National Toxicology Program

NTP

CURRENT DIRECTIONS and EVOLVING STRATEGIES

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ATSDR	Agency for Toxic Substances and Disease Registry
BSC	Board of Scientific Counselors
CDC	Centers for Disease Control and Prevention
CDM	Central Data Management
CERHR	Center for the Evaluation of Risks to Human Reproduction
CPSC	Consumer Product Safety Commission
DHHS	Department of Health and Human Services
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
HTS	High Throughput Screening
ICCEC	Interagency Committee for Chemical Evaluation and Coordination
ICCVAM	Interagency Coordinating Committee on the Validation of Alternative Methods
MLI	Molecular Libraries Initiative
MRI	Magnetic Resonance Imaging
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
NCP	NTP Center for Phototoxicology
NCTR	National Center for Toxicological Research
NICEATM	NTP Interagency Center for the Evaluation of Alternative Toxicological Methods
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PBPK	Physiologically Based Pharmacokinetic
PCB	Polychlorinated Biphenyl
RoC	Report on Carcinogens
SACATM	Scientific Advisory Committee on Alternative Toxicological Methods
TCDD	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin
TEF	Toxic Equivalency Factor
UV	Ultraviolet
WHO	World Health Organization

Overview

Mission and Goals

More than 80,000 chemicals are registered for use in the United States. Each year, an estimated 2,000 new substances are introduced for use in such everyday items as foods, personal care products, prescription drugs, household cleaners, and lawn care products. An estimated 500 to 600 new industrial chemicals are introduced annually to the U.S. commerce. We do not know the effects of many of these substances on our health, yet we may be exposed to them while manufacturing, distributing, using, and disposing of them or when they become pollutants in our air, water, or soil. While relatively few chemicals are thought to pose a significant risk to human health, safeguarding public health depends on identifying both what the effects of these substances are and at what levels of exposure they may become hazardous to humans—that is, understanding their toxicology.

The National Toxicology Program (NTP) was established in 1978 to (1) coordinate toxicology testing programs within the federal government, (2) strengthen the science base in toxicology, (3) develop and validate improved testing methods, and (4) provide information about potentially toxic chemicals to health, regulatory, and research agencies, scientific and medical communities, and the public. The NTP is an interagency program within the U.S. Department of Health and Human Services (DHHS) whose mission is to evaluate environmental substances of public health concern by developing and applying tools of modern toxicology and molecular biology. The program maintains an objective, science-based approach in dealing with critical issues in toxicology and is committed to using the best science available to prioritize, design, conduct, and interpret its studies. To that end, the NTP is continually evolving to remain at the cutting edge of scientific research, and to develop and apply new technologies.

Current Activities

The NTP maintains a number of complex, interrelated research and testing programs that provide unique and critical information needed by health, regulatory, and research agencies to evaluate potential human health effects from chemical and physical exposures. All of the NTP's activities are open to public scrutiny including communications with all interested parties. The NTP has always drawn strength and direction from the commitment of its scientists to exchange information openly, maintain impartiality, and apply rigorous, scientific peer review. This is a central priority of the program now and will remain so in the future.

The NTP seeks to maintain a balanced research and testing program that provides data on a wide variety of issues important to public health. In particular, the NTP seeks nominations of studies that

(1) fill significant gaps in the knowledge of the toxicity of chemicals or classes of chemicals, (2) address mechanisms of toxicity, or (3) enhance the predictive ability of future NTP studies. Currently, the NTP is focusing on several areas that have received inadequate attention in the past. Some examples include photoactive chemicals, contaminants of finished drinking water, endocrine-disrupting agents, and certain complex occupational exposures. The NTP is addressing potential safety issues associated with herbal medicines, radiofrequency radiation emissions from cellular telephones, perfluorinated compounds, and nanoscale materials. In general, these initiatives are broad-based and investigate various health-related effects.

The NTP continues to work to develop and validate alternative testing methods that will help identify environmental hazards using fewer test animals. This effort includes developing more efficient, mechanism-based testing strategies that provide information about how a substance affects biological processes, such as genetically engineered models for toxicology testing, and implementing gene expression technologies. The NTP is currently studying how to use *in vitro* high throughput assays for screening large numbers of substances for specific biological or toxic effects and for setting priorities for further toxicological evaluations. These methods hold the promise of providing a true mechanistic basis for identifying and studying environmental toxicants.

The NTP also evaluates whether human exposures to environmental agents cause adverse effects on reproduction, development, and the immune, respiratory, and central nervous systems. The NTP is expanding its effort to include routine investigations of changes in the immune system and the nervous system from exposures occurring during fetal development and early life.

The NTP continues to expand activities designed to place research and testing results from animals in a perspective that is more relevant to human health. This includes human exposure assessment, toxicokinetics, mechanism-based pharmacokinetic modeling, and interpreting results in molecular epidemiology for use in identifying human hazards (e.g., the Report on Carcinogens and the NTP's Center for the Evaluation of Risks to Human Reproduction). The NTP is also coordinating an effort to obtain "real-world" information about worker practices, complex occupational exposures, and potentially related adverse health effects. We need such information to identify areas for research and to design better laboratory studies on the potential health effects of chemicals, complex mixtures, and exposures people encounter in the workplace.

NTP Roadmap for the 21st Century

For more than 25 years, the NTP has been a leader in toxicology testing and research within the United States and has contributed significantly to the scientific knowledge upon which public health decisions are based. While the NTP has studied more than 2,500 substances, including more than 500 for cancer, relatively few of the existing and new substances can be evaluated fully for their potential to cause toxicity because the traditional methods used, while of great value for predicting biological responses, are time-consuming and labor intensive. Thus in August 2003, the NTP began reviewing its current activities to determine how to take advantage of new scientific technologies in its research and testing strategies, and broaden scientific knowledge on the link between mechanism and disease. The NTP created a vision for the program's future and in January 2005 released its roadmap to address the goals of that vision (available at http://ntp.niehs.nih.gov and select "NTP Vision & Roadmap").

The NTP's vision for the 21st century is to support the evolution of toxicology from an observational science based on disease-specific models to a predominantly predictive science focused on a broad inclusion of target-specific, mechanism-based, biological observations. The NTP Roadmap, developed with input from industry, academia, government, and advocacy groups, identifies current challenges and opportunities, and discusses future directions in three areas: (1) refinement of traditional toxicology assays, (2) development of rapid, mechanism-based, predictive screens for environmentally induced diseases, and (3) improvement in the overall utility of NTP products for public health decisions.

The NTP has now begun to implement the NTP Roadmap with workshops to address current toxicology and carcinogenicity testing strategies, a new high throughput screening initiative, and a focus on understanding host susceptibility. If initiated successfully, the NTP Roadmap should enable the NTP to broaden its testing activities to include more exposure scenarios, address susceptibility issues related to variability in human genetics, and provide better and more targeted scientific guidance for making public health decisions aimed at preventing or reducing adverse health effects.

Partnerships

Strengthening existing partnerships and forging new ones are important for the NTP to achieve its goals. The NTP has a critical role to provide scientific data, interpretations, and guidance on the appropriate uses of those data, and federal and state government agencies rely on the scientific knowledge base provided by the NTP to make credible decisions that protect public health. The NTP also works to (1) foster interagency collaborations in research and exposure assessment, (2) provide information to regulatory agencies about alternative methods for toxicity screening, and (3) explore new technologies for evaluating how environmental agents cause disease.

The NTP continues to develop international partnerships to establish efficient means to avoid duplicating effort(s) in toxicology testing. The NTP is collaborating with the European Ramazzini Foundation of Oncology and Environmental Sciences to create similar protocols, quality assurance, and reporting for laboratory studies on the health effects associated with long-term exposure to environmental agents. The NTP has a similar agreement with the Korea National Toxicology Program. The NTP is also participating in the World Health Organization's International Electric and Magnetic Fields Project to facilitate internationally coordinated research on the health effects of electric and magnetic fields, including those generated by cellular telephone technologies.

Organizational Structure and Oversight

Three agencies form the core of the NTP: (1) the National Center for Toxicological Research (NCTR) of the Food and Drug Administration (Figure 1), (2) the National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health, and (3) the National Institute for Occupational Safety and Health (NIOSH) of the Centers for Disease Control and Prevention. Each agency voluntarily provides resources to support NTP research, testing, centers, and outreach.

