

NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS

October 24, 1991

Summary Minutes

National Toxicology Program
Board of Scientific Counselors

October 24, 1991

Summary Minutes

<u>Contents</u>	<u>Page Numbers</u>
<u>Program Review of the Chemical Carcinogenesis Mechanisms Group, Division of Toxicology Research and Testing (DTRT), NIEHS</u>	1
I. <u>Research Activities of the Chemical Carcinogenesis Mechanisms Group</u>	1
END OF PROGRAM REVIEW	
II. <u>Report of the Director, NTP</u>	2
III. <u>Review of Chemicals Nominated for NTP Studies</u>	3
<u>Subcommittee Report</u>	
IV. <u>Technical Reports Review Subcommittee</u>	3
V. <u>Overview and Comments on the Heritable Effects Research Program, DTRT, NIEHS</u>	4
VI. <u>Concept Reviews, DTRT, NIEHS</u>	4
(1) Environmental Neurotoxicology	4
(2) Development and Evaluation of Rodent Strains with Inactivated Tumor Suppressor Genes in Carcinogenesis Studies	5
(3) Predictive Toxicology Methods Development	6
(4) Quality Assurance (QA) Inspection and Auditing Support Resource Contracts	6
Attachments 1-5	

SUMMARY MINUTES
NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS MEETING
October 24, 1991

The National Toxicology Program (NTP) Board of Scientific Counselors (the Board) met on October 24, 1991, 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. Daniel Longnecker (Chairman), Paul Bailey, Jay Goodman, Curtis Klaassen, Lawrence Loeb, Fumio Matsumura, Richard Miller, and Ellen Silbergeld. All members were present.

Program Review of the Chemical Carcinogenesis Mechanisms Group, Division of Toxicology Research and Testing (DTRT), NIEHS

I. Research Activities of the Chemical Carcinogenesis Mechanisms Group: Dr. James Selkirk, Group Leader, said the group's activities over the past few years had been concerned primarily with the metabolism, activation and detoxification of chemical carcinogens. He noted that most chemical carcinogens are biotransformed to electrophilic substances and patterns of metabolism and macromolecular binding are almost identical in all eukaryotic species. Yet, some cells exposed to carcinogens are susceptible to undergoing neoplastic transformation while other cells remain normal. Dr. Selkirk said the question they proposed to examine related to the expression of transformation after a mutagenic event had occurred and how this had to be due to some form of aberrant biochemistry, i.e., changes in the cell machinery through changes in enzymatic structure. He said that two-dimensional gel electrophoresis (2D gels) provided the methodology to isolate and identify a broad array of cellular proteins, both common and unique to normal and carcinogen treated cells. The advent of multiple gel technology and the concomitant use of computerized image analysis enabled a more sophisticated approach to analysis of the enormous amount of bio-molecular information present in 2D gels for both structural identification and comparative pattern analysis of proteins. Dr. Selkirk described two experiments using this technology in three cell lines derived from the C3H mouse, one being the parent line, one transformed and one resistant to transformation in response to treatment with benzo(a)pyrene. With the 2D gels, he demonstrated among the three lines that there were a large number of proteins common to all and smaller numbers either induced, repressed or down-regulated by treatment with B(a)p.

Dr. Selkirk discussed how they now and in the future would be focusing on oncogenes, especially oncoprotein detection and were

gearing their identification systems in this direction. He said they should be able to locate the translation products for three specific oncogenes in attempting to understand how the expression of these genes triggers the transformation process as well as alters enzymes and proteins essential for the phenotypic expression of transformation. Thus, it should be possible to connect structure with function and an attempt can be made to understand which biochemical pathways are being compromised by the expression of specific genes.

II. Report of the Director, NTP: Dr. Kenneth Olden reported that: (1) his choice of Dr. Richard Griesemer, Director, Division of Toxicology Research and Testing, NIEHS, to become Deputy Director, NIEHS, had been approved by the Director, NIH, and Dr. Griesemer had accepted the post; (2) the NIEHS, along with the rest of NIH, was operating under a continuing budget resolution through the end of November; (3) several internal administrative changes had been made including (a) selection of Dr. Andres Negro-Vilar as Clinical Director to coordinate collaborative research with clinical programs, initially at Duke University and the University of North Carolina at Chapel Hill, (b) selection of Dr. John Dement as Director of Prevention and Intervention Research, with a major initiative on lead toxicity underway, and (c) selection of Ms. Sandra Lange as Director of Communications as part of a challenge to increase the visibility of the Institute; (4) he was committed to making the reviews of laboratories and programs at the NIEHS as rigorous as peer reviews of university programs, and as such, he would take the recommendations of the Board of Scientific Counselors quite seriously in evaluations of programs and scientists; (5) he was initiating a review of the NTP by a special advisory committee to be made up of representatives of Federal research and regulatory agencies, industry, and academia as part of a goal to strengthen the NTP's role as the Nation's premier toxicology research and testing program. Dr. J. Donald Millar, Director, NIOSH, will chair the committee which will make recommendations on how (a) to improve the quality of chemicals nominated for testing by assuring that they have the greatest public health significance, (b) to assure that emphasis is placed on the mechanisms of toxicity and carcinogenicity, (c) to develop and validate better assays that may reduce the need for long-term testing in animals, and (d) to create new procedures for alerting regulatory agencies and the public about test results on important chemicals; (6) the Fourth Task Force for Research Planning in Environmental Health Sciences had met at the NIEHS in August and submitted a preliminary draft report in September for review by the Institute and its national advisory council. Issues specifically addressed include (a) emerging problems in environmental health that call for new research initiatives and approaches, (b) concepts and methods arising from recent scientific developments, and (c) strategic manpower and resource requirements of the research, with particular reference to needs and opportunities for preparing minority and women students for

