# National Toxicology Program
Board of Scientific Counselors Meeting
October 15-16, 1990
Summary Minutes

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SUMMARY MINUTES
NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS' MEETING
October 15 and 16, 1990

The National Toxicology Program (NTP) Board of Scientific Counselors met on October 15 and 16, 1990, at the National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina. (Attachment 1: Federal Register Meeting Announcement; Attachment 2: Agenda and Roster of Members.) Members of the Board are Drs. Arthur Upton (Chairman), Paul Bailey, Jay Goodman, John Little, Lawrence Loeb, Daniel Longnecker, Richard Miller, and Ellen Silbergeld. All were present on October 15. In Dr. Upton's absence, Dr. Longnecker chaired the meeting on October 16.

Committee and Meeting Reports

I. Technical Reports Review Subcommittee: Dr. Richard Irwin, NIEHS, 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. Irwin summarized the findings for toxicity and carcinogenicity from the Panel's meeting on April 25-26, 1990, at which there were six two year study reports reviewed. Of the six studies, the Panel concurred with staff recommendations for levels of evidence of carcinogenic activity on five, and recommended a change in the level of evidence for one of four experiments in the sixth study. Dr. Irwin gave a brief report on the seven two-year study and four short-term toxicity study reports to be reviewed by the Panel on November 19-20, 1990.

II. Reproductive and Developmental Toxicology Program Review Subcommittee: Dr. Jerrold Heindel, NIEHS, said the Chairman of the Subcommittee (currently Dr. Miller) usually reports to the Board on the last meeting but in this instance there had not been a Subcommittee meeting since the last Board meeting. The next meeting was scheduled for November 8 to 9 in Cincinnati with NIOSH as the host. He commented on the close collaboration and interaction among the three participating agencies (NIEHS, NIOSH and NCTR) in the area of reproductive and developmental toxicology. Dr. Heindel described the agenda for the November meeting. The first day was to be devoted to evaluation of NTP efforts in developmental toxicology and the second day would be focused on reproductive toxicology.

III. Conference on Mouse Lung Tumors: Dr. Darlene Dixon, NIEHS, reported on the background and substance of the Symposium on Mouse Pulmonary Carcinogenesis held at the NIEHS on March 27 and 28, 1990, in honor of the memory of Dr. Michael B. Shimkin. The symposium was cosponsored by the NIEHS and the Medical College of Ohio with the objective being to summarize research progress made during the last two decades in mouse lung tumorigenesis. Areas emphasized included investigations of the morphological development of lung tumors, genetics of lung tumor development in different strains of mice, application of mouse lung tumor bioassays for detection of environmental carcinogens, and studies of agents that either promote or inhibit development of
chemically induced lung tumors. Dr. Dixon said the proceedings of the symposium would be published in Experimental Lung Research, Vol. 17, No.2, March 1991, while a summary would be included in a future issue of Cancer Research.

Review of Chemicals Nominated for NTP Studies

Nominations of five 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. Upton chaired the review. Dr. William Eastin, NIEHS, Dr. Heindel, and Dr. H.B. Matthews, NIEHS, CEC Members, and Dr. Victor Fung, NTP Chemical Selection Coordinator, (by speaker phone from Bethesda, Maryland), served as resource persons. Board members served as principal reviewers for one chemical each, and following the presentation and discussion of each chemical, motions were made and voted upon. The Board's recommendations for the five chemicals are summarized in Attachment 4.

Concept Reviews - OTRT, NIEHS

I. Investigation of Molecular Mechanisms of Chemical Carcinogenesis and Evaluation of Chemicals in Mammalian Cell Systems -- (Attachment 5, pp. 2-3)

Dr. Judson Spalding, Experimental Carcinogenesis and Mutagenesis Branch, NIEHS, introduced the concept, and Dr. John Little, Board member, served as principal reviewer. Dr. Spalding said that mammalian cell transformation systems are proposed to be the in vitro models that most closely resemble the multistage process of tumorigenesis in vivo. The objectives of the concept proposal were (1) to utilize these models to create and characterize the properties of different phenotypes that represent discrete stages in the process of malignancy, (2) to use these phenotypes as targets to evaluate the effects of selected genotoxic and nongenotoxic carcinogens, and (3) to further develop the mammalian cell model to characterize biological properties of chemicals with emphasis on discriminating between nongenotoxic carcinogens and noncarcinogens. The model systems to be used are the Balb/c 3T3 mouse fibroblast transformation system and human fibroblast system. Dr. Spalding said that altered phenotypes would be used to examine the ability of the representative chemicals to induce a specific phenotype to acquire the characteristics of a "next stage" in progression toward malignancy.

Dr. Little thought this to be an exciting concept in that it proposes to use the large data base with the Balb/c system and the good data base with human fibroblasts to develop new information about the carcinogenesis process. Dr. Loeb suggested that only a few chemicals be studied but in depth to learn more about the process. Dr. Little moved that the concept be approved. Dr. Loeb seconded the motion which was approved unanimously by the Board.

II. Immunotoxicity of Workplace Xenobiotics in Humans -- (Attachment 5, p. 4)

Dr. Virginia Sanders, Systems Toxicity Branch, NIEHS, introduced the concept and Dr. Ellen Silbergeld, Board member, served as principal reviewer. Dr. Sanders said the objective of the proposal was to establish an immunological database for humans exposed to xenobiotics in the workplace through an Interagency Agreement (IAA) with NIOSH. Goals were: (1) to determine if a correlation exists between rodent and human immunotoxicity data so that rodent data can be used for risk assessment; (2) to determine if specific immune
parameters are altered by xenobiotic exposure so they can be utilized as biomarkers; and (3) to determine if xenobiotic-exposed populations with altered immune function have a higher probability of developing states of suppressed host resistance and/or clinical disease. The IAA would take advantage of NIOSH's inhouse immunotoxicology expertise and their access to exposed groups of workers in the field.