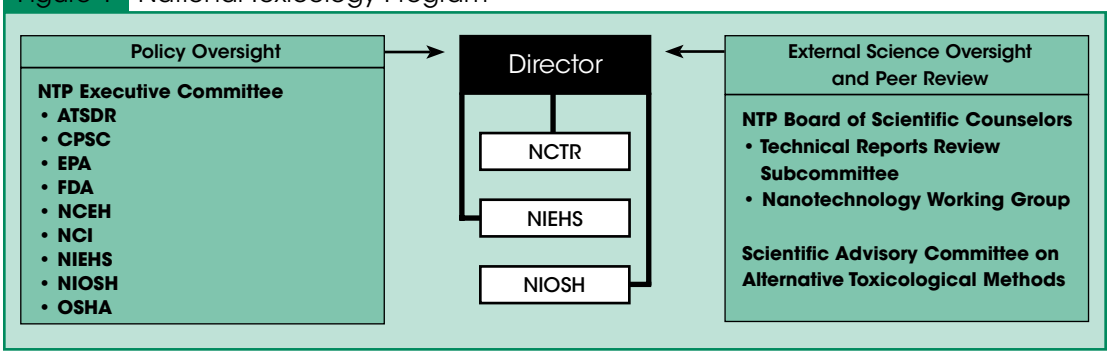
The NTP Executive Committee (Figure 1) provides oversight to the NTP for policy issues. This committee is composed of the heads (or their designees) of federal research and regulatory agencies. The NTP Board of Scientific Counselors (BSC) and the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) assure regular scientific and public peer review and input about NTP activities and priorities.

The BSC is a federally chartered advisory committee whose members are appointed by the secretary, DHHS. The BSC provides primary scientific oversight to the NTP director and evaluates the scientific merit of the NTP's intramural and collaborative programs. The Technical Reports Review Subcommittee of the BSC provides peer review for the NTP (1) long-term toxicology and carcinogenicity studies, (2) studies conducted in genetically modified models, and (3) as needed, short-term toxicity reports. These groups meet once or twice each year, and meetings are open to the public. In addition, the BSC, on occasion, convenes work groups to obtain an in-depth review of a specific topic.

The SACATM provides advice to the NIEHS director, the Interagency Coordinating Committee on the Validation of Alternative Methods, and the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods. This advice addresses priorities and directives related to the development, validation, scientific review, and regulatory acceptance of new or revised toxicological test methods, and ways to foster partnerships and communication with interested parties. The NIEHS director appoints members to this federally chartered advisory committee. The SACATM meets once or twice each year, and meetings are open to the public.

The NTP also uses special emphasis panels, as needed, to provide independent scientific peer review and advice to the NTP. These panels help ensure transparent, unbiased, and scientifically rigorous input to the program for its use in making credible decisions about human health hazards, setting research and testing priorities, and evaluating test methods for toxicity screening.

Figure 1 National Toxicology Program



Toxicology and Carcinogenicity Evaluations

The NTP has a broad mandate to characterize chemicals and other agents of public health concern. The NTP continually solicits and reviews nominations for toxicology studies for the specific categories listed in Table 1. The nomination process is open to all interested individuals and groups. Information about nominating a substance for testing by the NTP is available on the NTP website (http://ntp.niehs.nih.gov) or by contacting Dr. Scott Masten, Office of Chemical Nomination and Selection (for contact information, see inside back cover).

Table 1 Nomination Principles for NTP Studies

- Substances found in home, workplace, or ambient environments that are not associated with a single commercial organization.
- Naturally occurring substances that may not be adequately evaluated without federal involvement.
- Commercial products with significant exposure that were first marketed prior to current testing requirements or those that generate too little revenue to support further evaluations.
- Potential substitutes for existing chemicals or drugs that might not be developed without federal involvement.
- Mixtures of substances for which evaluations are not required of industry.
- Substances that will aid our understanding of chemical toxicities, or our understanding of the use of test systems to evaluate potential toxicities.
- Substances that should be evaluated to improve the scientific understanding of structure-activity relationships and thereby help limit the number of substances requiring extensive evaluations.
- Emergencies or other events that warrant immediate federal government evaluation of a substance.

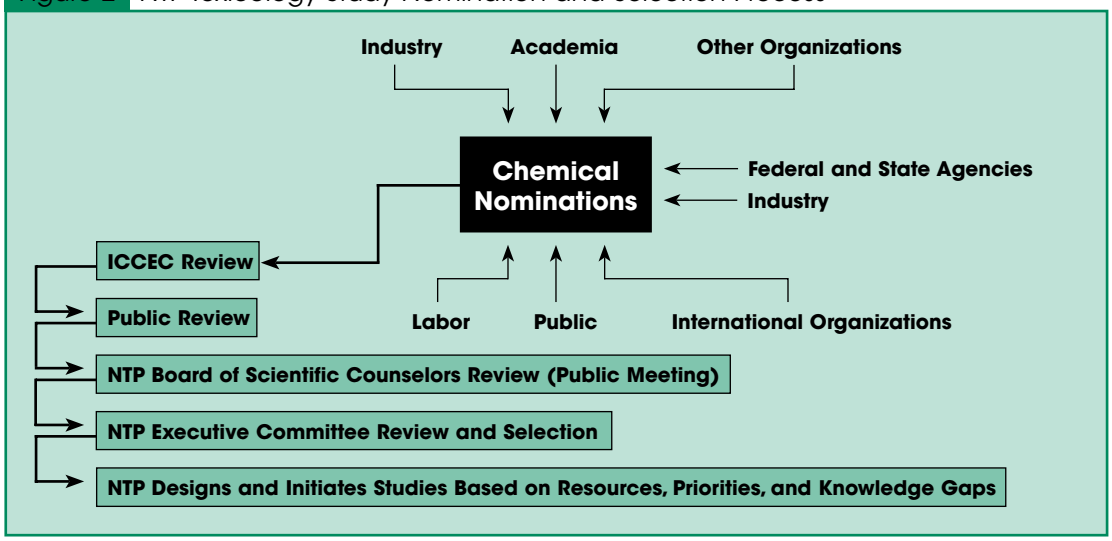
Nominations undergo several levels of review before the NTP selects agents for study (Figure 2). Representatives from federal agencies on the Interagency Committee for Chemical Evaluation and Coordination (ICCEC) and the BSC participate in the selection process. The NTP also solicits and considers public comment on nominations throughout this formal process. As the final step, the NTP Executive Committee reviews and evaluates the testing recommendations and the public comments for each nomination. The committee makes its own recommendations on the nominations: (1) to test, (2) not to test at this time, or (3) to defer testing until more information is received and considered. These steps help ensure that the NTP's testing program addresses toxicological concerns pertinent to all areas of public health and maintains balance among the types of substances evaluated.

The Executive Committee's recommendation of a substance for study does not automatically commit the NTP to its evaluation. The NTP strives to balance its selection of substances for study (e.g., occupational exposures, environmental pollutants, food additives, consumer products, and pharmaceuticals) and launches studies as time and resources permit. In reviewing and selecting nominated substances for study, the NTP also considers legislative mandates that require responsible private sector and commercial organizations to evaluate their products for human and environmental health effects. Also, a nomination selected for study may be deferred at any time if suitable data become available, if higher priority studies are identified, or if a study proves impractical.

The NTP evaluates substances for a variety of health-related effects, among them, general toxicity, reproductive and developmental toxicity, genotoxicity, immunotoxicity, neurotoxicity, and carcinogenicity. The NTP generally uses rodent models for study and conducts short-term studies for up to thirteen weeks and long-term studies for up to two years. For each agent studied, a project leader designs a comprehensive testing strategy to address the identified research and testing needs. A project review committee evaluates the testing strategy and proposes an appropriate mechanism for sponsoring the study (e.g., grant, contract, etc.).

The NTP publishes results of short-term rodent toxicology studies in the NTP Toxicity Report series and results of long-term studies, generally two-year rodent toxicology and carcinogenicity studies, as NTP Technical Reports or in peer-reviewed scientific journals. During 2003, the NTP began a new technical report series for reporting the results from studies conducted in genetically modified models such as genetically engineered mice. Completed reports are available electronically from the NTP website (http://ntp.niehs.nih.gov and select "Publications, Technical Reports, and Abstracts") or in hard copy from Central Data Management (for contact information, see inside back cover).