careers in the field; (7) he had visited several of the university-based Environmental Health Science centers and planned to visit the remainder in the near future. Centers visited were those at Harvard University, MIT, Oregon State University, University of California-Berkeley, and Rutgers University (University of Medicine and Dentistry of New Jersey); (8) he had met with the heads of most of the Federal health research and regulatory agencies as part of an aim to enhance program coordination. This will be followed by periodic meetings of the heads and key staff with Dr. Ronald Hart, Director, NCTR, scheduled to host the first meeting in early 1992; (9) Dr. Healy had convened a Director's retreat on September 10-11 to consider and discuss proposed initiatives for eleven "promising areas of science" to be contained in the NIH Strategic Plan. At the retreat, areas were revised and expanded to fourteen including a new initiative on "Basic Biology and the Environment", although nearly all of the other Science and Health Areas have environmental components. Forums will be held at three sites around the country (San Antonio, Los Angeles, Farmington, Connecticut) in February 1992 at which senior NIH staff will present information on the Strategic Plan and receive comments. Dr. Olden urged Board members to attend forums in their geographic area and voice support for environmental issues in the initiatives.

III. Review of Chemicals Nominated for NTP Studies: Nominations of six chemicals were considered by the Board. All had been reviewed previously by the NTP Chemical Evaluation Committee (CEC). (Summary data on the chemicals including CEC recommendations are provided in Attachment 3.) Dr. Longnecker chaired the review. Dr. William Allaben, NCTR, and Dr. Janet Haartz, NIOSH, CEC Members, and Dr. Victor Fung, NTP Chemical Selection Coordinator, served as resource persons. Board members served as principal reviewers for one or two chemicals each, and following the presentation and discussion of each chemical, motions were made and voted upon. The Board's recommendations for the six chemicals are summarized in Attachment 4.

Subcommittee Report

IV. Technical Reports Review Subcommittee: Dr. Richard Irwin, NIEHS, gave the Board a progress report on recent (July 9-10) and upcoming (November 21) meetings of the Subcommittee. He provided the Board written summary information noting that nine two-year toxicology and carcinogenesis study reports and three short-term toxicity study reports had been reviewed on July 9-10, while five two-year and four short-term study reports are scheduled for peer review by the Subcommittee on November 21. Dr. Longnecker noted that Dr. Curtis Klaassen, University of Kansas Medical Center, would assume the Chairmanship of the Subcommittee at the next meeting.

V. Overview and Comments on the Heritable Effects Research Program, DTRT, NIEHS: Dr. Michael Shelby, Experimental Carcinogenesis and Mutagenesis Branch, DTRT, presented an overview of the activities and accomplishments of the Heritable Effects Research Program over the past few years. He began by reporting that projects on germ cell mutagenesis had undergone technical review by an external panel of experts in September 1991. He said the primary goal of the Heritable Effects Research Group was to assess human health hazards that may result from exposures to chemicals that induce genetic damage in reproductive cells. This is accomplished by (1) identifying germ cell mutagens, (2) determining cell stages and gender affected, (3) investigating dose response and rate effects, (4) studying mechanisms of mutagenesis, and (5) developing methods that address health impact in the first generation. Dr. Shelby discussed the basis for concern about genetic hazards as they may affect fertility, fetal loss and health-affecting mutations in live births. He described briefly three projects and their accomplishments: Project I - use of the electrophoretic specific locus assay and its expansion in to development of a multiple-endpoint test system (Research Triangle Institute); Project II - detection of chromosomal effects of chemicals in mammalian germ cells (Oak Ridge National Laboratory); and Project III - detection and characterization of chemical induced, transmitted gene mutations in mice (Oak Ridge National Laboratory). Dr. Shelby summarized the contributions of the program to understanding the mechanisms of induced mutations, identification of genetic hazards, and generation of data for use by regulatory agencies in assessing genetic risks. He noted that the complete evaluation of an agent for the potential to induce heritable genetic effects requires the study of all germ cell stages in both males and females.

Dr. John Mulvihill, Chairman, Department of Human Genetics, University of Pittsburgh, discussed how human geneticists can use the NTP data and how difficult it is to obtain and define suitable cohorts of humans exposed to germ cell mutagens. He provided examples of the types of cohorts used which included offspring of cancer survivors who had been treated with radiation and/or chemotherapy and survivors of childhood cancer who had been treated with mutagenic therapies. Dr. Mulvihill concluded that the study of germ cell mutagenesis is important and relevant and had major public health and societal implications. Germ cell mutagenesis is relevant to women's health issues, to the epidemic of infertility and reproductive risks, to medical genetics and to the national genome project. He stated that the NIEHS has exerted international leadership and has been resourceful and innovative in working with excellent scientists to address an important and relevant issue.

VI. Concept Reviews, DTRT, NIEHS:

(1) Environmental Neurotoxicology -- (Attachment 5, pp. 2-3) Dr. Bernard Schwetz, Systems Toxicity Branch, introduced the

concept, and Dr. Ellen Silbergeld, Board member, served as principal reviewer. Dr. Schwetz said the objective of the proposal was to provide the NTP the capabilities for conducting animal studies to evaluate the neurotoxic potential of environmental chemicals. He noted that damage to the nervous system is an important consequence of exposure to certain environmental substances and research supported or conducted by NIEHS and other agencies has revealed remarkable vulnerability of the very young and the aging. Dr. Schwetz said the majority of the effort will be a second-tier level of work to characterize in greater detail the nature of the neurotoxic effects of specific chemicals, dose-reponse characteristics, species specificity, site of action, reversibility and other aspects of the neurotoxicity to aid in the risk assessment process.

Dr. Silbergeld said she strongly supported inhouse and contractual efforts in this area but noted that one area of need not spoken to was development of short-term and in vitro methodology. Further, she found it troubling that nervous system lesions could be observed on neuropathologic examination but often corresponding clinical effects were not observed. Dr. Schwetz responded that in vitro studies would be initiated inhouse and when through the validation stage could be incorporated into contract or other extramural efforts. Dr. Silbergeld moved that the concept be approved. Dr. Miller seconded the motion which was approved unanimously by the Board.

