharmacokinetic models (PBPK) in NTP technical reports is becoming routine, and such information should give guidance to regulatory agencies interested in extrapolation of data across species.

The NIEHS/NIH toxicokinetics faculty evaluates the appropriateness of a biologically based pharmacokinetic model for each chemical selected for NTP study. If a credible and potentially useful model can be constructed, then a study is designed to collect the appropriate data. The NTP's effort in risk

assessment is closely tied to its growing initiatives in mechanism-based toxicology (described earlier). This linkage provides opportunities to improve priority setting, use mechanistic information to establish risk or safety, clarify dose-response relationships in the "low dose" range, select the most appropriate experimental systems for estimating risk, and develop science-based models for specific subpopulations (e.g. age, gender, genetic predisposition, ethnicity, etc.). Information about models and projects related to risk assessment is available at http://www.niehs.nih.gov.

Human Exposure Assessment
The NTP increasingly recognizes the need for human data in its science base for decision-making. Information on human exposure to agents and their body burden is critical for a successful and scientifically sound approach to the evaluation of potential human health risks. However, the availability of human exposure assessment data is often the weakest component of risk assessment and limits the effective utilization of experimental data for making decisions about chemical exposures.

Advances in analytical methodologies now enable the detection of environmental and occupational chemicals in small biological samples (e.g. blood, urine, and hair). Taking advantage of such advances, the NTP is leading a new interagency human exposure assessment initiative in collaboration with NCEH/CDC, NIOSH/CDC, and EPA to quantify the body burdens of chemicals released into the environment and workplace. Efforts being undertaken in moving forward with this initiative are described below. This effort will benefit public health and priority setting by:

- allowing the prioritizing of chemicals and chemical mixtures to be studied by the NTP based on their occurrence in human tissue,
- providing data documenting exposure to children,
- identifying potentially "sensitive" subpopulations,
- strengthening the interpretation and use of animal toxicity data in quantifying the amount of chemical and/or active metabolite in blood and target tissues,
- allowing for refinement of human risk assessments through construction of physiologically based pharmaco/toxicokinetic models,
- examining relationships between health disparities and fiscal disparities,
- enhancing future epidemiological studies of exposure/disease relationships,
- allowing government agencies to determine the effectiveness of regulatory actions for environmental standards and clean-up sites, and
- linking these data with the NIEHS Environmental Genome Project.

The NIEHS Environmental Genome Project is a multi-center effort to identify systematically in the U.S. population the alleles of 200 or more environmental disease susceptibility genes. Information from this human exposure assessment initiative together with the environmental genome project will provide the science base essential for future, meaningful studies of gene/environment interactions in disease etiology.

Assessment of Endocrine Disruptors
As a part of the interagency human exposure assessment initiative, the NTP and the NCEH/CDC are collaborating on a pilot project for quantifying approximately 70 chemicals in either human blood or urine that are considered to be endocrine disruptors. The biological samples from the National Health and Nutrition Examination Surveys (NHANES) are being tested. This data will be used to estimate human exposure to endocrine disrupting agents within the U.S. population and to identify the ones of greatest public health concern. This information can be used in prioritizing chemicals for study and in developing biologically based models for estimating human risks.

Human Exposure Assessment and Environmental Disease Workshop
The NIEHS/NIH and NTP are sponsoring a workshop 22-24 September 1999 to bring together scientists and policy-makers from government agencies, academia, industry, and community groups who have an interest in exposure assessment issues. This workshop should provide information on disease-specific chemical exposure, highlight approaches for future research, and facilitate development of effective prevention and intervention strategies for chemical exposures. For additional information about this workshop visit the NTP web-site, http://ntp-server.niehs.nih.gov, or contact:
Dr. Scott Masten, NIEHS/NTP, P.O. Box 12233, Research Triangle Park, NC 27709
T: 919-541-5710, F: 919-541-7666, e-mail: masten@niehs.nih.gov.

Selected reading

1. Lucier GW, Schecter A. Human exposure assessment and the National Toxicology Program. *Environmental Health Perspectives* 106(10):623-627 (1998).

Report on Carcinogens

The *Report on Carcinogens* (*RoC*), previously called the *Annual Report on Carcinogens*, is prepared in response to Section 301 of the Public Health Service Act, as amended. This law 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 *RoC* 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 NTP solicits and encourages the broadest participation from interested individuals or parties in nominating agents, substances, mixtures, or exposure circumstances for listing in or delisting from the *RoC*. Nominations are requested to contain a rationale for listing or delisting. Appropriate supporting background documents (e.g. journal articles, NTP Technical Reports, International Agency for Research on Cancer listings, exposure surveys, release inventories, etc.) that support a nomination should be provided or referenced when possible. Anyone may nominate a substance to be considered for listing in or delisting from the *RoC* . The nominations should be submitted to Dr. C.W. Jameson, NTP, Report on Carcinogens, NIEHS/NIH, P.O. Box 12233, MD EC-14, Research Triangle Park, NC 27709, T: 919-541-4096, F: 919-541-0947, e-mail: jameson@niehs.nih.gov.