Dr. Silbergeld commented that this was an important area but expressed concern that our understanding of altered immunologic function in humans was not well enough developed to make the transfer from rodent to human studies. Therefore, she stated that the third goal should be deferred. Dr. Bailey suggested that it would be preferable to study humans receiving therapeutic agents as their exposure could be better quantitated than that of individuals exposed in the workplace. Dr. Sanders emphasized that the third goal was a long-term one. Dr. Silbergeld moved that the concept be deferred for revision and future consideration. Dr. Loeb seconded the motion which was approved unanimously by the Board.

III. Studies of Chemical Disposition in Mammals -- (Attachment 5, p. 5)

Dr. Burhan Ghanayem, Experimental Toxicology Branch, DTRT, NIEHS, introduced the concept and Dr. Jay Goodman, Board member, served as principal reviewer. These were ongoing studies where there was essentially no change in work to be performed or scope but concept review was required prior to recompeting the contracts in 1991. The objective is to provide for studies of chemical disposition in laboratory animals, primarily rats and mice. Studies are conducted both prospectively to provide data to support the design of subchronic and chronic studies and retrospectively to address questions raised by results of completed toxicology studies.

Dr. Goodman commented that the data provided by these types of studies were needed. He asked for one or two examples of prospective disposition studies that helped in better design of the subchronic or chronic study. Dr. Ghanayem discussed disposition studies with two chemicals which indicated that absorption of the chemical by test animals using the proposed vehicle and route of administration would have been poor. Dr. Goodman moved that the concept be approved. Dr. Miller seconded the motion which was approved unanimously by the Board.

NTP Quality Control and Quality Assurance Programs -- Long Term Animal Studies

I. NTP Quality Control Program: Dr. Gary Boorman, Chemical Carcinogenesis Branch, DTRT, gave an overview of the steps and procedures used to build quality into long-term (usually two-year) toxicity and carcinogenicity studies. He discussed why quality is important and also difficult to achieve. He pointed out controls used to ensure quality and ways to increase cost effectiveness while maintaining quality. Dr. Boorman concluded by describing support programs mainly in animal production and husbandry, chemistry support and pathology review that contribute to maintenance of quality in the long-term studies.

II. NTP Quality Assurance Program: Dr. Douglas Bristol, DTRT, defined quality assurance (QA) as a service function established to perform independent, objective assessments of activities and projects (internal audits), noting that QA has no authority or responsibility for the work they audit. He said the
purpose of QA was two fold, to assist management in determining a level of confidence, and to provide constructive feedback to project managers. Dr. Bristol listed the standards for auditing, discussed what is involved in QA evaluation of reports of long-term studies and evaluation of pathology specimens, and described the components of a QA site visit to a laboratory.

Report of the Director, NTP

Dr. David Hoel, Acting Director, in his report: (1) acknowledged the recent retirement of Dr. David Rall as NIEHS and NTP Director, commented on his preeminent contributions to the building of the NIEHS and role in the creation of the NTP, and noted his recent support in bringing to bear newer molecular biological techniques in evaluation of chemical toxicity; (2) announced that a search committee had been formed headed by Dr. Philip Chen, Associate Director for Intramural Affairs, NIH, to seek and evaluate nominations for Director, NIEHS, and encouraged Board members to help find good candidates; (3) announced formation of the Fourth Task Force for Research Planning in Environmental Health Science to be cochaired by Dr. Upton and Dr. Morton Lippmann, NYU; (4) spoke of a series of Superfund conferences including "Biodegradation of Hazardous Wastes" held at Utah State University in April, "Assessment of Human Exposure to Chemicals from Superfund Sites" at Michigan State University in June, and "Health Effects of Combustion Byproducts" held at NIH in October, as well as a NIEHS and NIOSH cosponsored conference on "Agricultural Chemical Utilization and Human Health" held in July; and (5) commented on the present uncertainty as to what the NIEHS budget would be, noting that the need for deficit reduction would undoubtedly have an impact on the final allocations.

Program on Cell Proliferation in Liver and Foregut Carcinogenesis

I. Introduction: Dr. Robert Maronpot, Experimental Carcinogenesis and Mutagenesis Branch, stated that studies of cell proliferation had been conducted by various investigators at NIEHS during the past seven years. He said the NIEHS has long been interested in using cell proliferation as an aid in understanding the carcinogenesis process, noting that it was one of many factors impacting on the process. Dr. Maronpot introduced the techniques used to measure cell proliferation including incorporation of tritiated thymidine or bromodeoxyuridine into DNA after pulse dosing or infusion with an osmotic minipump followed by autoradiography for tritiated thymidine or immunohistochemistry for bromodeoxyuridine. For measuring cell proliferation in tissues stored in the NTP archives, a technique called Proliferating Cell Nuclear Antigen (PCNA) allows labeling at different phases of the cell cycle and can be used with formalin-fixed, paraffin-embedded tissues. Another technique discussed was Nucleolar Organizing Regions as well as newer techniques for image analysis which may reduce the tedium and time required. Dr. Maronpot concluded by discussing the need for setting ground rules in advance.

II. Chemically-Induced Cell Proliferation by Mutagenic Noncarcinogens: Dr. Michael Cunningham, Experimental Toxicology Branch, DTRT, stated that results of studies in his laboratory indicate that cell proliferation may be important in the induction of hepatocarcinogenesis. He described studies with two mutagenic noncarcinogen:carcinogen pairs -- 2,6- and 2,4-diaminotoluene, and 1-and 2-nitropropane -- utilizing minipump infusion of bromodeoxyuridine (BrDU) and immunohistochemistry to quantitate incorporation of BrDU into hepatic DNA. They
concluded that the inability of 2,6-diaminotoluene to induce carcinogenesis was not due to low absorption or bioactivation in vivo, and induction of cell proliferation in the liver correlated better with the carcinogenic responses of 2,4- and 2,6-diaminotoluene and 1- and 2-nitropropane than did their mutagenicity in vitro. Dr. Cunningham concluded by discussing postulated mechanisms whereby induced cell proliferation may contribute to the multistage process of carcinogenesis.

