The National Toxicology Program

UPDATE

May 2003

Headquartered at the National Institute of Environmental Health Sciences NIH· HHS

New Database Available – NTP Invites Feedback

The NTP is creating a new database to allow searches of its study data using the web. Currently the NTP is developing programming tools for accessing the data and is interested in obtaining feedback from the public on the use of these new searches.

To access the database and do a search, go to the NTP homepage (http://ntp-server.niehs.nih.gov) and select "NTP Study Information." On this page are new options for accessing the database and doing a search.

Choose:
SEARCH THE NTP STUDIES DATABASE
(Hyperlinks on this page are shown here in italics)

- ***Available Data on Individual Studies***
- Pathology
  - ***Incidence rates*** for completed chronic and prechronic studies collected in the Toxicology Database Management System (TDMS)
  - ***Individual animal*** pathology data for completed chronic studies collected in the NTP's Toxicology Database Management System (TDMS) and Carcinogenesis Bioassay Data System (CBDS)

The first search category "Available Data on Individual Studies" allows the user to enter a chemical name and retrieve information about the types of studies (e.g., chronic exposure studies, reproductive/development, genetic toxicity, etc.) that are completed and to determine which studies have data available in electronic format. The data that might be available are clinical chemistry, hematology, organ weights, body weights, survival, clinical observations and pathology.

The second category "Pathology" includes two links to search through the NTP pathology databases. Under this heading the first link retrieves the incidence rates and the second link retrieves individual animal evaluations.

The NTP welcomes input from persons who try the database. Please send your queries, comments, and suggestions to: ntpwm@niehs.nih.gov

Society of Toxicologic Pathology Satellite Symposium

"An Exercise in Peer Review: The Pathology Working Group" is scheduled for Saturday, June 14, 2003, 8:30 AM – 4:30 PM at the Savannah Hotel, Savannah, Georgia. This symposium is aimed at providing continuing education on some basic and common lesions seen in toxicity and carcinogenicity studies and engendering active discussion about controversial and/or uncommon lesions.

Persons attending the satellite symposium will have the opportunity to participate in a mock pathology working group. Cases will be presented and after each case, the audience will vote on the diagnosis and the responses will be instantaneously collected and displayed. The cases will be available to registered attendees through the Society of Toxicologic Pathology web site (http://w2ww.toxpath.org) approximately one month prior to the meeting. Audience participation is limited to 100 voting attendees. Non-voting observers are also welcome, although space is limited.

Registration is required for both voting and non-voting attendees and there is no charge to attend. To reserve your spot, send your contact information (name, affiliation, telephone number and e-mail address) along with whether or not you wish to vote to Anne Marie Hauck, Experimental Pathology Laboratories, Inc., P.O. Box 12766, Research Triangle Park, NC by e-mail (ammotley@epl-inc.com). Don't delay - this symposium is sure to offer a stimulating good time.

This symposium is part of the annual meeting of the Society of Toxicologic Pathology and is being co-sponsored by the NTP and EPL, Inc.

Upcoming Peer Review of Draft NTP Technical Reports

The NTP Board of Scientific Counselors Technical Reports Review Subcommittee will peer review 6 draft NTP Technical Reports of NTP rodent toxicity and carcinogencity studies at its meeting on May 22, 2003 at the National Institute of Environmental Health Sciences (NIEHS). The meeting begins at 8:30 a.m. and is open to the public.

The reports tentatively scheduled for review include:

- Propylene glycol mono-***t***-butyl ether – used as a solvent
- 2-Methylimidazole – used as a chemical and pharmaceutical intermediate
- Triethanolamine – used in a variety of industrial and manufacturing applications
- Stoddard solvent IIC – used as a paint and dry cleaning solvent
- Aspartame – used as an artificial sweetener
- Acesulfame potassium – used as an artificial sweetener

The draft reports are available for public review, free-of-charge though ehpOnline (http://ehp.niehs.nih.gov). A limited number of printed reports are available from Central Data Management at the NIEHS (T: 919-541-3419, fax: 919-541-3687, CDM@niehs.nih.gov). This meeting can be viewed via the Internet at http://www.niehs.nih.gov/external/video.htm. Persons needing special assistance in order to attend are asked to contact the Executive Secretary (T: 919-541-0530, e-mail: wolfe@niehs.nih.gov) seven business days prior to the meeting.

