NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS

March 13 and 14, 1990
Summary Minutes
National Toxicology Program
Board of Scientific Counselors Meeting
March 13 and 14, 1990
Summary Minutes

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SUMMARY MINUTES
NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS MEETING
March 13 and 14, 1990

The National Toxicology Program (NTP) Board of Scientific Counselors met on March 13 and 14, 1990, at the National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina. (Attachment 1: Federal Register Meeting Announcement; Attachment 2: Agenda and Roster of Members and Expert Consultants.) Members of the Board are Drs. Arthur Upton (Chairman), Jay Goodman, John Little, Daniel Longnecker, Richard Miller, Adrianne Rogers, Robert Scala, and Ellen Silbergeld. Dr. Scala was unable to attend the meeting.

Program Review of the Experimental Toxicology Branch (ETB), Division of Toxicology Research and Testing (DTRT), NIEHS

I. Introduction and Overview: Dr. Richard Griesemer, Director, DTRT, described the components of the NTP and the major objectives of the Program. Within the DTRT, the NIEHS component of the NTP, there are four branches of which the ETB is one. Dr. Griesemer noted the extensive collaborative activity between the DTRT and the Division of Biometry and Risk Assessment (DBRA), NIEHS, as well as interactions with the Divisions of Intramural and Extramural Research.

Dr. H.B. Matthews, Chief, Experimental Toxicology Branch, said the ETB was created recently to place increased emphasis on non-cancer endpoints of chemical toxicity, and as such, the Branch is responsible for the design, conduct, and reporting the results of toxicity studies on chemicals nominated from within and outside of the Institute. There are five work groups within the ETB: Chemical Disposition, General Toxicology, Toxicologic Pathology, Mutagenesis, and Clinical Pathology. Dr. Matthews reported on several new initiatives in the ETB including (1) a class study on three oximes which exert toxicity in humans through inhibition of alcohol and aldehyde dehydrogenases, and (2) a collaborative study with NIOSH to assess the bioavailability of lead sulfide and lead oxide, as the pure salts and as found in ores from several geographic areas.

The review format combined platform presentations by work group leaders and selected staff with a poster session which allowed more informal and indepth interactions among reviewers and program staff. The Board was supplemented by five ad hoc consultants with expertise in the program areas being reviewed. The names and affiliations of the consultants are given in Attachment 2.

II. Chemical Disposition Work Group: Dr. L.T. Burka, Acting Group Leader, said major objectives were to characterize disposition of chemicals nominated and selected by the Program including absorption and tissue distribution after administration by various routes, determination of rates and routes of elimination including half lives after single or, more often,
multiple dosing, and investigation of metabolism of the chemicals with identification of major metabolites. Further studies are concerned with evaluating mechanisms of toxicity/carcinogenicity. Dr. Burka reviewed studies ongoing or completed during the two previous years. He described the six contracts and one interagency agreement utilized. To facilitate extrapolation of laboratory data to humans, three of the contracts are concerned with comparative studies of the in vitro metabolism of chemicals by rodent and human tissues, usually either hepatocytes or liver slices.

Future plans and directions include: (1) continuing to provide chemical disposition information for NTP studies; (2) continuing mechanistic studies; (3) developing cell proliferation studies as a mechanistic tool; (4) increasing emphasis on pharmacokinetics and pharmacokinetic modeling; and (5) acquiring expertise for studying metals/metal complexes/organometallic compounds.

III. General Toxicology Work Group: Dr. John Bucher, Group Leader, said the purpose of the group is to ensure that a basic core of toxicity information exists for chemicals under study by the NTP. He introduced members of the group and discussed their expertise, and described the process of study design. Options for study performance include utilizing inhouse laboratory capabilities or various contract mechanisms. He noted that ETB Toxicity Study contracts were under development which eventually would become the primary means for carrying out short-term toxicity studies. Plans are: (1) to continue to provide complete toxicity characterizations on selected chemicals; (2) to move toward better integration of chemical disposition and metabolism information, along with clinical and anatomic pathology data, and genetic toxicity data when available; and (3) to provide an appropriate balance of mechanistic studies and hazard identification studies.

IV. Toxicologic Pathology Work Group: Dr. Michael Elwell, Group Leader, said the group is composed of toxicologic pathology, the histology laboratory, and the electron microscopy laboratory. The latter two laboratories provide primarily support and service not only to DTRT but also to the rest of the NIEHS. Objectives of the group are: (1) to participate in the design and conduct of toxicity studies; (2) to provide evaluation and interpretation of final pathology results from studies performed; and (3) to investigate mechanisms of toxicologic lesion formation. During FY 1989, 46 prechronic studies were reviewed. Among plans were: (1) further studies of cell proliferation in prechronic studies as part of an early assessment of toxicity before morphologic changes are observed; (2) continued incorporation of prechronic pathology results into the Toxicology Data Management System (TDMS); and (3) continued development of an expanded toxicologic pathology data base.

V. Mutagenesis Work Group: Dr. Errol Zeiger, Group Leader, said the group is responsible for the design and conduct of short-term in vitro and in vivo genetic toxicity studies and incorporation of in vivo studies into the overall toxicologic characterization of chemicals of interest. He said this was done through: (1) developing and monitoring contracts for research, testing chemicals, and developing and validating test methods; (2) using results of testing to characterize test systems for their ability to predict
other end points such as carcinogenicity; (3) studying mechanisms of mutagenesis intramurally; and (4) testing chemicals of interest. Dr. Zeiger described their rather extensive database of short-term test results including some of the recent in vivo cytogenetic results and how the database was and is used in various research studies.

Dr. Zeiger said future plans under the contract program include: (1) expansion of in vivo genetic toxicity testing and integration into toxicity testing protocols; (2) developing and evaluating short-term tests to identify carcinogens that do not appear to be mutagens or clastogens; and (3) continuing to support the NTP by providing and interpreting short-term data. In inhouse research they planned to (1) continue studies on mutagenicity and peroxidizing ability of thiols in cultured cells and extend to studies in rat liver, and (2) investigate mechanisms of mutagenicity of thiols, bisulfite, and metal ions to determine their similarities and differences and whether they are all mutagenic through formation of free radicals.

