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Overview

Mission and Goals

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

The National Toxicology Program (NTP) was established by the U.S. Department of Health and Human Services (HHS) in 1978 to coordinate toxicological testing programs within the Department, strengthen the science base in toxicology, develop and validate improved testing methods, and 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 whose mission is to evaluate agents 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.

Focusing on the Future

The NTP provides information that improves the nation’s ability to evaluate potential human health effects from chemical and physical exposures. 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 protect public health. 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 exchanging information openly, maintaining impartiality, and applying rigorous scientific peer review. This will remain a central priority of the program now and in the future.
The NTP seeks to maintain a balanced research and testing program that provides data on a wide variety of issues that are important to public health. In particular, the NTP seeks nominations of studies that enhance the predictive ability of future NTP studies, address mechanisms of toxicity, or fill significant gaps in the knowledge of the toxicity of chemicals or classes of chemicals. Currently, the NTP is focusing on several areas that have received inadequate attention in the past, including 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, hexavalent chromium, and DNA-based therapies. 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 chemical hazards using fewer test animals. This effort includes developing more efficient, mechanism-based testing strategies, such as transgenic models for toxicology testing, and implementing microchip-based genomic technologies. Future initiatives in mechanism-based toxicology research will integrate information from traditional and gene-expression-based studies to develop new testing strategies for identifying and studying environmental toxicants. These studies hold the promise of providing a true mechanistic basis for hazard identification using short-term, practical assays applied over the broad range of environmental agents to which we are exposed.

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. Reproductive studies are being refined to address emerging knowledge of the subtle effects caused by low doses of endocrine-active chemicals.

The NTP continues to expand activities designed to place research and testing results from animals into a more relevant human health perspective. This includes human exposure assessment, toxicokinetics, mechanism-based pharmacokinetic modeling, and the interpretation of results in molecular epidemiology for use in human hazard identification (e.g., Report on Carcinogens and the NTP 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.
Role in Shaping Public Health Policy

Over the past two decades, the NTP has developed an increasingly interactive relationship with regulatory agencies. Through this relationship, the NTP plays an important, although indirect, role in shaping public health policy. Federal and state government agencies rely on the scientific knowledge base provided by the NTP to make credible decisions that protect public health without unnecessarily increasing the regulatory burden on industry. The NTP plays a critical role in providing needed scientific data, interpretations, and guidance on the appropriate uses of these data to regulatory agencies and other groups involved in health-related research. The NTP also plays an important role in fostering interagency collaborations in research and exposure assessment, providing information to regulatory agencies about alternative methods for toxicity screening, and exploring new technologies for evaluating how environmental agents cause disease.

Organizational Structure and Oversight

Three agencies form the core of the NTP: 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) (Figure 1). Each agency voluntarily provides resources to support NTP research, testing, centers, and outreach. Program contacts for each agency are Dr. Christopher J. Portier (NIEHS/NIH), Dr. Albert E. Munson (NIOSH/CDC), and Dr. William T. Allaben (NCTR/FDA). The NTP is administratively located at the NIEHS/NIH. The Director of the NIEHS/NIH, Dr. Kenneth Olden, serves as Director of the NTP and reports to the Secretary, HHS. The National Cancer Institute of the National Institutes of Health (NCI/NIH) was a charter agency for the NTP and continues to serve on the NTP Executive Committee.

The NTP Executive Committee (Figure 1) provides oversight to the NTP for policy issues. This committee is composed of the heads of federal research and regulatory agencies. External advisory groups provide review and advice to the NTP. The NTP Board of Scientific Counselors (“the Board”), its subcommittees, and the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) assure regular scientific and public peer review and input about activities and priorities.

The Board provides primary scientific oversight to the Director regarding the NTP, the NTP Center for the Evaluation of Risks to Human Reproduction (CERHR), and the NTP Center for Phototoxicology (NCP), and it evaluates the scientific merit of the NTP’s intramural and collaborative programs. The Technical Reports Review Subcommittee of the Board provides peer review for the
NTP long-term toxicology and carcinogenesis studies and short-term toxicity study reports. The Report on Carcinogens Subcommittee of the Board provides external scientific evaluation of substances nominated for listing in or delisting from the Report on Carcinogens. These groups each meet once or twice each year, and all meetings are open to the public.

The SACATM is a new advisory committee that was chartered in January 2002 to fulfill requirements specified in the ICCVAM Authorization Act of 2000 (Public Law 106-545) for providing advice to the Interagency Coordinating Committee for the Validation of Alternative Methods (ICCVAM). The ICCVAM is an NIEHS interagency coordinating committee under the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (see page 19). The SACATM provides advice to the Director of the NIEHS, the ICCVAM, and the NICEATM on priorities and directives related to the development, validation, scientific review, and regulatory acceptance of new or revised toxicological test methods and on ways to foster partnerships and communication with interested parties. The SACATM replaces the Advisory Committee on Alternative Toxicological Methods which previously provided external input to the NTP on these issues. Members of the SACATM are appointed by the Director of the NIEHS. The SACATM will meet two to three times each year, and all meetings will be open to the public.