The NTP conducts toxicology and carcinogenesis studies of agents of public health concern. Any scientist, organization, or member of the public may nominate a chemical for NTP testing (see article below, ***What is the NTP Testing Program?***). The results of short-term rodent toxicology studies are published in the NTP Toxicity Report series and from longer-term rodent carcinogenicity studies, generally two years, are published in the NTP Technical Report series. The NTP will unveil a new Technical Report series of shorter-term carcinogenicity studies at the upcoming meeting. The studies of aspartame and acesulfame potassium will be the first two studies reported in the new series.

The Technical Reports Review Subcommittee is a standing subcommittee of the NTP Board of Scientific Counselors. Subcommittee actions and summary minutes from the meeting will be posted on the NTP web site (http://ntp-server.niehs.nih.gov) or available in hardcopy from the NTP Executive Secretary (T: 919-541-0350).

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What is the NTP Testing Program?

The NTP has a broad mandate to provide toxicological characterizations for chemicals and other agents of public health concern. The program continually solicits the nomination of toxicological studies from all interested groups, such as labor unions, academia, federal and state agencies, industry, and the general public. Study nominations are welcome for specific substances or general issues related to potential human health hazards of occupational or environmental exposures.

The NTP Office of Chemical Nomination and Selection handles the receipt of study nominations and comments on testing initiatives or nominations (contact information below). As possible, the NTP asks that nominators provide a rationale for study, background information describing sources of exposure and possible adverse health effects or concerns associated with exposure, and for specific substances, the chemical name and Chemical Abstract Service (CAS) registry number.

Details about the nomination process are available on the NTP web site (http://ntp-server.niehs.nih.gov, select "How to Nominate Substances") or by contacting the NTP Office of Chemical Nomination and Selection. All nominations undergo several levels of review before the NTP selects agents for study and designs and implements toxicological studies. These steps of review help to 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 agents evaluated.

Current areas of focus in the NTP's testing program include potential hazards associated with herbal dietary supplements, radio-frequency radiation emissions from cellular telephones, hexavalent chromium in drinking water, photoactive chemicals, certain complex occupational exposures, dioxin-like compounds, contaminants of finished drinking water, and endocrine-disrupting agents.

Contact information: Dr. Scott Masten, Office of Chemical Nomination and Selection, NIEHS, P.O. Box 12233, MD A3-07, 111 TW Alexander Dr., Research Triangle Park, NC 27709; T: 919-541-5710; masten@niehs.nih.gov

NTP Workshop on Transgenics

On February 21, 2003, as part of an ongoing process to evaluate the utility of genetically modified animal models, the NTP hosted a workshop, "Genetically Modified Rodent Models for Cancer Hazard Identification: Selecting Substances for Study and Interpreting and Communicating Results" in Washington, DC. Approximately 100 persons with both national and international representation attended, including invited staff from NTP-participating regulatory and science agencies, members of various NTP and NIEHS external advisory committees, representatives from animal welfare groups, foreign governments, and the pharmaceutical, chemical, and academic communities. Many of these persons have participated in other efforts to evaluate the utility of genetically modified mouse models (Robinson and MacDonald, 2001).

The goal of this workshop was two-fold:

1) To solicit comment on a proposed process for selection of appropriate nominated substances to undergo cancer hazard evaluation in genetically modified or "transgenic" models
2) To solicit comment on issues related to the proper interpretation of results from genetically altered mouse cancer models, the implications of these findings for public health decisions, and the most appropriate interpretive language to describe the results of such studies to the scientific/regulatory communities and the public.

The workshop opened with plenary talks outlining the current understanding of biology of the tumor responses to carcinogens exhibited by three commonly used genetically modified mouse (GMM) models - Tg.AC, the p 53+/- and the Hras2, followed by a short history of the use of GMM models within the NIEHS and specifically in the NTP cancer bioassay program. The workshop attendees then split into two breakout groups to consider the issues posed above and ultimately reconvened to discuss the separate deliberations in an afternoon plenary session.

Since the early 1990s, scientists at the NIEHS/NTP have been working to develop rodent cancer screening models using GMM models. The NTP has conducted a number of assays on chemicals for which no long-term cancer bioassays exist using two widely studied models, the Tg.AC and p53 (+/-).