III. Ethyl Acrylate- and Acrylic Acid-Induced Cell Proliferation: Correlation with Forestomach Carcinogenesis: Dr. Burhan Ghanayem, Experimental Toxicology Branch, said that ethyl acrylate administered by gavage in corn oil for two years caused significant increases in forestomach tumors in both male and female rats and mice, with no neoplastic lesions detected at any other site. He described more recent short-term (13-week) studies in male F344 rats administered ethyl acrylate by gavage with concurrent cell proliferation measured by BrDU incorporation. Results indicated that ethyl acrylate caused a significant dose- and time-dependent increase in epithelial cell proliferation of the forestomach after 13-weeks but minimal increase in a nontarget organ for neoplasia, liver. In animals dosed for 13 weeks and sacrificed 19 months later, the forestomachs appeared relatively normal. Apparently, sustained forestomach cell proliferation for 13 weeks was insufficient to result in increased incidence of tumors after 19 months of recovery. Thus, the relationship between ethyl acrylate-induced forestomach lesions and carcinogenicity has not yet been resolved.

IV. Methylene Chloride Studies: Dr. Maronpot reported that methylene chloride was a high volume industrial solvent for which NTP two-year inhalation studies had been completed several years ago. For B6C3F1 mice, there was clear evidence of carcinogenic activity in both males and females based on increased incidences of lung and liver tumors. He then described the results from a new 2-year study with methylene chloride in female B6C3F1 mice. This study was primarily designed to obtain liver and lung tumors for oncogene analysis although other important endpoints were added. Although there was an increased incidence of liver tumors, there were no alterations in H-ras oncogenes between chemically-induced and spontaneous (control) tumors. There was an increase in liver/body weight ratio due mainly to increased glycogen deposition and storage in hepatocytes. Finally, there was an almost two-fold increase in cell proliferation at 52 weeks but not at 26 or 78 weeks in treated mice compared with controls as measured by hepatocyte labeling with bromodeoxyuridine. These findings do not resolve whether or not cell proliferation could be a significant factor associated with liver tumor induction by methylene chloride.

V. Overview of Cell Proliferation in Liver Carcinogenesis: Division of Biometry and Risk Assessment (DBRA) Plans: Dr. Ronald Melnick, DBRA, reported that a thorough review of the literature was undertaken to assess the relationship between cell proliferation and liver carcinogenesis in rodents. Emphasis was given to evaluating literature on nongenotoxic hepatocarcinogens since some authors had suggested that neoplasia induced by high doses of nongenotoxic chemicals resulted predominantly from cell proliferation due to toxicity which increased spontaneous somatic mutations. The liver is the most common site of chemical carcinogenesis in rats and mice. Among the conclusions that could be drawn from this review, Dr. Melnick stated that quantitative correspondence between sustained cell proliferative responses and carcinogenic
responses have not been well demonstrated. Thus, sufficient data are not available to support the hypothesis that chemically-induced cell proliferation is the primary mechanism by which nongenotoxic chemicals cause liver cancer. Future plans for exploring this issue include: (1) establishing a contract for use by all NIEHS divisions to provide a consistent and efficient resource for assessment of cell proliferation; (2) obtaining dose-response data for chemically-induced liver cell proliferation over extended exposure durations and at doses which bracket the carcinogenic doses of the compounds to be evaluated; (3) determining the effect of protocol variations on cell proliferation and/or development of preneoplastic foci; (4) examining the relationship between chemically-induced cell proliferation and carcinogenesis in other organs, e.g., kidney; and (5) organizing a conference on the validity of cell proliferation as a predictor of chemical carcinogenesis.

Program on Toxicity and Carcinogenesis

I. Introduction: Dr. James Huff, DBRA, discussed findings and conclusions drawn based on an indepth examination of the chemical carcinogenesis database of the NTP aimed at exploring the inter-relationship between toxicity, genotoxicity, and carcinogenicity in laboratory rodents and published (Hoel, Haseman, Hogan, Huff and McConnell, The impact of toxicity on carcinogenicity studies: implications for risk assessment. Carcinogenesis vol.9, no. 11, pp.2045-2052, 1988). Dr. Huff said that to their knowledge this was the first attempt to integrate these factors and evaluate their implications for the process of risk assessment. The evaluation was based on information obtained from 2-year studies involving 99 chemicals of which 53 gave a positive response for carcinogenicity in at least one experimental group. Conclusions drawn were that: (1) only seven of the 53 chemicals had target organ toxicity at all sites of carcinogenicity; (2) only three chemicals displayed carcinogenic effects at the top exposure with no supporting evidence of tumors at lower doses; (3) mutagenicity in Salmonella did not correlate with 'high dose only' carcinogenic effects; (4) the number of chemical carcinogens with some 'indirect (or secondary) mechanism' (toxicity) is small; (5) histopathology diagnoses are not fully adequate for justifying mechanistic assumptions; and (6) to differentiate chemicals into categories of carcinogenesis (e.g., 'primary and secondary') for purposes of risk assessment is premature.

II. Toxicity and Carcinogenicity Induced by Mutagens and Nonmutagens: Dr. Raymond Tennant, Experimental Carcinogenesis and Mutagenesis Branch, presented background on the evolving use of short-term genetic toxicology tests, most notably the Salmonella mutagenesis assay, for attempting to predict carcinogenicity of chemicals. He described the extensive body of work emanating from his laboratory, much in collaboration with Dr. John Ashby (Imperial Chemical Industries) that had defined the relationship between chemical structure ('structural alerts') and carcinogenicity/mutagenicity for a large number of chemicals in the NTP database. This led to the concept that knowledge about chemical structure combined with limited short-term genotoxicity and toxicity test results can be used to predict potential carcinogens and noncarcinogens. Dr. Tennant discussed a current paper using 44 chemicals for which toxicology and carcinogenesis studies by the NTP are currently in process that will enable evaluation of the concept. He opined that these studies should provide a way to challenge the relationship between carcinogenicity and subchronic and chronic toxicity.
Dr. Michael Elwell, Experimental Toxicology Branch, described a recent study that evaluated the possible relationship between toxicity and carcinogenicity for a group of 31 chemicals that had been subjected to subchronic and chronic exposure experiments in rodents by the NTP and for which the results had been peer reviewed. Of the 31, 22 were carcinogenic and nine were noncancerous. He noted that 87% of the 31 prechronic studies in rats showed toxicity while 70% of 27 studies in mice had toxicity; approximately one-third of the two-year studies were dosed at levels where toxicity was seen in the prechronic study. Dr. Elwell focused the rest of his presentation on the rat studies, reporting that 80% manifested chronic toxicity compared with 55% that had both chronic toxicity and carcinogenicity. He reviewed concordances or lack of concordances between toxicity (both chronic and subchronic) and carcinogenicity further broken down by target sites and mutagenicity or nonmutagenicity.

