NATIONAL TOXICOLOGY PROGRAM

BOARD OF SCIENTIFIC COUNSELORS

November 30 and December 1, 1989

Summary Minutes

National Toxicology Program
Board of Scientific Counselors Meeting

November 30 - December 1, 1989

Summary Minutes

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SUMMARY MINUTES
NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS MEETING
November 30 and December 1, 1989

The National Toxicology Program (NTP) Board of Scientific Counselors met on November 30 and December 1, 1989, at the National Institute of Environmental Sciences (NIEHS), Research Triangle Park, North Carolina. (Attachment 1: Federal Register Meeting Announcement; Attachment 2: Agenda and Roster of Members.) 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. Silbergeld was unable to attend the meeting.

Division of Toxicology Research and Testing (DTRT), NIEHS -- Program Progress and Concept Reviews

I. Introduction and Overview: Dr. Richard Griesemer, Director, DTRT, said the principal aims during the first day were to provide some orientation about the NTP to new members and discuss program planning and restructuring within the Division, the NIEHS component of the NTP, as well as to present some research highlights from the different branches. Further, the Board would be asked to review four project concepts. Concept reviews are needed for new projects, for recompetitions with changes in statements of work, and for projects ongoing for five years or more since the last concept review. Dr. Griesemer listed the major objectives of the NTP and described the mechanisms for policy and scientific oversight. The Board and its subcommittees are the primary bodies for providing scientific oversight.

Dr. Griesemer reported that over the past year, DTRT staff had engaged in a series of formal and informal reviews of program activities and conducted a series of short courses to increase general awareness among the staff of advances and opportunities in selected fields of biomedical research. Foremost among the results of the reviews were the reaffirmation that important problems were being worked on and national needs being responded to, and that our study results are generally of high quality and utility to public health. Also, concerns were identified in both research and management aspects of the program. From this, staff recommendations included: (1) integration of chemical disposition and toxicity studies was needed; (2) toxicologic studies should be designed for hypothesis testing when possible; (3) advances in molecular biology, carcinogenesis, and germ cell mutagenesis should be exploited; and (4) the matrix organizational structure of the division should be replaced with multidisciplinary groups or teams for each major toxicologic endpoint. Dr. Griesemer said there would be presentations by the chiefs of the four major branches and selected senior staff while more detailed information on a number of projects would be available in a poster session the second day.

II. General Toxicology: Dr. H. B. Matthews, Chief of the proposed Experimental Toxicology Branch (ETB), said the ETB was created to place increased emphasis on short-term studies of chemical toxicity through a team approach with a staff which includes senior investigators in general toxicology, genetic toxicology, pathology, clinical chemistry and chemical disposition. He described current studies on tris-(2-chloroethyl) phosphate to illustrate

approaches used, including detailed chemical disposition, behavioral toxicology, and neuropathologic evaluations, all of which aided in explaining species differences in the characteristic brain (hippocampal) lesions.

A. Concept Reviews:

(1) In Vitro Methods to Assess Human Metabolism of Chemical Xenobiotics -- (Attachment 3, pp. 3-4)

Dr. Leo T. Burka introduced the concept and Dr. Robert Scala, Board member, served as principal reviewer. The objective is to provide data which supports or refutes the suitability of studies on the fate of chemicals in animals for prediction of their fate in humans. The proposed contract though similar to ongoing contracts will differ in emphasis by (a) use of liver slices, (b) increased emphasis on metabolite identification, (c) emphasis on developing data useful for pharmacokinetic studies, and (d) doing research on cryopreservation of tissue slices.

Dr. Scala supported the concept as needed for shedding light on human metabolism of xenobiotics and useful for risk assessment. His one reservation concerned the low success rate to date in cryopreservation. In response to a question by Dr. Goodman about use of these approaches in extrapolation, Dr. Burka described recent studies with benzene. Dr. Miller suggested placenta as an accessible source of human tissue.

Dr. Scala moved that the concept be approved. Dr. Little seconded the motion which was approved unanimously by the Board.

(2) General Toxicity Testing and Research Onsite at the NIEHS -- (Attachment 3, p. 7)

Dr. Bernard Schwetz introduced the concept and Dr. Arthur Upton, Board member, served as principal reviewer. The objective is to have the capability onsite to evaluate toxicity of selected chemicals and conduct research to better understand site and mode of action. An onsite contract allows for a more rapid and multi-disciplinary response to public health needs.

Dr. Upton supported the need for having rapid capability to fill data gaps and respond to needs for mechanistic data. Other Board members affirmed their support for quick response capability.

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

III. Systems Toxicity: Dr. Bernard Schwetz, Chief, Systems Toxicity Branch, said the new branch differed mainly from its predecessor, the Systemic Toxicology Branch, by having added a neurotoxicology group while no longer having the chemical disposition group. He said he and other senior staff would focus in their discussions on activities of the groups in developmental toxicology, reproductive toxicology and immunotoxicology.

A. Reproductive and Developmental Toxicology -- Dr. Schwetz said there were a number of questions that could be asked about the area, including availability of and experience with established test methods, predictiveness across species, concordance with human effects of chemicals, availability of established prescreens, what understanding there is of site/mode of action of toxicity, and how does answering these questions provide information for developing a risk assessment model? He discussed the available technology in reproductive toxicology for answering these questions, especially the older multigeneration assay and the more current reproductive assessment by continuous breeding assay along with semen analysis in both animals and humans. Regarding developmental toxicology, Dr. Schwetz described the extensive experience over the past 25 years with the standard protocol, the "Segment II" screen. He commented on the workshop held at NIEHS, September 21-22, 1989, to evaluate in vitro teratology methodology, noting that points of agreement or disagreement revolved around the usefulness of prescreens, performance characteristics of the assays, and status of validation efforts. Future efforts should focus on studying chemicals in parallel in in vivo and in vitro teratology systems. Also needed was a new list of reference agents. Dr. Schwetz discussed the rodent lactation model, pointing out preliminary data which suggest that the rat is a good model for the excretion of chemicals into human milk. He mentioned initial efforts in an understudied area, developmental immunotoxicology.