Toxicology and Carcinogenesis Evaluations

The NTP has a broad mandate to provide toxicological characterizations for chemicals and other agents of public health concern. The NTP continually solicits and reviews nominations for toxicology studies in the specific categories given 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 web site (http://ntp-server.niehs.nih.gov) or by contacting Dr. Scott Masten, Office of Chemical Nomination and Selection (for contact information, see back flap).

Nominations undergo several levels of review before the NTP selects agents for study and designs and implements toxicological studies (Figure 2). Representatives from federal agencies on the Interagency Committee for Chemical Evaluation and Coordination (ICCEC) and the Board participate in the selection process. The NTP also solicits and considers public comment on nominations throughout this formal process. As the final step of selection, the NTP Executive Committee reviews and evaluates the testing recommendations and the public comments for each nomination and makes its own recommendations to test, to not test at this time, or to defer testing until additional 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 helps maintain 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 initiates 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.

### Table 1: Nomination Principles for NTP Studies

- 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
- Commercial chemicals 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
- Substances that occur as mixtures for which evaluations cannot be required of industry
- Chemicals that should be evaluated to improve the scientific understanding of structure-activity relationships, and thereby help limit the number of chemicals requiring extensive evaluations
- Emergencies or other events that warrant immediate government evaluation of a chemical or agent
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, metabolism, disposition,
and carcinogenicity. The NTP generally uses
rodent models for study, and performs short-term
studies for up to thirteen weeks and chronic, 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 performing
the study (grant, contract, etc.).

The NTP publishes results of short-term rodent
toxicology studies in the NTP Toxicology Report series,
and results of longer-term studies, generally two-year
rodent toxicology and carcinogenesis studies, as NTP
Technical Reports or in peer-reviewed scientific journals.
The Technical Reports Review Subcommittee of the
Board (Figure 1) formally reviews these reports in open
public meetings. Table 2 lists candidates for peer review

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**Table 2**  
Candidate Chemicals for Peer Review

<table>
<thead>
<tr>
<th>2002</th>
<th>2003</th>
</tr>
</thead>
</table>
| • trans-Cinnamaldehyde  
• Decalin  
• Dipropylene glycol  
• Elmiron  
• Pentaerythritol triacrylate  
• Trimethylolpropane triacrylate  
• Urethane + Ethanol | • 2-Methylimidazole  
• 3,3',4,4',5-Pentachlorobiphenyl  
• Propylene glycol β-butyl ether  
• Stoddard solvent (Type Ic)  
• 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)  
• Triethanolamine |
The NTP conducts research on a broad range of high-priority agents and issues of public health concern. Below are brief overviews of some current NTP initiatives.

**Radiofrequency Radiation Emissions from Cellular Phones**

Over 100 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 hand-held 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 radiofrequency radiation exposure guidelines. These guidelines are based on protecting the user from acute injury from thermal effects produced by radiofrequency radiation. Current data are insufficient to determine whether these guidelines are adequate for protecting against potential adverse effects of long-term exposure.

Studies in laboratory animals are crucial for understanding whether exposure to radiofrequency radiation may pose a danger to human health. Other research groups are performing several long-term animal studies addressing this issue. In addition, the NTP plans to conduct laboratory research to help clarify any potential health hazard for the U.S. population. The NTP is working with technical experts from the National Institute of Standards and Technology to test the suitability of various radiofrequency radiation exposure systems for these studies.

**Hexavalent Chromium**

Chromium is a naturally occurring element present in various valence states. Trivalent chromium is an essential nutrient, and chromium occurs most commonly in nature in this state. Hexavalent chromium compounds are the next most stable form; however, they rarely occur naturally and are typically associated with industrial sources.

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 carcinogenic potential of hexavalent chromium administered in drinking water. Hexavalent chromium is an established human carcinogen in certain occupational settings, presumably as a result of inhalation exposure. However, we do not know the long-term consequences of exposure to hexavalent chromium compounds in the water supply. Data currently available on the chronic toxicity and carcinogenicity of hexavalent chromium given orally are not sufficient to establish or characterize any hazard. The NTP studies will include both short- and long-term administration of hexavalent chromium to...
laboratory animals as sodium dichromate dihydrate in drinking water, as well as studies on hexavalent chromium’s tissue absorption. Data from the absorption studies and outlines of the designs of all studies on hexavalent chromium are accessible on the NTP web site (http://ntp-server.niehs.nih.gov/).

Children’s Health
The NTP continues to be a leader in issues related to children’s health through research and the NTP Center for the Evaluation of Risks to Human Reproduction (CERHR; see page 18). The NTP has ongoing efforts to evaluate effects of various agents on developing immune and nervous systems through laboratory studies of pesticides, water disinfectant by-products, and endocrine-disrupting agents. The program is expanding these efforts by establishing study protocols where perinatal animals will be given these agents and then examined for developmental immunotoxicology, neurotoxicology, and reproductive effects. Toxicokinetic data from mothers, fetuses, and newborns will be used to develop physiologically based pharmacokinetic models of risks to humans from environmental toxicants during perinatal development.