The workshop attendees commented favorably on a proposal to actively solicit nominations of substances to be studied for carcinogenic potential in GMM models during all phases of the NTP nomination review process (http://ntp-server.niehs.nih.gov/NomPage/noms.html). They recommended that the NTP gather as much information as possible about the rationale for a study early in the process to allow adequate evaluation of the request. They agreed that the NTP staff scientist and the study design teams should have responsibility for selecting the appropriate model(s) and designing the study protocols to be used.

Both breakout groups addressed the issues for the second goal through consideration of hypothetical case studies. These case studies were examples in the p53 +/-, the Tg.AC, and the Hras2 models of tumor responses of varying strengths, from none to strong, and of dose-related increases in benign and malignant tumors. The examples were designed to stimulate discussions that might reveal the current level of acceptance of these models for cancer hazard identification. The NTP also hoped to gain input about what types/level of pathologic response in the GMM models would be needed in order to apply the same categories for defining strength of evidence to the results as are currently used for 2-year bioassays using traditional rodent models.

Initial discussions revealed that neither breakout group willingly accepted the premise that results of studies with GMM models are equivalent to the results from a traditional 2-year rodent assay. Because these models possess oncogenes or disabled tumor suppressor functions, there was reluctance to accept that a positive outcome indicated that the responsible chemical is a "carcinogen." Suggestions on how to convey this lowered state of confidence took several directions. One breakout group described positive findings with the p53+/- and the Hras2 models as indicating a "neoplastic" or "tumorigenic" response, although the slight majority favored use of the term "carcinogenic activity." This latter term is currently used to characterize a positive tumor finding in the 2-year NTP rodent bioassay. The other breakout group also preferred "carcinogenic activity" to "neoplastic response," but placed a condition on the use of this term. This group requested that a preamble statement be added to reports of studies with GMM models indicating that the results should not be accorded the same weight of evidence as a standard 2-year rodent cancer bioassay.

When considering the best terminology to describe the strength of response in the GMM models, the majority of the workshop participants accepted the terminology used in the 2-year bioassay, i.e., "clear evidence," "some evidence," "equivocal evidence," or "no evidence." There was a suggestion that a tumorigenic response sufficient to achieve a call of "clear evidence" in a 2-year study, might only deserve a call of "some evidence" in a GMM model because of concerns outlined earlier; however, this suggestion did not receive widespread support.

Both breakout groups struggled to find appropriate language to describe findings with the Tg.AC model. The primary tumorigenic endpoint in this model is papilloma development in the skin, and its assay

developers have frequently termed Tg.AC a “reporter phenotype” (Tennant ***et al***., 2001). Papillomas arise following activation of a zeta-globin promoted v-Ha-ras transgene that appears to be inserted in an inducible form in skin, forestomach and bone marrow. In contrast to the opinions for p53+/- and rasH2, the majority in both breakout groups was uncomfortable with the term "carcinogenicity activity," for describing the model’s response, even when the observed response is malignant skin neoplasms. A minority felt that "carcinogenic activity" is an appropriate descriptor in this case. Suggestions for how to describe a positive papilloma response ranged from “tumor promoter response” or “neoplastic response,” to the very nonspecific “biological activity,” reflecting the opinion that activation of the zeta-globin gene, whether a discriminator for carcinogens or not, cannot be characterized as a cancer response.

One of the major topics of discussion at the International Life Sciences Institute/HESI workshop the previous day concerned proposals to alter the designs of the assays with GMM models to improve their sensitivity to detect carcinogens. Pritchard ***et al. (***2003) raised concerns about this issue and showed that failures of the GMM models to provide a correct classification of substances that are ***known*** or ***reasonably anticipated to be human carcinogens*** are more likely to stem from false negatives rather than false positives. Because of lingering doubts about the true meaning of negative results in these models, some of the case studies examined by the breakout groups included situations where no tumor response occurred. The NTP included these cases to determine whether the attendees felt that the results would be best described as showing “no evidence” of a tumor response under the conditions of the study, or as studies that should be considered “inadequate” to demonstrate a lack of “carcinogenic activity.” The breakout groups showed little support for calling studies with negative findings in GMM models “inadequate” studies, rather the attendees seemed comfortable with the call of “no evidence” of carcinogenic activity/ neoplastic response/biological activity, as the case may be, as long as the study duration is clearly stated and the conclusion clearly reflects the assay conditions.