VI. Clinical Pathology Work Group: Dr. Morrow Thompson, Group Leader, said the group is responsible for the design, conduct, evaluation and interpretation of clinical pathology studies in support of the ETB and the NTP, and this includes both inhouse studies and the clinical pathology studies conducted by the contract laboratories. He noted that the Statement of Work that applies to clinical pathology studies conducted by contract laboratories had been significantly revised to reflect the importance of documentation, standardization and quality control. Dr. Thompson described the assays in the core hematology and clinical chemistry profile, noting that other assays can be added when indicated. The group's philosophy is to obtain samples from animals not only at the end of a study but also early on and midway through the study, usually at 4, 21 and 90 days.

VII. Selected ETB Research Projects:

(1) Structural, Metabolic, and Cellular Basis of 2-Butoxyethanol Induced Toxicity -- Dr. Burhan Ghanayem, Chemical Disposition Group, described studies designed to characterize the toxicity of 2-butoxyethanol (BE, ethylene glycol monobutyl ether). The chemical is metabolized primarily to a glucuronide conjugate and butoxyacetic acid (BAA) via alcohol and aldehyde dehydrogenases. Primary toxicity in rodents is a hemolytic anemia. By using an inhibitor of the dehydrogenases, the toxicity was shown to be caused mainly by BAA. Dr. Ghanayem reported on structure-toxicity relationship studies which showed the four carbon side chain is optimal and the ether linkage essential for inducing hematotoxicity. He concluded by describing studies which indicated the mechanism of toxicity by BAA involved a depletion of ATP and a corresponding increase of calcium concentrations inside the red blood cell.

(2) Mechanisms of Mutagenesis by Glutathione -- Dr. Zeiger reported on studies led by Dr. Avi Stark, a recent visiting scientist in his laboratory. He said glutathione (GSH) is mutagenic to Salmonella when incubated with purified fractions from kidney but not from liver due to the activity of the enzyme gamma-glutamyl transpeptidase (GGT) with the cysteinyl glycine formed being the mutagenic species. The GSH-GGT system can induce lipid peroxidation and since the enzymes horse radish peroxidase or catalase inhibit mutagenic
activity, hydrogen peroxide was implicated. Dr. Zeiger further mapped out the reaction chain. Mutagenicity studies with GSH have been extended to mammalian cells; specifically, a Chinese hamster ovary cell line. He commented that studies were planned to test whether lipid peroxidation can be induced in GGT-rich preneoplastic liver foci in rodents when challenged with GSH as a possible model for liver tumor promotion or progression.

(3) Bile Acids as Indicators and Initiators of Hepatic Toxicity -- Dr. Thompson noted the physiological importance of bile acids in lipid digestion and absorption and said this was a two part study with one part being to examine the analysis of bile acids in serum as a sensitive measure of specific types of hepatobiliary damage while on the other hand doing studies to determine the potential of bile acids to initiate or perpetuate hepatic toxicity and preneoplasia. With regard to use of bile acids as diagnostic tools, he described a complex study in which groups of rats received 12 different treatments to produce as many different types of impairment of hepatobiliary function. Using assays developed in his laboratory, they were able to identify 95% of the animals with the appropriate treatment group based on the serum bile acid profile. Dr. Thompson then described experiments in which chenodeoxycholic acid (CDCA) mixed in the feed promoted the formation of hepatocellular foci. This was the first demonstration of a promotional effect by a primary bile acid. Because high concentrations of CDCA can develop in animals with certain types of hepatocellular diseases, the relevance of this finding in conditions that produce high endogenous concentrations of CDCA will be investigated.

(4) Cell Proliferation in Rat Liver by the Mutagenic Carcinogen: Noncarcinogen Pair, 2,4-Diaminotoluene and 2,6-Diaminotoluene -- Dr. Michael Cunningham, Chemical Disposition Group, said the research question he was concerned with was what is the basis for the apparent lack of correlation between the results from short-term genotoxicity assays and the results of rodent bioassays. He described a series of studies aimed at determining the basis including using an immunocytochemical method to measure cell proliferation in the liver. Cell proliferation studies done with this pair as well as other chemicals or pairs of chemicals have led to the following conclusions: (1) the inability of 2,6-diaminotoluene to induce carcinogenesis is not due to poor absorption or bioactivation in vivo; (2) induction of cell proliferation in the liver correlates better with carcinogenicity of 2,4- and 2,6-diaminotoluene and 1-and 2-nitropropane than does their mutagenicity in vitro; and (3) induction of cell proliferation correlates better with the tissue specific carcinogenesis (forearm vs. liver) of ethyl acrylate than does its mutagenicity in vitro.

END OF PROGRAM REVIEW

VIII. Report of the Director: Dr. David Rall reported that: (1) Dr. Robert Scala, Board Member and Chair, Technical Reports Review Subcommittee, was absent due to having suffered a heart attack recently. He was home, recovering well and expected to return to work in a few weeks; (2) Dr. Dorothy Canter was joining the Office of the Assistant Administrator for Solid Waste and Emergency Response, EPA, where she will be involved with the Superfund program, and he noted her nearly 10 years service with NIEHS/NTP; (3) among recent and upcoming conferences at NIEHS were (a) "Application of
Molecular Markers in Epidemiology" held February 21-22, (b) a symposium on "Mouse Pulmonary Carcinogenesis" in honor of the memory of Dr. Michael Shimkin cosponsored by Medical College of Ohio to be held March 27-28, and (c) an international workshop sponsored by the Scientific Group on Methodologies for the Safety Evaluation of Chemicals on "Methods for the Estimation of Cross Species Differences in DNA Damage and Repair in the Context of Pharmacokinetic Mechanisms" to be held March 19-24; (4) Dr. Norton Nelson had died recently and Dr. Rall commented on what a great loss this was to many at NIEHS personally as well as to the field of environmental health (Dr. Nelson was the first chairman of the NTP Board); and (5) the Board's Technical Reports Review Subcommittee and associated ad hoc Panel of Experts would meet on April 25 to peer review NTP draft Technical Reports on DL-amphetamine sulfate, 3,3'-dimethylbenzidine dihydrochloride, ethylene thiourea, sodium azide, and tris(2-chloroethyl) phosphate, and on April 26 to review the Report of the studies on sodium fluoride. As this was the last meeting for Dr. Adrianne Rogers as a member of the Board, Dr. Rall presented her a certificate and thanked her on behalf of the Program for her service.