Dr. Robert Chapin, NIEHS, described ongoing contract activities in male reproductive toxicology, especially the primary screen, the reproductive assessment by continuous breeding (RACB) protocol, and a short term in vivo reproductive toxicity screen which would serve as a prescreen for RACB and also has some usefulness in initial identification of developmental toxicants. He commented about how RACB data fits into intramural research, e.g., site and mechanism of action studies with boric acid. Dr. Chapin briefly discussed the use of rabbits as the best animal model for studying effects of chemicals on seminal biochemistry and sperm viability parameters.

Dr. Steven Schrader, NIOSH, described their studies of reproductive function in humans noting that NIOSH has been carrying out field studies since 1983 of men occupationally exposed to toxicants. Focus has been in five major areas: (1) the neuroendocrine system, primarily hormone levels; (2) testicular effects, primarily sperm count, morphology, motility, etc.: (3) accessory sex glands, through evaluation of biochemical markers in semen; (4) measures of genetic damage to sperm cells; and (5) effects on libido. He reported on field studies with ethylene dibromide and glycol ethers, and mentioned planned studies with boric acid. Dr. Schrader then discussed the more recent initiation of studies to evaluate effects of chemical exposure on the reproductive system in human females, where the focus is on effects on fertility. He described a pilot study aimed at assessing effectiveness of methodology for detecting toxicant effects on the central nervous system, pituitary gland, ovary and uterus. Future studies will attempt to enlarge the human cohort and particularly identify chemical exposures with worker populations that can be studied.

Dr. Jerrold Heindel, NIEHS, discussed intramural research on female reproductive toxicity, including whole animal studies, mechanistic studies, and evaluating ways to extrapolate from animal data to humans. He noted that estrus cyclicity was the only established endpoint of female fertility but his group was investigating pseudopregnancy, superovulation and ovarian histology as possible

other endpoints which could help define site of action of a toxicant. The ovarian histology studies were being done collaboratively with NCTR. Dr. Heindel discussed mechanistic studies concerned with toxicity of phthalate esters to ovarian granulosa cells and mentioned collaborative efforts with researchers at Duke University evaluating human granulosa cells to aid in extrapolation of animal data to humans.

Dr. Schwetz concluded with comments on future directions. In reproductive toxicology, these were to: (1) give more attention to the animal-human interface; (2) give increased emphasis to studies in females; and (3) do more mechanistic studies. In developmental toxicology, future directions include: (1) more emphasis on the relationship between lactation and neonatal toxicity; (2) continuing evaluation of methodology for in vitro teratology; and (3) increased commitment to the field of developmental neurotoxicology.

B. Immunotoxicology -- Dr. Michael Luster, NIEHS, described the types of immunotoxic effects and current issues in immunotoxicology, particularly relating to immunosuppression and hypersensitivity. He reviewed approaches used to detect immune alterations, these being primarily toxicologic endpoints, measures of immune function, and measures of host resistance to challenge. He discussed the immunotoxicity studies being done on AIDS therapeutics in collaboration with the NCI. Dr. Luster discussed three types of cell systems and endpoints being used in intramural research studies, macrophage activation, B cell maturation, and T cell maturation, and studies being performed with the first two systems. With regard to immunotoxicity testing of chemicals by the NTP over the past 10 years, he reported that of 54 tested, 30 showed altered immune function and 28 showed altered host resistance. Dr. Luster concluded by talking about new research and development efforts.

IV. Carcinogenesis: Dr. Gary Boorman, Chief of the proposed Chemical Carcinogenesis Branch, said the branch would encompass toxicologists, pathologists, chemists, contract specialists and others concerned with long-term carcinogenesis studies in rodents. He said that rodent carcinogenicity studies had gained a significant degree of acceptance as a means of identifying potentially hazardous chemicals for humans, and noted great progress over the last 20 years with standardization of study conduct and pathology, and improved evaluation and reporting. Dr. Boorman said the branch would be organized between study conduct and study evaluation. Facets of study conduct include: (1) setting priorities for testing after chemicals have been approved by inhouse and extramural review committees; (2) study design; (3) selection of laboratories; and (4) monitoring of studies. He discussed opportunities to improve the quality of the studies and enhance understanding of the results, including better definition of chemicals selected for study, improvement of diets, more efficient data management, and followup studies to better define certain lesions observed in the two-year studies.

Dr. Scot Eustis, NIEHS, discussed the study evaluation aspect of the Chemical Carcinogenesis Branch. He reviewed the status of two year studies in progress noting that most were two species, three dose with some having interim sacrifices and a few being stop studies. He commented on how important it was that the data derived from the two-year studies be accurate and correct in that conclusions drawn about carcinogenicity of a chemical were often based on small numbers of lesions. Thus, he emphasized the importance of data verification and

quality assurance in describing the steps involved in the pathology data audit and pathology specimens audit, histopathology quality assessment, and the pathology working group (PWG) review. Dr. Eustis concluded by discussing evolution and change in the studies process including improvement of rodent diets to enhance longevity and health of the animals, modification in study design, inclusion of techniques for looking at the molecular biology of neoplasia, and looking for ways to improve the efficiency and cost effectiveness of the studies process.