Figure 2 NTP Toxicology Study Nomination and Selection Process



Current Directions

The NTP conducts research on a broad range of high-priority agents and issues of public health concern. Information about NTP studies, including standard protocols, fact sheets, and data from completed studies, is available on the NTP website (http://ntp.niehs.nih.gov). Below are brief overviews of some current initiatives.

Radiofrequency Radiation Emissions from Cellular Phones

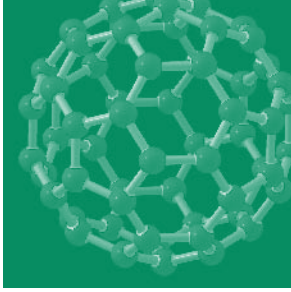
More than 200 million Americans currently use wireless communication devices, with thousands of new users added daily. Personal (cellular) telecommunications is a rapidly evolving technology that uses microwave radiation to communicate between a fixed base station and a mobile user. Most systems employ a handheld cellular telephone, with the radiation antenna held close to the user's head.

The Federal Communication Commission requires cellular phones and other wireless communication devices to meet its guidelines for exposure to radiofrequency radiation. These guidelines are based on protecting the user from immediate injury from the heat produced by radiofrequency radiation. However, we currently do not have enough data to determine whether these guidelines will also protect against potential adverse effects of long-term exposure.

Studies in laboratory animals are crucial for understanding whether long-term exposure to radiofrequency radiation may pose a danger to human health. The NTP is studying the toxic and carcinogenic effects of chronic exposure to cellular phone radiofrequency radiation emissions in laboratory animals. The NTP worked with technical experts from the National Institute of Standards and Technology to demonstrate the suitability of using reverberation chambers to expose animals to uniform fields of cellular phone radiofrequency radiation. These studies will test radiofrequency signals that simulate exposures of cellular phone users to help clarify any potential health hazard for the U.S. population.

Children's Health

The NTP continues to be a leader in issues related to children's health through research and the NTP's Center for the Evaluation of Risks to Human Reproduction. The NTP has ongoing efforts to evaluate effects of various agents on the developing immune and nervous systems through laboratory studies of pesticides, water disinfectant by-products, and endocrine-disrupting agents. The program has expanded these efforts by establishing study protocols where perinatal animals will be given these



agents and then examined for toxic effects, including developmental immunotoxicity, neurotoxicity, and reproductive effects. Toxicokinetic data from animal studies of mothers, fetuses, and newborns will be used to develop pharmacokinetic models based on physiology. These models will help evaluate risks to humans from exposure to environmental toxicants during early development.

Phototoxicology

The U.S. public is increasingly exposed to ultraviolet (UV) radiation or sunlight through more frequent use of tanning booths and more leisure time spent in outdoor activities. The NTP is coordinating an effort between the NIEHS and the NCTR to study how sunlight or UV radiation affects the toxicity (phototoxicology) and carcinogenicity (photocarcinogenicity) of substances nominated to the NTP, including those of high priority to the Food and Drug Administration (FDA). These studies use the SKH-1 hairless mouse as the primary model, and new models are also under investigation. The NTP Center for Phototoxicology also conducts studies to learn how these toxic and carcinogenic effects might occur.

The NTP Center for Phototoxicology is studying the possible acute toxicity and carcinogenicity of topically applied plant extracts of the aloe vera plant or topically applied retinyl palmitate in combination with simulated sunlight. Many products, including cosmetics and dietary supplements, contain portions of the aloe vera plant. Retinyl palmitate is included in some cosmetics as an "anti-wrinkle" compound, and its safety in the presence of sunlight needs further study. Also, the NTP Center for Phototoxicology is designing and conducting studies of other cosmetic ingredients, including topically applied Padamate O used in cosmetic and sunscreen preparations, furocoumarin compounds found in lemon and lime oils, nanoscale particles used in sunscreens (zinc oxide and titanium dioxide), and permanent makeup inks.

Herbal Medicines

Herbs are among our oldest medicines, and their increasing use in recent years is evidence of public interest in alternatives to conventional medicine. The use of herbal medicines and other dietary supplements has increased substantially since passage of the 1994 Dietary Supplement Health and Education Act. Herbal medicines are a major market in U.S. pharmacies and constitute a multi-billion-dollar industry. Although botanicals are sold as dietary supplements or ethnic traditional medicines, herbal formulations are not subjected to FDA premarket approval to ensure their safety or efficacy.

The NTP is planning or is conducting research on several medicinal herbs and compounds found in herbs (listed in Table 2) to examine toxic effects associated with exposures to high acute doses and chronic low doses, including carcinogenicity, reproductive toxicity, neurotoxicity, and immunotoxicity. NTP studies include both traditional toxicological research and studies to understand how effects might occur.

Table 2 Herbals and Herbal Components under Study by the NTP

Aloe vera gel	Widely used for centuries as a treatment for minor burns and is increasingly being used in products for internal consumption.
Bitter orange extract	Bitter orange peel and its constituent synephrine are in dietary supplements used for weight loss.
Black cohosh	Used to treat symptoms of premenstrual syndrome, dysmenorrhea, and menopause.
Bladderwrack	A source of iodide used in the treatment of thyroid diseases and also found as a component of weight-loss preparations.
Blue-green algae	Claims to prevent cancer and heart disease and boost immunity. Use has been promoted for children to treat attention deficit disorder.
Comfrey	Used externally as an anti-inflammatory agent in the treatment of bruises, sprains, and other external wounds. Consumed in teas and as fresh leaves for salads. Based in part on NTP studies on the alkaloid components of comfrey, the FDA recommended that manufacturers of dietary supplements containing this herb remove them from the market.
***Echinacea purpurea* extract**	Used as an immunostimulant to treat colds, sore throat, and flu.
Ephedra	Also known as Ma Huang. Traditionally used as a treatment for symptoms of asthma and upper respiratory infections. Often found in weight-loss and "energy" preparations, which usually also contain caffeine. The FDA has prohibited the sale of dietary supplements containing ephedra.
***Ginkgo biloba* extract**	Ginkgo fruit and seeds have been used medicinally for thousands of years to promote improved blood flow and short-term memory, and to treat headache and depression.
Ginseng and Ginsenosides	Ginsenosides are thought to be the active ingredients in ginseng. Ginseng has been used as a laxative, tonic, and diuretic.
Goldenseal root	Traditionally used to treat wounds, digestive problems, and infections. Current uses include as a laxative, tonic, and diuretic.
Green tea extract	Used for its antioxidative properties.
Kava kava extract	A widely used medicinal herb with psychoactive properties sold as a calmative and antidepressant. A recent report of severe liver toxicity has led to restrictions of its sale in Europe.
Milk thistle extract	Used to treat depression and several liver conditions, including cirrhosis and hepatitis, and to increase breast milk production.
Pulegone	A major terpenoid constituent of the herb pennyroyal. Has been used as a carminative, insect repellent, emmenagogue, and abortifacient.
Senna	Laxative with increased use due to the removal of a widely used, chemical-stimulant type laxative from the market.
Thujone	Terpenoid found in a variety of herbs, including sage and tansy, and in high concentrations in wormwood.

Nanoscale Materials

Nanotechnology has become an increasing focus of U.S. and global research and development efforts. As with many technological advances, new materials are created, and as a result, the potential exists for new and unanticipated exposures for which the impact on human health is unknown. The NTP has begun a broad-based research program to address potential human health hazards associated with the manufacture and use of nanoscale materials.

Nanoscale materials are a broadly defined set of substances where at least one critical dimension is less than 100 nanometers and they possess unique optical, magnetic, or electrical properties. The NTP's research program focuses on manufactured nanoscale materials of current or projected commercial importance. Nanoscale materials can, in theory, be engineered from nearly any chemical substance; semiconductor nanocrystals, organic dendrimers, carbon fullerenes ("buckyballs"), and carbon nanotubes are a few of the many examples. They are already appearing in commerce as industrial and consumer products, and as novel drug delivery formulations.