IX. Review of Chemicals Nominated for NTP Studies: There were nine chemical nominations considered by the Board. Two of chemicals were evaluated by the NTP Chemical Evaluation Committee (CEC) on August 2, 1989, reviewed by the Board on November 30, 1989, and deferred so that further information could be obtained. The other seven chemicals were evaluated by the CEC on January 24, 1990, (Summary data on the chemicals including CEC recommendations are provided in Attachment 3.) Dr. Upton chaired the review. Dr. William Allaben, NCTR, Dr. Dorothy Canter, NIEHS, and Dr. Janet Haartz, NIOSH, CEC members, and Dr. Victor Fung, NIEHS, NTP Chemical Selection Coordinator, served as resource persons. Board members served as principal reviewers for one or two chemicals, and following the presentation and discussion of each chemical, motions were made and voted on. The Board's recommendations for the nine chemicals are summarized in Attachment 4.

X. Concept Reviews - NIEHS-DTRT: Three project concepts dealing with germ cell mutagenesis were presented by members of the Heritable Effects Research Group and peer reviewed by the Board. All three concepts represented a combination of ongoing work that had been concept-approved in past meetings of the Board and work that represented new directions based on results of earlier experiments and the applications of new technologies. Concept review was required because the work statements had been modified. Background information on concept review is given in Attachment 5, p. 1.

(1) Chemical Induction of Genetic Transposition -- (Attachment 5, pp. 3-4)

"Chemical Induction of Genetic Transposition" - Dr. James Mason introduced the concept and Dr. Arthur Upton, Board member, served as principal reviewer. Dr. Mason said the objectives of the project were (a) to determine if induction of genetic transposition by chemicals can be induced, (b) to identify chemicals or classes of chemicals that can induce transposition, and (c) to investigate the mechanism(s). He reported that a simple genetic assay devised in Drosophila has provided evidence that representatives of two families of transposable elements are induced to transpose in germ cells after treatment with chemical mutagens. The concept proposes to support further experiments
in Drosophila while extending studies to mice to determine whether chemicals induce transposition of endogenous transposons in the germ line of mammals.

Dr. Upton supported the concept noting that the technology and resources appeared to be available and that there were many practical implications for the findings. After brief discussion by other Board members, Dr. Little moved that the concept be approved. Dr. Rogers seconded the motion which was approved unanimously by the Board.

(2) Chemical Induction of Chromosome Damage in Mouse Germ Cells -- (Attachment 5, pp. 5-6)

"Chemical Induction of Chromosome Damage in Mouse Germ Cells" - Dr. Michael Shelby introduced the concept and Dr. Richard Miller, Board member, served as principal reviewer. The objectives of the project are to test chemicals for the induction of chromosomal damage in mammalian germ cells, to characterize chromosome aberrations at the cytogenetic and molecular levels, and to identify developmental defects associated with heritable chromosomal damage. Changes proposed are: (a) additional effort is proposed for karyotypic analysis of breakpoints associated with reciprocal translocations and other chromosomal rearrangements; and (b) development of methods for detecting induction and germ cell transmission of aneuploidy.

Dr. Miller thought this to be an exciting concept with many potential applications to human studies and development of information useful for risk extrapolation. He asked whether chemicals to be tested would be limited to those to which humans are exposed. Dr. Shelby replied that only chemicals of environmental importance would be evaluated in the testing component; however, any chemical of scientific interest could be looked at in the applied research aspect of the project.

Dr. Miller moved that the concept be approved. Dr. Rogers seconded the motion which was approved unanimously by the Board.

(3) Investigation of Spontaneous and Induced Mutations in Mouse Germ Cells -- (Attachment 5, pp. 7-8)

"Investigation of Spontaneous and Induced Mutations in Mouse Germ Cells" - Dr. Michael Shelby introduced the concept and Dr. John Little, Board member, served as principal reviewer. The objectives are to continue testing chemicals for mutagenicity in mammalian germ cells using the mouse morphological specific locus test, to expand the spectrum of mutational endpoints used and to characterize at the molecular level the lesions associated with the mutations recovered. Four primary changes or expansions to the work statement were proposed, being: (a) to perform a mutagenesis experiment which will combine several selected endpoints to permit detection of several classes of mutations in a single experiment; (b) to place greater emphasis on the application of molecular techniques to the induction, detection and characterization of mutations; (c) mapping of new genomic insertions via in situ hybridization techniques; and (d) establishment and maintenance of a transgenic mouse data base.

Dr. Little endorsed the concept and said that the new directions described in expanding the scope would provide valuable information for improving
characterization of induced lesions at the molecular level, especially those involving insertional mutations. Dr. Little moved that the concept be approved. Dr. Rogers seconded the motion which was approved unanimously by the Board.
Pursuant to Public Law 92-463, notice is hereby given of a meeting of the National Toxicology Program (NTP) Board of Scientific Counselors, U.S. Public Health Service, in the Conference Center, Building 101, South Campus, National Institute of Environmental Health Sciences (NIEHS), 111 Alexander Drive, Research Triangle Park, North Carolina on March 13 and 14, 1980.

The meeting will be open to the public from 8:45 a.m. until adjournment on March 13. The preliminary agenda with approximate times are as follows:

**Review of Experimental Toxicology Branch (ETB), Division of Toxicology Research and Testing, NIEHS**

8:45 a.m.-9:30 a.m. — Introduction and Overview of Objectives and Purposes of the ETB

9:30 a.m.-11:30 a.m. — Descriptions of Objectives and Activities for ETB Work Groups in Chemical Disposition, Clinical Pathology, General Toxicology, in Vitro Toxicity, and Toxicologic Pathology

12:30 p.m.-2:00 p.m. — ETB Poster Session

2:00 p.m.-4:00 p.m. — Scientific Presentation on Selected ETB Research Projects

4:00 p.m.-5:00 p.m. — General Discussion and Concluding Remarks.

In accordance with the provisions set forth in sections 522(c)(4) and 522b(c)(6) title 5, U.S.C. and section 10(d) of Public Law 92-463, for the review, discussion and evaluation of individual grant applications. These applications and the discussion could reveal confidential trade secrets or commercial property such as patentable material and personal information concerning individuals associated with the applications the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

Mrs. Winifred J. Lumadue, Committee Management Officer, National Cancer Institute, 9000 Rockville Pike, Building 31, Room 10A08, National Institutes of Health, Bethesda, Maryland 20892 (301/496-5708), will provide a summary of the meeting and roster of the Board members, upon request.