The review of agents, substances, mixtures, or exposure circumstances for listing in or delisting from the *RoC* involves a multi-phased, peer review process.

Public comment on the nominations is solicited several times during the review process. Briefly, two Federal scientific review groups independently evaluate all available data relevant to the inclusion or exclusion of candidate agents and vote on each agent. A subcommittee of the NTP Board of Scientific Counselors also evaluates the data independently and votes on classification during an open, public meeting that also provides an opportunity for public comment. All comments and recommendations are presented to the NTP Executive Committee for review and comment. The NTP Director makes the final recommendation for listing and/or delisting in the final draft of the *RoC* and submits it to the Office of Secretary, DHHS for approval.

The criteria used for listing in the *RoC* are as follows:

Known to be Human Carcinogens:

- There is sufficient evidence of carcinogenicity from studies in humans which indicates a causal relationship between exposure to the agent, substances or mixture and human cancer.

Reasonably Anticipated to Be Human Carcinogens:

- There is limited evidence of carcinogenicity from studies in humans which indicates that a causal interpretation is credible but that alternative explanations such as chance, bias or confounding factors could not be adequately excluded; or
- There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors: (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site or type of tumor or age at onset; or
- There is less than sufficient evidence of carcinogenicity in humans or laboratory animals; however, the agent, substance or mixture belongs to a well defined, structurally-related class of substances whose members are listed in a previous *Report on Carcinogens* as either a *known to be human carcinogen* or *reasonably anticipated to be human carcinogen* or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgement, with consideration given to all relevant information. Relevant information includes, but is not limited to dose-response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub-populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals but there are compelling data indicating that the agent acts through mechanisms which do not operate in human and would therefore not reasonably be anticipated to cause cancer in humans.

The most recent *RoC* is the 8th Edition that was published in 1998. The *8th RoC* is available on the NTP home page at http://ntp-server.niehs.nih.gov or may be obtained by contacting the Environmental Health Information Service (EHIS, see page 19). The 9th Report is scheduled for publication in late 1999. A list of the nominations under consideration for listing in or delisting from the *9th RoC* is given in Table 5.

Nominations to be considered in 1999 and 2000 for listing and delisting in the 10th Edition of the *RoC* will be announced for public comment early in 1999. Publication of the 10th Edition is anticipated for 2001.

Table 5
*Summary of the Agents, Substances, Mixtures, or Exposure Circumstances Reviewed for Possible Listing in or Delisting from the 9th Report on Carcinogen**

Reviewed in 1997	*Reviewed in 1998*
Benzidine-based dyes as a class	Alcoholic beverage consumption
1,3-Butadiene	Boot and shoe manufacture and repair
Cadmium and Cadmium compounds	Diesel exhaust particulates
Chloroprene	Environmental tobacco smoke
Phenolphthalein	Ethyl Acrylate
Saccharin	Ethylene Oxide
Smokeless tobacco	Isoprene
Solar radiation and exposure to sunlamps and sunbeds	
Sulfuric acid mist	Methyl-*t*-Butyl Ether
Tamoxifen	Nickel compounds

Tetrafluoroethylene	Silica, crystalline (respirable size)
Tobacco smoking	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCCD)
Trichloroethylene	

*These agents were reviewed by three groups, the NIEHS/NIH Review Group for the *RoC*, NTP Executive Committee Working Group, and NTP Board of Scientific Counselors Subcommittee for the *RoC*. Actions by each of the groups can be found at the NTP web-site, http://ntp-server.niehs.nih.gov

New NTP Centers

Two new administrative centers, The Center for the Evaluation of Alternative Toxicological Methods and The Center for the Evaluation of Risks to Human Reproduction, have been established within the NTP.

The Center for the Evaluation of Alternative Toxicological Methods
The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) was established in 1997 in response to the 1993 NIH Revitalization Act to reduce, refine, or replace the use of animals in research and testing. ICCVAM has membership from 14 Federal agencies and programs (ATSDR, CPSC, Departments of Defense, Energy, Interior, and Transportation, EPA, FDA, NCI/NIH, NIEHS/NIH, NIH, NIOSH/CDC, National Library of Medicine/NIH, and OSHA). The Committee functions to provide cross-agency communication and coordination on issues relating to validation, acceptance, and national/international harmonization of toxicological testing methods.