(2) Development and Evaluation of Rodent Strains with Inactivated Tumor Suppressor Genes in Carcinogenesis Studies -- (Attachment 5, pp. 4-5) Dr. Richard Paules, Experimental Carcinogenesis and Mutagenesis Branch, introduced the concept, and Dr. Jay Goodman, Board member, served as principal reviewer. Dr. Paules said one of the goals of the NTP is to characterize the carcinogenic potential of environmental insults accurately, rapidly and with minimal use of whole animals. He reviewed current multistep models of neoplastic development including deletion of genes whose products are negative regulators of cellular proliferation, i.e., tumor suppressor genes. The objective of the project would be to utilize strains of rodents with inactivated tumor suppressor genes in evaluating the carcinogenic potential of chemicals of interest. Rodent strains would be generated through targeted homologous recombination techniques, or other appropriate means. Such strains might be more sensitive to carcinogenic properties of chemicals, since the animals would have already undergone one of the presumed heritable alterations involved in neoplastic progression. Their use could reduce the time of bioassays and possibly the number of animals needed.

Dr. Goodman commented that he supported basic research on tumor suppressor genes but had strong reservations about their use now in a test system for carcinogenic effects, and saw potential for

misuse in creating a 'hypersensitive animal'. The proposed studies could be valuable if used to examine mechanisms. Dr. Klaassen thought the issue was sensitivity vs. predictivity. Dr. Raymond Tennant, Experimental Carcinogenesis and Mutagenesis Branch, said the aims of this proposal were consonant with the Branch goal of helping to reduce dependence upon the rodent bioassay. Dr. Goodman requested that the concept be reoriented toward research on mechanisms of carcinogenesis and away from testing. He moved that the concept be approved with the title changed to read: "Development and Evaluation of Rodent Strains with Inactivated Tumor Suppressor Genes for Studies Aimed at Discerning Mechanisms Involved in Carcinogenesis," and with references to assays and tests deleted from the concept statement. Dr. Matsumura seconded the motion which was approved unanimously by the Board.

(3) Predictive Toxicology Methods Development -- (Attachment 5, pp. 6-7) Dr. Douglas Bristol, Experimental Carcinogenesis and Mutagenesis Branch, stated that the objective of the proposal was to develop and validate structure-activity relationship (SAR) methods that predict the toxicologic effects of a broad range of diverse (non-congeneric) chemicals. He discussed the potential benefits deriving from development of SAR correlative methods, and noted that the existence of the extensive NTP database was essential with primary focus to be on using organ-specific toxicity data from animal studies of the most recent 200 chemicals. Dr. Bristol described an approach for modeling non-congeneric chemicals, and said two types of contracts would be considered - one which would extend existing SAR methods to the analysis of organ toxicity data, and a second type which would apply knowledge-based computer technology to the development of SAR systems that sort chemicals objectively, e.g., neural networks or expert systems.

Dr. Klaassen commented on the complexities and limitations of SAR methods, urged that adequate biological data be incorporated into the models, and expressed concern about the problems of cross species predictability, noting that rats often don't predict even for mice. However, he thought this to be a project worth doing as a research tool. Dr. Klaassen moved that the concept be approved. Dr. Bailey seconded the motion which was approved by five yes to one no vote (Dr. Loeb). Dr. Silbergeld was not present for the vote.

(4) Quality Assurance (QA) Inspection and Auditing Support Resource Contracts -- (Attachment 5, p. 8) Mr. David Bridge, Chemical Carcinogenesis Branch, said the goal of the concept proposal is to continue to meet the NTP's Quality Assurance program objectives: (1) to independently assess study conduct compliance with Good Laboratory Practice (GLP) regulations and standards, (2) to validate data and results for NTP studies, and (3) to provide feedback to help improve overall conformance to

NTP requirements and cost effectiveness of NTP studies. This project will provide the NTP with independent support for conducting QA site visits and retrospective audits that will address the documentation and conduct of funded research relative to NTP requirements and standards. The system for providing monitoring and assessment information creates an ongoing cycle for continuous improvement including the control and reduction of adverse events occurring in studies at the contract laboratories.

Dr. Bailey noted that this was not a new concept but a continuation of an ongoing project, and he strongly supported continuation. In response to a question about whether inhouse studies were audited, Dr. Bernard Schwetz, NIEHS, commented that QA audits had been and would continue to be done on inhouse studies where judgements were being made on safety as opposed to those studies concerned with mechanistic work. Dr. Bailey moved that the concept be approved. Dr. Silbergeld seconded the motion which was approved unanimously by the Board.

(Catalog of Federal Domestic Assistance Program No. 93.121, Dental Research Institute, National Institutes of Health)

Dated: September 24, 1991.

Samuel C. Rawlings,

Acting Committee Management Officer, NIH.
[FR Doc. 91-24094 Filed 10-4-91; 8:45 am]

BILLING CODE 4140-01-M

Division of Research Grants; Meeting

Pursuant to Public Law 92-463, notice is hereby given of the meetings of the following study sections:

Safety and Occupational Health, Dr. Gopal Sharma, Westwood Bldg., rm. 219C, Tel. 301-496-6723, Oct. 16-18, 8 a.m., Holiday Inn, Bethesda, MD
Lung Biology and Pathology, Dr. Anne Clark, Westwood Bldg., rm. A10, Tel. 301-496-4673, Oct. 21-23, 8 a.m., Holiday Inn, Bethesda, MD

The meetings will be open to the public to discuss administrative details relating to study section business for approximately one hour at the beginning of the first session of the first day of the meetings. Attendance by the public will be limited to space available. The meetings will be closed thereafter in accordance with the provisions set forth in sections 552b(c)(4) and 552b(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 discussions 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.