Other information pertaining to this meeting can be obtained from the Executive Secretary, Dr. Brian Kimes, National Cancer Institute, National Institutes of Health, Research Plaza North, Room 300, Bethesda, Maryland 20892 (301/496-8527), upon request.

This notice is being published less than 15 days prior to the meeting due to the difficulty of coordinating the attendance of members due to unforeseen conflicting schedules.

Dated: February 20, 1980.

Betty J. Beveridge,
Committee Management Officer, NIH.

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**Public Health Service**

**National Toxicology Program; Board of Scientific Counselors; Meeting**

Pursuant to Public Law 92-463, notice is hereby given of a meeting of the National Toxicology Program (NTP) Board of Scientific Counselors, U.S. Public Health Service, in the Conference Center, Building 101, South Campus, National Institute of Environmental Health Sciences (NIEHS), 111 Alexander Drive, Research Triangle Park, North Carolina on March 13 and 14, 1980.

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4:00 p.m.-5:00 p.m. — General Discussion and Concluding Remarks.

In accordance with the provisions set forth in sections 522(c)(4) and 522b(c)(6) title 5, U.S.C. and section 10(d) of Public Law 92-463, the meeting will be closed to the public on March 14 from 8:45 a.m. until 2:15 p.m. for further evaluation of research activities in the NIEHS Experimental Toxicology Branch, including the consideration of individual qualifications and performance, the competence of individual investigators, and similar items, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

The meeting on March 14 will be open to the public from 2:30 p.m. to 4:30 p.m. The preliminary agenda is as follows:

**Review of NTP Studies**

Nine chemicals will be reviewed. Seven of the chemicals were evaluated by the NTP Chemical Evaluation Committee (CEC) on January 24, 1980, and are (with CAS Nos. in parentheses): (1) Bisphenol A Glycidyl Ether (107-54-9); (2) 2-Bromo-3-nitropropane (2183-13-7); (3) C.I. Acid Red 87 (10769-22-8); (4) C.I. Acid Red 111 (68355-57-2); (5) C.I. Basic Brown 1 (1062-38-6); (6) C.I. Basic Brown 2 (6358-93-4); and (7) C.I. Direct Black 80 (8030-56-8). Two of the chemicals were evaluated by the CEC on August 2, 1982, reviewed by the Board on November 30, 1982, and deferred so that further information could be obtained. The chemicals are: (1) p-Amino-benzoic Acid (150-13-0) and (2) Elmiron (37319-17-8).

The Executive Secretary, Dr. Larry G. Hart, National Toxicology Program, P.O. Box 12233, Research Triangle Park, North Carolina 27709, telephone (919) 541-3671, will have available a roster of Board members and expert consultants and other program information prior to the meeting, and summary minutes subsequent to the meeting.

Dated: February 6, 1980.

David P. Raff,
Director, National Toxicology Program.

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**National Toxicology Program Board of Scientific Counselors Meetings; Draft Technical Reports Projected for Public Peer Review From April 1990 Through October 1991**

To inform the public earlier and allow interested parties to comment or obtain information on long-term toxicology and carcinogenesis studies and short-term toxicity studies prior to public peer review, the National Toxicology Program (NTP) again publishes in the Federal Register a current listing of draft Technical Reports projected for evaluation by the Peer Review Panel during their next six meetings from April 1990 through October 1991. The listing will continue to be updated with announcements in the Federal Register approximately twice a year. The meeting dates for 1990 are April 25-26, July 10-11, and November 13-14. Specific dates for the 1991 meetings will be established at a later time.

The attachment gives draft Technical Reports of studies on chemicals listed alphabetically within known or estimated dates of reviews and includes Chemical Abstracts Service registry numbers, responsible National Toxicology Program staff scientists with telephone numbers, NTP report numbers (if assigned), primary use(s), species, route of administration, and exposure levels used.

Those interested in having more information about any of the studies listed in this announcement, or wanting to provide input, should contact the particular NTP staff scientist as early as possible by telephone or by mail to:
AGENDA
BOARD OF SCIENTIFIC COUNSELORS
NATIONAL TOXICOLOGY PROGRAM
March 13 and 14, 1990

CONFERENCE CENTER, BUILDING 101, SOUTH CAMPUS
NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES
RESEARCH TRIANGLE PARK, NORTH CAROLINA

Tuesday, March 13, 1990

8:45 a.m.- 8:55 a.m. Report of the Director, NTP
Dr. D. P. Rall, NIEHS

8:55 a.m.-9:00 a.m. Introductory Remarks
Dr. R. Griesemer, NIEHS

9:00 a.m.-9:30 a.m. Introduction and Overview of
Objectives and Purposes of
the ETB
Dr. H. B. Matthews

9:30 a.m.-11:30 a.m. Objectives and Activities
of ETB WorkGroups
A. Chemical Disposition
Dr. L. Burka
B. General Toxicology
Dr. J. Bucher
C. Toxicologic Pathology
Dr. M. Elwell
D. Mutagenesis
Dr. E. Zeiger
E. Clinical Pathology
Dr. M. Thompson

11:30 a.m.-12:30 a.m. Lunch

12:30 p.m.-2:00 p.m. ETB Poster Session

2:00 p.m.-4:00 p.m. Selected ETB Research Projects

1. Structural, Metabolic, and Cellular Basis of
2-Butoxyethanol Induced Toxicity
Dr. B. Ghanayem

2. Somatic Mutagenesis
Dr. E. Zeiger

3. Bile Acids as Indicators and Initiators of Hepatic Toxicity
Dr. M. Thompson
4. Cell Proliferation in Rat Liver by the Mutagenic: Noncarcinogen Pair, 2,4-Diaminotoluene and 2,6-Diaminotoluene

4:00 p.m.- 5:00 p.m. General Discussion and Concluding Remarks

Dr. H. B. Matthews

Wednesday, March 14, 1990

8:15 a.m.-12:30 p.m. Evaluation of Programs and Personnel in the Experimental Toxicology Branch, NIEHS