NTP studies will evaluate the toxicological properties of major classes of nanoscale materials that represent a cross section of composition, size, surface coatings, and physicochemical properties. The NTP will investigate fundamental questions concerning if and how nanoscale materials can interact with biological systems. The program includes studies to evaluate the biological disposition of "quantum dots" (nanoscale crystalline fluorescent semiconductors), long-term toxicology studies of carbon-based nanoscale materials (e.g., single- or multi-walled nanotubes, fullerenes), and phototoxicology studies of representative nanoscale metal oxide particles used in industrial settings and consumer products (e.g., titanium dioxide). The NTP will use the data to develop mathematical models to predict the absorption, distribution, metabolism, and elimination of nanoscale materials in humans. The NTP has also established a Nanotechnology Working Group under the NTP Board of Scientific Counselors to bring interested parties together to learn about this initiative.

Safe Drinking Water

More than 200 million Americans are estimated to use municipally treated drinking water, so the availability of safe drinking water is of enormous importance to public health. Many agents occur (1) naturally in water (e.g., arsenic, aluminum), (2) because of contamination (e.g., methyl *tert*-butyl ether and other gasoline additives, pesticides, organic tin compounds), or (3) with environmental changes (e.g., cyanobacterial toxins from algal blooms in surface waters). The NTP is designing long-term toxicology and toxicokinetic studies on several of these agents, including aluminum complexes, organic tin compounds, and the two most common cyanobacterial toxins (microcystin-LR and cylindrospermopsin).

Because of concerns by a number of California legislators, the California Environmental Protection Agency, and the California Health and Human Services Agency, the NTP is studying the potential of hexavalent chromium in drinking water to cause cancer. Hexavalent chromium compounds rarely occur naturally and are typically associated with industrial sources. Hexavalent chromium is an established human carcinogen in certain occupational settings, presumably as a result of inhalation exposure. Data currently available on the chronic toxicity and carcinogenicity of hexavalent chromium given orally are not sufficient to establish or characterize any hazard for it in the water supply. NTP studies include both short- and long-term administration of hexavalent chromium to laboratory animals (sodium dichromate dihydrate in drinking water), as well as studies on tissue absorption of hexavalent chromium.

Occupational Exposures

The NTP is coordinating an effort between the NIEHS and NIOSH to better understand worker exposures, educate workers, and identify occupational health research gaps. Current efforts are addressing worker exposure to welding fumes, abrasive blasting materials, and metalworking fluids.

Studies of diseases in workers suggest that occupational exposure to welding fumes may cause adverse health effects. More information is needed to evaluate the relationship between timing and amount of exposure and the adverse effects that result, and to understand the specific causes of these effects. The NIOSH has constructed a computer-controlled, automated robotic system to generate tightly controlled, well-characterized welding fumes, for investigating fumes caused by different welding processes and materials. These studies will examine the physical and chemical composition of the generated fumes and gases, as well as evaluate which exposure conditions, or welding processes and materials cause acute biological responses in laboratory animals.

Alternatives to silica sand for abrasive blasting are frequently recommended to reduce workers' risk for acquiring fibrotic lung disease and cancer. NIOSH recommends the use of coal slag, garnet, steel grit, crushed glass, and specular hematite as safe alternatives to silica sand for abrasive blasting. The NTP will evaluate the relative effects of these alternatives for causing lung disease, and NIOSH will use this information as guidance for developing exposure limits for workers.

Millions of gallons of metalworking fluids are used each day in industry for cutting, milling, drilling, stamping, and grinding, and as a result, workers potentially are exposed to a wide variety of formulations through their skin and in the air they breathe. The NTP will evaluate the acute and long-term health effects of several commercial products in laboratory animals.

The NIOSH is planning a National Exposures at Work Survey that will be conducted in a nationally representative sample of workplaces across all industries, starting with the health services industry. This survey will collect data on chemical, physical, and biological agents to which workers could be exposed, as well as data on ways to control exposure, and health and safety practices. Information from this initiative will be used to educate workers, identify occupational health knowledge gaps, and help target areas where research is likely to reduce workplace illness.

DNA-Based Products

DNA-based therapies are being developed to treat a wide range of human diseases. However, by their very nature, they pose a risk of interacting with the host's genes, or disrupting normal cellular processes in unexpected, unpredictable, and potentially harmful ways. Examples of DNA-based products include (1) vaccines against viruses and bacteria that have been made from plasmid DNA, (2) synthetic oligonucleotides to modulate gene expression, and (3) viral carriers for gene therapy. The FDA has only limited authority to require evaluation of long-term effects of these therapies. Presently, the NTP is collaborating with the FDA and sister NIH institutes to study the safety of DNA-based products. These studies address lifelong risks presented by their use and the potentials for reproductive toxicities, for transmission of altered genetic material to subsequent generations, and for DNA-based products to cause autoimmune disease or immune dysfunction.

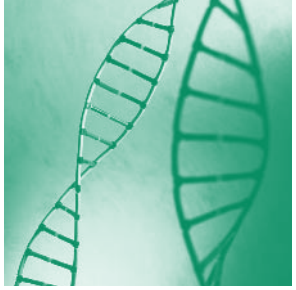
Polybrominated Flame Retardants

The NTP is studying how exposure to polybrominated flame retardants might affect human health. The class of brominated flame retardants called polybrominated diphenyl ethers (PBDE) is structurally similar to the dioxin-like polychlorinated biphenyls raising concern for carcinogenic potential and developmental toxicity. In addition, there is evidence that they similarly accumulate in human and animal tissues. The substances under evaluation include the PBDE isomers found in DE-71, the most widely used commercial formulation of a PBDE-based flame retardant, as well as two other brominated flame retardants: tetrabromobisphenol A and tetrabromobisphenol A-bis (2,3-dibromopropyl) ether.

Perfluorinated Compounds

Perfluorinated compounds or their chemical precursors have been used since the 1950s as surfactants and emulsifiers in commercial products, including stain or water protectors for carpets, textiles, auto interiors, camping gear, and leather, and in food packaging and other paper containers. Perfluorinated compounds such as perfluorooctyl sulfonate (PFOS) and perfluorooctanoic acid (PFOA) have been found globally in human tissues and the environment. They are persistent in the environment, resistant to heat and chemical stress, and insoluble in both water and oil. Although much is known about the toxicity of PFOS and PFOA, the same cannot be said for other members of this class. For this reason, the NTP is collaborating with the Environmental Protection Agency (EPA) to study perfluorinated compounds as a class, including several perfluorinated sulfonates and carboxylic acids, as well as fluorotelomeric alcohol derivatives (potential precursors of perfluorinated carboxylic acids).

This initiative includes studies on reproduction and development in laboratory animals, as well as studies to characterize how these chemicals behave inside the body to learn whether members of this class of compounds have similar modes of action. The NTP will explore the use of *in vitro* assays in conjunction with information from studies in laboratory animals to predict adverse responses to chemicals within this class. If common modes of action exist among these chemicals, then a cumulative risk assessment might be more appropriate than individual chemical assessments to evaluate the health effects of perfluorinated compounds in the environment.



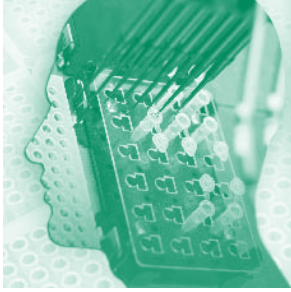
Evolving Strategies

Considering the large number of chemicals in commercial use, the NTP must continually set priorities and develop research strategies to characterize toxicants and identify hazards that make the best use of available resources. Using new testing strategies that provide more or better information can strengthen the scientific knowledge on which regulatory decisions are based. The NTP core agencies develop and validate new testing methods, and university-based researchers also participate in these efforts through NIEHS extramural grants.

Many testing strategies focus on more rapid screening tests, alternative or complementary *in vivo* tests for rodent bioassays, and less use of two-year rodent studies to determine toxicities. Strategies include molecular screening methods, non-mammalian test species, genetically engineered animal models, genetically engineered *in vitro* cell systems, microchip-based genomic technologies, and computer-based predictive toxicology models. Such techniques can provide insight into the molecular and biological events associated with a chemical's toxic effect, as well as mechanistic information for assessing human risk. They can also help clarify dose-response relationships, make species comparisons, and identify sources of variations among individuals. Below are brief overviews of some current and emerging NTP initiatives highlighting new research tools.