The Office of Committee Management, Division of Research Grants, Westwood Building, National Institutes of Health, Bethesda, Maryland 20892, telephone 301-496-7534 will furnish summaries of the meetings and rosters of committee members. Substantive program information may be obtained from each scientific review administrator.

(Catalog of Federal Domestic Assistant Program Nos. 13.306, 13.333, 13.337, 13.393-13.396, 13.837-13.844, 13.846-13.878, 13.892, 13.893, National Institutes of Health, HHS)

Dated: September 24, 1991.

Samuel C. Rawlings,

Acting Committee Management Officer, NIH.
FR Doc. 91-24095 Filed 10-4-91; 8:45 am]

BILLING CODE 4140-01-M

Public Health Service

National Toxicology Program (NTP) 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 October 24, 1991.

The meeting will be open to the public from 9 a.m. to 3 p.m. in the Conference Center. The preliminary agenda topics with approximate times are as follows:

- 9 a.m.-10:30 a.m.—Review of Research Activities on Protein Modulation During Cell Transformation of the Chemical Carcinogenesis Mechanisms Group, Division of Toxicology Research and Testing, NIEHS.
- 10:45 a.m.-11:45 a.m.—Review of Chemicals Nominated for NTP studies. Six chemicals will be reviewed. Five of the chemicals were evaluated by the NTP Chemical Evaluation Committee (CEC) on August 8, 1991, and are (with CAS Nos. in parentheses): (1) Benzophenone (119-61-9); (2) Benzyltrimethylammonium Chloride (58-93-9); (3) 1,2,3,4-Butanetetracarboxylic Acid (1703-58-8); (4) Halazone (80-13-7); and (5) Pentaerythritol Triacrylate (3524-68-3). One chemical was reviewed by the CEC on March 13, 1991: Trimethylolpropane Triacrylate (15625-89-5).
- 12:45 p.m.-1 p.m.—Report of the Director, NTP
- 1 p.m.-1:15 p.m.—Update on Activities of the Technical Reports Review Subcommittee
- 1:15 p.m.-2 p.m.—Overview and Comments on the Heritable Effects Research Program, DTRT, NIEHS
- 2 p.m.-3 p.m.—Concept Reviews
 - A. Development and Evaluation of In Vivo Rodent Model Systems Utilizing Targeted Gene "Knock-Out" of Potential Suppressor Genes
 - B. Neurotoxicity Evaluation of Environmental Agents
 - C. Quality Assurance Audit Report
 - D. Predictive Toxicology Methods Development

In accordance with the provisions set forth in section 552b(c)(6) title 5 U.S. Code and section 10(d) of Public Law 92-463, the meeting will be closed to the public on October 24 from 8:15 a.m. to 9 a.m. and from 3:15 p.m. to adjournment for further evaluation of the research activities in the Chemical Carcinogenesis Mechanisms Group, DTRT, NIEHS, including the consideration of personnel 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 Executive Secretary, Dr. Larry C. Hart, National Toxicology Program, P.O. Box 12233, Research Triangle Park, North Carolina 27709, telephone 919-541-3971, FTS 629-3971, 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: September 16, 1991.

Kenneth Olden,

Director, National Toxicology Program.
[FR Doc. 91-24096 Filed 10-4-91; 8:45 am]

BILLING CODE 4140-01-M

ADVISORY COUNCIL ON HISTORIC PRESERVATION

Meetings

AGENCY: Advisory Council on Historic Preservation.

ACTION: Notice of meeting.

SUMMARY: Notice is hereby given that the Advisory Council on Historic Preservation will meet on Friday, October 18, 1991. The meeting will be held in the Monterey Room at the Sir Francis Drake Hotel, 450 Powell Street, San Francisco, California, beginning at 9 a.m.

The Council was established by the National Historic Preservation Act of 1966 (16 U.S.C. 470) to advise the President and the Congress on matters relating to historic preservation and to comment upon Federal, federally assisted, and federally licensed undertakings having an effect upon properties listed in or eligible for inclusion in the National Register of Historic Places. The Council's members are the Architect of the Capitol; the Secretaries of the Interior, Agriculture, Housing and Urban Development, Treasury, and Transportation; the Director, Office of Administration; the Chairman of the National Trust for Historic Preservation; the President of the National Conference of State Historic Preservation Officers; a Governor; a Major; and eight non-Federal members appointed by the President.

The agenda for the meeting includes the following:

- I. Chairman's Welcome/Opening
- II. Council Business
- III. Section 106 Cases
- IV. New Business
- V. Adjourn

Note: The meetings of the Council are open to the public. If you need special

AGENDA
BOARD OF SCIENTIFIC COUNSELORS
NATIONAL TOXICOLOGY PROGRAM

October 24, 1991

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

CLOSED MEETING

8:15 a.m.- 9:00 a.m.	Evaluation of Program and Personnel in the Chemical Carcinogenesis Mechanisms Group, Division of Toxicology Research and Testing (DTRT), NIEHS	Board and Consultants
----------------------	--	-----------------------

OPEN MEETING

9:00 a.m.-10:30 a.m.	Research Activities of the Chemical Carcinogenesis Mechanisms Group, DTRT, NIEHS	Dr. J. Selkirk
10:30 a.m.-10:45 a.m.	BREAK	
10:45 a.m.-11:45 a.m.	Review of Chemicals Nominated for NTP Studies	Board Dr. V. Fung
11:45 a.m.-12:45 p.m.	LUNCH	
12:45 p.m.- 1:00 p.m.	Report of the Director, NTP	Dr. K. Olden
1:00 p.m.- 1:15 p.m.	Update on Activities of the Technical Reports Review Subcommittee	Dr. D. Longnecker, Board Dr. R. Irwin
1:15 p.m.- 2:00 p.m.	Overview and Comments on the Heritable Effects Research Program, DTRT, NIEHS	Dr. M. Shelby Dr. J. Mulvihill, Univ. of Pittsburgh
2:00 p.m.- 3:00 p.m.	Concept Reviews, DTRT, NIEHS Procedures and Principles	Dr. R. Griesemer Dr. W. Johnston
	I. Environmental Neurotoxicology	Dr. B. Schwetz