Board and Consultants

OPEN MEETING

1:30 p.m.- 3:00 p.m. Review of Chemicals Nominated for NTP Studies

Board

Dr. D. Canter

3:00 p.m.- 4:00 p.m. Concept Review - DTRT Procedures and Principles

I. Chemical Induction of Genetic Transposition

II. Chemical Induction of Chromosome Damage in Mouse Germ Cells

III. Investigation of Spontaneous and Induced Mutation in Mouse Germ Cells

Dr. W. Johnston

Dr. J. Mason

Dr. M. Shelby

Dr. M. Shelby

Adjourn
NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
March 13 and 14, 1990

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New York University Medical School
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* Not Present
AD HOC REVIEWERS FOR NTP BOARD OF SCIENTIFIC COUNSELORS REVIEW OF EXPERIMENTAL TOXICOLOGY BRANCH, NIEHS

March 13 and 14, 1990

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NTP BOARD OF SCIENTIFIC COUNSELORS MEETING

Conference Center, Building 101, South Campus
National Institute of Environmental Health Sciences
Research Triangle Park, North Carolina

March 13, 1990
NTP BOARD OF SCIENTIFIC COUNSELORS MEETING

Conference Center, Building 101, South Campus
National Institute of Environmental Health Sciences
Research Triangle Park, North Carolina

March 14, 1990

H art    Rall    Upton    Griesemer
  Longnecker
  Rogers
  Little
  Haartz
  Allaben

  Stage

  Tennant
  Miller
  Goodman
  Silbergeld
  Canter
  Fung
**Summary Data on Chemicals for Review by the Board of Scientific Counselors on March 14, 1990**

<table>
<thead>
<tr>
<th>Chemical (CAS Number)</th>
<th>Nomination Source</th>
<th>Domestic Production (lbs.)</th>
<th>Estimated Worker Exposure</th>
<th>NTP Testing Status</th>
<th>Chemical Evaluation Committee Recommendations (Priority)</th>
<th>NTP Selection Principles</th>
<th>Rationale/Remarks</th>
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<tbody>
<tr>
<td><strong>A. Chemicals for Reconsideration</strong></td>
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<tr>
<td>1. p-Aminobenzoic acid (150-13-0)</td>
<td>NIEHS</td>
<td>&gt;5.0x10^3 (1986-1988)</td>
<td>4,448</td>
<td>Negative in Salmonella</td>
<td>No testing</td>
<td>--</td>
<td>Significant decrease in use and potential for exposure. NTP is testing structurally-related compounds, p-nitrobenzoic acid and p-nitrotoluene.</td>
</tr>
<tr>
<td>2. Elmiron (37319-17-8)</td>
<td>FDA</td>
<td>No definitive production data available</td>
<td>--</td>
<td>--</td>
<td>Carcinogenicity (Moderate-High)</td>
<td>2</td>
<td>Potential as treatment for interstitial cystitis. FDA has granted chemical &quot;orphan drug status.&quot; Lack of carcinogenicity data.</td>
</tr>
<tr>
<td><strong>B. New Chemicals</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Bisphenol A diglycidyl ether (DGEBA) (1675-54-3)</td>
<td>NIEHS</td>
<td>0-1.0x10^3 (1977)^c</td>
<td>23,706</td>
<td>Positive in Salmonella</td>
<td>Carcinogenicity studies</td>
<td>--</td>
<td>High production. Significant human exposure. EPA proposing testing by industry under TSCA Section 4 test rule. Refer testing recommendation to EPA. Check status of EPA testing after one year.</td>
</tr>
<tr>
<td>2. 2-Bromo-2-nitropropane-1,3-diol (52-51-7)</td>
<td>Private individual</td>
<td>No definitive production data available</td>
<td>On test in Salmonella</td>
<td>No testing</td>
<td>--</td>
<td>Chemical not expected to have toxic effects at the concentrations used. Available toxicity data indicate no cause for concern.</td>
<td></td>
</tr>
<tr>
<td>Chemical (CAS Number)</td>
<td>Nomination Source</td>
<td>Domestic Production (lbs.)</td>
<td>Estimated Worker Exposure</td>
<td>NTP Testing Status</td>
<td>Chemical Evaluation Committee Recommendations (Priority)</td>
<td>NTP Selection Principles</td>
<td>Rationale/Remarks</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------------</td>
<td>-----------------------------</td>
<td>---------------------------</td>
<td>-------------------</td>
<td>----------------------------------------------------------</td>
<td>-------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>3. C.I. Acid Red 97 (10169-02-5)</td>
<td>NCI</td>
<td>$1.0 \times 10^4$</td>
<td>1,450</td>
<td>--</td>
<td>-Chemical analysis -Metabolism</td>
<td>3</td>
<td>-Low production -Limited occupational exposure -Scientific interest in disulfonil benzidine moiety -Determine impurities in commercially available product and identify metabolites prior to considering toxicological studies</td>
</tr>
<tr>
<td>4. C.I. Acid Red 111 (6358-57-2)</td>
<td>NCI</td>
<td>Listed in TSCA Inventory but no production volume reported</td>
<td>--</td>
<td>--</td>
<td>-No testing</td>
<td>--</td>
<td>-Low production -Low potential for exposure</td>
</tr>
<tr>
<td>5. C.I. Basic Brown 1 (1052-38-6)</td>
<td>NCI</td>
<td>$1.0 \times 10^3$</td>
<td>--</td>
<td>--</td>
<td>-Carcinogenicity (Low)</td>
<td>3</td>
<td>-Structural interest -Low production -Low potential for exposure</td>
</tr>
<tr>
<td>6. C.I. Basic Brown 2 (6358-83-4)</td>
<td>NCI</td>
<td>Zero</td>
<td>--</td>
<td>--</td>
<td>-No testing</td>
<td></td>
<td>-No longer produced in U.S. -Low potential for exposure</td>
</tr>
<tr>
<td>7. C.I. Direct Black 80 (8003-69-8)</td>
<td>NCI</td>
<td>$2.1 \times 10^4$</td>
<td>--</td>
<td>--</td>
<td>-Dermal absorption (High)</td>
<td>3,8</td>
<td>-High production -Potential for human exposure -Substitute for C.I. Direct Black 3B, a known animal carcinogen -Consider for carcinogenicity studies only if dye is absorbed by dermal route</td>
</tr>
</tbody>
</table>
Footnotes


c) U.S. Environmental Protection Agency. Non-confidential portion of the Initial TSCA Chemical Substances Inventory. Washington, DC


e) Personal communication from Dr. T. Helmes, Ecological and Toxicological Association of the Dyestuffs Manufacturing Industry (ETAD) to Dr. V. Fung, NTP.
NTP CHEMICAL SELECTION PRINCIPLES