Phototoxicology
Because of the public’s increasing exposure to ultraviolet (UV) radiation from sunlight and other sources (e.g., tanning booths), the NTP has begun research on whether any toxic effects might occur from such exposures. The NTP is coordinating an effort between the NIEHS/NIH and NCTR/FDA to study the phototoxicity and photocarcinogenicity of substances nominated to the NTP, including those of high priority to the FDA. In general, these studies investigate the effects on gene expression, toxicity, and carcinogenicity of sunlight combined with either topically or systemically applied substances in the SKH-1 hairless mouse. Much of this research is being carried out at the NTP Center for Phototoxicology (NCP; see page 19).

Phototoxicology studies are in progress at the NCP for topically applied alpha-hydroxy and beta-hydroxy acids (chemoexfoliating acids) and aloe vera. Many cosmetics include alpha-hydroxy and beta-hydroxy acids, in some cases, to correct or improve the appearance of “sun-aged” skin. The relation of skin cancer to their continuous use along with exposure to sunlight is not known. Studies underway at the NCP are using glycolic and salicylic acids to represent alpha-hydroxy and beta-hydroxy acids, respectively. The NCP is also studying possible acute toxicity and photocarcinogenesis of topically applied plant fractions of the aloe vera plant in combination with simulated sunlight. Numerous products including cosmetics and dietary supplements include portions of the aloe vera plant.

The NTP is currently designing studies on the phototoxicity and photocarcinogenicity of other cosmetic ingredients including topically applied retinyl palmitate (a vitamin A derivative), tattoo ink chemicals, and fluorescein-based dyes.

Animal models for testing the role of specific UV wavelengths and chemicals in the development of human malignant skin melanoma do not yet exist. We therefore do not yet understand the effects on melanoma development of chemicals combined with exposure to sunlight. The NCP is studying a transgenic mouse [TP-nts (+) p16/INK4a (+/−)] as an animal model for studying melanoma development.

Herbal Medicines
Medicinal herbs are among our oldest medicines, and their increasing use in recent years is evidence of public interest in alternatives to conventional medicine. Approximately one third of the U.S. population is
believed to use some form of alternative medicine, including herbal remedies. The use of herbal medicines and other dietary supplements has increased substantially since passage of the 1994 Dietary Supplement Health and Education Act. Although approximately 1,500 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 conducting research on several medicinal herbs and compounds found in herbs (listed in Table 3) to examine carcinogenicity, reproductive toxicity, neurotoxicity, immunotoxicity, or toxic effects associated with exposures to high acute doses and chronic low doses.

**Safe Drinking Water Program**

More than 200 million Americans are estimated to use municipally treated drinking water, so the availability

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**Table 3  Herbs and Herbal Components under Study by the NTP**

<table>
<thead>
<tr>
<th>Herb/Component</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Aloe vera gel</td>
<td>Seventh most widely used herb; used as a dietary supplement, a component of cosmetics, and a treatment for minor burns.</td>
</tr>
<tr>
<td>Black cohosh</td>
<td>Used to treat symptoms of pre-menstrual syndrome (PMS), dysmenorrhea, and menopause.</td>
</tr>
<tr>
<td>Black walnut extract</td>
<td>Found in hair dye formulations and walnut oil stain; juglone is a major constituent.</td>
</tr>
<tr>
<td>Comfrey</td>
<td>Consumed in teas and as fresh leaves for salads; contains pyrrolizidine alkaloids that are known to be toxic; based in part on NTP studies of the alkaloid components of comfrey, the FDA has recommended that manufacturers of dietary supplements containing this herb remove them from the market.</td>
</tr>
<tr>
<td>Echinacea purpurea extract</td>
<td>A common medicinal herb in the United States; used to treat colds, sore throat, and flu.</td>
</tr>
<tr>
<td>Ginkgo biloba extract</td>
<td>Among the five or six most frequently used medicinal herbs.</td>
</tr>
<tr>
<td>Ginseng and ginsenosides</td>
<td>Fourth most widely used medicinal herb; ginsenosides are thought to be the active ingredients in ginseng, which has been associated with adverse health effects.</td>
</tr>
<tr>
<td>Goldenseal</td>
<td>Second or third most popular medicinal herb used in this country; used as a laxative, tonic, and diuretic.</td>
</tr>
<tr>
<td>Grape seed extract and pine bark extract</td>
<td>Widely used herbs; used to promote health of the cardiovascular system.</td>
</tr>
<tr>
<td>Kava kava</td>
<td>Reported to be the fifth most widely used medicinal herb; has psychoactive properties and is sold as a calmative and antidepressant.</td>
</tr>
<tr>
<td>Milk thistle extract</td>
<td>Used to treat depression and several liver conditions and to increase breast milk production.</td>
</tr>
<tr>
<td>Pulegone</td>
<td>A toxic compound found in pennyroyal.</td>
</tr>
<tr>
<td>Thujone</td>
<td>A toxic compound of wormwood; also found in other herbs, including sage and tansy.</td>
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</table>
of safe drinking water is of enormous importance to public health. Although chlorination is one of the major public health advances of the twentieth century, by-products of chlorination or other disinfection processes (disinfection by-products, DBPs) may cause health problems such as cancer. In addition, some agents found naturally in water or that contaminate public water systems may pose a threat to public health.