This workshop was the first of a series that the NTP plans to hold dealing with various issues related to the appropriate use of GMM models in cancer hazard identification and risk estimation. A topic on the immediate horizon is how the results from GMM models should be used in listing substances as ***known*** or ***reasonably anticipated human carcinogens*** in the NTP Report on Carcinogens.

References

Pritchard JB, French JE, Davis BJ. Haseman, JK. 2003. Transgenic mouse models: Their role in carcinogen identification. Environ. Health Perspect. 111(4) 444-454.

Robinson DE, MacDonald JS. 2001. Background and framework for ILSI’s collaborative evaluation program on alternative models for carcinogenicity assessment. Toxicol. Pathol. 29 (suppl 1) 13-19.

Tennant RW, Stasiewicz S, Eastin, WC, Mennear, JH, Spalding, JW. 2001. The Tg.AC (v-Ha-ras) transgenic mouse: Nature of the model. Toxicol. Pathol. 29 (suppl 1) 51-59.

How to Subscribe to the NTP List-server

The NTP Update is issued approximately 4 times each year. To subscribe to the “list-server” and receive the NTP Update as well as other NTP news and announcements electronically, register online at http://ntp-server.niehs.nih.gov or send email to ntpmail-request@list.niehs.nih.gov with the word “subscribe” as the body of the message, or contact the NTP Liaison and Scientific Review Office.

Additional information about the NTP along with announcements of meetings, publications, study results and its centers is available on the Internet at http://ntp-server.niehs.nih.gov.

The ehpOnline maintains issues of the Report on Carcinogens and the library of NTP Technical Reports and NTP Toxicity Reports and adds new reports as available. The electronic PDF files of completed reports are available free-of-charge and printed reports can be purchased through ehpOnline. To gain access to these reports, go to http://ehp.niehs.nih.gov or call 866-541-3841 or 919-653-2595.

Contact information: NTP Liaison and Scientific Review Office, NIEHS, P.O. Box 12233, MD A3-01, Research Triangle Park, NC 27709; T: 919-541-0530; F: 919-541-0295; liaison@starbase.niehs.nih.gov

NTP Center for the Evaluation of Risks to Human Reproduction (CERHR)

New NTP-CERHR Monograph Series

The CERHR announces the availability of the "NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Di-***n***-Butyl Phthalate (DBP)." This monograph is the first in the NTP-CERHR monograph series and includes three parts:

1) the NTP brief, which presents the NTP's interpretation of the available data and its conclusions on the potential for DBP to cause adverse developmental and reproductive effects in humans,
2) the expert panel report, and
3) all public comments on the expert panel report.

The NTP utilized information provided in the expert panel report, public comments, as well as information from studies, published since the expert panel meeting, to reach its conclusions on DBP.

The monograph is posted electronically on the CERHR website: http://cerhr/niehs/nih/gov and a limited number of copies in printed text are available from the CERHR.

Monographs on six additional phthalates [butyl benzyl phthalate (BBP), di(2-ethylhexyl) phthalate (DEHP),di-isodecyl phthalate (DIDP), di-isononyl phthalate (DINP), di-***n***-hexylphthalate (DnHP), and di-***n***-octyl phthalate (DnOP)] are in production and will be available soon.

Experts Find Little Concern for Ethylene Glycol and Propylene Glycol

The CERHR convened an expert panel on February 11-13, 2003, in Alexandria, Virginia, to evaluate whether or not exposure to ethylene glycol or propylene glycol is a reproductive and/or developmental hazard.

The expert panel concluded for ethylene glycol that there was "negligible concern" for developmental toxicity and reproductive toxicity at current estimated levels of human exposure.that there was "negligible concern" for developmental toxicity and reproductive toxicity at current estimated levels of human exposure.

For propylene glycol, the expert panel concluded "that current estimated exposures to propylene glycol are of negligible concern for [causing] reproductive or developmental toxicity in humans."

Ethylene glycol was selected for evaluation because it is a high production volume chemical, there is a potential for widespread occupational and general population exposures due to its use in heating and cooling systems (e.g., automotive antifreeze), and there is published evidence from laboratory studies of developmental toxicity resulting from exposure to ethylene glycol.

Propylene glycol is used commercially as an intermediate in the manufacture of unsaturated polyester resins and in the production of plasticizers. Propylene glycol was evaluated because of its similarity in structure to ethylene glycol and the potential for widespread human exposure through its use in food, tobacco, pharmaceutical products, cosmetics, various paints and coatings and as an antifreeze and de-icing solution.