Dr. Maronpot then discussed the findings for the 27 of 31 chemicals which were studied in mice. Like in the rat, kidney and forestomach were common sites of toxicity. Ovary was a target site for both toxicity and carcinogenicity unique to mice in this study. Dr. Maronpot summarized and drew conclusions for the 31 chemical study: (1) there was some concordance between sites of subchronic toxicity and carcinogenicity; (2) however, there was more discordance than concordance overall; and (3) toxic lesions were generally proliferative and regenerative. The data presented indicate that proliferative responses were not always predictive of chemical carcinogenesis.

III. General Discussion: There was an extensive discussion among the Board members, staff and others around the issues discussed pertaining to relationships between cell proliferation and carcinogenesis, toxicity and carcinogenesis, and cell proliferation and toxicity. Among questions raised were: does the definition of "toxicity" imply the existence of a visible lesion, or should there be more subtle endpoints?; does cell proliferation always equate with toxicity?; and a specific suggestion was offered that the NTP consider routinely incorporating cell proliferation studies into the design of 90-day studies on chemicals.
Federal Register / Vol. 55, No. 191 / Tuesday, October 2, 1990 / Notices

National Institutes of Health

Consensus Development Conference On Diagnosis and Management of Asymptomatic Primary Hyperparathyroidism

Notice is hereby given of the NIH Consensus Development Conference on "Diagnosis and Management of Asymptomatic Primary Hyperparathyroidism" which will be held on October 29-31, 1990 in the Masur Auditorium of the National Institutes of Health, 8000 Rockville Pike, Bethesda, Maryland 20892. This conference is sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases and the NIH Office of Medical Applications Research.

Hyperparathyroidism is increasingly being recognized in asymptomatic patients as a result of widespread use of multiphasic screening tests that lead to detection of hypercalcemia. Because the disease is now known to be more common than previously appreciated, with two new cases occurring per thousand women over 60 years of age per year, primary care physicians as well as endocrinologists are increasingly interested in the correct diagnosis and proper management of patients with hyperparathyroidism.

Physicians are often uncertain about the management of patients with subtle or absent signs and symptoms and a clear biochemical diagnosis of hyperparathyroidism. Especially difficult are decisions about indications for surgery and how patients should be monitored to detect silent organ damage, particularly progressive bone loss. Data are now available on the natural history of asymptomatic hyperparathyroidism, but controversy exists about the interpretation of this information and its implications for patient management.

This conference will bring together endocrinologists, surgeons, radiologists, epidemiologists, health care providers and the public to examine issues related to the diagnosis and management of asymptomatic primary hyperparathyroidism.

Following a day and a half of presentations by experts and discussion by the audience, a Consensus Panel will weigh the scientific evidence and write a draft statement in response to the following questions:

- What is the most accurate, cost-effective method of diagnosing hyperparathyroidism?
- Are there patients with asymptomatic hyperparathyroidism who can safely be followed? Should they be?
- If not operated on, how should asymptomatic patients be monitored and managed?
- What are the indications for surgery in patients with asymptomatic hyperparathyroidism?
- What is the role of gland localization technology in management of patients with asymptomatic hyperparathyroidism?
- What research should be done to clarify issues in diagnosis and management of hyperparathyroidism?

On the third day of the conference, following deliberation of new findings or evidence that might have been presented during the meeting, the panel will present its final consensus statement.

Information on the program may be obtained from: Judy Corbett, Prospect Associates, 1821 Rockville Pike, Suite 500, Rockville, Maryland 20852, (301) 498-6555.

Dated September 24, 1990.

William Rash, Acting Director, NIT.

National Toxicology Program, Board of Scientific Counselors' Meetings

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 15 and 16, 1990.

The meeting will begin at 1:30 p.m. on October 15 and will be open to the public from 1:30 p.m. to 6 p.m. The preliminary agenda topics with approximate times are as follows:

1:30 p.m.-2:30 p.m.: Update on Activities of the Technical Reports Review Subcommittees

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

Symposium Report—Mouse Pulmonary Carcinogenesis

2:20 p.m.-3:20 p.m.—Review of Chemicals Nominated for NTP Studies. The nominations of five chemicals will be reviewed. The chemicals were evaluated by the NTP Chemical Evaluation Committee on September 12, 1990, and are (with CAS Nos. in parentheses): (1) Dichlorodiphenylsulfone (80-07-9); (2) Dicyclohexylamine (77-78-6); (3) Methylene Blue (61-73-4, 7220-79-3); (4) Phosphine (7903-51-2); and (5) Propylene Glycol T-Butyl Ether (57018-52-2).

3:45 p.m.-4:15 p.m.: Concept Reviews

A. Investigation of Molecular Mechanisms of Chemical Carcinogenesis in Mammalian Cell Systems

B. Immunotoxicity of Workplace Xenobiotics in Humans

C. Studies of Chemical Disposition in Mammals

4:15 p.m.-5 p.m.

NTP Quality Control and Quality Assurance Programs—Long-term Animal Studies

The meeting on October 15 will be open to the public from 8:30 a.m. until adjournment. The preliminary agenda topics with approximate times are as follows:

8:30 a.m.-8:45 a.m.: Report of the Director NTP

8:45 a.m.-11:30 a.m.: Program on Cell Proliferation in Liver and Foresomach Carcinogenesis

11:30 a.m.-12 Noon: Program on Toxicity and Carcinogenesis

1 p.m.-3:30 p.m.: Program on Toxicity and Carcinogenesis (cont'd.)