V. Genetic Toxicology: Dr. Raymond Tennant, Chief, proposed Experimental Carcinogenesis and Mutagenesis Branch, said the new branch was derived from the existing Cellular and Genetic Toxicology Branch with a primary goal being to develop methods and concepts to reduce dependence on traditional rodent bioassay systems for detecting carcinogens and germ cell mutagens. One approach has been to evaluate the predictivity of short-term tests for carcinogens. He hoped that a legacy of the Branch would be in establishing the concept of assay specificity, i.e., determining the frequency with which assays detect noncarcinogens. A strategy for the new Branch would have three components: (1) to learn more about neoplastic processes, particularly how they are perturbed by chemicals, especially nongenotoxic substances; (2) empirically to develop new methods to detect nonmutagens; and (3) to use the large NTP data base to identify additional factors that are predictive of carcinogenicity such as those based on chemical structure and biologic activity. Ongoing bioassays will be used to prospectively test the validity of those factors. Dr. Tennant briefly described the organizational components of the branch which were groups concerned with evaluation of (1) mechanisms of carcinogenesis, (2) transgenic mouse models for characterization of mutagens and carcinogens, (3) in vitro mammalian cell culture systems for characterization of carcinogens, and (4) heritable effects-germ cell mutagenesis.

Dr. Robert Maronpot, NIEHS, spoke about the group concerned with mechanisms of carcinogenesis. He described a paradigm for the evolution of malignancy based on the concept that cancer is a phenotypic expression of accumulated genetic damage that he thought represented a suitable framework upon which to build a research effort concerned with mechanisms of carcinogenesis. The group's action plan would be to (1) sort out and categorize which genetic events are common to various cancers and which are important, and (2) determine how chemicals affect these. Tools and approaches would include: (1) use of transgenic technology; (2) study of adducts on transcriptionally active genes; (3) use of tissue culture systems; (4) study of the role of suppressor genes; (5) continuing study of oncogene activation and expression; (6) using specific animal models; and (7) determining parallel paths to malignancy in rodents and humans.

Dr. Michael Shelby, NIEHS, described the activities of the heritable effects group. He mentioned the four in vivo mouse germ cell assays, and listed the major accomplishments of the group over the past years. He discussed ongoing studies evaluating chromosomal effects, projects using the morphological specific locus test. and the more recently initiated studies in the multiple endpoint project. Dr. Shelby described planned initiatives of the heritable effects group: (1) applying recombinant DNA methods to development of human germ cell mutation assays; (2) developing parallel animal model assays which will allow the same endpoints to be studied in both mice and humans; (3) continuing to evaluate germ cell mutagens in animal models; and (4) supporting human population studies.

Review of Chemicals Nominated for NTP Studies

There were six chemical nominations 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 4.) Dr. Upton chaired the review. Dr. William Allaben, NCTR, Dr. Dorothy Canter, NIEHS, and Dr. Janet Haartz, NIOSH, CEC members, and Dr. Victor Fung, NTP Chemical Selection Coordinator, served as resource persons. As orientation for new Board members, Dr. Canter described the NTP chemical nomination and selection process. Board members served as principal reviewers for one chemical each, and following the presentation and discussion of each chemical, motions were made and voted on. The Board's recommendations for the six chemicals are summarized in Attachment 5.

Update on Activities of the Technical Reports Review Subcommittee

Dr. Eustis gave the Board a progress report on recent and upcoming activities of the Technical Reports Review Subcommittee and associated ad hoc Panel of Experts (Peer Review Panel). Dr. Eustis summarized the findings for carcinogenicity from the Panel's meetings on June 27 and November 20-21,1989, at which there were 14 two-year studies and 5 short-term toxicity study reports reviewed. Of the 14 two -year studies, the Panel concurred with staff recommendations for levels of evidence of carcinogenic activity on 11 studies, recommended a change in the levels for one, and recommended deferral for two (amphetamine sulfate and ethylene thiourea). Dr. Eustis discussed in more detail two of the studies reviewed at the November meeting, tetranitromethane and ethylene thiourea.

Dr. Scala, Chair of the Panel, commented on the two reports deferred at the November meeting, noting that the deferral was not so much for scientific reasons but more because of inadequate presentation. He then discussed a number of issues that have arisen over the past several Panel meetings and which the Panel has asked the Program to consider or provide information on. These issues included: maximum tolerated dose (MTD) and how to use it in setting doses; use of genetic toxicology data and historical control data in the reports; voting procedures, especially reasons for abstentions; levels of evidence; the role of irritation/hyperplasia in tumor response; and chemical selection especially those found as contaminants of the diet.

Report of the Director, NTP

Dr. David Rall reported that the NIEHS expected to be able to fund 28-29 % of approved grants which was considerably better than a 10 % funding rate for NIH grants projected in an article in Science magazine. However, the Gramm-Rudman deficit reduction act will result in a 1.7 % slash in the Institute budget causing NIEHS to effect reductions of about 10 % in both continuing and approved renewals.