High Throughput Screening

The NTP promotes improvements in toxicology test methods that will enhance the program's ability to evaluate the large number of substances in our environment that potentially pose hazards for human health. As part of its activities to implement the NTP Roadmap, the NTP seeks to identify or develop rapid, mechanism-based assays that can be used to screen large numbers of environmental substances for their potential biological activity (high throughput screening or HTS). The concept of HTS is based on the use of automated processes to evaluate hundreds to thousands of substances rapidly using *in vitro* systems. The NTP hopes to use the data from HTS assays to (1) identify mechanisms of action for further investigation, (2) develop models to predict how substances might react in biological systems, and (3) prioritize substances for more extensive toxicological evaluation. The HTS initiative will also generate the scientific information and understanding needed by health regulatory agencies to make decisions on potentially toxic materials in order to protect public health. The NTP is currently in the process of identifying specific assays to include in the HTS program.



In August 2005, the NTP, through the NIEHS, became a formal participant in the NIH Molecular Libraries Initiative (MLI), part of the NIH Roadmap for Medical Research. Although the MLI was originally conceived as a strategy to help the HTS initiative identify chemical probes for use in medical and basic science research, the NTP is working with MLI project leaders to expand the effort by adding toxicity testing capabilities. Through this collaboration, the NTP can link information on the biological activity of environment substances, generated from HTS assays, with toxicity effects identified in the NTP's toxicology testing program.

To date, the NTP has provided approximately 1,400 chemicals to the MLI, as well as six HTS cell-based screening assays (three that measure steps integral to apoptosis, two that assess cytotoxicity, and one that measures cell membrane P-glycoprotein activity), and is working to identify other commercially available HTS assays that can be adapted to a robotics-based system. Data collected on these chemicals from the HTS assays will be maintained in a database accessible to the NTP and the MLI for future analysis. To help guide this process, the NTP sponsored the HTS Assays Workshop on December 14-15, 2005, to discuss the usefulness of this technology for the NTP and toxicology.

Caenorhabditis elegans

The NTP is interested in developing rapid, sensitive, and specific tests for screening environmental agents. A current focus is the nematode *Caenorhabditis elegans (C. elegans)*. The NTP is investigating the response of *C. elegans* when exposed to known or suspected toxicants and is monitoring the effects of these toxicants on its growth, size, reproduction, and movement. The goal is to determine the possibility of using the nematode as a practical and efficient model in toxicology studies. The *C. elegans* system has now been used to measure the toxicological effects of transition metals, common laboratory solvents, chemical oxidants, and organochlorine pesticides. A publicly accessible database is currently under construction to share the results from the *C. elegans* studies.

NTP Research Databases

A primary goal of the NTP is to evaluate agents of public concern for their potential toxicity or carcinogenicity. Some studies address general toxic effects in laboratory animal species, whereas others focus on specific immune, neurological, reproductive, and developmental effects. Data from general toxicology and carcinogenicity studies are publicly available on the NTP website (http://ntp.niehs.nih.gov). The NTP is expanding the public's access to its data to include all study types (general toxicology, carcinogenesis, genetic toxicity, and organ systems). The NTP provides access to the data in a common

format using web-based applications that allow users to query data, conduct simple statistical manipulations, and export the information. Basic tools are available on the website to allow users to search for studies on specific substances and retrieve data for individual animals. The NTP is also developing tools for conducting systematic searches of specific effects or chemicals, both within and across studies. This type of search will allow comparison of effects among individual chemicals or classes of chemicals.

Magnetic Resonance Imaging

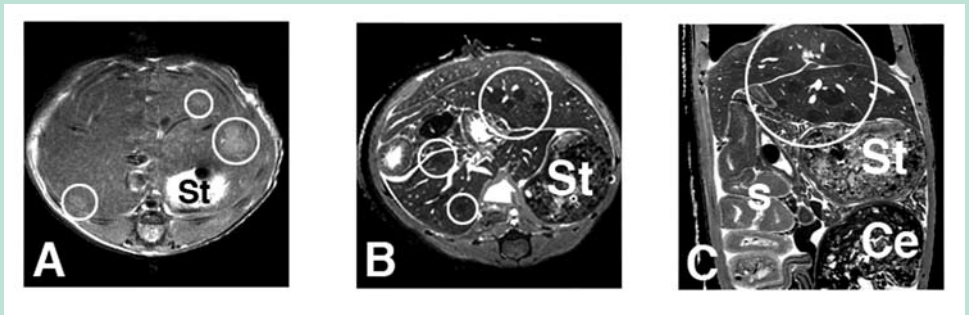
Traditionally in NTP toxicology and carcinogenicity studies, lesions are evaluated with conventional optical microscopy of collected tissue samples. Representative samples are collected because examining all the tissue involved is impractical. Because of recent advances in the technology for imaging, magnetic resonance imaging (MRI) of the entire body at microscopic resolution is now possible. The NTP is investigating MRI for imaging laboratory animals (see Figure 3). MRI microscopy is three-dimensional, can examine the same specimens at different angles, and measures the volume of tissues and organs. MRI of live animals permits acquisition of imaging data at different times over an animal's lifetime. Because the images are digital, web-based viewing is easier.

MRI is a noninvasive technique that will permit the NTP to perform a more complete and thorough examination of tissues and organs from test animals without destroying the samples, and may also allow more information to be gathered from studies than before. Anticipated uses include monitoring lesions and examining the morphology and functionality of genetically engineered mice. The NTP has completed pilot studies of birth defects and developmental neurotoxicity studies and is currently completing a pilot study to monitor long-term the development of liver tumors by *in vivo* images of mice over time.

Risk Assessment Methodology

Risk assessment involves using scientific information to determine whether exposures to agents in the environment or workplace are hazardous to the health of individuals or populations, and if so, to what extent. Mathematical models that accurately represent physiological and biochemical processes in laboratory animals and humans can provide a scientifically sound basis for using data from studies

Figure 3 MRI Microscopy of Mice with Multiple Small Liver Tumors



A. Transverse MRI slice through the liver of a live mouse. Spinal cord is at 6 o'clock. Liver tumors are circled. St = stomach.

B. Transverse MRI slice through the liver of a mouse after perfusion fixation. Liver tumors are circled. St = stomach.

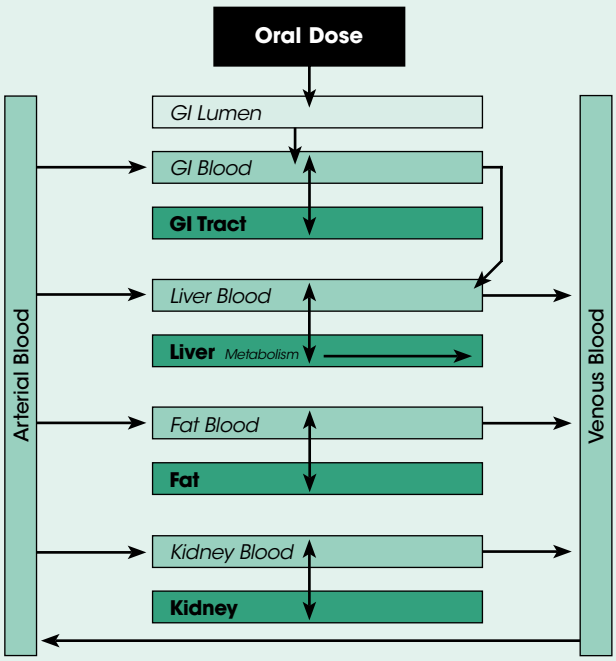
C. Dorso-ventral slice through the liver of the same mouse after perfusion fixation. Multiple liver tumors are circled. St = stomach. Ce = cecum. S = small intestines.

in animals to determine if and how an exposure might cause health effects in humans. Physiologically based pharmacokinetic (PBPK) models measure the biological processes of absorption, distribution, metabolism, and elimination of an agent in animals or humans (Figure 4). The NIEHS continues to develop PBPK models to evaluate relationships between environmental exposures and carcinogenicity, and developmental and reproductive toxicities (Table 3). PBPK models are often included in NTP Technical Reports or are published in the peer-reviewed literature.

Toxic Equivalency Factors

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) and dioxin-like compounds comprise a large class of structurally related environmental contaminants that include some polychlorinated biphenyls (PCBs), as well as polychlorinated dibenzodioxins and polychlorinated dibenzofurans. These are persistent substances that remain in human tissues and in the environment for extended periods of time. TCDD, a known human carcinogen, and other dioxin-like compounds bind to the same aryl hydrocarbon receptor (AhR). Evaluating effects of exposure to mixtures of these compounds is more complex than evaluating exposures to individual compounds. The Toxic Equivalency Factor (TEF), an approach established by the World Health Organization (WHO), has been widely accepted as the best method to evaluate potential health risks associated with exposure to mixtures of dioxin-like compounds. The TEF approach ranks the toxicity of a dioxin-like compound relative to the most potent dioxin TCDD.