The expert panel reports are posted on the CERHR website (http://cerhr.niehs.nih.gov) and available from the CERHR in printed text. The CERHR invites public comment on the reports and their conclusions. Following this comment period, the CERHR will prepare a NTP-CERHR monograph on each chemical.

Future Evaluations of Fluoxetine Hydrochloride and Acrylamide

The CERHR is planning future expert panel evaluations of fluoxetine hydrochloride (Prozac®; Sarafen™, CAS RN 54910-89-3) and acrylamide (CAS RN 79-06-1). The expert panel will evaluate the potential reproductive and/or developmental toxicity of each chemical.

Fluoxetine hydrochloride (Prozac®; Sarafem™; CAS RN 54910-89-3), an antidepressant, was selected for expert panel evaluation due to sufficient reproductive and developmental animal data, human exposure information, and public concern. Fluoxetine hydrochloride, under the name Sarafem™, is being prescribed to treat premenstrual dysphoric disorder (PMDD), potentially increasing the number of exposures to women of childbearing age. The FDA also recently approved its use in 7-17 year-olds. It is anticipated that the expert panel evaluation will occur late in 2003.

Acrylamide (CAS RN 79-06-1) is used in the production of polyacrylamide, which is used in water treatment, pulp and paper production, and mineral processing. It is used in the synthesis of dyes, adhesives, contact lenses, soil conditioners, permanent press fabrics and in molecular biology procedures such as electrophoresis. Acrylamide is a neurotoxicant and in animal studies has been shown to be a carcinogen, germ cell mutagen, and reproductive toxicant. It was selected for expert panel evaluation due to recent public concern for human exposures through its presence in starchy foods treated at high temperatures, e.g., french fries, potato chips. There are recent data available on occupational exposure, bioavailability, and reproductive toxicity. It is anticipated that the expert panel evaluation will occur in 2004.

The CERHR invites the nomination of qualified scientists to serve on each of the two expert panels. Panelists are primarily drawn from the CERHR Expert Registry and/or the nomination of other scientists who meet the criteria for listing in that registry, including formal academic training and experience in a relevant scientific field, publications in peer-reviewed journals, membership in relevant professional societies, certification by an appropriate scientific board or other entities, and participation in similar committee activities.

Scientists on the expert panel will be selected to represent a wide range of expertise, including developmental toxicology, reproductive toxicology, epidemiology, general toxicology, pharmacokinetics, exposure assessment, and biostatistics. Nominations received by July 17, 2003 will be considered for the fluoxetine hydrochloride and acrylamide panels and for inclusion in the CERHR Expert Registry. Nominations should be forwarded to Dr. Shelby at the address below.

The CERHR also invites comment from the public and other interested parties on fluoxetine hydrochloride and acrylamide, including toxicological information from completed and ongoing studies and planned studies and information about current production levels, human exposure, use patterns, and environmental occurrence. Information and comments should be forwarded to the CERHR. Information and comments received by July 17, 2003 will be made available to the CERHR staff and the expert panel for consideration in the evaluation and posted on the CERHR web site.

***Contact information*: Dr. Michael Shelby, Director, CERHR, NIEHS, P.O. Box 12233, MD EC-32, 79 TW Alexander Drive, Research Triangle Park, NC 27709; T: 919-541-3455; shelby@niehs.nih.gov**

Upcoming Events

May 22, 2003	NTP Board of Scientific Counselors Technical Reports Review Subcommittee meeting NIEHS, Research Triangle Park, NC
June 14, 2003	Satellite Symposium “An Exercise In Peer Review: The Pathology Working Group” At the annual meeting of the Society of Toxicologic Pathology, Savannah, GA
August 12-13, 2003	Scientific Advisory Committee on Alternative Toxicological Methods NIEHS, Research Triangle Park, NC
September 10-11, 2003	NTP Board of Scientific Counselors meeting NIEHS, Research Triangle Park, NC
October 14-15, 2003	NTP Board of Scientific Counselors Report on Carcinogens Subcommittee meeting Washington, DC
November 5-6, 2003	NTP Board of Scientific Counselors Technical Reports Review Subcommittee meeting NIEHS, Research Triangle Park, NC