- II. Development and Evaluation of Rodent Studies with Inactivated Tumor Suppressor Genes in Carcinogenesis Studies Dr. R. Paules
- III. Predictive Toxicology Methods Development Dr. D. Bristol
- IV. Quality Assurance Inspection and Auditing Support Resource Contracts Mr. D. Bridge

3:00 p.m.- 3:15 p.m. BREAK

CLOSED MEETING

3:15 p.m.- 4:30 p.m. Evaluation of Program and Personnel in the Chemical Carcinogenesis Mechanisms Group, DTRT, NIEHS Board and Consultants

Adjourn

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS

October 24, 1991

Dr. Paul T. Bailey
Mobil Oil Corporation
Toxicology Division
P. O. Box 1029
Princeton, NJ 08543-1029

Dr. Jay I. Goodman
Professor
Department of Pharmacology and
Toxicology
Michigan State University
8440 Life Sciences Bldg.
East Lansing, MI 48824-1317

Dr. Curtis Klaassen
Professor
Department of Pharmacology & Toxicology
University of Kansas Medical Center
39th and Rainbow Blvd.
Kansas City, KS 66103

Dr. Lawrence A. Loeb
Professor and Director
Gottstein Memorial Laboratory and
Department of Pathology SM-30
University of Washington D-525 HSB
Seattle, WA 98195

Dr. Daniel S. Longnecker, Chairperson
Professor
Department of Pathology
Dartmouth Medical School
217 Remsen
Hanover, NH 03756

Dr. Fumio Matsumura
Professor
Department of Environmental
Toxicology
University of California
Davis, CA 95616

Dr. Richard K. Miller
Department of Obstetrics, Gynecology
Box 668
University of Rochester
601 Elmwood Avenue
Rochester, NY 14642

Dr. Ellen K. Silbergeld
University of Maryland
Medical School
Howard Hall - 544
660 West Redwood Street
Baltimore, MD 21201

AD HOC REVIEWERS

Chemical Carcinogenesis Mechanisms Group, DTRT, NIEHS

October 24, 1991

Dr. Dennis Reeder, Group Leader
Biochemical Measurements
National Institute of Standards and Technology
Gaithersburg, MD 20899

Dr. Leigh Anderson
Large Scale Biology Corp.
Rockville, MD 20850

SUMMARY DATA ON CHEMICALS FOR REVIEW BY BOARD OF SCIENTIFIC COUNSELORS
ON OCTOBER 24, 1991

Chemical (CAS Number)	Nomina- tion Source	Domestic Production (lbs)	Estimated Worker Exposure ^a	NTP Testing Status	Chemical Evaluation Committee Recommendations (Priority)	NTP Chemical Selection Princi- ples	Rationale/Remarks
1. Benzophenone (119-61-9)	NIEHS	3.0 x 10 ⁵ - 3.0 x 10 ⁶ (1983) ^b	41,520	-Negative in <u>Salmonella</u>	-Toxicity -Carcinogen- icity (Moderate) -Teratogen- icity (High)	3, 6, 8	-High production -Potential for occupation- al and consumer exposure -Air and water pollutant -Structural interest as an aromatic ketone
2. Benzyltrimethyl- ammonium chloride (56-93-9)	NIEHS	1.5 x 10 ⁶ - 1.5 x 10 ⁷ (1983) ^b 4.0 x 10 ⁶ (Annual production for 1986 - 1989) ^c	5,001	-Negative in <u>Salmonella</u>	-Toxicity (including neurotoxi- city) -Carcinogen- icity -Teratogen- icity (Moderate)	3, 8	-High production -Potential for human exposure -Lack of toxicity data -Structural interest in quaternary ammonium compounds
3. 1,2,3,4-Butane- tetracarboxylic acid (1703-58-8)	NCI	2.0 x 10 ³ - 2.1 x 10 ⁴ (1983) ^b 3.0 x 10 ⁶ (annual product- ion) ^d	--	-Selected for <u>Salmonella</u>	-Toxicity -Reproductive and develop- mental effects (High)	2, 8	-High production -Potential for human exposure -Potential substitute for formaldehyde -Lack of toxicity data

Chemical (CAS Number)	Nomina- tion Source	Domestic Production (lbs)	Estimated Worker Exposure ^a	NTP Testing Status	Chemical Evaluation Committee Recommendations (Priority)	NTP Chemical Selection Principles	Rationale/Remarks
4. Halazone (80-13-7)	NIEHS	Listed in TSCA Inventory but no production volume data available ^b	--	-Positive in <u>Salmonella</u>	-No testing	--	-Limited exposure -Compound undergoes rapid hydrolysis -Lack of suspicion of toxicity
5. Pentaerythritol triacrylate (3524-68-3)	NCI	1.5 x 10 ⁵ - 1.0 x 10 ⁶ (1983) ^b	62	-Negative in <u>Salmonella</u>	-Chemical disposition and metabo- lism (High) -Carcinogen- icity (Moderate)	3, 8	-High and increasing production and use -Potential for occupation- al exposure -Suspicion of carcinogen- icity as a member of the multifunctional acrylate chemicals class; some members of this class were shown to be carcino- genic or have potential for carcinogenic activity in dermal studies in mice