Public Comments—Persons wanting to make remarks from the floor during time allowed for public comments must notify the Executive Secretary by telephone or by mail no later than October 10, 1990, and provide a copy of any written remarks by October 12, 1990. Oral presentations should supplement written statements and will be restricted to five minutes.

The Executive Secretary, Dr. Larry C. Hart, National Toxicology Program, P.O. Box 12233, Research Triangle Park, North Carolina 27709, telephone (919) 541-3671, FTS 628-3671, will have available a roster of Board members and other program information prior to the meeting and summary minutes subsequent to the meeting.
National Toxicology Program, Availability of Technical Report on Toxicology and Carcinogenesis Studies of Benzofuran

The HHS' National Toxicology Program announces the availability of the NTP Technical Report on toxicity and carcinogenesis studies of benzofuran, used as an intermediate in the polymerization of coumarone-indene resins found in various corrosion-resistant coatings such as paints and varnishes, in water-resistant coatings, and in paper products and fabrics, and in adhesives approved for use in food contact.

Toxicology and carcinogenesis studies were conducted by administering to groups of 50 male rats 0.30, 0.60 mg/kg benzofuran in corn oil by gavage, 5 days per week for 103 weeks. Groups of 50 female rats were administered 0.60, or 120 mg/kg on the same schedule. Groups of 50 male mice were administered 0.30, or 120 mg/kg and groups of 50 female mice were administered 0.120, or 240 mg/kg on the same schedule.

Under the conditions of these 2-year gavage studies, there was no evidence of carcinogenic activity of benzofuran for male F344/N rats receiving doses of 30 or 60 mg/kg per day. There was some evidence of carcinogenic activity of benzofuran for female F344/N rats, based on increased incidences of tubular cell adenocarcinomas of the kidney. There was clear evidence of carcinogenic activity for male and female B6C3F1 mice, based on increased incidences of neoplasms of the liver, lung, and forestomach.

Exposure to benzofuran increased the severity of nephropathy in male rats, increased the incidences of nephropathy in female rats, and induced hepatocellular metaplasia in the pancreas in female rats. Nonneoplastic lesions observed in mice exposed to benzofuran included synchronous alteration of the liver, bronchiolar epithelial hyperplasia, and epithelial hyperplasia of the forestomach.

The study scientist for these studies is Dr. Richard Irwin. Questions or comments about this Technical Report should be directed to Dr. Irwin at P.O. Box 12233, Research Triangle Park, NC 27709 or telephone (919) 541-3340.

Copies of Toxicology and Carcinogenesis Studies of Benzofuran in F344/N Rats and B6C3F1 Mice (Gavage Studies) (TR 370) are available without charge from the NTP Public Information Office, MD B2-04, P.O. Box 12233, Research Triangle Park, NC 27709.

Dated: September 28, 1990
David P. Rall, M.D., Ph.D.
Director, National Toxicology Program
### AGENDA

**BOARD OF SCIENTIFIC COUNSELORS**

**NATIONAL TOXICOLOGY PROGRAM**

October 15-16, 1990

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

**Monday, October 15, 1990**

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<td>1:30 p.m.</td>
<td>Welcome, Introduction of New Board Members and Announcements</td>
<td>Dr. A. Upton, Board&lt;br&gt;Dr. L. Hart, NIEHS</td>
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<td>1:35 p.m.</td>
<td>Committee and Other Reports</td>
<td>Drs. J. Goodman, E. Silbergeid, Dr. S. Eustis, NIEHS</td>
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<td>(2) Reproductive and Developmental Toxicology Program Review Subcommittee</td>
<td>Dr. R. Miller Board&lt;br&gt;Dr. B. Schwetz, NIEHS</td>
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<td>(3) Conference on Mouse Lung Tumors</td>
<td>Dr. D. Dixon, NIEHS</td>
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<tr>
<td>2:20 p.m.</td>
<td>Review of Chemicals Nominated for NTP Studies</td>
<td>Board&lt;br&gt;Dr. V. Fung, NIEHS</td>
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<tr>
<td>3:20 p.m.</td>
<td>Break</td>
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<tr>
<td>3:45 p.m.</td>
<td>Concept Reviews, Division of Toxicology, Research and Testing Procedures and Principles</td>
<td>Dr. R. Griesemer, NIEHS&lt;br&gt;Mr. W. Johnston, NIEHS</td>
</tr>
<tr>
<td></td>
<td>I. Investigation of Molecular Mechanisms of Chemical Carcinogenesis in Mammalian Cell Systems</td>
<td>Dr. J. Spalding, NIEHS</td>
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<td></td>
<td>II. Immunotoxicity of Workplace Xenobiotics in Humans</td>
<td>Dr. V. Sanders, NIEHS</td>
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<tr>
<td></td>
<td>III. Studies of Chemical Disposition in Mammals</td>
<td>Dr. B. Ghanayem, NIEHS</td>
</tr>
</tbody>
</table>
4:15 p.m. - 4:30 p.m. NTP Quality Control Program -- Long-Term Animal Studies
Dr. G. Boorman, NIEHS

4:30 p.m. - 5:00 p.m. NTP Quality Assurance Program -- Long-Term Animal Studies
Dr. D. Bristol, NIEHS

Tuesday, October 16, 1990

8:30 a.m. - 8:45 a.m. Director's Report
Dr. D. Hoel, NIEHS

Program on Cell Proliferation in Liver and Forestomach Carcinogenesis

8:45 a.m. - 9:10 a.m. Introduction
Dr. R. Maronpot, NIEHS

9:10 a.m. - 9:30 a.m. Diaminotoluenes, Nitropropanes, Mirex
Dr. M. Cunningham, NIEHS

9:30 a.m. - 10:00 a.m. Ethyl Acrylate, Acrylic Acid
Dr. B. Ghanayem, NIEHS

10:00 a.m. - 10:30 a.m. Break

10:30 a.m. - 10:50 a.m. Methylene Chloride
Dr. R. Maronpot, NIEHS

10:50 a.m. - 11:10 a.m. Overview of Cell Proliferation in Liver Carcinogenesis: Division of Biometry and Risk Assessment Plans
Dr. R. Melnick, NIEHS