Update on Activities of the Reproductive and Developmental Toxicology Program Review Subcommittee and Concept Reviews

Dr. Miller, Board representative to the Subcommittee, noted the diversity of the members with expertise ranging from clinical studies to basic science, and then introduced Dr. Claude Hughes, Subcommittee member from Duke University Medical

Center, who reported on the last meeting held at NIEHS, September 20, 1989. The purposes of this meeting were to review results using the reproductive assessment by continuous breeding protocol (RACB), review concepts for initiatives in female reproductive toxicology, and to receive updates and discuss ongoing and new research projects on male and female fertility assessment, developmental immunotoxicity, developmental toxicology, and post-natal toxicology. Dr. Hughes stated that the RACB protocol was still the core methodology for the program and the Subcommittee recommended only minor modifications in the RACB, including addition of a short-term component (14-28 days) and broadening the protocol to being able to use rats. He commented on the development of a rabbit model for fertility assessment of males. Dr. Hughes discussed recently initiated NTP efforts in female reproductive assessment, noting the NIOSH pilot study in humans and NIEHS studies in rats using the vertically integrated scheme. He discussed NIEHS studies using ovarian granulosa cells from rats in culture as well as work with human cell lines.

A. Concept Reviews:

(1) Reproductive Toxicity Testing and Methods Development -- (Attachment 3, p. 5)

Dr. Robert Chapin introduced the concept and Dr. Richard Miller, Board member, served as principal reviewer. The objectives of the concept are to continue the capability for the screen, Reproductive Assessment by Continuous Breeding (RACB), while maintaining the flexibility to use other established assays and providing for defining new model systems to aid in prescreening chemicals as candidates for RACB testing. The RACB is considered to be the definitive screen for detecting reproductive toxicity in rodents.

Dr. Miller said this was a laudable concept and noted that the RACB develops more information than the typical multigenerational study. After brief discussion by other Board members, Dr. Miller moved that the concept be approved. Dr. Scala seconded the motion which was approved unanimously by the Board.

(2) Site and Mechanism Studies of Reproductive Toxicants -- (Attachment 3, p. 6)

Dr. Jerrold Heindel introduced the concept and Dr. Richard Miller, Board member, served as principal reviewer. The objectives of this concept project are to determine the site and mechanism of known reproductive toxicants to improve extrapolation of animal data to humans. Although much work can be done inhouse, there is a need for a contract(s) to have access to organs, tissues or cells from various species including humans and to carry out specialized studies, e.g., with human ovarian granulosa cells.

Dr. Miller stated that this proposal had great potential for generating useful data in reproductive toxicology. In response to his concern about inclusion of chemical disposition and metabolism studies, Dr. Heindel replied that such studies have been and will continue to be conducted.

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

The entire meeting will be open to the public from 9:00 a.m. to 4:30 p.m. The one-day meeting will include: an orientation to the history, current structure and functions of the Division of Research Grants; and a discussion of study section procedures and practices, especially as related to priority scores and percentile rankings. Attendance by the public will be limited to space available.

The Office of Committee Management, Division of Research Grants, Westwood Building, National Institutes of Health, Bethesda, Maryland 20892, telephone (301) 496-7534, will furnish a summary of the meeting and a roster of the committee members.

Dr. Samuel Joseloff, Executive Secretary of the Committee, Westwood Building, Room 449, National Institutes of Health, Bethesda, Maryland 20892, phone (301) 496-7441, will provide substative program information upon request.

Dated: October 26, 1989.

Betty J. Beveridge,

Committee Management Officer, NIH.

[FR Doc. 89-25806 Filed 11-1-89; 8:45 am]

BILLING CODE 4140-01-M

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), Research Triangle Park, North Carolina, on November 30 and December 1, 1989.

The meeting will be open to the public from 9:00 a.m. to 5:00 p.m. on November 30. The preliminary agenda topics with approximate times are as follows:

9:00 a.m.-10:00 a.m.—Program Orientation for New Board members

10:00 a.m.-12:30 p.m.—Program Progress and Concept Reviews—NIEHS Division of Toxicology Research and Testing (DTRT):

A. General Toxicology;

B. Reproductive and Development Toxicology;

C. Immunotoxicology;

1:30 p.m.-4:00 p.m.—Program Progress and Concept Reviews—DTRT cont.

D. Carcinogenesis;

E. Genetic Toxicology;

4:00 p.m.-5:00 p.m.—Review of Chemicals Nominated for NTP Studies.—The nominations of six chemicals will be reviewed. The chemicals were evaluated by the NTP Chemical Evaluation Committee on August 2, 1989, and are (with CAS Nos. in parentheses): (1) 4-Acetylaminofluorene (28322-02-3); (2) p-Aminobenzoic Acid (150-13-0); (3) Elmiron (37319-27-8); (4) Ethanol (64-17-1); (5) Monochloroacetone (78-95-5); and (6) Propylene Glycol Monomethyl Ether (107-98-2).

The meeting on December 1 will be open to the public from 9:00 a.m. until adjournment. The preliminary agenda topics with approximate times are as follows:

9:00 a.m.-9:15 a.m.—Report of the Director, NTP

9:15 a.m.-9:45 a.m.—Update on Activities of the Technical Reports Review Subcommittee (Peer Review Panel);

9:45 a.m.-10:45 a.m.—DTRT Poster Session

10:45 a.m.-11:15 a.m.—Update on Activities of the Reproductive and Developmental Toxicology Program Review Subcommittee

The Executive Secretary, Dr. Larry G. 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 other program information prior to the meeting, and summary minutes subsequent to the meeting.

Dated: October 29, 1989.

David P. Rall,

Director, National Toxicology Program.

[FR Doc. 89-25807 Filed 11-1-89; 8:45 am]

BILLING CODE 4140-01-M

DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT

Office of Administration

[Docket No. N-89-2079]

Submission of Proposed Information Collection to OMB

AGENCY: Office of Administration, HUD.