The EPA is responsible for setting water standards for DBPs. To provide scientific data for setting sound standards for water quality, the NTP is collaborating with the EPA on a research program to assess potential risks from human exposure to DBPs. This program includes a systematic, mechanism-based, toxicological evaluation of DBPs focusing on reproductive toxicity, immunotoxicity, neurotoxicity, and carcinogenicity. The program selects DBPs for study based on their presence in drinking water, occurrence with different disinfection processes, chemical structures, and class of DPB: trihalomethanes, haloacetic acids, and haloacetonitriles. Table 4 lists DBPs currently under study by the NTP.

Besides DBPs, many agents occur naturally (e.g., arsenic, aluminum), or because of contamination (e.g., gasoline additives such as methyl t-butyl ether, pesticides, organic tin compounds), or with environmental changes (e.g., cyanobacterial toxins from algal blooms in surface waters). The NIEHS/NIH and EPA are considering toxicology studies on several of these agents, including aluminum complexes, organic tin compounds, and the two most common cyanobacterial toxins (microcystin-LR and cylindrospermopsin), for further study by the NTP.

### Occupational Exposures

The NTP is coordinating an effort between the NIEHS/NIH and NIOSH/CDC to better understand worker exposures, educate workers, and identify occupational health research gaps. Current efforts are addressing worker exposure to asphalt fumes and 1-bromopropane.

Asphalt fumes generated during road paving have been linked to acute irritation of mucous membranes and skin, but to date no cancer risk has been established. Using a system designed to produce asphalt fumes similar to those found in the field, the NIOSH/CDC has developed methods for characterizing these fumes and for monitoring asphalt fume exposure in inhalation toxicity studies. Laboratory inhalation studies are evaluating the effects of exposure to asphalt fumes in animals.

An industry consortium has petitioned the EPA to list 1-bromopropane as an alternative for ozone-depleting solvents. This could vastly increase the exposure of workers and the public to this compound. To obtain information on exposures to this chemical, the NIOSH/CDC is conducting an industry-wide study targeting adhesive users, the metal degreasing and electronics industry, and chemical, aerosol, and adhesive manufacturers. Study sites will be selected based on quantity and type of 1-bromopropane use, number of workers exposed, type of manufacturing process, and how well the site represents the industry. Exposure will be studied using inhalation, exhaled breath, and biological measures. The NTP Center for the Evaluation of Risks to Human Reproduction (CERHR; see page 18) recently held an external scientific peer review to evaluate the evidence for potential reproductive and developmental toxicity caused by exposure to 1-bromopropane and 2-bromopropane.

### Table 4: Water Disinfection By-Products under Study

<table>
<thead>
<tr>
<th>Water Disinfection By-Products under Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bromochloroacetic acid</td>
</tr>
<tr>
<td>• Bromodichloromethane</td>
</tr>
<tr>
<td>• Chloramine</td>
</tr>
<tr>
<td>• Chloroform</td>
</tr>
<tr>
<td>• Dibromoacetic acid</td>
</tr>
<tr>
<td>• Dibromoacetonitrile</td>
</tr>
<tr>
<td>• Dichloroacetic acid</td>
</tr>
<tr>
<td>• Sodium bromate</td>
</tr>
<tr>
<td>• Sodium chlorate</td>
</tr>
<tr>
<td>• Sodium chlorite</td>
</tr>
</tbody>
</table>
The NIOSH/CDC is planning a National Exposures at Work Survey (NEWS), 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 exposure controls 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.

**Endocrine-Disrupting Agents**

Endocrine disruptors are naturally occurring or man-made substances that may mimic or interfere with natural hormones in the body. Endocrine disruptors may turn on, turn off, or modify signals that hormones carry and thus affect the normal functions of tissues and organs. The NTP is involved in several efforts to strengthen the scientific knowledge base within this field.

The NIEHS/NIH and the National Center for Environmental Health of the CDC are collaborating to quantify approximately 70 chemicals found in human blood or urine that are considered endocrine-disrupting agents, including phthalates and phytoestrogens. The biological samples are collected as part of the National Health and Nutrition Examination Survey (NHANES), which includes men and women of various age, socioeconomic, and ethnic groups. The first edition of the CDC’s National Report on Human Exposure to Environmental Chemicals, released in 2001, presents levels of 27 environmental chemicals measured in NHANES samples, including phthalate metabolites. This study complements the recently completed scientific peer review by the NTP Center for the Evaluation of Risks to Human Reproduction (CERHR; see page 18) on the potential reproductive and developmental toxicity of phthalates.

Endocrine-disrupting chemicals are of interest to the FDA, and through an interagency agreement the NIEHS/NIH supports toxicology studies being conducted at the NCTR/FDA. Chemicals under study include the phytoestrogen genistein, the pesticide vinclozolin, the drug ethinyl estradiol, and the industrial chemical nonylphenol. These studies assess effects on reproduction, development of hormone-sensitive organs, and cancer in rodents over several generations, as well as behavioral and immunological effects.

As required by the 1996 Food Quality Protection Act, the EPA is in the process of choosing appropriate assays to screen endocrine-active agents and developing standardized, validated protocols for those assays. One concern is the adequacy of current guidelines for assessing the reproductive and developmental toxicities of chemicals at environmental levels. On behalf of the EPA, the NTP organized a scientific peer review in 2000 to evaluate reported health-related effects and dose-response relationships for endocrine-disrupting chemicals studied using dosing regimens lower than those normally recommended under the EPA’s standard toxicity testing guidelines. The peer review report is posted on the NTP web site (http://ntp-server.niehs.nih.gov). A limited number of printed reports are available from the NTP Liaison and Scientific Review Office (for contact information, see back flap).