The NTP Center for the Evaluation of Alternative Toxicological Methods (NICEATM) was established in 1998 to provide operational support for ICCVAM and to coordinate committee-related review panels and workshops. ICCVAM and NICEATM work to promote the validation and regulatory acceptance of toxicological test methods that are more predictive of human and ecological effects than those currently available and to communicate with stakeholders and the public. The desired outcomes from these new methods are the improvement in agencies abilities to assess risk and make regulatory decisions, and the refinement, reduction, and replacement of animals in toxicological testing. The Advisory Committee on Alternative Toxicological Methods established by DHHS meets biannually to provide ICCVAM and NICEATM advice on activities and priorities. It is composed of knowledgeable representatives from academia, industry, public interest and animal welfare organizations, other agencies, and the international community.

Workshops are held, as needed for evaluation of adequacy of existing methods, identification of areas needing alternative methods, and evaluation of proposed validation studies. A formal, scientific review process is in place for evaluation of the validation status of proposed alternative testing methods. Briefly,

- ICCVAM considers whether a proposed alternative method should be evaluated.
- Peer review panels are convened and charged with development of a scientific consensus on the usefulness, limitations, and validation status of the proposed test method.
- ICCVAM reviews the panels document on scientific validity and potential acceptability of a test method and forwards the report to regulatory agencies. Each agency decides the regulatory acceptability of a new method according to its own mandates.

Two alternative methods have been brought to ICCVAM and the Center for consideration. The murine Local Lymph Node Assay (LLNA), a method for assessing allergic contact dermatitis of chemicals, was reviewed in September 1998 and the final report is available. The peer review panel concluded that the LLNA is a valid alternative to the currently accepted guinea pig test methods and also provides for the refinement and reduction of animal use. Unlike traditional guinea pig test methods, this mechanistic test quantifies the proliferation of lymphocytes in the regional lymph nodes in response to a chemical and can be used to evaluate its relative potency. From an operational and economic viewpoint, the LLNA also appears to be more efficient, quicker, cost less, use fewer animals, and subject the animals to less pain and distress. Individual regulatory agencies will now decide the acceptability of this method according to their own mandates. An *in vitro* method, Corrositex^{R}, used for assessing the dermal corrosivity potential of chemicals, was reviewed by a peer review panel in January 1999. The panel concluded that the method could be used for assessing the corrosivity of certain chemical classes and used in a tiered testing approach for other classes; the report will be available in June 1999 or accessible from a link on the NTP homepage, htt;://ntp-server.niehs.nih.gov.

Information about ICCVAM and NICEATM is found at http://iccvam.niehs.nih.gov or contact:
NICEATM, NIEHS/NIH, P.O. Box 12233, MD EC-17, Research Triangle Park, NC 27709
T: 919-541-3398, F: 919-541-0947, e-mail: NICEATM@niehs.nih.gov.

For inquiries regarding nominations of alternative testing methods contact:

Dr. William S. Stokes
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F: 202-260-1847
e-mail: hill.richard@epamail.gov

Selected reading

1. Clay, R. New tricks for an old assay. *Environmental Health Perspectives* 106(10):A488-489 (1998).

2. Twombly R. New NTP centers meet the need to know. *Environmental Health Perpectives* 106(1):A480-483 (1998).
3. NTP. Validation and Regulatory Acceptance of Toxicological Test Methods, A Report on the Ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods. NIH Publication No. 97-3981. Research Triangle Park: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program, 1997.
4. Chhabra, R.S., Bucher, J.R., and Stokes, W.S. US National Toxicology Program strategies for use of alternate test systems. van Zutphen, L.F.M. and Balls, M. (eds.) *Animal Alternatives, Welfare and Ethics*, Elsevier Science, B.V. pp. 607-615 (1997).

The Center for the Evaluation of Risks to Human Reproduction

The Center for the Evaluation of Risks to Human Reproduction (CERHR) was established in June 1998 through the NIEHS/NIH and NTP in response to an increasing awareness of the public and scientific community about possible adverse effects of environmental exposures on fertility and childbearing. The NTP Board of Scientific Counselors provides oversight for the Center. The CERHRs goal is to provide the public, scientific community, regulatory agencies, and public health policy makers a compilation of available information for a chemical or mixture and an objective scientific assessment on its reproductive risk(s) and to identify critical gaps in the science base and special research needs. Two to three chemicals are evaluated per year, and the Center follows a formal process for their nomination, selection, and review including:

- call for nomination of chemicals for evaluation,
- compilation of available scientific information on nominated chemicals,
- evaluation of whether or not to move forward with formal review of the agent,
- review of background documents and information by a Scientific Review Panel with diverse scientific expertise, and
- preparation of evaluation documents by the Scientific Review Panel.