Chemical (CAS Number)	Nomina- tion Source	Domestic Production (lbs)	Estimated Worker Exposure ^a	NTP Testing Status	Chemical Evaluation Committee Recommenda- tions (Priority)	NTP Chemical Selection Princi- ples	Rationale/Remarks
6. Trimethylolpro- pane triacrylate (15625-89-5)	NCI	1.2 x 10 ⁵ - 1.2 x 10 ⁶ (1983) ^b	4,179	--	-Chemical disposition -Carcinogen- icity -Reproductive and develop- mental effects (Moderate to high)	3, 8	-Increasing use -Potential for human exposure -Lack of adequate data on carcinogenicity, repro- ductive and developmental effects -Representative multi- functional acrylate -Suspicion of carcinogen- icity as a member of the multifunctional acrylate chemicals class; some members of this class were shown to be carcino- genic or have potential for carcinogenic activity in dermal studies in mice

FOOTNOTES

- a) National Occupational Exposure Survey, conducted by National Institute for Occupational Safety and Health between the years 1981 and 1983.
- b) U.S. Environmental Protection Agency, TSCA Inventory, public file, Washington, D.C.
- c) U.S. International Trade Commission, Synthetic Organic Chemicals. Washington, D.C.
- d) Personal communication from L. Brotherton, Ortec, Inc., to C. Tighe, A. D. Little, Inc. April 22, 1991.

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 NTP BOARD OF SCIENTIFIC COUNSELORS
On October 24, 1991

Chemical (CAS Number)	Nomination Source	Testing Recommendations (Priority)	Rationale/Remarks
1. Benzophenone (119-61-9)	NIEHS	-Toxicity -Carcinogenicity (Moderate) -Teratogenicity (High)	-High production -Potential for human exposure -Air, soil, and water pollutant -Interest in toxicity of aromatic ketones class
2. Benzyltrimethyl- ammonium chloride (56-93-9)	NIEHS	-Toxicity (including neuro- toxicity) -Reproductive and teratogenicity (High) -Carcinogenicity (Moderate)	-High production -Potential for worker and consumer exposure -Lack of toxicity data -Current interest in agents that affect central, nicotinic, and muscarinic cholinergic receptors and potential linkage with neuro-degenerative diseases such as dementia -Opportunity for NTP to structure chronic studies to include sensitive endpoints in neurotoxicity and neurologic development
3. 1,2,3,4-Butane- tetracarboxylic acid (1703-58-8)	NCI	-Toxicity -Reproductive and teratogenicity -Carcinogenicity (Moderate)	-Potential for human exposure -Potential substitute for formaldehyde -Lack of toxicity data -Before performing toxicological studies, NTP should verify use of the chemical as a substitute for formaldehyde and ascertain whether testing by industry may be requested by an EPA significant new use rule

Chemical (CAS Number)	Nomination Source	Testing Recommendations (Priority)	Rationale/Remarks
4. Halazone (80-13-7)	NIEHS	-No testing	-Limited exposure -Chemical undergoes rapid degradation in water -Lack of suspicion of toxicity
5. Pentaerythritol triacrylate (PETA) (3524-68-3)	NCI	-Chemical disposition and metabolism (High) -Carcinogenicity (Low)	-High production but production volume has leveled off in recent years -Potential for occupational exposure -Suspicion of carcinogenicity as a member of the multifunctional acrylates chemical class; some members of this class were shown to be carcinogenic or have potential for carcinogenic activity in dermal studies in mice -Chemical disposition and metabolism studies should allow comparison of the activity of PETA with other acrylates -Defer carcinogenicity studies of PETA until the carcinogenicity studies of other multifunctional acrylates are completed by industry
6. Trimethylolpropane triacrylate (TMPTA) (15625-89-5)	NCI	-Chemical disposition -Carcinogenicity -Reproductive and developmental effects (Moderate to high)	-High production and increasing use -Potential for human exposure -Lack of adequate data on carcinogenicity, reproductive and developmental effects -Representative multifunctional acrylate -Suspicion of carcinogenicity as a member of the multifunctional acrylates chemical class; some members of this class were shown to be carcinogenic or have potential for carcinogenic activity in dermal studies in mice

BACKGROUND CONCEPT REVIEWS

The Division of Toxicology Research and Testing currently has 120 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. Twenty-five concepts have been reviewed by the Board since March 1989.

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.

NATIONAL TOXICOLOGY PROGRAM CONCEPT REVIEW

CONTRACT TITLE: Environmental Neurotoxicology

PROJECT OFFICER: B.A. Schwetz (919) 541-7992

OBJECTIVE: To provide the NTP the capabilities for conducting animal studies to evaluate the neurotoxic potential of environmental chemicals. Because there isn't a widely accepted protocol for routine evaluation of neurotoxicity, flexibility is required to design test strategies that are suited to the specific question and test agent. While part of this effort will be designed to serve as an initial screen for neurotoxicity (perhaps similar to the Functional Observational Battery suggested in EPA guidelines), the majority of this effort will be used as a second-tier of work to address more specific questions to characterize in greater detail the nature of the neurotoxic effect, the dose-response characteristics, species specificity, site of action, reversibility and other aspects of the neurotoxicity to help in the risk assessment process.

CONCEPT STATEMENT: Damage to the nervous system is an important consequence of exposure to certain environmental substances. NIOSH lists neurotoxic disorders among the ten leading causes of work-related diseases and injury; about one-third of the industrial chemicals studied affect the nervous system under some condition of employment. Neurotoxicants are also found among drugs, food additives, pesticides, and substances of abuse but relatively few of the many potentially hazardous substances have been identified and characterized so that preventive measures can be taken.

EPA's listing of most prevalent pollutants released by industry shows that 17 of the top 25 have neurotoxic potential (Office of Technology Assessment Brief, April 1990), many pesticides are neurotoxic, and NIOSH reports millions of workers are exposed to neurotoxic chemicals. There has been a dramatic increase in mortality from motor neuron disease; Parkinson's disease may be related to environmental factors; Minamata Bay mercury poisoning is a dramatic environmental neurotoxic poisoning (Neurotoxicity, identify and controlling poisons of the nervous system, Office of Technology Assessment, OTA-BA-436, Washington, DC, April 1990).