ACTION: Notice.

SUMMARY: The proposed information collection requirement described below has been submitted to the Office of Management and Budget (OMB) for review, as required by the Paperwork Reduction Act. The Department is soliciting public comments on the subject proposal.

ADDRESS: Interested persons are invited to submit comments regarding this proposal. Comments should refer to the proposal by name and should be sent to: John Allison, OMB Desk Officer, Office of Management and Budget, New Executive Office Building, Washington, DC 20503.

FOR FURTHER INFORMATION CONTACT: David S. Cristy, Reports Management Officer, Department of Housing and Urban Development, 451 7th Street, Southwest, Washington, DC 20410, telephone (202) 755-6050. This is not a toll-free number. Copies of the proposed forms and other available documents submitted to OMB may be obtained from Mr. Cristy.

SUPPLEMENTARY INFORMATION: The Department has submitted the proposal for the collection of information, as described below, to OMB for review, as required by the Paperwork Reduction Act (44 U.S.C. chapter 35).

The Notice lists the following information: (1) The title of the information collection proposal; (2) the office of the agency to collect the information; (3) the description of the need for the information and its proposed use; (4) the agency form number, if applicable; (5) what members of the public will be affected by the proposal; (6) how frequently information submissions will be required; (7) an estimate of the total numbers of hours needed to prepare the information submission including number of respondents, frequency of response, and hours of response; (8) whether the proposal is new or an extension, reinstatement, or revision of an information collection requirement; and (9) the names and telephone numbers of an agency official familiar with the proposal and of the OMB Desk Officer for the Department.

Authority: Section 3507 of the Paperwork Reduction Act, 44 U.S.C. 3507; section 7(d) of the Department of Housing and Urban Development Act, 42 U.S.C. 3535(d).

Dated: October 27, 1989.

John T. Murphy,

Director, Information Policy and Management Division.

Proposal: Actions to Reduce Losses in FHA Programs, FR-2491.

Office: Housing.

Description of the need for the Information and its proposed use: This rule would require a mortgagee, when notified by the FHA Commissioner that the mortgagee had a higher than normal rate of early serious defaults and claims in the preceeding year, to submit a report to the Commissioner; and, if applicable, a plan and timetable for necessary corrective actions.

AGENDA

NTP BOARD OF SCIENTIFIC COUNSELORS

November 30 and December 1, 1989

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

Thursday, November 30, 1989

9:00 a.m. - 9:05 a.m.	Welcome and Introduction of New Board Members and Chairman	Dr. D. Rall, NIEHS
9:05 a.m. - 9:15 a.m.	Procedures and Principles of Concept Reviews	Dr. L. Hart, NIEHS Mr. W. Johnston, NIEHS
9:15 a.m. - 10:00 a.m.	Program Orientation for New Members	Dr. R. Griesemer, NIEHS

Division of Toxicology Research and Testing (DTRT) - Program Progress and Concept Reviews

10:00 a.m. - 10:45 a.m.	A. General Toxicology	Dr. H. Matthews, NIEHS
	Concept Reviews - DTRT I. In Vitro Methods to Access Human Metabolism of Chemical Xenobiotics	Dr. L. Burka, NIEHS
	II. General Toxicity Testing and Research Onsite at the NIEHS	Dr. B. Schwetz, NIEHS
10:45 a.m. - 11:00 a.m.	Break	
11:00 a.m. - 12:00 noon	B. Reproductive and Developmental Toxicology	Dr. B. Schwetz & Dr. J. Heindel, NIEHS
12:00 noon - 12:30 p.m.	C. Immunotoxicology	Dr. M. Luster, NIEHS
12:30 p.m. - 1:30 p.m.	Lunch	

1:30 p.m. - 2:15 p.m.	D. Carcinogenesis	Dr. G. Boorman & Dr. S. Eustis, NIEHS
2:15 p.m. - 3:00 p.m.	E. Genetic Toxicology	Dr. R. Tennant, Dr. R. Maronpot & Dr. M. Shelby, NIEHS
3:00 p.m. - 3:30 p.m.	Break	
3:30 p.m. - 4:00 p.m.	F. Summary and Future Program Plans	Dr. R. Griesemer & Dr. J. Selkirk, NIEHS
4:00 p.m. - 5:00 p.m.	Review of Chemicals Nominated for NTP Studies	Dr. D. Canter, NIEHS Board

Friday, December 1, 1989

9:00 a.m. - 9:15 a.m.	Report of the Director, NTP	Dr. D. Rall, NIEHS
9:15 a.m. - 9:45 a.m.	Update on Activities of the Technical Reports Review Subcommittee (Peer Review Panel)	Dr. R. Scala, Board Dr. S. Eustis, NIEHS
9:45 a.m. - 11:00 a.m.	Break/Poster Session	
11:00 a.m. - 12:00 noon	Update on Activities of the Reproductive and Developmental Toxicology Program Review Subcommittee	Dr. R. Miller, Board Dr. B. Schwetz, NIEHS Dr. S. Schrader, NIOSH Dr. C. Hughes, Duke University
	Concept Reviews - DTRT III. Reproductive Toxicity Testing and Methods Development	Dr. J. Heindel, NIEHS
	IV. Site and Mechanism Studies of Reproductive Toxicants	Dr. J. Heindel, NIEHS