11:10 a.m. - 11:30 a.m. General Discussion

Program on Toxicity and Carcinogenesis

11:30 a.m. - 12:00 Noon Introduction
Drs. J. Huff, R. Tennant, and J. Spalding, NIEHS

12:00 Noon - 1:00 p.m. Lunch

1:00 p.m. - 3:00 p.m. Evaluation of Associations for 31 Substances
Drs. R. Maronpot, M. Elwell, R. Tennant, J. Spalding, and R. Griesemer, NIEHS

3:00 p.m. - 3:30 p.m. Break

3:30 p.m. - 4:30 p.m. General Discussion

Adjourn
Dr. Paul T. Bailey (3/94)  
Mobil Oil Corporation  
Toxicology Division  
P. O. Box 1029  
Princeton, New Jersey 08543-1029  
(Toxicology)

Dr. Jay I. Goodman (3/92)  
Professor  
Department of Pharmacology and Toxicology  
Michigan State University  
East Lansing, Michigan 48824  
(Toxicology)

Dr. John B. Little (3/91)  
Professor  
Department of Cancer Biology  
Harvard School of Public Health  
Boston, Massachusetts 02115  
(Experimental Carcinogenesis)

Dr. Lawrence A. Loeb (3/94)  
Professor and Director  
Gottstein Memorial Laboratory and Department of Pathology SM-30  
University of Washington D-525 HSB  
Seattle, WA 98195  
(Carcinogenesis)

Dr. Daniel S. Longnecker (3/93)  
Professor  
Department of Pathology  
Dartmouth Medical School  
Hanover, New Hampshire 03756  
(Experimental Pathology)

Dr. Richard K. Miller (3/92)  
Department of Obstetrics, Gynecology Box 668  
University of Rochester  
601 Elmwood Avenue  
Rochester, New York 14642  
(Reproductive & Developmental Toxicology)

Dr. Ellen K. Silbergeld (3/93)  
University of Maryland Medical School  
Howard Hall - 544  
660 West Redwood Street  
Baltimore, Maryland 21201  
(Developmental Neuroscience)

Dr. Arthur C. Upton, (Chairperson)  
Director, Institute of Environmental Medicine  
New York University Medical School  
550 First Avenue  
New York, New York 10016  
(Experimental Carcinogenesis)
### SUMMARY DATA ON CHEMICALS FOR REVIEW BY BOARD OF SCIENTIFIC COUNSELORS ON OCTOBER 15, 1990

<table>
<thead>
<tr>
<th>Chemical (CAS Number)</th>
<th>Nomination Source</th>
<th>Domestic Production (lbs)</th>
<th>Estimated Worker Exposure*</th>
<th>NTP Testing Status</th>
<th>NTP Chemical Evaluation Committee Recommendations (Priority)</th>
<th>NTP Chemical Selection Principles</th>
<th>Rationale/Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. p,p'-Dichlorodiphenylsulphone (80-07-9)</td>
<td>NCI</td>
<td>- No production volume found*</td>
<td>--</td>
<td>--</td>
<td>- Subchronic studies - Mutagenicity (High)</td>
<td>3,8</td>
<td>- High production - Potential for increased use - Lack of toxicological data - Lack of information on residues (if any) of the chemical in polymeric products and whether the monomer is released from the polymers at high temperatures - ITC will recommend chemical to EPA for physical/chemical testing by industry</td>
</tr>
<tr>
<td>2. Dicyclopentadiene (77-73-6)</td>
<td>NCI</td>
<td>5.3x10^6 to 282x10^6 (1977)* 130x10^6 (1988)*</td>
<td>1,122</td>
<td>- Negative in Salmoella</td>
<td>- Carcinogenicity - Reproductive and teratogenicity studies (Moderate)</td>
<td>3,8</td>
<td>- High and increasing production and use - Found in ground water and surface water - Potential for exposure - Lack of toxicological data</td>
</tr>
<tr>
<td>Chemical (CAS Number)</td>
<td>Nomination Source</td>
<td>Domestic Production (lbs)</td>
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<tr>
<td>3. Methylene Blue (61-73-4; 7720-79-3)</td>
<td>NCI</td>
<td>1.2X10^4 to 1.2X10^5 (1977)^o</td>
<td>69,563</td>
<td>--</td>
<td>- Carcinogenicity - Reproductive and teratogenicity studies - Determine whether neurotoxicity studies are needed (High)</td>
<td>3,4,6</td>
<td>- Widespread uses - Some medical and veterinary applications of the chemical have not been approved by FDA - Potential for exposure - Lack of carcinogenicity data</td>
</tr>
</tbody>
</table>
### SUMMARY DATA TABLE (CONT'D)

<table>
<thead>
<tr>
<th>Chemical (CAS Number)</th>
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<th>Domestic Production (lbs)</th>
<th>Estimated Worker Exposure*</th>
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<th>NTP Chemical Selection Principles</th>
<th>Rationale/Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. Phosphine (7803-51-2)</td>
<td>NCI</td>
<td>1.0x10^4 to 1.1x10^7 (1977)^o</td>
<td>9,234</td>
<td>--</td>
<td>No testing</td>
<td>--</td>
<td>-Chemical is highly reactive and readily decomposes to toxic products even under high vacuum; thus, it is not clear if human exposure is to phosphine or its decomposition products -Generation of pure test material will be difficult -Some human data are available -Chromosomal aberrations observed in fumigant applicators exposed to phosphine and other fumigants -NCI epidemiological study of grain workers indicated an increased incidence of non-Hodgkin's lymphoma, and suggestions of leukemia and pancreatic cancer. Workers were exposed to phosphine and a mixture of carbon disulfide and carbon tetrachloride -NCI and EPA are now jointly designing a five year prospective study of 150,000 workers in the grain handling industry. Phosphine will be one of the few compounds which will be spotlighted in this study.</td>
</tr>
<tr>
<td>Chemical (CAS Number)</td>
<td>Nomination Source</td>
<td>Domestic Production (lbs)</td>
<td>Estimated Worker Exposure*</td>
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<tr>
<td>5. Propylene glycol t-butyl ether (57018-52-7)</td>
<td>CPSC</td>
<td>No production data found</td>
<td>--</td>
<td>--</td>
<td>-Carcino-genicity</td>
<td>2,3,8</td>
<td>-Widely used solvent -Replacement for ethylene glycol monoalkyl ethers, which cause reproductive and teratogenic effects in animals -Potential for both worker and consumer exposure -Lack of toxicological data -Dermal route of exposure is more important than inhalational route</td>
</tr>
</tbody>
</table>
Footnotes for Table


b) p,p'-Dichlorodiphenylsulfone is used in the production of engineering plastics. 1,491,228,000 pounds of these plastic products were produced in 1988.