The NTP Executive Committee operates under the principle that industry will test chemicals for health and environmental effects as intended and mandated by the Congress under legislative authorities. Therefore, the NTP, acting under its chemical selection principles, will test:

1. Chemicals found in the environment that are not closely associated with commercial activities;

2. Desirable substitutes for existing chemicals, particularly therapeutic agents, that might not be developed or tested without Federal involvement;

3. Chemicals that should be tested to improve scientific understanding of structure-activity relationships and thereby assist in defining groups of commercial chemicals that should be tested by industry;

4. Certain chemicals tested by industry, or by others, the additional testing of which by the Federal government is justified to verify the results;

5. Previously tested chemicals for which other testing is desirable to cross-compare testing methods;

6. "Old chemicals" with the potential for significant human exposure which are of social importance but which generate too little revenue to support an adequate testing program (some of these may be "grandfathered" under FDA laws);

7. Two or more chemicals together, when combined human exposure occurs (such testing probably cannot be required of industry if the products of different companies are involved); and

8. In special situations, as determined by the Executive Committee, marketed chemicals which have potential for large-scale and/or intense human exposure, even if it may be possible to require industry to perform the testing.

The selection of a chemical by the Executive Committee does not automatically commit the NTP to testing the chemical. The NTP is committed to ascertain the specific toxicologic and regulatory concerns; evaluate the adequacy of existing data or current efforts in government, academic, or private laboratories; and then propose and conduct specific tests that are needed. Occasionally new information is obtained that answers the questions posed in the nomination and selection process. Sometimes testing is not done because chemicals are withdrawn by the nominator, because others are or will be testing the chemical, or because the chemical is not available, or no longer produced.
Testing Recommendations for Chemicals Reviewed by Board of Scientific Counselors on March 14, 1990

<table>
<thead>
<tr>
<th>Chemical Name</th>
<th>Nomination Source</th>
<th>Testing Recommendations (Priority)</th>
<th>Rationale/Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-Aminobenzoic acid (150-13-0)</td>
<td>NIEHS</td>
<td>No testing</td>
<td>Significant decrease in use, low potential for exposure, NTP testing structurally-related chemicals, p-nitrobenzoic acid and p-nitrotoluene</td>
</tr>
<tr>
<td>Bisphenol A diglycidyl ether (DGEBPA)</td>
<td>NIEHS</td>
<td>Carcinogenicity studies by industry through EPA test rule (High)</td>
<td>High production, high human exposure, EPA proposing testing by industry under TSCA Section 4 test rule, refer testing recommendation to EPA, check status of EPA testing after one year</td>
</tr>
<tr>
<td>2-Bromo-2-nitropropane-1,3-diol (52-51-7)</td>
<td>Private individual</td>
<td>No testing</td>
<td>No significant toxicity effects observed in available studies, chemical not expected to have toxic effects at concentration used</td>
</tr>
<tr>
<td>C.I. Acid Red 97 (10169-02-5)</td>
<td>NCI</td>
<td>Chemical analysis - Metabolism (Low)</td>
<td>Low production, limited occupational exposure, scientific interest in disulfonil benzidine moiety, determine impurities in commercially available products and identify metabolites prior to considering toxicological studies</td>
</tr>
<tr>
<td>C.I. Acid Red 111 (6358-57-2)</td>
<td>NCI</td>
<td>No testing</td>
<td>Low production, low potential for exposure</td>
</tr>
<tr>
<td>Chemical (CAS Number)</td>
<td>Nomination Source</td>
<td>Testing Recommendations (Priority)</td>
<td>Rationale/Remarks</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-------------------</td>
<td>------------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>6. C.I. Basic Brown 1 (1052-38-6)</td>
<td>NCI</td>
<td>-Chemical analysis</td>
<td>-Structural interest</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Chemical disposition (Low to moderate)</td>
<td>-Low production</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-Low potential for exposure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-Determine impurities in commercially available product and identify metabolites prior to considering for carcinogenicity studies</td>
</tr>
<tr>
<td>7. C.I. Basic Brown 2 (6358-83-4)</td>
<td>NCI</td>
<td>-No testing</td>
<td>-Not currently produced in U.S.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-Low potential for exposure</td>
</tr>
<tr>
<td>8. C.I. Direct Black 80 (8003-69-8)</td>
<td>NCI</td>
<td>-Dermal absorption (High)</td>
<td>-High production</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-Potential for human exposure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-Used as substitute for C.I. Direct Black 38, a known animal carcinogen</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-Consider for carcinogenicity studies only if dye is absorbed by dermal route</td>
</tr>
<tr>
<td>9. Elmiron (37319-17-8)</td>
<td>FDA</td>
<td>-Carcinogenicity</td>
<td>-Potential for treatment for interstitial cystitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Teratogenicity (Moderate to high)</td>
<td>-FDA has granted chemical &quot;orphan drug status&quot;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-Lack of carcinogenicity data</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-NTP should keep abreast of clinical trials</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-Carcinogenicity studies pending results of clinical trials</td>
</tr>
</tbody>
</table>

a) On November 30, 1989, the Board deferred p-aminobenzoic acid to obtain additional information on its use as a sunscreen, and the level of human exposure to the chemical from this use.

b) On November 30, 1989, the Board deferred Elmiron to obtain more information on the efficacy and use of the drug, type of people using it, results of animal studies, and clinical trials.
BACKGROUND CONCEPT REVIEWS

The Division of Toxicology Research and Testing currently has 160 research and resource contracts and interagency agreements. These contracts and agreements support a variety of activities — toxicologic characterization, testing, methods development, and program resources (i.e. chemistry, occupational health and safety, animal production, pathology, quality assurance, archives, etc).

Prior to issuance of a Request for Proposal (RFP), a project concept review is required by Public Health Service regulations. These project concepts in many instances consist of more than one contract or interagency agreement. Concept reviews are needed for new projects, for recompetitions with changes in statements of work, and for projects ongoing for 5 years or more since the last concept review. Fifteen concepts were reviewed and approved by the NTP Board of Scientific Counselors (BSC) in March 1989. Four concepts were reviewed and approved at the November 1989 BSC Meeting.