Adjourn

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS

November 30 and December 1, 1989

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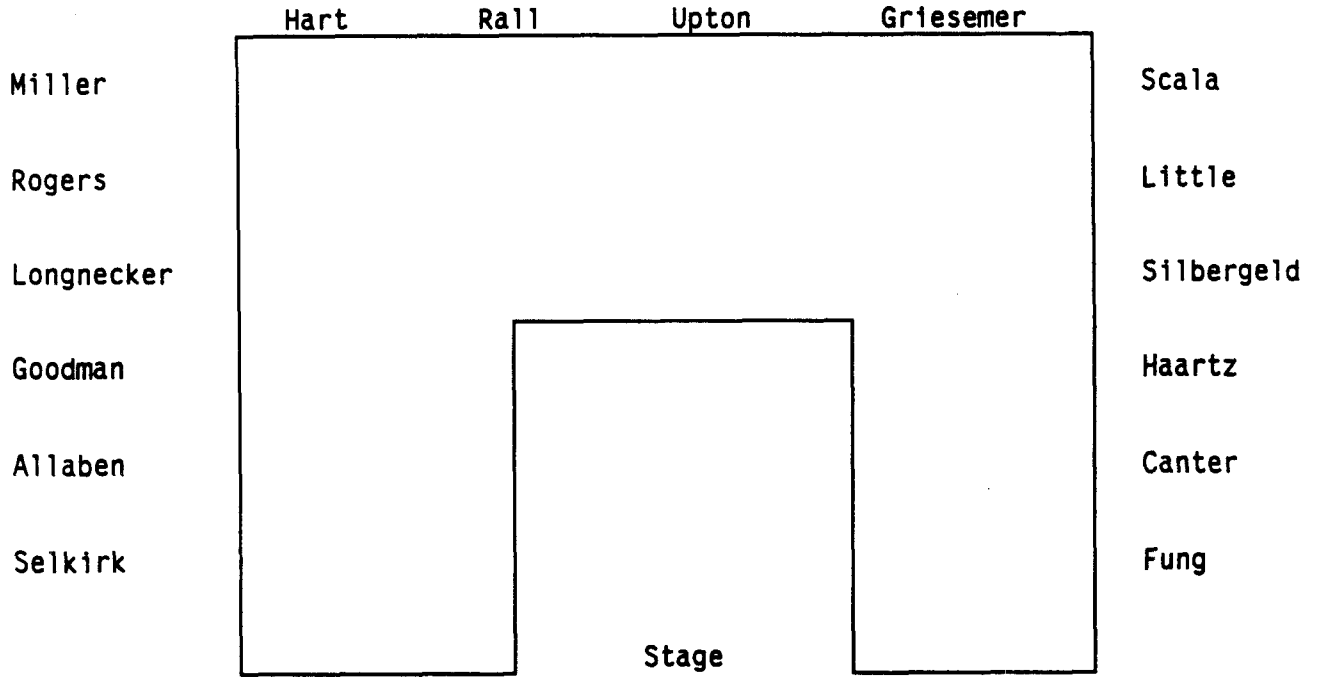
NTP BOARD OF SCIENTIFIC COUNSELORS MEETING

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

Novemer 30 and December 1, 1989



NTP BOARD OF SCIENTIFIC COUNSELORS

REVIEW OF PROJECT CONCEPTS

November 30 - December 1, 1989

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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 are to be reviewed 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.

d. where pertinent, adequacy of the methodology to be used in performing the activity.

National Toxicology Program Board of Scientific Counselors
Review of Concepts

November 30 - December 1 1989

NATIONAL TOXICOLOGY PROGRAM CONCEPT REVIEW

CONTRACT TITLE: In Vitro Methods to Assess Human Metabolism of Chemical Xenobiotics

PROJECT OFFICER: L. T. Burka, (919) 541-4667

OBJECTIVE: The objective of all research in the Chemical Disposition Group is to provide data suitable for extrapolation to predict human risks resulting from exposure to hazardous chemicals. The objective of work done under the proposed contract is to provide data which supports or refutes the suitability of studies on the fate of chemicals in animals for prediction of their fate in humans. That is, in vitro metabolism of chemical xenobiotics in human tissue preparations will be compared to results obtained with similar preparations from animal species most commonly used in laboratory research and testing. Data obtained can be used to extrapolate more accurately results from toxicity/carcinogenicity studies to predict possible human health risks.

CONCEPT STATEMENT: Since the disposition of toxic chemical xenobiotics cannot be done in humans, appropriate studies of chemical disposition are conducted in laboratory animals. Results obtained from these studies are then extrapolated to predict the fate of the chemicals of interest in humans. In all species, rates and pathways of metabolism (most frequently hepatic metabolism) are primary determinants of chemical disposition. Hepatic metabolism of chemical xenobiotics may result in activation or deactivation of toxic properties and may vary considerably with species. Species dependent variations in chemical metabolism frequently account for variations in species sensitivity to chemical toxicity. Therefore, the validity and accuracy of animal to human extrapolation is enhanced if either the animal model and humans handle the subject chemical in a similar way, or, if we have adequate data to document and quantify the relevent differences.

In the past four years we have had in place three contracts to develop methods to investigate the in vitro metabolism of chemical xenobiotics in tissues from humans and other species. These contracts have looked into the use of S-9, microsomes, whole cells and tissue slices; primarily from liver, but also other organs. The human tissue has been obtained from donor organs for which there was no suitable recipient and from surgery waste tissue. Biopsy material and cadaver tissue were also considered and rejected as useful sources of tissue.

The methods developed to prepare hepatocytes from rodent liver have been modified to allow preparation of hepatocytes from large lobes of human liver or even whole livers. Methods have also been developed for the use of tissue slices for metabolism studies. Using both these preparations, metabolic profiles of several model compounds have been determined. In recent years, this work has concentrated on metabolic profiles of compounds of specific interest to the NTP and profiles for several compounds have been obtained.