The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM; see page 19) is involved in preparing background documents for the EPA on current in vitro methods for assessing androgenic and estrogenic activities of chemicals. A peer review of these methods is planned for 2002.

**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 genome or disrupting normal cellular processes in unexpected, unpredictable, and potentially harmful ways. Examples of DNA-based products include vaccines against viruses and bacteria made of plasmid DNA encoding one or more antigenic proteins, synthetic oligonucleotides to modulate gene expression, and viral carriers for gene therapy. Presently, the NTP is collaborating with the FDA and sister NIH institutes to study the safety of DNA-based products. These studies address life-long 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.
Evolving Strategies

Considering the large number of chemicals in commercial use, the NTP must continually set priorities and develop research strategies for toxicological characterization and hazard identification that make the best use of available resources. Using new testing strategies that provide additional or better information can strengthen the scientific knowledge on which regulatory decisions are based. The NTP core agencies are developing and validating new testing methods, and in addition, university-based researchers are participating in these efforts through NIEHS/NIH 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, transgenic 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 to make better use of these new research tools.

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 effects on the immune, neurological, and reproductive and developmental systems. Data from general toxicology and carcinogenesis studies are publicly available on the NTP web site (http://ntp-server.niehs.nih.gov/). The NTP is expanding public accessibility to NTP data to include all study types (general toxicology, carcinogenesis, genetic toxicity, and organ systems). The NTP will make the data available in a common format and will provide web-based applications that allow users to query data, conduct simple statistical manipulations, and export the information.

Toxicogenomics

New molecular technologies have brought the NTP into the arena of toxicogenomics, a new scientific field that examines how the entire genome is involved in organisms’ responses to environmental toxicants. Toxicogenomics applies genetic knowledge 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 (mRNA) profiling (by microarray analysis), cell-wide or tissue-wide protein profiling
(proteomics), genetic susceptibility, and computational models to illustrate the roles of gene-environment interactions in disease. This field could have a revolutionary impact on environmental health, drug safety, and risk assessment.

To centralize activities in toxicogenomics, the NIEHS/NIH established the National Center for Toxicogenomics (NCT) in 2000. Complementary DNA (cDNA) microchip-based technology will enable the NCT to assess the genetic impact of toxicants. Microarrays containing genes from common test animals and organisms, including mice, rats, and yeast, are currently in use at the NIEHS/NIH, and the NIOSH/CDC has compiled a hepatic microarray.

Gene arrays are being evaluated against known toxicants and building a database of expression information to determine the typical genetic changes or “signature” profiles produced by these toxicants. Identification of such changes in gene expression on a genome-wide basis could provide a global perspective on how an organism responds to a specific stress, drug, or toxicant. As this technology continues to improve, it will help NTP scientists evaluate and compare compounds under study. Such information could define cellular networks of response genes, identify target molecules of toxicity, provide future biomarkers and alternative testing procedures, and identify individuals who are sensitive to drugs or environmental agents.

Transgenic Animals

For more than three decades, the NTP has conducted studies in laboratory rodents (bioassays) to identify carcinogens thought to pose risks to human health. New genomic technologies enable transgenic models that 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 than conventional rodent strains, and within a time frame in which few, if any, spontaneous tumors would arise. Target or reporter genes 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 is evaluating the usefulness of a number of transgenic rodent models for studies of carcinogenesis [p16INK4a, p53def (p53 +/−), Tg.AC (v-Ha-ras), and Tg.NK (MMTV/c-neu)] and mutagenesis [C57BL/6J-TgN (phiX174am3, cs70) 54Hvm]. The p53def and Tg.AC models appear to be able to identify known human carcinogens. The p53def has demonstrated preferential identification of genotoxic/mutagenic carcinogens, and the Tg.AC has responded to both genotoxic and nongenotoxic carcinogens. As understanding progresses of the complex signaling pathways turned on or off during carcinogenesis, the NTP will be able to select transgenic animal models that best mimic human tissue processes, providing a firmer foundation for applying hazard data from animals to humans. Efforts are also underway to develop transgenic cell lines and to evaluate the usefulness of transgenic fish as alternates to mouse or cultured cell models.

Risk Assessment Methodology

Risk assessment involves using facts to determine whether exposure to hazardous agents affects the health of individuals and populations, and if so, how much. Biologically based mathematical models for estimating human risk are useful to risk assessment. These models are mathematical representations of physiological and biochemical processes known to occur in laboratory animals and humans. These models can provide a scientifically
sound basis for evaluating data in animals and then applying that information across species to determine if and how exposure to an agent might cause health effects in humans.