Figure 4 Physiologically Based Pharmacokinetic Model



This model represents the uptake, distribution, and metabolism of an environmental agent administered orally.

Table 3 Substances with PBPK Models Developed by the NTP

Anthraquinone	Methyleugenol
Butadiene	2-Methylimidazole
Bromochloroacetic acid	4-Methylimidazole
Bromodichloromethane	Naphthalene
Chromium picolinate monohydrate	3,3',4,4',5-Pentachlorobiphenyl
Decalin	2,3,4,7,8-Pentachlorodibenzofuran
Dibromoacetic acid	PCB mixtures
Dichloroacetic acid	Pentabromodiphenyl oxide
p,p'-Dichlorodiphenyl sulfone	Primidone
Divinylbenzene	Propylene glycol mono-*t*-butyl ether
2,2',4,4',5,5'-Hexachlorobiphenyl	Sodium nitrite
Isoprene	Sodium dichromate dihydrate
Melatonin	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin
Mercury	Urethane

The NTP evaluated the TEF approach in its long-term toxicology and carcinogenicity studies by testing TCDD, 3,3',4',4',5-pentachlorobiphenyl (PCB 126), and 2,3,4,7,8-pentachlorodibenzofuran, individually and in combination with each other. Dose-response analyses showed that for liver, lung, and oral mucosal tumors, effects for doses of any one of the three individual compounds were the same as for a similar potency-adjusted dose of the mixture. Also, the tumor response by dose for the mixture could be predicted by combining the effects of potency-adjusted doses of the individual chemicals. This evaluation affirmed the need to base health standards on mixtures rather than on single chemicals and supported the appropriateness of assuming that the effects of dioxins should be added together when using TEFs for cancer risk assessments for dioxins.

Humans are exposed to mixtures of not only dioxin-like PCBs but also PCBs that have either weak or no dioxin-like activity. The TEF scheme deals only with PCBs with dioxin-like activity and assumes that there is no interaction between these and the non-dioxin-like PCBs. The NTP is currently addressing interactions between PCBs. The results from studies of the non-dioxin-like PCB 153 (2,2',4,4',5,5'-hexachlorobiphenyl) in combination with PCB 126 indicate that the potency of PCB 126 can be both increased and decreased, depending upon the tumor endpoint examined, by co-exposure with PCB 153. Studies to evaluate how the weak-dioxin PCB 118 (2,3',4,4',5-pentachlorobiphenyl) affects the potency of PCB 126 are ongoing.

Other compounds, in addition to dioxins, furans, and PCBs, also have the ability to bind to the AhR, but are not currently included in the WHO TEF scheme. The NTP is evaluating such compounds with weak-dioxin-like activity (including polychlorinated naphthalenes, tetrachloroazobenzene, hexachlorobenzene, and indole-3-carbinol) to determine if they have chronic toxicological and carcinogenic effects similar to those of TCDD, which would argue for their inclusion in dioxin cancer risk assessments.

Transgenic Animals

For more than three decades, the NTP has conducted studies in laboratory rodents to identify carcinogens thought to pose risks to human health. Genetically engineered animal models based on new gene technologies are being evaluated as alternatives or complements to rodent bioassays. Genetically altered or transgenic mouse models carry activated oncogenes or inactivated tumor

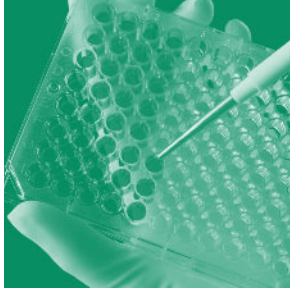
suppressor genes known to be involved in neoplastic (tumor-causing) processes in both humans and rodents. This trait may allow these mice to respond or show the effects of carcinogens more quickly and more reliably than conventional rodent strains. Target or reporter genes in the animals also allow direct molecular and cellular analysis of a chemical's effects and can provide additional mechanistic information about its mode of action.

The NTP sought input from its advisory groups and the public about the usefulness of a number of transgenic rodent models for short-term studies of carcinogenicity [p53(+/–), Tg.AC (v-Ha-ras), and RasH2]. In general, there is support for using the p53(+/-) and RasH2 models to evaluate the carcinogenic potential of chemical or physical agents. The NTP will continue to consider transgenic models when designing the testing strategy for substances under study. As understanding increases of the complex signaling pathways that are turned on or off during carcinogenesis, the NTP will be able to select transgenic animal models that best mimic human tissue responses. This strategy should provide a firmer foundation for applying hazard data from animals to humans.

Toxicogenomics

New molecular technologies have brought the NTP into the arena of toxicogenomics, a new scientific field that examines how the entire genetic structure, or genome, is involved in an organism's response to environmental toxicants. Toxicogenomics applies knowledge of genetics to environmental medicine by studying the effect of toxicants on gene activity and specific proteins produced by genes. It combines information from studies of genomic-scale messenger RNA profiling (by microarray analysis), cell-wide or tissue-wide protein profiling (proteomics), genetic susceptibility, and computational models. This information helps illustrate how interactions between genes and the environment affect the onset and progression of disease. This field could revolutionize environmental health, drug safety, and risk assessment.

Initial efforts by the NTP include studying variables that affect gene expression in the liver. To date, the NTP has studied individual variation in hepatic gene expression in male rats, including the effect of circadian rhythm, the effect of age, variability due to conducting studies on different days and in different laboratories, and the effect of feed (pellets or mash) on hepatic gene expression. This information is crucial in understanding how environmental agents may affect the disease process. The study of agents that might promote or cause cancer is one of the more time-consuming and costly NTP efforts. Therefore, several studies have been launched to determine whether the analyses of hepatic gene expression may allow earlier detection and greater understanding of the role of the environment on the onset and progression of hepatocellular cancer. The NTP is also evaluating gene expression after exposure to substances known to affect the immune system and natural products known to cause cancer in humans.



Centers

NTP Center for Phototoxicology

The NTP Center for Phototoxicology (NCP), established in 2000, conducts research on how light affects the toxicology and carcinogenicity of substances nominated to the NTP and on the mechanisms that underlie these effects. Current research initiatives are described on page 11 under "Phototoxicology." Research in this area is very important because of the public's increasing exposure to UV radiation or sunlight through more frequent use of tanning booths and more leisure time spent in outdoor activities.

The NCP's state-of-the-art laboratory can study the potential toxic or carcinogenic effects of a test substance in combination with UV or visible radiation from several light sources. The NCP also conducts mechanistic studies to learn how these effects might occur. The laboratory can simulate natural sunlight using filtered 6.5-kilowatt xenon-arc lamps, which enable researchers to duplicate human exposure conditions. The facility can also perform studies using light from different types of fluorescent tubes, such as those used in fluorescent lamps and suntan-bed lamps.

The NTP Board of Scientific Counselors advises the NCP on its programs and priorities. Substances selected for testing are nominated directly from the FDA and from outside submissions to the NTP. The FDA's Chemical Selection Working Group prioritizes nominations and forwards them to the NTP for formal consideration in its nomination and selection process. More information about the NCP is available by contacting Dr. Paul C. Howard, director, NCP (for contact information, see inside back cover).

Center for the Evaluation of Risks to Human Reproduction

Established in 1998, the NTP's Center for the Evaluation of Risks to Human Reproduction (CERHR) serves as an environmental health resource to the public, and to regulatory and health agencies. The NTP Board of Scientific Counselors advises the CERHR on its processes, priorities, and direction.

The CERHR provides scientifically based, uniform assessments of the potential for adverse effects on reproduction and development caused by human exposure to chemicals. It follows a formal, open process for nomination, selection, and review of chemicals, and public input is encouraged. The CERHR selects chemicals for review based on several factors, including how much is produced, how many people are exposed, public concern about the chemical hazard, and published evidence of reproductive or developmental toxicities.

Assessed through rigorous evaluations by independent scientific panels in public forums, these evaluations are intended to:

- Interpret scientific evidence and provide information to the public about the strength of the evidence that a given exposure or circumstance poses a hazard to reproduction, or to the health and welfare of children.
- Provide regulatory agencies with objective and scientifically sound assessments of data related to the reproductive/developmental health effects associated with exposure to specific chemicals or classes of chemicals, including descriptions of any uncertainties associated with these assessments.
- Identify knowledge gaps to help establish research and testing priorities.