Public input is important in this process and can occur through 1) the nomination of chemicals for evaluation, 2) public comments on nominations and the prioritizing and selecting of chemicals nominated for evaluation, and 3) public comments on the evaluation of a particular chemical at the time of the expert panel meetings. The public is encouraged to nominate chemicals or chemical mixtures for review through the Center and/or suggest scientists to be added to an Expert Registry from which reviewers will be appointed to serve on the ad hoc panels that assess the reproductive and developmental toxicity of selected agents. Nominations of chemicals or chemical mixtures should be accompanied by a justification for the nomination, and whenever possible, include appropriate background information, data, or literature citations. Scientists names suggested for addition to the Expert Registry should be accompanied by a description of their expertise and curriculum vitae. All chemical nominations and suggestions for the Expert Registry should be forwarded to:
NTP Center for the Evaluation of Risks to Human Reproduction, Attn: Dr. John A. Moore, 1800 Diagonal Road, Suite 500, Alexandria, VA, 22314
T: 703-838-9440, F: 703-684-2223, e-mail: jmoore@sciences.com, web address: http://cerhr.niehs.nih.gov. The Centers web-site is operational and is accessible directly or through links with the NIEHS and NTP home pages, http://www.niehs.nih.gov and http://ntp-server.niehs.nih.gov.

Scientific Review Panel reports of evaluated chemicals will be published in *Environmental Health Perspectives* and will also be available on the Centers web-site. The first evaluation to be conducted will deal with a selected group of phthalates that are widely used in consumer products. It is anticipated that the first review will be conducted in the summer 1999.

For additional information about the Center contact:
Dr. Michael D.Shelby, Director CERHR, NIEHS/NTP, P.O. Box 12233, MD B3-09, Research Triangle Park, NC 27709
T: 919-541-3455, F: 919-541-4634, e-mail: shelby@niehs.nih.gov.

Selected reading

1. Twombly R. New NTP centers meet the need to know. *Environmental Health Perspectives* 106(1):A480-483 (1998).

Communication and Public Outreach

Maintaining open communications and ensuring dialogue with Federal and State agencies, industry, stakeholders, academia, and the public are goals of the NTP. The NTP Board of Scientific Counselors, its subcommittees for review of Technical Reports and the *Report on Carcinogens* (*RoC*), and the newly established Advisory Committee on Alternative Toxicological Methods assure regular scientific and public peer review and input. NTP conferences and workshops 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 remain a priority. Emphasis continues on ensuring broad dissemination of the results of NTP research and testing and in communicating information about its evolving programs and priorities. The distribution of NTP testing and research results and its program plans, initiatives, announcements, and publications occur through mailings, Federal Register announcements, and the world-wide-web that includes a subscription-based NTP List-Server. The NTP home page, http://ntp-server.niehs.nih.gov, offers access to information about the NTP, and links are available that detail and highlight ongoing and future initiatives, NTP centers, NTP documents, *Report on Carcinogens*, and announcements.

On-line, searchable access, as well as printed copies of NTP publications including the *Report on Carcinogens*, NTP Technical Reports, NTP Toxicology Reports, and other NTP documents, is available through the Environmental Health Information Service (EHIS) at http://ehis.niehs.nih.gov. Subscription packages to the EHIS include access to NTP publications, as well as *Environmental Health Perspectives* (primary issues and supplements), the Rodent Historical Controls Database, the Chemical Health and Safety Database, and a variety of other services. To purchase single copies or to subscribe on-line, visit the EHIS at http://ehis.niehs.nih.gov, e-mail: ehis@niehs.nih.gov, or call 1-800-315-3010.

The Central Data Management Office oversees distribution, upon request, of specific chemical study information and NTP documents including the NTP Annual Plan and Annual Plan Summary, NTP Study Status Reports, pre-peer review copies of draft NTP Technical Reports, background documents for chemicals nominated to the NTP, and summaries of minutes from NTP meetings including the Board of Scientific Counselors, and its subcommittees. Requests for these documents should be directed to:
Central Data Management, NIEHS/NIH, P.O. Box 12233, MD E1-02, Research Triangle Park, NC 27709
T: 919-541-3419, F: 919-541-3687, e-mail: cdm@niehs.nih.gov.

The NTP is interested in stakeholder input into its programs and priorities. Nominations, inquiries, and comments from the public and other interested parties

are welcome at any time. The NTP Liaison and Scientific Review Office serves as the focal point for receiving input to the Program and for overseeing the distribution of information about programs, workshops, initiatives, etc. Questions regarding the program, comments, and input can be submitted to:
NTP Liaison and Scientific Review Office, NIEHS/NIH, P.O. Box 12233, Research Triangle Park, NC 27709, T: 919-541-0530, F: 919-541-0295, e-mail: liaison@starbase.niehs.nih.gov.

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