Research supported or conducted by NIEHS and other agencies has revealed remarkable vulnerability of the very young and the aging. In the unborn fetus and continuing through early childhood, environmental agents such as lead, mercury, and ionizing radiation may have profound effects on mental development including learning disabilities. In the elderly, environmental agents may contribute to the early occurrence of degenerative brain disorders and may contribute to progressive mental disabilities.

The work proposed under this concept will provide the necessary data to help the NTP characterize the neurotoxicity of chemicals through a series of contracts and interagency agreements. The work will be done primarily in rodent models but may be done in other species, such as subhuman primates, if warranted. In

addition to studies in young adult males and females, evaluations in the immature and aged rodents will be conducted as specifically justified by situations of human exposure. For those chemicals which are already identified by screening tests as a neurotoxicant, further tests of motor activity, neuropathology, operant behavior, delayed neurotoxicity, and neurochemical and neurophysiological evaluations will also be considered on a chemical-by-chemical basis.

NATIONAL TOXICOLOGY PROGRAM CONCEPT REVIEW

CONTRACT TITLE: Development and Evaluation of Rodent Strains with Inactivated Tumor Suppressor Genes in Carcinogenesis Studies

PROJECT OFFICERS: Richard S. Paules, (919) 541-3710
Raymond W. Tennant, (919) 541-4141

OBJECTIVE:

To utilize strains of rodents with inactivated tumor suppressor genes in evaluating the carcinogenic potential of test chemicals or substances of interest to the National Toxicology Program. Rodent strains shall be generated through targeted homologous recombination techniques, or other appropriate means, to render a potential tumor suppressor gene (or other similar regulatory gene) product nonfunctional. Once identified, animals would be characterized for pathology resulting from the genetic alteration, with particular reference to spontaneous tumor incidences, and then evaluated in carcinogenesis studies with both genotoxic and non-genotoxic agents.

CONCEPT STATEMENT:

Proposed is the identification and use in carcinogenesis studies of strains of rodents whose genomes contain inactivated tumor suppressor genes or other proliferation regulatory genes. Such rodents which would carry these genetic alterations in every cell of the animal could be generated by homologous recombination techniques, or other suitable means. Recent advances in homologous recombination technology with pluripotent embryonic stem (ES) cells (Capecchi, 1989; Hasty, *et al.*, 1991) have allowed for the generation of transgenic mice with targeted disruptions of a number of genes implicated in growth control, including the *c-src*, *c-myb*, *Hox-2.6*, *c-myc*, *N-myc*, and *pim-1* genes. Utilizing this technology, efforts for this proposal would likely involve the introduction (by electroporation, microinjection, or other suitable means) of cloned, altered rodent tumor suppressor genes in appropriate selectable replacement or insertion vectors into ES cells. Cells that have undergone an inactivating homologous recombination event in the target gene would be identified and clonally expanded. Such ES cell lines could, themselves, be useful in *in vitro* carcinogenesis studies. Recombinant ES cells would be injected into recipient blastocysts which would then be implanted in a foster mother to develop into a chimeric offspring and bred to generate transgenic rodent lines. Strains of rodents that have lost one or both functional alleles of a tumor suppressor gene may be hypersensitive to carcinogenic properties of exogenous agents, since the animals would have already undergone one of the presumed requisite, heritable alterations of its genome involved in neoplastic progression (Marshall, 1991). Such rodents could be extremely useful to the NTP by reducing both the time of rodent carcinogenesis

bioassay studies and possibly the number of animals required to yield significant results. Furthermore, using appropriate breeding strategies, rodent strains could be generated that contain more than one genetic alteration and that could potentially reflect the genetic background of specific genetically-susceptible human populations. These rodents would then be extremely useful for evaluating the consequences of exposure to specific environmental insults for certain at-risk human populations.

Capecchi, M.R. (1989). Altering the genome by homologous recombination. *Science*, **244**, 1288-1292.

Hasty, P., Rivera-Perez, J., Chang, C., and Bradley, A. (1991). Target frequency and integration pattern for insertion and replacement vectors in embryonic stem cells. *Mol. Cell. Biol.*, **11**, 4509-4517.

Marshall, C.J. (1991). Tumor suppressor genes. *Cell*, **64**, 313-326.

NATIONAL TOXICOLOGY PROGRAM CONCEPT REVIEW

CONTRACT TITLE: Predictive Toxicology Methods Development

PROJECT OFFICER: Douglas W. Bristol, (919) 541-2756

OBJECTIVE: Apply knowledge-based computer methodologies to the analysis of NTP data to develop and validate structure-activity relationship (SAR) methods that predict the toxicologic effects of a broad range of diverse (non-congeneric) chemicals.

CONCEPT STATEMENT: Studies that correlate the structure of organic chemicals with systematic changes in the physicochemical properties or biological effects that they exhibit date back to the earliest days of organic chemistry. More than a century later, Hall and Kier pointed out that the form-and-function relationship for chemicals is one of the most ubiquitous in natural science and it serves as the basis for all SAR work. Significant progress in SAR research has occurred over the last two decades and the correlative-method approach has gained widespread acceptance as a versatile scientific tool. SAR methods have been developed and used to great advantage in the pharmaceutical and agricultural-chemical industries to screen and predict desirable biologic activities, kinetics, and effects of chemicals as a means of reducing the effort, time, and cost of developing new products. In regulatory circles, the Environmental Protection Agency (EPA) utilizes SARs as part of the hazard assessment procedure that was developed to review chemical premanufacture notifications received under TSCA, Section 5.