The project concept reviews are conducted by the NTP Board of Scientific Counselors and are open to the public so long as discussions are limited to review of the general project purposes, scopes, goals, and various optional approaches to pursue the overall program objectives. The meeting will be closed to the public, however, if the concept discussions turn to the development or selection of details of the projects or RFPs, such as specific technical approaches, protocols, statements of work, data formats, or product specifications. Closing the session is intended to protect the free exchange of the advisory group members' opinions and to avoid premature release of details of proposed contract projects or RFPs.

The Board members are asked to review the project concepts for overall value and scientific relevance as well as for fulfilling the program goal of protecting public health. Specific areas should include:

a. scientific, technical or program significance of the proposed activity;

b. availability of the technology and other resources necessary to achieve required goals;

c. extent to which there are identified, practical scientific or clinical uses for the anticipated results; and

d. where pertinent, adequacy of the methodology to be used in performing the activity.
INTRODUCTION TO GERM CELL MUTAGENESIS CONCEPTS

Three concept statements dealing with germ cell mutagenesis are being presented to the Board for approval. All three concepts represent a combination of ongoing work that has been concept-approved in past meetings of the Board of Scientific Counselors and work that represents new directions based on results of earlier experiments and the applications of new technologies. Concept review is required at this time because the work statements have been modified.

The two projects on induced mutations and chromosome damage in mouse germ cells each include two primary components, one dealing with testing of chemicals for germ cell mutagenicity and the other with basic investigations into the processes of mutagenesis in mammalian germ cells. The third project, which includes studies on the induction of transposable elements in mouse and Drosophila, is designed to investigate a mechanism of chemically-induced mutations that is of potential importance in germ cell mutagenesis.

The concept statement for a fourth project was reviewed by the Board last March. A portion of the minutes of that meeting, indicating approval of the concept to expand the electrophoretic specific locus test into a multiple endpoint assay, is included in this package of information. That concept along with the three being presented at this meeting encompass the germ cell mutagenicity projects supported by Heritable Effects Research Group.
NATIONAL TOXICOLOGY PROGRAM CONCEPT REVIEW

CONTRACT TITLE: Chemical Induction of Genetic Transposition

PROJECT OFFICERS: James M. Mason, (919) 541-4483
Jack B. Bishop, (919) 541-1876

OBJECTIVE: Recent evidence suggests that transposable genetic elements that reside in the genomes of many organisms may be induced to transpose in response to chemical treatment. The objectives of the proposed projects are (1) to determine if transposition can be induced by chemicals, and, if induction can be demonstrated, (2) to identify chemicals or classes of chemicals that are capable of inducing transposition, and (3) to investigate the mechanism(s) of chemically-induced transposition.

CONCEPT STATEMENT: Where it has been investigated, a significant proportion of naturally occurring mutations has been found to result from insertion of a transposable element. In Drosophila, for example, that proportion is close to 50% Although the database is small, there are a few examples of spontaneous gene mutations in the mouse that resulted from insertion of transposable elements. Further, chemical induction of endogenous retrotransposons has been demonstrated in cultured mouse cells and in lower eukaryotes.

In NTP supported studies, a simple genetic assay has been devised in Drosophila that will allow the identification of individuals with a new transposon insertion. This assay has provided evidence that representatives of two different transposable element families are induced to transpose in germ cells after treatment with chemical mutagens. The assay may be used to identify chemicals that induce transposition and to investigate the relationship between chemical treatment and transposition. Preliminary evidence from other NTP supported studies suggests that chemical treatment of mouse zygotes (around the time of sperm entry or early pronuclear stages) induces MuLV retroviruses to transpose.

In other studies supported by the NTP, high incidences of developmental abnormalities and death among mid- to late-gestation mouse fetuses have been observed following exposure of zygotes to mutagenic chemicals. Cytogenetic evaluation of pronuclear metaphases, early cleavage embryos and abnormal mid-gestation fetuses failed to show structural or numerical chromosome abnormalities that would account for these events. A possible explanation of these developmental abnormalities is that they are causally related to mutagen-induced transposition.
It is proposed to support further experiments in Drosophila and mice to determine whether chemicals induce transposition of endogenous transposons in the germ line of higher eukaryotes, and if chemical induction of transposition can be verified, to investigate the molecular basis of the genetic events.
CONTRACT TITLE: Chemical Induction of Chromosome Damage in Mouse Germ Cells

PROJECT OFFICERS: Jack B. Bishop (919) 541-1876
                         Michael D. Shelby (919) 541-4667

OBJECTIVE: The objectives of the work to be conducted under the proposed interagency agreement are to test chemicals for the induction of chromosomal damage in mammalian germ cells, to characterize chromosomal aberrations at the cytogenetic and molecular levels, and to identify developmental defects associated with heritable chromosomal damage and to relate these defects to human developmental anomalies that may result from similar chromosome damage. Results of these studies on the induction of chromosome damage in mammalian germ cells serve as a major resource for regulatory agencies evaluating the health risk of chemicals to which humans are exposed.

CONCEPT STATEMENT: Among the naturally occurring and synthetic chemicals to which humans are exposed are those with the capacity to interact with DNA and give rise to mutations. Exposure of humans to mutagenic chemicals may give rise to mutations in germ cells, the transmission of these mutations to subsequent generations, and a resultant increase in frequencies of genetic diseases in the population. Determining the risk of such health effects presently must be approached through whole mammal assays because tests using lower organisms or mammalian cells in vitro do not address transmission of induced mutations through the germ cells, germ cell stage specificity, and the various unique metabolic, physiological, and transport factors that exist in conjunction with mammalian reproductive cells.

The in vivo mammalian mutagenesis program conducted by the Heritable Effects Research Group is the primary source of chemical germ cell mutagenicity data in the U.S. This database serves as a major resource for regulatory agencies in assessing risks for increased incidence of inherited diseases and birth defects associated with human exposure to environmental mutagens. The mammalian germ cell mutagenesis program supported by the NTP has made numerous contributions to this area of genetic toxicology in recent years. The number of chemicals on which germ cell mutagenicity data are available has increased substantially through the current interagency agreement and characterization of the mutants recovered in our studies have led to a deeper understanding of mutagenesis in mammalian germ cells.