Developing biologically based models relies on first developing a simple model based on available data and then testing predictions of the model experimentally. As more data become available from studies in cell cultures, animals, and humans, the model is continually adjusted or expanded. Physiologically based pharmacokinetic (PBPK) models quantify the biological processes of absorption, distribution, metabolism, and elimination of an agent resulting from exposure in animals or humans (Figure 3). The NIEHS/NIH has created or is developing PBPK models to evaluate exposure-response relationships for carcinogenicity and developmental and reproductive toxicities (listed in Table 5). PBPK models are now often included in NTP Technical Reports. This information helps regulatory agencies assess the human risk from exposure to environmental agents.

Combining PBPK models with models that measure changes in cells in target tissues under different concentrations of test agents helps define dose-response relationships and determine the likelihood of adverse effects from “low-dose” exposure. These models also help to assess variation among individuals in specific groups (e.g., same or similar age, gender, genetic predisposition, or ethnicity). The NIEHS/NIH has developed mechanistic models of aryl hydrocarbon receptor-dependent changes in gene expression for the carcinogen 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). TCDD is the most potent member of the dioxin class of chemicals. Dioxins are unwanted, but widely occurring, by-products of chemical processes that involve reactions of chlorine and hydrocarbons (e.g., produced by paper and pulp bleaching or incineration of hospital and municipal wastes). They are also contaminants in some pesticides, herbicides, and wood preservatives. The EPA used this model in its TCDD cancer risk assessment, which serves as its basis for regulating human exposure to this environmental hazard. NTP initiatives in human exposure and new toxicogenomic technologies should provide human and animal mechanistic data for developing and improving biologically based models.

### Figure 3
**Physiologically Based Pharmacokinetic Model**

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

### Table 5
**Physiologically Based Toxicokinetic Modeling**

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Route of Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthraquinone</td>
<td>Oral in feed</td>
</tr>
<tr>
<td>Butadiene</td>
<td>Inhalation</td>
</tr>
<tr>
<td>p,p'-Dichlorodiphenylsulfone</td>
<td>Oral in feed</td>
</tr>
<tr>
<td>Isoprene</td>
<td>Inhalation</td>
</tr>
<tr>
<td>Melatonin</td>
<td>Endogenous</td>
</tr>
<tr>
<td>Mercury (pregnant rat)</td>
<td>Inhalation</td>
</tr>
<tr>
<td>Methyleugenol</td>
<td>Oral by gavage</td>
</tr>
<tr>
<td>Naphthalene</td>
<td>Inhalation</td>
</tr>
<tr>
<td>Polychlorinated biphenyls (209 congeners)</td>
<td>Multiple routes</td>
</tr>
<tr>
<td>Primidone</td>
<td>Oral in feed</td>
</tr>
<tr>
<td>Sodium nitrite</td>
<td>Oral in drinking water</td>
</tr>
<tr>
<td>2,3,7,8-Tetrachlorodibenzo-p-dioxin</td>
<td>Oral and dermal</td>
</tr>
</tbody>
</table>
Human Reproduction

The NTP Center for the Evaluation of Risks to Human Reproduction (CERHR), established in 1998, serves as an environmental health resource to the public and to regulatory and health agencies. It provides scientifically based, uniform assessments of the potential for adverse effects on reproduction and development caused by agents to which humans are exposed. The NTP Board of Scientific Counselors (“the Board”) advises the CERHR on its processes, priorities, and direction.

The CERHR follows a formal, open process for nomination, selection, and review of chemicals; public input is encouraged. The CERHR selects chemicals for review based on several factors, including production volume, extent of human exposures, public concern about the chemical hazard, and published evidence of reproductive or developmental toxicities. The CERHR carries out these assessments through rigorous evaluations by independent scientific panels in public forums. These evaluations are intended to

- interpret scientific evidence to the public and provide information about the strength of the evidence that a given exposure or circumstance poses a hazard to reproduction or 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; and
- identify knowledge gaps to help establish research and testing priorities.

The CERHR’s first expert panel evaluated evidence that seven selected phthalates [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] may pose a reproductive and/or developmental risk for people exposed to these chemicals. Phthalates are widely used as plasticizers in consumer products such as shower curtains, medical devices, upholstery, raincoats, and soft-squeeze toys. Other expert panels have addressed potential reproductive and/or developmental toxicity of methanol (October 2001) and 1-bromopropane and 2-bromopropane (December 2001). Methanol is a commercially important, high-production-volume chemical with potential for occupational, consumer, and environmental exposure. 1-Bromopropane has various industrial uses and is being considered as a replacement for ozone-depleting chemicals such as hydrochlorofluorocarbons and chlorinated solvents. 2-Bromopropane has no industrial uses in the United States but is a contaminant in 1-bromopropane. A future CERHR evaluation is planned for ethylene glycol, a high-production-volume chemical used chiefly in antifreeze for heating and cooling systems.
Expert panel reports are posted on CERHR’s web site (http://cerhr.niehs.nih.gov) and are available in hard copy from the CERHR. As a final step in its review of a chemical, the NTP prepares an NTP-CERHR Report. This report gives the NTP’s interpretation of the potential for the chemical to cause adverse reproductive and/or developmental effects for humans exposed to it. The NTP-CERHR Reports are transmitted to federal and state agencies, interested parties, and the public and will be available on the center’s web site. NTP-CERHR Reports are currently being developed for the seven phthalates, methanol, and the bromopropanes.

