Planning, Implementation, & Evaluation

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How does NTP test potentially dangerous substances? There is no single methodology that applies in all instances, but careful planning, implementation, and evaluation are the three essential components of our process. Explore the items below to learn about the techniques, approaches and methodologies we employ during each stage of testing.

The NTP Planning Process

Problem Identification

Over the course of any given year, NTP receives various requests for the study of potentially harmful substances. These requests are submitted by:

- Advocacy groups
- Agencies represented on the NTP Executive Committee
- Colleges and universities
- Companies and industry associations
- Concerned individuals
- Federal and state regulatory agencies
- Health agencies
- Labor unions

Often, a substance or chemical comes to the attention of NTP because it is "in the news": for example, an unusual number of factory workers working with a specific chemical

The NTP Problem Identification Process: Hexavalent Chromium

In October 2000, California State Representative Adam Schiff nominated hexavalent chromium for NTP study, stating that "the safety of the drinking water in several California cities is being questioned as a result of hexavalent chromium compound contamination. Definitive data on whether hexavalent chromium administered in drinking water is carcinogenic is needed."

Shortly thereafter, in February 2001, the California branch of the Environmental Protection Agency (EPA) filed its own request. In addition to the reasons cited by Rep. Schiff, the California EPA noted "the limited animal and human carcinogenicity data available" pertaining to hexavalent chromium.

Finally, in March 2001, the U.S. Congressional delegation from California filed yet a third request, noting that "the NTP carcinogenicity tests will contribute to the development of a scientifically sound standard for hexavalent chromium in drinking water."

develop cancer, or local supplies of drinking water are found to be contaminated.

Problem Selection

Substances and circumstances are continually reviewed by the NTP Office of Nomination and Selection to determine whether they have been adequately tested or previously considered by NTP. This process usually involves one or more of the following steps:

- A review of toxicological literature is prepared, which evaluates available information about the substance.
- A Federal Register notice (FRN) is published, including preliminary study recommendations and a solicitation for public comments.
- NTP develops a Research Concept, which outlines a proposed research program.
- The NTP Board of Scientific Counselors (BSC) considers the request for testing. If necessary, representatives from affected industries are allowed input into the process.
- The NTP Executive Committee makes a final recommendation to the NTP Director on whether to proceed with, or defer, the recommended study.

The NTP Problem Selection Process: Gum Guggul Extract

Gum guggul is a non-FDA-approved dietary supplement that is also widely used to treat arthritis, obesity, heart disease, and acne. It was brought to NTP's attention because of its widespread use by U.S. consumers and the lack of available information about its safety in humans.

The NTP Research Concept for gum guggul, published in 2005, discussed eight possible areas of gum guggul research:

- Effects on various organ systems
- Effects on gene expression (toxicogenomics)
- Interaction with nuclear receptors
- Potential drug-drug and drug-chemical interactions
- Effects on enzymes involved in sex-hormone biosynthesis
- Effects on reproduction and development
- Immunotoxicity studies using the Salmonella array
- Use of hyperlipidemic and/or obesity models

The NTP study group recommended a tiered approach to gum guggul research. Tier I included high-priority studies, while Tier II comprised studies that could be reconsidered as data became available from Tier I studies.

The NTP Implementation Process

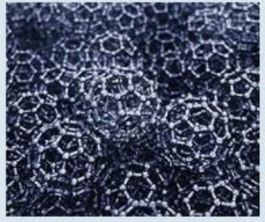
Study Design

Substances approved for NTP study are assigned to a staff scientist from either NIEHS, the Food and Drug Administration (FDA), or the National Institute for Occupational Safety and Health (NIOSH).

This individual assembles a Study Design Team composed of staff from NTP, NIEHS, and other government agencies. If the study is deemed warranted, this team presents a detailed proposal to a joint NIEHS/NTP Project Review Committee.

In certain instances, the Study Design Team may recommend **not** pursuing a given study, due to technical difficulties in acquiring suitable test samples or carrying out specific methodologies.

The NTP Study Design Process: Multiwalled Carbon Nanotubes



In May 2014, an NTP Study Design team discussed the proposed testing protocol for multiwalled carbon nanotubes. Unlike the typical chemicals and compounds considered by NTP, multiwalled carbon nanotubes are a product of nanotechnology processes, and so present unique challenges when considering their potential health effects.

The team reviewed plans for:

- A two-year chronic inhalation study
- A 30-day inhalation systems toxicity study
- Co-visualization of carbon nanotubes and nickel (which can be used as a surrogate to detect carbon nanotubes in lung tissue)

With the approval of the NIEHS project leader, it was decided that the agreed-upon study plan would be presented to the joint NIEHS/NIH Project Review Committee.