The chromosomal effects project will continue to include the testing of chemicals for the induction of chromosomal damage in the male and female germ cells and in zygotes. The basic tests used for these studies will include the dominant lethal and heritable translocation tests and cytogenetic analyses of somatic and reproductive cells. Beyond the testing activities, areas of investigation will include research on (1) the chromosomal basis for developmental anomalies resulting from mutagen treatment of pronuclear stage zygotes and (2) identifying and characterizing developmental anomalies associated with heritable translocations.
PROPOSED CHANGES TO THE CURRENT STATEMENT OF WORK:

There are two primary changes proposed for the work statement. They are: (1) additional effort is proposed for karyotypic analysis of breakpoints associated with reciprocal translocations and other chromosomal rearrangements recovered from the heritable translocation test; localization of these breakpoints will assist in the molecular analysis of these genomic regions, and (2) development of methods for detecting induction and germ cell transmission of aneuploidy.
CONTRACT TITLE: Investigation of Spontaneous and Induced Mutations in Mouse Germ Cells

PROJECT OFFICERS: Michael D. Shelby, (919) 541-3345
                  Jack B. Bishop, (919) 541-1876
                  James M. Mason, (919) 541-4483

OBJECTIVE: The objectives of the work to be conducted under the proposed interagency agreement are to test chemicals for mutagenicity in mammalian germ cells, to expand the spectrum of mutational endpoints used in mutagenicity tests and to characterize, at the molecular level, the lesions associated with the mutations recovered. The results of these studies on mutagenicity in mammalian germ cells serve as a major resource for regulatory agencies evaluating the health risks of chemicals to which humans are exposed.

CONCEPT STATEMENT: Among the naturally occurring and synthetic chemicals to which humans are exposed are those with the capacity to interact with DNA and give rise to mutations. Exposure of humans to mutagenic chemicals may give rise to mutations in germ cells, the transmission of these mutations to subsequent generations, and a resultant increase in the frequency of genetic diseases in the population. Determining the risk of such health effects presently must be approached through whole mammal assays because tests using lower organisms or mammalian cells in vitro do not address transmission of induced mutations through the germ cells, germ cell stage specificity, and the various unique metabolic, physiological, and transport factors that exist in conjunction with mammalian reproductive cells.

The in vivo mammalian mutagenesis program conducted by the Heritable Effects Research Group is the primary source of chemical germ cell mutagenicity data in the U.S. This data base serves as a major resource for regulatory agencies in assessing risks for increased incidence of inherited diseases and birth defects associated with human exposure to environmental mutagens. The mammalian germ cell mutagenesis program supported by the NTP has made numerous contributions to this area of genetic toxicology in recent years. The number of chemicals on which germ cell mutagenicity data are available has been increased substantially through the current interagency agreement and characterization of the mutants recovered in our studies have led to a deeper understanding of mutagenesis in mammalian germ cells.

We are proposing to continue the testing of chemicals for germ cell mutagenicity using the mouse morphological specific locus test with treatments involving male mice, female mice and mouse zygotes. Testing of chemicals for germ cell mutagenicity, as well as studies with radioactive and fluorescent labeled tags to define the molecular target dose of selected chemicals in the germ line and the use of unscheduled DNA synthesis as a biomarker to demonstrate that the chemical reaches the germline target, are expected to continue at approximately their current level.
PROPOSED CHANGES TO THE CURRENT STATEMENT OF WORK:

There are four primary changes proposed for the work statement. They are: 1) to perform a mutagenesis experiment in which the "Assessment of Dominant Damage (ADD)" approach is combined with other selected endpoints into a multiple-endpoint assay to permit detection of several classes of mutations in a single experiment and to make more efficient use of animals; 2) place greater emphasis on the application of molecular techniques to the induction, detection and characterization of mutations; 3) mapping of new genomic insertions via in situ hybridization techniques to facilitate subsequent molecular analysis of the genomic regions surrounding these insertions and 4) the establishment and maintenance of a transgenic mouse data base that will include information on the nature of the transgene inserted, the phenotype of the transgenic stocks and a variety of other information. An expected benefit of the latter three additions is an improved characterization of induced lesions at the molecular level, especially those involving insertional mutations such that structural and functional changes associated with new mutations may be related to adverse health outcomes which might be expected with similar changes in the human genome.
LIST OF CONCEPTS APPROVED BY
NTP BOARD OF SCIENTIFIC COUNSELORS
March 1989 and November 1989

Toxicity and Carcinogenicity Studies in Animals
Chemical Repository and Safety Support
Chemistry Support Services
Rodent Disease Diagnostic Laboratories
Genetic Monitoring on Inbred Rodents
Pathology Support
Pathology Archive
Statistical Analysis of Laboratory Studies
Expired Breath Analysis in Chemical Toxicity Assessment
Immunotoxicity of Environmental Chemicals and Therapeutics
Neurotoxicology Methods Validation
Mutagenicity Studies with Salmonella
In Vivo Cytogenetics
Mammalian Germ Cell Mutagenesis
Identification of Rodent Tumor Suppressor Genes
In Vitro Methods to Assess Human Metabolism of Chemical Xenobiotics
Reproductive Toxicity Testing and Methods Development
Site and Mechanism Studies of Reproductive Toxicants
General Toxicity Testing and Research On-Site at the NIEHS
Experimental Toxicology:

- Testing the Urine of Rats in the 14-Day Prechronic Test for Mutagenic Activity
- In Vitro Cytogenetics
- Studies of Chemical Disposition in Mammals

Systems Toxicity:

- Developmental Toxicity Testing:
  - Range Finding
  - Testing and Research

Mutagenesis and Experimental Carcinogenesis:

- Mutagenesis Assays Using Transgenic Mice
- Heritable Translocation Test in Mice
- Drosophila Mutagenesis Testing
- Response of Centromeres to DNA Damaging Agents
- Mammalian Cell (Mouse Lymphoma) Mutagenesis Assays
- Transformation Assays
- DNA Adducts and DNA Modifications
- Development of Detection Methods for Non-Electrophilic Carcinogens
- Validation of Chemicals in Drosophila and Yeast Aneuploidy Detection Assays

Resources:

- Pathology Quality Assurance
- Health and Safety