The center’s web site 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 or scientists for its expert registry. Information about the CERHR and the nomination process is available from its web page or by contacting Dr. Michael Shelby, Director, CERHR (for contact information, see back flap).

NTP Center for Phototoxicology
The NTP Center for Phototoxicology (NCP) was established in 2000 to conduct mechanistic-based research and phototoxicology and photocarcinogenesis studies on substances nominated to the NTP. Many of these compounds are of regulatory importance to the FDA. Research in this area is very important because of the public’s increasing exposure to ultraviolet (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 electromagnetic radiation from several light sources. The NCP also conducts mechanistic studies to learn how these effects might occur. The laboratory can simulate sunlight using 6.5 kilowatt xenon-arc lamps that can mimic terrestrial solar light for most latitudes. Emulating terrestrial light enables researchers to experimentally duplicate human exposure conditions, which is critical for such research. 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 Phototoxicology Chemical Selection Working Group prioritizes nominations and forwards them to the NTP for formal consideration in its nomination and selection process. Current research initiatives are described on page 9 under “Phototoxicology.” Additional information about the NCP is available through the NCP web site (http://www.fda.gov/nctr/science/phototox.htm) or by contacting Dr. Paul C. Howard, Director, NCP (for contact information, see back flap).

NTP Interagency Center for the Evaluation of Alternative Toxicological Methods
Toxicity testing is absolutely necessary to assess the hazards and safety of substances in our food, air, and water, in the workplace, and at home. Developing, validating, accepting, and harmonizing new and revised toxicological test methods are coordinated throughout the federal government through the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). The ICCVAM was established in 2000 (ICCVAM Authorization Act of 2000: Public Law 106-545) as a permanent interagency coordinating committee of the NIEHS/NIH under the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM).
The ICCVAM consists of the heads of 15 federal agencies or their designees (Table 6).

The NICEATM and the ICCVAM facilitate the development, scientific review, and validation of new and revised toxicological test methods that may predict human health risks better than currently used methods, improve our understanding of toxicity, save time and money, and even refine, reduce, or replace animal use. The NICEATM also promotes information sharing and communication among the agencies and other interested parties.

The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM), established in January 2002, provides advice on the activities of the ICCVAM and the NICEATM.

The ICCVAM has a formal process for evaluating new or revised toxicological test methods. The NICEATM and the ICCVAM convene workshops and expert panel meetings to evaluate how well current methods work, to identify areas needing improved or new methods, to assess the current status of new methods, and to recommend additional research, development, and validation. These meetings are open to the public and have opportunity for public comment. Meeting reports, public comments, and ICCVAM recommendations regarding 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.

The Local Lymph Node Assay (LLNA) was the first method evaluated under the ICCVAM peer review process. The panel concluded that the LLNA is a valid substitute for currently accepted guinea pig test methods. The EPA, the Occupational Safety and Health Administration, and the FDA announced their acceptance of the LLNA as an alternative method in October 1999. Compared to the traditional test, the LLNA can be completed in a shorter timeframe, provides dose-response information, reduces the number of animals required, and eliminates animal pain and distress.

The NICEATM and the ICCVAM recently held a peer review on the Up-and-Down Procedure (UDP) for assessing acute oral toxicity. The peer review panel recommended the UDP as a substitute for the conventional LD50 test for hazard classification testing. The UDP will reduce the number of animals used for acute toxicity testing. The ICCVAM agreed with the panel’s conclusion and will now develop test recommendations and forward them to the appropriate federal agencies for their consideration. In October 2000, the NICEATM and ICCVAM organized an international workshop to review and evaluate in vitro methods for assessing acute systemic toxicity. The workshop experts recommended in vitro cytotoxicity methods as an approach that could be used to estimate starting doses for in vivo acute toxicity studies, which will further reduce numbers of animals used. The ICCVAM agreed with this recommendation and will develop and forward test recommendations to the appropriate federal agencies for their consideration. As follow-up to both reviews, a workshop on the implementation of acute toxicity test methods was held in February 2002 at the NIH. The NICEATM will hold an expert panel meeting in May 2002 to assess the validation status of several in vitro assays proposed for possible use in the EPA’s Endocrine Disruptor Screening Program.

Additional information about NICEATM and ICCVAM, meeting schedules, meeting reports and minutes, and information on nominating alternative toxicological methods is available through the ICCVAM/NICEATM web site (http://iccvam.niehs.nih.gov) or by contacting Dr. William S. Stokes, Director, NICEATM (for contact information, see back flap).

Table 6  ICCVAM

- Agency for Toxic Substances and Disease Registry
- Food and Drug Administration
- National Institute for Occupational Safety and Health/Centers for Disease Control and Prevention
- National Institutes of Health
- National Cancer Institute/National Institutes of Health
- National Institute of Environmental Health Sciences/National Institutes of Health
- National Library of Medicine/National Institutes of Health
- Occupational Safety and Health Administration
- U.S. Consumer Product Safety Commission
- U.S. Department of Agriculture
- U.S. Department of Defense
- U.S. Department of Energy
- U.S. Department of the Interior
- U.S. Department of Transportation
- U.S. Environmental Protection Agency
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, HHS delegated responsibility preparing the RoC to the NTP, which prepares the report with assistance from other federal health and regulatory agencies and nongovernment institutions.