c) U.S. Environmental Protection Agency TSCA Inventory, public file, Washington, D.C.


e) Production volume of cyclopentadiene is included in this figure.
<table>
<thead>
<tr>
<th>Chemical (CAS Number)</th>
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<th>Rationale/Remarks</th>
</tr>
</thead>
</table>
| p,p'-Dichlorodiphenyl sulfone (80-07-9) | NCI | Defer | -High production  
-Although the chemical is used in a closed system in the manufacture of polymers and other products, there is the possibility for sudden massive release of the chemical  
-It is difficult to evaluate the potential for human exposure because there is a lack of information on the amount (if any) of monomeric residues in polymeric products, and whether the chemical is released from these products  
-Deferred in order to ascertain whether the Organization for Economic Cooperation and Development has information on chemical properties and toxicity studies |
| Dicyclopentadiene (77-73-6) | NCI | -Carcinogenicity  
-Reproductive and teratogenicity studies (Moderate) | -High and increasing production and use  
-Identified in ground water and surface water  
-Potential for exposure  
-Need to fill toxicological data gaps  
-Previous chronic, reproductive and teratogenicity studies used mammals not usually used for risk evaluation for human health |
<table>
<thead>
<tr>
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<tr>
<td>3. Methylene Blue (61-73-4; 7720-79-3)</td>
<td>NCI</td>
<td>-Carcinogenicity (High) -Reproductive studies (Moderate)</td>
<td>-Widely used compound -Potential for exposure -Lack of carcinogenicity data -Previous neurotoxicity studies are sufficient</td>
</tr>
<tr>
<td>4. Phosphine (7803-51-2)</td>
<td>NCI</td>
<td>No testing</td>
<td>-Phosphine is unstable and decomposes readily; exact nature of decomposition products to which humans are exposed is not known -Generation of pure test material would be difficult in animal studies -NCI and EPA are collaborating on an epidemiological study of workers in the grain handling industry which will examine the issue of phosphine toxicity</td>
</tr>
<tr>
<td>Chemical (CAS Number)</td>
<td>Nomination Source</td>
<td>Testing Recommendations (Priority)</td>
<td>Rationale/Remarks</td>
</tr>
<tr>
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<td>-------------------</td>
</tr>
<tr>
<td>5. Propylene glycol t-butyl ether (57018-52-7)</td>
<td>CPSC</td>
<td>-Carcinogenicity -Chemical disposition by dermal and oral routes (High) -Reproductive studies (High if no information is found on testicular effects in previous subchronic rat studies; moderate if such data are available)</td>
<td>-Widely used solvent -Replacement for ethylene glycol monoalkyl ethers, which cause reproductive and teratogenic effects in animals -Potential for human exposure -Lack of carcinogenicity data -Good model for analysis of structure-activity relationships of glycol chemical class -Review available prechronic rat studies to ascertain whether histopathology indicated testicular effects -Adequate teratogenicity data are available -Perform chemical disposition studies prior to other toxicology studies</td>
</tr>
</tbody>
</table>
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. Twenty-two 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: Investigation of Molecular Mechanisms of Chemical Carcinogenesis and Evaluation of Chemicals in Mammalian Cell Systems

PROJECT OFFICERS: Judson W. Spalding (919) 541-7936
Raymond W. Tennant (919) 541-4141

OBJECTIVE: Mammalian cell transformation systems are the in vitro models that most closely resemble the multistage process of tumorigenesis in vivo. The objectives of this proposal are (1) to utilize these models to create and characterize the properties of different phenotypes that represent discrete stages in the process of malignancy, (2) to use these phenotypes as targets to evaluate the effects of selected genotoxic and nongenotoxic carcinogens identified in the NTP toxicology and carcinogenesis studies program, and (3) to further the development of the mammalian cell model to characterize the biological properties of chemicals with emphasis on discriminating between nongenotoxic carcinogens and noncarcinogens.

CONCEPT STATEMENT: Cultured cells can be transfected with cellular protooncogenes and activated oncogenes to create different phenotypes. In NTP supported studies, human fibroblasts have been transfected with both normally expressed and over-expressed activated ras-oncogenes and the resulting phenotypes are being characterized. Other distinct phenotypes have been derived from the parent human fibroblast line as a result of spontaneous events or chemical treatment. After confirmation of the presence and expression of the transfected oncogenes, the phenotypes are characterized according to such criteria as growth factor requirements, anchorage independent clonal growth in soft agar, and benign or malignant expression in a thymic mice. While the characterization of these different phenotypes has just begun, already there is evidence that some of the phenotypes represent discrete and separate stages in the spectrum of the normal to malignant stages in tumorigenesis. The nonmalignant phenotypes offer unique and important targets for assessing chemically induced lesions in both the normal cellular protooncogenes and the transfected oncogenes. It is of special interest to determine the specific molecular effects of selected genotoxic and nongenotoxic carcinogens identified in the NTP toxicology and carcinogenesis studies program. The nongenotoxic carcinogens which comprise over 30% of the NTP rodent carcinogens are an especially important group because our understanding at the molecular level of how they may induce tumors is very speculative.