Chemicals reviewed to date by the CERHR expert panels are listed in Table 4. Future reviews include genistein and soy formula, bisphenol A, and hydroxyurea.

The NTP-CERHR Monograph series reports the findings for chemicals evaluated by the CERHR. Each monograph includes the NTP Brief, the Expert Panel Report, and public comments on the Expert Panel Report. The brief gives the NTP's interpretation of the potential for the chemical to cause adverse reproductive and/or developmental effects in exposed humans, and is based on the Expert Panel Report, public comments, and new information available after the expert panel meeting. NTP-CERHR monographs are transmitted to appropriate federal and state agencies and are made available to the public. Expert Panel Reports and NTP-CERHR monographs are posted on the CERHR website (http://cerhr.niehs.nih.gov) and are available in hard copy and CD-ROM from the CERHR.

The CERHR conducts workshops bringing together experts to discuss important topics relative to the effects of environmental agents on reproduction and development. The CERHR website has information on various environmental exposures and their potential to affect pregnancy and child development, as well as links to other resources.

The CERHR welcomes nominations of chemicals for review, as well as scientists for its registry of experts. Information about the CERHR and the nomination process is available from its website or by contacting Dr. Michael Shelby, director, CERHR (for contact information, see inside back cover).

Table 4 Chemicals Reviewed by CERHR Expert Panels

Acrylamide	Used in production of polyacrylamide that is used in water treatment, pulp and paper production, and mineral processing. Also used in the synthesis of dyes, adhesives, contact lenses, soil conditioners, and permanent press fabrics and in electrophoresis.
Amphetamines	Central nervous system stimulants. Amphetamine is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy. Methamphetamine is indicated for the treatment of ADHD and for short-term treatment of obesity.
1-Bromopropane	Solvent in spray adhesives and cold bath degreaser. Potential use as a replacement for ozone-depleting hydrochlorofluorocarbons and chlorinated solvents.
2-Bromopropane	Contaminant in 1-bromopropane. Used in synthesis of pharmaceuticals and dyes.
Di-(2-ethylhexyl) phthalate	High production volume chemical. Used in polyvinyl chloride-based consumer products such as building products, car products, children's products (but not in toys intended for mouthing), clothing, food packaging, and in medical devices.
Ethylene glycol	High production volume chemical used chiefly in the production of polyester compounds and widely used as antifreeze for heating and cooling systems.
Fluoxetine	Used primarily as an antidepressant in adults; is approved for use in children 7 to 17 years old. Also used to treat premenstrual dysphoric disorder.
Methanol	Used primarily in chemical synthesis and racecar fuels. Has potential use as a vehicle fuel or fuel additive.
Methylphenidate	A central nervous system stimulant approved by the FDA for the treatment of ADHD and narcolepsy in persons 6 or more years of age.
Phthalates (7)*	Primary plasticizers in a wide range of polyvinyl chloride-based consumer products.
Propylene glycol	Used in production of polyester resins, such as antifreeze and de-icing solution, and in paints and coatings. Also approved for use as a food additive and for use in some drugs and cosmetics.
Styrene	High production volume chemical used in the production of polystyrene resins. Is found in foam cups, dental fillings, ion exchange filters, and construction materials.

* butyl benzyl phthalate, di(2-ethylhexyl) phthalate, di-isodecyl phthalate, di-isononyl phthalate, di-*n*-butyl phthalate, di-*n*-hexyl phthalate, and di-*n*-octyl phthalate

NTP Interagency Center for the Evaluation of Alternative Toxicological Methods

Toxicity testing is necessary to assess the hazards and safety of substances in our environment. Developing, validating, accepting, and harmonizing new, alternative, and revised toxicological test methods are coordinated throughout the federal government by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). Established in 2000, ICCVAM consists of representatives from 15 federal agencies (Table 5). The NTP Interagency Center for the Evaluations of Alternative Toxicological Methods (NICEATM) provides scientific and operational support for ICCVAM and its activities. The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) provides advice on the activities of NICEATM and ICCVAM.

NICEATM and ICCVAM work together to evaluate new, revised, and alternative toxicological test methods that may (1) predict human health risks better, (2) save time and money, and (3) refine (cause less pain and distress), reduce, or replace animal use. NICEATM also promotes information sharing and communication among government agencies, industry, the public, and the international community.

ICCVAM has a formal process for nominating and submitting new, revised, and alternative toxicological test methods for evaluation. Once test methods are accepted for evaluation, NICEATM and ICCVAM convene independent, scientific, peer review panels to assess their usefulness and limitations. Workshops and expert panel meetings are also convened to (1) evaluate how well current safety assessment methods are working, (2) identify areas needing improved or new methods, (3) assess

the current validation status of new methods, and (4) recommend appropriate research, development, and validation. These meetings are open to the public and provide an opportunity for public comment. Meeting reports, public comments, and ICCVAM recommendations on the scientific validity and potential acceptability of alternative test methods are forwarded to federal agencies for their consideration. Each agency determines the regulatory acceptability of a method according to its own statutory mandates. ICCVAM also works to achieve international acceptance of test methods that it finds to be scientifically valid for specific uses. Test methods evaluated by the ICCVAM process or those under consideration for review are listed in Table 6. ICCVAM has developed a process for establishing performance standards for validated and accepted test methods. These standards can be used to determine the acceptability of other proposed test methods that are based on similar scientific principles, and measure or predict the same biological or toxic effect.

More information about NICEATM and ICCVAM, meeting schedules, meeting reports and minutes, and information on nominating alternative toxicological methods are available through the ICCVAM/NICEATM website (http://iccvam.niehs.nih.gov) or by contacting Dr. William S. Stokes, director, NICEATM (for contact information, see inside back cover).

Table 5 ICCVAM

- **Agency for Toxic Substances and Disease Registry**
- **Consumer Product Safety Commission**
- **Department of Agriculture**
- **Department of Defense**
- **Department of Energy**
- **Department of the Interior**
- **Department of Transportation**
- **Environmental Protection Agency**
- **Food and Drug Administration**
- **National Cancer Institute**
- **National Institute of Environmental Health Sciences**
- **National Institutes of Health**
- **National Library of Medicine**
- **National Institute for Occupational Safety and Health**
- **Occupational Safety and Health Administration**

Table 6 Test Methods Evaluated or under Consideration by ICCVAM

Test Method	Regulatory Application
Murine Local Lymph Node Assay	Substitute for currently accepted guinea pig test methods for allergic contact dermatitis. Received regulatory acceptance by U.S. agencies in 1999 and adopted by the international Organisation for Economic Co-operation and Development in 2002.
Corrositex®, EpiDerm™, EPISKIN™, and Transcutaneous Electrical Resistance Assay	*In vitro* methods to determine dermal corrosivity. Corrositex® received regulatory acceptance by U.S. agencies in 2000.
Up-and-Down Procedure	Alternative method for assessing acute oral toxicity and replacement for the conventional LD50 test for hazard classification testing. Received regulatory acceptance by U.S. agencies in 2003.
In vitro cytotoxicity methods	Used to estimate doses for assessing acute systemic toxicity in animals.
In vitro androgen receptor and transcriptional activation assays	EPA's Endocrine Disruptor Screening Program for identifying potential endocrine-disrupting chemicals.
In vitro estrogen receptor and transcriptional activation assays	EPA's Endocrine Disruptor Screening Program for identifying potential endocrine-disrupting chemicals.
FETAX (Frog Embryo Teratogenesis Assay: *Xenopus*)	*In vitro* method to determine the developmental toxicity of chemicals and mixtures.
Bovine Corneal Opacity and Permeability Test, Hen's Egg Test-Chorioallanotoic Membrane Test, Isolated Chicken Eye Test Method or Chicken Enucleated Eye Test Method, and the Isolated Rabbit Eye Assay	*In vitro* methods to assess ocular corrosiveness and severe irritation.
In vitro pyrogenicity test methods (PBMC/IL-6, WB/IL-1, cryo WB/IL-1, WB/IL-6, MM6/IL-6)	*In vitro* methods proposed to replace currently accepted tests that require the use of rabbits or an *in vitro* test that requires the use of horseshoe crabs.