In addition to the development of metabolic profiles, during the first years of the contract considerable effort was expended in an effort to cryopreserve the human tissue. The intent was to have a moderate number of preparations on hand so that interindividual variation in metabolism of specific xenobiotics could be

assessed more easily. While methods were developed that would cryopreserve rat hepatocytes or rat liver slices moderately well, the same methods were unsuccessful in cryopreserving human hepatocytes or liver slices.

PROPOSED CHANGES TO THE CURRENT STATEMENT OF WORK: The proposed contract, while a derivative of the original three, has a somewhat different emphasis. 1) The major component of this contract will be to provide comparative data for metabolism of chemical xenobiotics in human and rodent liver slice preparations. This work will make considerable use of tissue slices because the slice method is technically simpler than hepatocyte preparation; an excellent coupling of Phase 1 and Phase 2 metabolism has been observed in this system; and metabolism can be made to proceed for longer times. This latter feature is especially important for slowly metabolized substrates. In addition, cryopreservation of slices shows more promise than cryopreservation of hepatocytes. 2) The proposed contract will place increased emphasis on the chemical identity of metabolites formed by both animal and human tissue. In most cases, metabolism of the compound in question has been studied, standards are available, and identities need only be verified. In rare cases we may wish to undertake identification of particularly interesting unknown metabolites. 3) The proposed contract will also place increased emphasis on the development of data suitable for use in pharmacokinetic studies. Since relative rates of metabolism will change with concentration, there needs to a range of concentrations studied. With metabolism data at a number of concentrations, kinetic parameters such as Km and Vmax can be estimated. These parameters can be used in physiologically based pharmacokinetic models, thus facilitating interspecies extrapolation. 4) Even though initial efforts at cryopreservation have not been fully successful we have not lost interest in that area. Further research on cryopreservation of tissue slices is still needed. At present, the proposed metabolism studies can be carried out if fresh tissue is routinely available. Even so, metabolism studies are spread out over weeks or longer to obtain enough replicates to assess interindividual variation. However, performing incubations using tissue from several different sources at the same time provides logistical as well as statistical advantages. This will be possible only if cryopreservation techniques are developed. Therefore, a small research component in the contract will be devoted to developing these techniques.

NATIONAL TOXICOLOGY PROGRAM CONCEPT PROPOSAL

CONTRACT TITLE: Reproductive Toxicity Testing and Methods Development

PROJECT OFFICERS: Jerrold J. Heindel (919) 541-5130
Robert E. Chapin (919) 541-3742

OBJECTIVE: To test chemicals specifically for reproductive toxicity and to develop new methods to aid in this process.

CONCEPT STATEMENT: The testing of chemicals for reproductive toxicity and the development of new methods to enhance the sensitivity, specificity and efficiency of these tests falls within the NTP mandate to broaden and coordinate the federal government's efforts to characterize the toxicity of chemicals. To this end, the NTP has developed and validated a definitive screen for detecting reproductive toxicity in rodents. This screen, called Reproductive Assessment by Continuous Breeding (RACB), has improved upon the existing multigeneration studies by increasing the number of litters deliverable by the test animals, adding a specific battery of endpoints at necropsy to increase the sensitivity of the test, and by adding a crossover mating trial to determine the affected sex. It is proposed to continue reproductive toxicity testing by the NTP utilizing this basic RACB design with modifications developed to improve its ability to more fully characterize the reproductive hazard of a chemical.

It is also proposed that the NTP continue to define new model systems both in vivo and in vitro in order to more effectively prescreen chemicals which are candidates for RACB testing, to aid in the extrapolation process to humans, to improve our ability to determine overall reproductive toxicity, affected sex and site of action, to reduce the numbers of animals required for testing and to reduce the time and cost of testing.

NATIONAL TOXICOLOGY PROGRAM CONCEPT PROPOSAL

PROPOSED TITLE: Site and Mechanism Studies of Reproductive Toxicants

PROJECT OFFICER: Jerrold J. Heindel and members of the Developmental and Reproductive Toxicology Group

OBJECTIVE: To determine the site and mechanism of known reproductive toxicants in order to improve the extrapolation of animal data to humans and to aid in determining structure-activity relationships.

CONCEPT STATEMENT: In order to carry out the NTP's mandate to characterize the toxicity of chemicals it is necessary to not only determine which chemicals are reproductive toxicants but also to determine, when possible, the active component, the compounds' site of action and its mechanism of action. The ability to carry out a vertically integrated approach (from whole animal testing (RACB) to mechanism of action in isolated cell types) is a unique and important part of the NTP program in Reproductive Toxicology. We propose therefore to continue to utilize this vertically integrated approach for the determination of the site and mechanism of action of male and female reproductive toxicants. These studies may include whole animal, organ cultures, isolated cell cultures, mixed cell cultures or isolated enzyme preparations from males and females of various species and strains.

These studies aimed at determining the site and mechanism of action of reproductive toxicants will help the NTP provide regulatory agencies with an improved ability to extrapolate both between species and between chemical types (i.e., structure-activity relationship).

NATIONAL TOXICOLOGY PROGRAM CONCEPT PROPOSAL

CONTRACT TITLE: General Toxicity Testing and Research On-Site at the NIEHS

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

OBJECTIVE: To evaluate the toxicity of selected chemicals, and to conduct applied research to better understand the site and mode of action of chemical-induced toxicity.