The resources of another contract already in place provide the capability to create a variety of specific retroviral vectors that carry different cellular protooncogenes or activated oncogenes. These vectors can be used to create other unique phenotypes in the human fibroblast cell system. In addition cell cultures derived from different tissues of transgenic mice that carry specific protooncogenes or activated oncogenes can provide another source of unique phenotypic targets for characterizing chemical effects.
In another NTP supported study, over 150 chemicals have been evaluated for cytotoxicity and activity in the Balb/c 3T3 mouse fibroblast transformation assay. Most of the chemicals were selected from the NTP bioassay program and tested under code. A standard cytotoxicity assay was developed that accurately measures survival and estimation of an LD-50 value under conditions of the transformation assay. This also permits the ranking of all of the chemicals in the data base according to their relative toxicity. It was discovered that the transformation assay did not have the power to discriminate between carcinogens and noncarcinogens if the LD-50 concentration exceeded 5.0 mM. This is an important finding because for the first time, a clearly defined effective concentration range has been described for a short-term genotoxicity test that defines the limitations of the power of the assay. The new modified Balb/c 3T3 transformation assay has a high sensitivity for identifying genotoxic carcinogens. Furthermore, the activity of these carcinogens which represented a diversity of chemical classes was detected in the ABSENCE of an exogenous metabolic activation system. The assay has also exhibited the ability to detect cytotoxic nongenotoxic carcinogens. Another important accomplishment is that the conversion of induced transformation frequencies to t-statistic values, permits all of the chemicals in the data base to be rank-ordered according to relative potency.

Several other and different protocols have been developed using Balb/c 3T3 cells which detect chemicals characterized as having promoter activity, but to date only a few chemicals have been evaluated in these assays. In a collaborative effort, this Balb/c 3T3 transformation data base is currently undergoing structure activity analysis in the CASE program. An important preliminary finding is that the molecular descriptors that define activity in the transformation assay are different than the descriptors that define the activity of these same chemicals in the Salmonella mutagenicity assay. This structure activity analysis exercise is very important because it provides the opportunity to evaluate the power of structure activity analysis to correctly predict the activity of a new chemical-set and validate that prediction for cytotoxicity and transformation in the Balb/c 3T3 assay.

It is proposed to continue to create and characterize different oncogene derived phenotypes and examine the ability of representative chemicals to induce a specific phenotype to acquire the characteristics of a “next stage” in progression toward malignancy. It is important and timely to continue these studies in order to gain a better understanding of some of the molecular mechanisms associated with chemical-oncogene interactions in carcinogenesis. The Balb/c 3T3 cell transformation system has the potential for detecting and discriminating between some classes of nongenotoxic carcinogens and noncarcinogens. It is important to continue chemical evaluation in this system and develop a larger data base of nonmutagenic carcinogens especially in those other protocols that characterize the properties of promoter activity.
CONTRACT TITLE: Immunotoxicity of Workplace Xenobiotics in Humans

PROJECT OFFICERS: Virginia M. Sanders, Ph.D. (919) 541-0165
Michael I. Luster, Ph.D. (919) 541-4188

OBJECTIVE: The objective of the proposed project is to establish an immunological database for humans exposed to workplace xenobiotics.

CONCEPT STATEMENT: An extensive database has been established on the effect of xenobiotics on the non-human immune system. Although a number of xenobiotics have been shown to induce immunotoxicity in rodents, the relationship of these findings to humans has not been determined. For this reason, we propose to establish a coordinated effort between NIEHS and NIOSH to both validate a battery of immunological tests designed to assess human immune function and apply these tests to selected human populations exposed to workplace xenobiotics suspected of being immunotoxic.

The goals of this coordinated effort shall be the following: 1) To determine if a correlation exists between rodent and human immunotoxicity data so that rodent data can be used confidently for human risk assessment; 2) To determine if specific immune parameters are altered by xenobiotic exposure so that they can be utilized as biomarkers of exposure; and 3) To determine if xenobiotic-exposed populations with altered immune function have a higher probability of developing states of suppressed host resistance and/or clinical disease.

Biological samples from exposed individuals shall be obtained by NIOSH epidemiologists and physicians who will identify suitable populations for study. The choice of human populations for study shall be guided by immunotoxicological results already validated in rodents. Immunotoxicological expertise shall be coordinated between NIEHS and NIOSH in order to establish, validate and apply a battery of immunological tests which shall assess the function of the major human immune cell types involved in the maintenance of immune homeostasis. These cell types include T and B lymphocytes, macrophages, and natural killer cells.
CONTRACT TITLE: Studies of Chemical Disposition in Mammals

PROJECT OFFICER: Burhan Ghanayem, Ph.D.

ALTERNATE PROJECT OFFICER: Leo T. Burka, Ph.D.

OBJECTIVE: To provide for studies of chemical disposition in laboratory animals, primarily rats and mice.

CONCEPT STATEMENT: Determination of the fate of a chemical in a test species is integral to the toxicological characterization of the respective chemical and is fundamental to an accurate extrapolation of toxicity data from laboratory animals to predict risks to humans. Therefore, an integral part of the ETB evaluation of research needs to characterize the toxicity of chemicals nominated to the NTP is to determine the need for studies of the metabolism and disposition and toxicokinetics of respective chemicals. When appropriate data is not available in the literature, studies are designed to determine such factors as rate and degree of absorption, metabolism and the likely involvement of reactive metabolites and the potential for bioaccumulation. These studies also determine the impact of such factors as dose and route of exposure, as well as species, sex, and age of the test animal on the toxicity and metabolism of chemicals.

APPROACH: Studies are conducted both prospectively to provide data to support the design of subchronic and chronic studies and retrospectively to address questions raised by results of completed studies. Selections of candidate chemicals are primarily based upon the chemicals nominated to the program for toxicity and carcinogenicity studies. Since each chemical is different and the data required varies from study to study, no standard protocol is used, only a general protocol is provided to guide investigators in the design of the most appropriate studies. Progress on each project conducted is followed through regular phone conversations between the Project Officer and the Principal Investigator and finalized in detailed written preliminary and final reports which are made available to all interested parties upon request.

PROPOSED CHANGES TO THE CURRENT STATEMENT OF WORK: The work to be performed during the next five years is expected to be essentially the same as in the preceding period.
LIST OF CONCEPTS APPROVED BY
NTP BOARD OF SCIENTIFIC COUNSELORS

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
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