Report on Carcinogens

The Report on Carcinogens (RoC) is prepared every two years in response to Section 301 of the Public Health Service Act, as amended. The RoC lists all substances that either are known to be human carcinogens or may reasonably be anticipated to be human carcinogens, and to which a significant number of people living in the United States are exposed. The secretary, DHHS delegated responsibility for preparing the RoC to the NTP. The NTP prepares the report with help from other federal health and regulatory agencies and nongovernmental institutions.

The RoC is an informational, scientific, and public health document identifying and discussing agents, substances, mixtures, and exposure circumstances that may pose a carcinogenic hazard to human health. It compiles relevant and useful data on the listed substances, including carcinogenicity, genotoxicity, and biological mechanisms in humans and/or animals, the potential for exposure to them, and federal regulations to limit exposures.

The NTP solicits and encourages broad participation from individuals or groups interested in nominating agents, substances, mixtures, or exposure circumstances for listing in or delisting (removal) from the RoC. Anyone may submit a nomination for consideration. The preparation and review process for each RoC takes about three years. Review of the nominations for listing in or delisting from the RoC follows a formal process that includes many phases of scientific peer review and opportunities for public comment. The review groups evaluate each nomination according to specific RoC criteria. The NTP director evaluates all review group recommendations, public comments, and other information in developing a recommendation to the secretary, DHHS.

The 11th RoC was released January 31, 2005, and is available on the NTP website (http://ntp.niehs.nih.gov and select “Report on Carcinogens”), or in hard copy or printed text from Central Data Management (CDM) (for contact information, see inside back cover). Nominations under consideration for the 12th RoC are listed in Table 7.

The NTP holds public meetings to gain input regarding procedures used for the review of nominations for listing in or delisting from the RoC and on the criteria used for evaluation of the nominations. These meetings provide an opportunity for the public to present its views to the NTP. The most recent public meeting was held in January 2004. Information concerning this meeting, including the public comments received, the meeting transcript, and the NTP response to issues identified at this meeting, is posted on the NTP website.

More information about the RoC, how to obtain copies of the report, and how to submit a nomination for listing in or delisting from the RoC, is available through the NTP website or by contacting Dr. C.W. Jameson, director, RoC (for contact information, see inside back cover).

Table 7 Nominations to the 12th Report on Carcinogens

Review for possible listing	
Aristolochic acid	Principle extract from *Aristolochia sp.* Is a mixture of nitrophenanthrene carboxylic acids.
Herbal remedies containing aristolochic acid	Used as a traditional Chinese herbal remedy to promote health, weight loss, and for a wide range of medical conditions.
Captafol	Fungicide widely used since 1961 for the control of fungal diseases in fruits, vegetables, and some other plants. Use in the United States was banned in 1999.
Cobalt–tungsten carbide powders and hard metals	Used to make cutting tools and wear-resistant products.
Etoposide	A DNA topoisomerase II inhibitor used in chemotherapy for non-Hodgkin's lymphoma, small-cell lung cancer, testicular cancer, lymphomas, and a variety of childhood malignancies.
Etoposide in combination with cisplatin and bleomycin	Used to treat testicular germ cell cancers.
Metalworking fluids	Used to cool and lubricate tools and working surfaces in a variety of industrial machining and grinding operations.
ortho-Nitrotoluene	Used to synthesize agricultural and rubber chemicals, azo and sulfur dyes, and dyes for cotton, wool, silk, leather, and paper.
Riddelliine	A member of a class of toxic pyrrolizidine alkaloids found in some plants growing in western United States. Cattle, horses, and sheep ingest these plants and residues have been found in milk and honey.
Styrene	Used in the production of polystyrene, acrylonitrile-butadiene-styrene resins, styrene-butadiene rubbers and latexes, and unsaturated polystyrene resins.
Teniposide	A DNA topoisomerase II inhibitor used mainly in the treatment of adult and childhood leukemia.
Review for possible reclassification of listing	
Certain glass wool fibers	Used in thermal, electrical, and acoustical insulation, weatherproofing, and filtration media. Some special purpose glass wool fibers are used for high-efficiency air filtration media and acid battery separators.
Di-(2-ethylhexyl) phthalate	Used mainly as a plasticizer in flexible polyvinyl chloride (PVC) products. Plasticized PVC is used in many consumer items and building products such as floor tiles, furniture upholstery, shower curtains, table cloths, toys, and many other products, and in plastic medical devices.
Formaldehyde	Used in the production of resins for use in different products including plastics, adhesives, and binders for wood products, pulp and paper, synthetic fibers, and in textile finishing. Also used as a disinfectant and preservative and as an intermediate for many industrial chemicals.

Outreach

Open communication with federal and state agencies, industry, academia, advocacy groups, and the public is crucial for the success of NTP activities. Partnerships with sister federal agencies are ongoing, and the NTP continues to collaborate with the private sector. NTP conferences and workshops give researchers, regulators, policy makers, and the public the chance to examine issues together, exchange information, and reach agreement on future directions for toxicology and risk assessment.

The NTP is interested in input from the public and all interested parties on its programs and priorities. Nominations, inquiries, and comments are welcome at any time. The NTP Liaison and Scientific Review Office collects input, represents the program through exhibits at national and international meetings, publishes the quarterly newsletter *NTP Update*, and oversees the distribution of information about programs, workshops, initiatives, and other projects. In addition, this office manages scientific peer review for the NTP and organizes workshops on scientific and public health topics. General inquiries and requests for information can be directed to this office (for contact information, see inside back cover).

The NTP website (http://ntp.niehs.nih.gov) provides searchable access to NTP activities and offers access to information about the NTP, with links that detail and highlight ongoing and future initiatives and the NTP centers. The NTP distributes testing and research results, program plans, and other publications through mailings, *Federal Register* announcements, and the NTP website. Also, individuals can subscribe free of charge to the NTP listserv by registering online through the website or by sending e-mail to ntpmail-request@list.niehs.nih.gov with "Subscribe" as the message. The NTP listserv notifies subscribers by e-mail about the release of new NTP publications and about upcoming events such as advisory committee meetings, peer reviews, expert panel meetings, and workshops.

The Central Data Management (CDM) oversees distribution (on request) of specific chemical study information and NTP documents including the NTP Annual Report, NTP study status reports, background documents for chemicals nominated to the NTP for study, and copies of draft NTP Technical Reports, NTP Toxicity Reports, and NTP Genetically Modified Models Reports. To request any of these documents, contact the CDM (for contact information, see inside back cover).

Contact Information

Primary Contact:

NTP Liaison and Scientific Review Office
P.O. Box 12233, MD A3-01
Research Triangle Park, NC 27709
Telephone: (919) 541-0530
E-mail: liaison@starbase.niehs.nih.gov

Program Contacts:

NTP Center for the Evaluation of Risks to Human Reproduction
P.O. Box 12233, MD EC-32
Research Triangle Park, NC 27709
Telephone: (919) 541-3455
E-mail: cerhr@niehs.nih.gov
Website: http://cerhr.niehs.nih.gov

NTP Center for Phototoxicology
NCTR/FDA, HFT-110
3900 NCTR Road
Jefferson, AR 72079
Telephone: (870) 543-7672
E-mail: phoward@nctr.fda.gov
Website: www.fda.gov/nctr/science/centers/phototoxicology

NTP Interagency Center for the Evaluation of Alternative Toxicological Methods
P.O. Box 12233, MD EC-17
Research Triangle Park, NC 27709
Telephone: (919) 541-2384
E-mail: niceatm@niehs.nih.gov
Website: http://iccvam.niehs.nih.gov

Office of Chemical Nomination and Selection
P.O. Box 12233, MD A3-01
Research Triangle Park, NC 27709
Telephone: (919) 541-5710
E-mail: ntpnomin@niehs.nih.gov

Report on Carcinogens
P.O. Box 12233, MD EC-14
Research Triangle Park, NC 27709
Telephone: (919) 541-4096
E-mail: jameson@niehs.nih.gov

Central Data Management
P.O. Box 12233, MD EC-03
Research Triangle Park, NC 27709
Telephone: (919) 541-3419
E-mail: cdm@niehs.nih.gov

National Toxicology Program

NTP

Headquartered at the
National Institute of Environmental Health Sciences
National Institutes of Health
P.O. Box 12233
Research Triangle Park, NC 27709
Website: http://ntp.niehs.nih.gov

Public Health Service
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