CONCEPT STATEMENT: Toxicological findings through studies conducted by the NTP or reported in the open literature often stimulate the need to conduct additional studies to enhance the data or permit more informed interpretation of data. This might include studies in other animal species, by other routes or modes of exposure, including inhalation, and studies designed for more in-depth investigation of specific toxic responses. Many studies are interdisciplinary in nature and draw on the expertise and research interests of a wide range of NIEHS scientists who collaborate in these studies. Studies are selected on the basis of Program needs and are conducted on-site with the help of the Contractor staff. Capabilities are sufficiently flexible to permit testing and research related to a broad spectrum of toxicological endpoints, frequently using non-routine study designs tailored to meet the needs for individual chemicals.

Summary Data on Chemicals for Review by the Board of Scientific Counselors
on November 30, 1989

Chemical (CAS Number)	Nomination Source	Domestic Production(lbs)	Estimated Worker Exposure	NTP Testing Status	Other	Chemical Evaluation Committee Recommendations (Priority)	NTP Chemical Selection Principles	Rationale/Remarks
1. 4-Acetyl-aminofluorene (28322-02-3)	CIIT[a]	-Not produced in the U.S.[b]	--	-Positive in mouse lymphoma in three independent studies; another study in progress -Negative for chromosomal aberrations and positive for sister chromatid exchanges in Chinese hamster ovary cells *in vitro*	-Extensively tested for genotoxicity in *in vivo* an *in vitro* assays as part of International Program for the Evaluation of Short-Term Tests for Carcinogenicity	No testing	--	-Research chemical -Very low production-would need custom synthesis to provide sufficient chemical for NTP testing -Low potential for human exposure -Testing of 4-AAF not expected to provide significant data to validate short-term *in vivo* assays
2. p-Amino-benzoic acid (150-13-0)	NIEHS	$1.2x10^4$-$1.2x10^5$ (1977)[c]	4,448[d]	-Negative in *Salmonella*	--	No testing	--	-Significant decrease in use and potential for exposure -NTP is testing structurally-related compounds, p-nitro-benzoic acid and p-nitrotoluene
3. Elmiron (37319-17-8)	FDA	-No definitive production data [c,e]	--	--	-Carcinogenicity (Moderate-High)		2	-Potential as treatment for interstitial cystitis -FDA has granted chemical "orphan drug status" -Lack of carcinogenicity data

ATTACHMENT 4

Chemical (CAS Number)	Nomination Source	Domestic Production(lbs)	Estimated Worker Exposure	NTP Testing Status	Other	Chemical Evaluation Committee Recommendations (Priority)	NTP Chemical Selection Principles	Rationale/Remarks
4. Ethanol (64-17-5)	NIEHS	8.3×10^6-2.7×10^9 (1977)[c] 5.74×10^8 (1988)[e]	987,777[d]	-Continuous breeding study: no significant effect on mating or fertility; significant reduction in litter size -Inhalation teratology; no teratogenic effect observed	IARC concluded that there is sufficient evidence for carcinogenicity of alcoholic beverages in humans	No testing	--	-Epidemiological studies indicate association between consumption of ethanol-containing beverages and variety of human cancers -Toxicity of ethanol studied extensively
5. Monochloroacetone (78-95-5)	NCI	1.0×10^5-1.0×10^6 (1977)[c]	4,354[d]	--	--	No testing	--	-Chemical manufactured and used in closed systems -Limited occupational exposure -Lack of evidence for consumer exposure -If exposure can be substantiated, CEC will re-evaluate chemical
6. Propylene glycol methyl ether (107-98-2)	NCI	1.0×10^6-1.0×10^8 (1977)[c]	91,396[d]	-No effect observed in continuous breeding study	--	-Carcinogenicity (Moderate-High)	3,8	-Increasing use as solvent (replacement for other glycol ethers shown to have toxic effects -Potential for exposure -Lack of carcinogenicity data

a) Chemical Industry Institute of Toxicology
b) Hazardous Substances Data Bank. On-line printout. National Library of Medicine, National Institutes of Health.
c) U.S. Environmental Protection Agency. Non-confidential portion of Initial TSCA Chemical Substances Inventory.
d) National Occupational Exposure Survey conducted by NIOSH between 1981 and 1983.
e) U.S. International Trade Commission. Synthetic Organic Chemicals. U.S. Production and Sales.

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 addtional 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 November 30, 1989

Chemical (CAS Number)	Nomination Source	Testing Recommendations (Priority)	Rationale/Remarks
1. 4-Acetylaminofluorene (28322-02-3)	Chemical Industry Institute of Toxicology	-No testing	-Research chemical -Limited use -Low potential for human exposure
2. p-Aminobenzoic acid (150-13-0)	NIEHS	-Defer	-Obtain additional information on amount of use and level of human exposure
3. Elmiron (37319-17-8)	FDA	-Defer	-Obtain more information on efficacy and use of drug, type of people using it, results of animal studies, and clinical trials.
4. Ethanol (64-17-5)	NIEHS	-No testing	-Animal studies indicate co-carcinogenic effects -Epidemiological studies identify association between consumption of ethanol-containing beverages and variety of human cancers
5. Monochloroacetone (78-95-5)	NCI	-No testing	-Limited production -Low potential for human exposure
6. Propylene glycol methyl ether (107-98-2)	NCI	-Carcinogenicity (Moderate to high)	-Replacement as solvent for other glycol ethers shown to have toxic effects -Use as solvent is increasing -Potential for exposure -Lack of carcinogenicity data

ATTACHMENT 5