The RoC is an informational, scientific and public health document that identifies and discusses agents, substances, mixtures, and exposure circumstances that may pose a carcinogenic hazard to human health. It compiles meaningful and useful data on the agents listed, 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 groups or individuals interested in nominating agents, substances, mixtures, or exposure circumstances for listing in or delisting from the RoC. Anyone may submit a nomination for consideration by the NTP.

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 many opportunities for public comment (Figure 4). 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, HHS.

The 9th RoC was initially released May 15, 2000, with an addendum published on January 19, 2001, and is available on the Environmental Health Perspectives web site (http://ehponline.org; for contact information, see back flap). The scientific review of nominations to the 10th RoC is complete and we anticipate publication in 2002 (see list in Table 7).

The preparation and review process for each RoC takes approximately three years. Table 8 lists the nominations under consideration for the 11th RoC; review of these nominations is underway, and publication is scheduled for 2004.

Additional information about the RoC, including 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 web page (http://ntp-server.niehs.nih.gov) or by contacting Dr. C.W. Jameson, Head, Report on Carcinogens (for contact information, see back flap).
Table 7  Summary of the Agents, Substances, Mixtures, or Exposure Circumstances for Possible Listing in or Delisting from the 10th Report on Carcinogens

<table>
<thead>
<tr>
<th>Reviewed in January 2000</th>
<th>Reviewed in December 2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 2-Amino-3-methylimidazo[4,5-f]quinoline (IQ)</td>
<td>• Broad-spectrum UV radiation, UVA, UVB, and UVC</td>
</tr>
<tr>
<td>• Beryllium and beryllium compounds</td>
<td>• Chloramphenicol</td>
</tr>
<tr>
<td>• 2,2-Bis-(Bromomethyl)-1,3-propanediol</td>
<td>• Estrogens, steriodal</td>
</tr>
<tr>
<td>• 2,3-Dibromo-1-propanol</td>
<td>• Nickel and nickel compounds</td>
</tr>
<tr>
<td>• Dyes metabolized to 3,3'-dimethoxybenzidine (dimethoxybenzidine dyes as a class)</td>
<td>• Methyleneugenol</td>
</tr>
<tr>
<td>• Dyes metabolized to 3,3'-dimethylbenzidine (dimethylbenzidine dyes as a class)</td>
<td>• Trichloroethylene</td>
</tr>
<tr>
<td>• Styrene-7,8-oxide</td>
<td>• Wood dust</td>
</tr>
<tr>
<td>• Vinyl bromide</td>
<td></td>
</tr>
<tr>
<td>• Vinyl fluoride</td>
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</tbody>
</table>

Table 8  Summary of Nominations under Consideration for the 11th Report on Carcinogens

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• 1-Amino-2,4-dibromo-anthraquinone</td>
<td>• Naphthalene</td>
</tr>
<tr>
<td>• 2-Amino-3,4-dimethylimidazo[4,5-f]quinoline (MeIQ)</td>
<td>• Neutrons</td>
</tr>
<tr>
<td>• 2-Amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx)</td>
<td>• Nitrobenzene</td>
</tr>
<tr>
<td>• Cobalt sulfate heptahydrate</td>
<td>• Nitromethane</td>
</tr>
<tr>
<td>• Diazaoaminobenzene</td>
<td>• Occupational exposure to lead or lead compounds</td>
</tr>
<tr>
<td>• Diethanolamine</td>
<td>• Phenylimidazopyridine (PhIP)</td>
</tr>
<tr>
<td>• Hepatitis B virus</td>
<td>• 4,4'-Thiodianiline</td>
</tr>
<tr>
<td>• Hepatitis C virus</td>
<td>• X-radiation and gamma (γ)-radiation</td>
</tr>
<tr>
<td>• High-risk human papillomaviruses</td>
<td></td>
</tr>
</tbody>
</table>
Communication and Public Outreach

Open communication with federal and state agencies, industry, academia, and the public is crucial for the success of NTP activities. Partnerships with sister federal agencies are increasing, 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, and oversees the distribution of information about programs, workshops, initiatives, and other projects. General inquiries and requests for information can be directed to this office.

The NTP web site (http://ntp-server.niehs.nih.gov) 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 web site. In addition, individuals can subscribe free-of-charge to the NTP listserv by registering online through the web site or by sending e-mail to ntpmail-request@list.niehs.nih.gov with “subscribe” as the message.

The Central Data Management (CDM) oversees distribution (on request) of specific chemical study information and NTP documents, including the NTP Annual Plan, NTP Study Status Reports, pre-peer review copies of draft NTP Technical Reports, background documents for chemicals nominated to the NTP for study, and minutes from meetings of the NTP Board of Scientific Counselors and its subcommittees. To request any of these documents, contact the CDM.

The Environmental Health Perspectives (EHP) web site (http://ehponline.org) provides searchable access and printed copies of NTP publications, including the Report on Carcinogens, NTP Technical Reports, and NTP Toxicity Reports. EHP subscription packages include access to NTP publications, Environmental Health Perspectives journal, the Rodent Historical Controls Database, and the Chemical Health and Safety Database. For additional information, contact EHP.
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