The primary advances in SAR research have been derived from approaches that involve the human-guided selection of molecular descriptors that adequately model the physicochemical properties or biological effects of structurally similar chemicals (i.e., congeners or chemical classes). Such SAR investigations are based on Hansch (linear free energy), pattern-recognition (multivariate regression analysis), or similar mathematical approaches and are widely used; however, their application in predictive toxicology is restricted to relatively small, congeneric groups of chemicals, because they rely on the human selection of appropriate descriptors to embrace the myriad factors involved in producing toxicologic effects. When extended to make predictions for molecular structures whose properties are not adequately covered by the descriptors, the congeneric SAR model will inevitably fail. Of greater relevance to the National Toxicology Program's (NTP) broad mission is the development of non-congeneric SAR methodologies that can predict the toxicologic effects expected for at least some, if not many, of the diverse universe of chemicals. Such methods must be able to identify appropriate molecular descriptors independently and objectively at the first level of analysis and may include a variety of complementary modeling tools to incorporate more specific information in a coherent fashion at subsequent levels of analysis.

Progress in two separate areas during the past 15 years offers great promise for developing non-congeneric SAR models. First, advances in computer software and hardware engineering have led to the development of knowledge-based expert systems that offer the ability to identify parameters and make SAR correlations automatically from data entered as a learning set. Such systems,

exemplified by decision-making and neural network software, utilize human guidelines for searching (heuristic approach to discovery), "learn" objectively from the data, establish causal relationships (select descriptors) , and are thus ideally suited to identifying correlations that are embedded in large amounts of diverse information. Second, the NTP has generated extensive, high-quality data for groups of from 50 to 1000 individual chemicals by conducting various standardized in vivo and in vitro tests that characterize toxicologic effects. The recent publication by Tennant et al., "Prediction of the Outcome of Rodent Carcinogenicity Bioassays Currently Being Conducted on 44 Chemicals by the NTP," has stimulated 6 other groups to make their best predictions utilizing different approaches. This activity indicates that the development of SAR methodology to predict the toxic effects of non-congeneric chemicals is at a new threshold.

The proposed project has four related steps. Initially we wish to develop, extend, and apply the most promising knowledge-based computer methodologies to the SAR analysis of both nonneoplastic and neoplastic organ-specific toxicity effects from recent NTP rodent studies on 200 chemicals. The strengths and weaknesses of the non-congeneric predictive methods developed will be assessed prospectively by comparing organ toxicity predictions with actual results from rodent toxicity studies. As methods are validated, they will be adapted or extended to model other biological end points for NTP studies, such as genotoxicity, developmental toxicity, reproductive toxicity, immunotoxicity, etc. Ultimately, validated predictive methods will be incorporated as a complementary tool for managing NTP testing.

Extraordinary benefits are possible from this concept. In the broadest sense, success in developing non-congeneric predictive methods will help propel toxicology from a science based on empirical testing, which utilizes dose-response and statistical parameters for determining the health effects of individual chemicals, to one based on modeling, mechanistic inference, hypothesis testing, and validation of theory. More immediately, the development of predictive toxicology methods for incorporation into the NTP as scientific tools that aid the selection of chemicals and the identification of their specific testing needs will help to minimize the use of laboratory animals, maximize the information derived from testing that is conducted, and enable resources to be managed most effectively for accomplishing the extensive mission of the NTP.

NATIONAL TOXICOLOGY PROGRAM CONCEPT REVIEW

CONTRACT TITLE: Quality Assurance (QA) Inspection and Auditing Support Resource Contracts

PROJECT OFFICER: David A. Bridge, (919) 541-4102

OBJECTIVE: The goal is to continue to meet the NTP's Quality Assurance program objectives: 1) independently assess study conduct compliance with Good Laboratory Practice (GLP) regulations and standards, 2) validate data and results for NTP studies, and 3) provide feedback to help improve overall conformance to NTP requirements and cost effectiveness of NTP studies.

CONCEPT STATEMENT: Effective quality management of resources depends upon the use of objective and pertinent information in making decisions that affect the technical performance of any operation. This project will provide the NTP with independent support for conducting QA Site Visits and Retrospective Audits that will address the documentation and conduct of funded research relative to NTP requirements and standards (including Federal GLPs). The NTP will be better informed to take action to assure the high quality of studies, ascertain areas of vulnerabilities in the conduct and documentation of studies, and develop acceptance standards for the performance of high quality studies.

QA site visits, which include inspections of procedures and audits of data, will be made at designated laboratories to assess the extent to which study activities are conducted in contractual compliance and that the documentation supports their complete and accurate reconstruction. QA site visits provide the NTP with evaluations of internal systems regarding a laboratory's adherence to protocols and Standard Operating Procedures (SOPs); compliance with requirements of study contracts and the NTP General Statement of Work; and assurance of the quality for data generation, collection, and storage.

Retrospective audits will be conducted in steps corresponding to the progression of events associated with the conduct and reporting of long-term studies. These audits will involve chronic study records generated by contract laboratories and the NTP to assess their completeness, consistency, accuracy, and compliance with the NTP General Statement of Work which includes FDA Good Laboratory Practice Regulations. Audits of other NTP studies will follow protocols designed to fit the needs of each specific project. Thus, retrospective audits provide the NTP with study-specific assessments used to ensure quality as well as provide a broad base of information about study performance for evaluations of contractor laboratories.

LIST OF CONCEPTS APPROVED BY
NTP BOARD OF SCIENTIFIC COUNSELORS

March 1989 to May 1991

March 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

November 1989

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

March 1990

Chemical Induction of Genetic Transposition
Chemical Induction of Chromosome Damage in Mouse Germ Cells
Investigation of Spontaneous and Induced Mutation in Mouse Germ Cells

October 1990

Investigation of Molecular Mechanisms of Chemical Carcinogenesis in Mammalian Cell Systems
Studies of Chemical Disposition in Mammals

May 1991

Immunotoxicity of Workplace Xenobiotics in Humans

Experimental Toxicology:

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

Systems Toxicity:

Developmental Toxicity Testing:
Range Finding
Testing and Research

Mutagenesis and Experimental Carcinogenesis:

Mutagenesis Assays Using Transgenic 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