Conduct

NTP has a wide variety of test methodologies at its disposal, including:

- Toxicology/carcinogenicity, evaluating dose-response relationships between exposed and unexposed organisms
- Chemical disposition and toxicokinetics, tracking absorption, distribution, metabolism, and excretion
- Developmental and reproductive toxicity, evaluating organ development and reproductive systems
- Genetic toxicology, assessing damage to DNA
- Immunotoxicity, assessing damage to the immune system
- Neurotoxicity, assessing neurodevelopmental and neurodegenerative disorders
- Toxicogenomics, examining the expression of genes, proteins, and metabolites in living cells
- Alternative testing methodologies, including predictive toxicology models, *in vitro* cell- and tissue-based systems, and transcriptomic profiling

The results of NTP tests are subjected to statistical analysis and quality assurance protocols, assuring that the data obtained is of the highest caliber.

The NTP Conduct Process: Sulfolane

An industrial chemical identified in Alaskan groundwater, sulfolane was nominated for NTP testing in 2011. We have conducted, or are currently conducting, five separate studies of this substance, including:

- A 28-day toxicity study to determine the sensitivity of test animals to sulfolane, as well as the appropriate dosing levels for longer-term studies
- An absorption, distribution, metabolism and excretion study to track the progress of sulfolane via different routes of exposure
- A two-year subchronic toxicity study to identify the effects of sulfolane on development, reproduction, and the immune system
- A chronic toxicity study to determine the carcinogenetic effects of long-term sulfolane exposure
- A three-month immunotoxicity study to determine sulfolane's effects on mouse immune systems

The NTP Evaluation Process

Review

Completed NTP studies are subject to intensive, multi-stage, internal and external review. The stages of this process may include:

- Pathology review – examination of tissue slides by NTP pathologists
- NTP evaluation – vetting of results by NTP scientific staff
- Peer review – evaluation of results by committees of outside experts

These criteria also apply if the study yields inconclusive or negative results. Even if a given substance is shown to have no little or no impact on human health (extrapolating from rodent models), publicizing this data this still adds to the body of knowledge of the medical and toxicological communities.

The NTP Peer Review Process: Cell Phone Radiation

One of the most ambitious peer-review meetings in NTP history was held in March 2018, to discuss the results of our cell phone radiofrequency radiation (RFR) studies. This three-day meeting was attended by over 100 participants from government, industry, and academia, who discussed such issues as:

- The reverberation chamber technology used to evaluate the effects of cell phone RFR exposure in rats and mice
- The pathology peer-review process for two-year cell phone RFR studies
- Whether the studies' experimental design, conduct, and findings supported NTP's conclusions regarding carcinogenic activity

In the course of the meeting, oral comments were submitted by representatives from:

- The Environmental Working Group
- The Environmental Health Trust
- The California Brain Tumor Association
- McGill University
- The Phonegate Alert Association
- The Korean Institute of Electromagnetic Engineering and Science

Dissemination

Once a study has been reviewed and evaluated, the results are posted on the NTP website. Occasionally, a substance or chemical is the object of sufficient public or regulatory interest as to warrant a press release. This was the case, for example, with recent studies of cell phone radiation and bisphenol A, a chemical used in epoxy resins.

The NTP Dissemination Process: The Elk River Chemical Spill

In January 2014, approximately 10,000 gallons of chemicals used to process coal spilled from a storage tank into the Elk River in West Virginia. The Elk River is a municipal water source which serves about 300,000 people in the Charleston area.

NTP carried out a research program to predict the toxicity of these spilled chemicals—employing rodent studies, toxicity tests in cells, and computer modeling, among other approaches. Here is an excerpt from a 2015 press release from the Department of Health and Human Services:

> "The scientific results of the NTP studies released today upheld the drinking water advisory issued during the Elk River chemical spill, which is good and reassuring news for West Virginia residents who reside in the affected communities," said Dr. Rahul Gupta, Commissioner for the Bureau for Public Health and State Health Officer.
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> "All together, the NTP findings support the adequacy of the drinking water advisory levels established at the time of the spill," said John Bucher, Ph.D., NTP Associate Director. "The results identified an opportunity to evaluate a potential health effect in the affected communities. NTP used a comprehensive suite of state-of-the-art toxicology tools to look at the spilled chemicals, and found very little reason for concern about long-term health effects."

Impact

The final data from published NTP reports are made available to the public, and can be downloaded for further analysis by industry, academia, government bodies, and scientific research organizations. NTP does not, itself, issue any recommendations or warnings about a given substance; rather, we present the conclusions of our studies fairly and impartially and leave it to other bodies to formulate policies or take action (if needed).

The NTP Impact: Hexavalent Chromium

In May 2009, a paper by NTP researcher Matthew Stout, "Hexavalent Chromium Is Carcinogenic to F344/N Rats and B6C3F1 Mice after Chronic Oral Exposure," was published in the journal Environmental Health Perspectives, and has since garnered over 150 citations. The TOX-72 and TR-546 reports, summarizing three-month and two-year studies, have also been cited numerous times in scientific journals.

NTP's findings about hexavalent chromium have had a marked influence on public policy. In 2011, the U.S. Department of Defense issued a rule minimizing the use of materials containing hexavalent chromium, and the Occupational Safety and Health Administration amended its existing hexavalent chromium standards. Our research also inspired the nation's first-ever drinking-water standards for hexavalent chromium, adopted by California in 2014.