

**SUMMARY MINUTES  
NATIONAL TOXICOLOGY PROGRAM  
BOARD OF SCIENTIFIC COUNSELORS' MEETING**

*October 18, 1994*

The National Toxicology Program (NTP) Board of Scientific Counselors (the Board) met on October 18, 1994, 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. Curtis Klaassen (Chairman), Arnold Brown, Elaine Faustman, David Hoel, Claude Hughes, Fumio Matsumura, Franklin Mirer, Kenneth Reuhl, and Peter Working. All members were present except Dr. Working.

I. Report of the Director, Environmental Toxicology Program (ETP), NIEHS: Dr. George Lucier, Director, ETP, gave an overview of current and evolving NTP initiatives, most of which are described in the draft FY 1995 NTP *Annual Plan* which had been sent to the Board prior to the meeting and was to be discussed later in the morning. These included:

— Chemical Nomination and Selection: emphasis given to selecting chemicals for which there is significant human exposure and chemicals which will enable us to test hypotheses, e.g., role of cell proliferation in carcinogenesis.

— Chronic Bioassay Studies: there is a Congressional mandate to increase study starts while incorporating more mechanistic considerations with level budget requiring more efficiency in study conduct.

— Priority Setting for Chronic Bioassays: discussed need to use existing extensive toxicology data bases along with mechanistic findings in setting priorities.

— Dose Selection: Dr. Lucier reported on a workshop cosponsored by the NIEHS on "NTP Studies: Principles of Dose Selection and Applications to Mechanism-Based Risk Assessment" to be held at the 1995 Society of Toxicology Annual Meeting.

— Risk Assessment Research: Dr. Lucier reported on a workshop titled "Mechanism-Based Toxicology in Cancer Risk Assessment: Implications for Research, Regulation and Legislation" to be held in Chapel Hill, North Carolina, on January 11-13, 1995. A series of plenary lectures will precede breakout into five workgroups that will develop recommendations and identify areas of consensus, disagreement, and knowledge gaps, and ways to address those gaps. Each workgroup will have co-chairs, to allow expertise in regulatory issues and the science.

— Alternative/Complementary Models: the NIH Revitalization Act of 1993 reinforces NTP activity in development and validation of alternative methods.

— NTP Grants: RFAs in developmental gene expression where grants have already been awarded and in mechanistically-based alternative methods in toxicology in process complement more applied studies conducted through contracts and interagency agreements.

— *Biennial Report on Carcinogens*: NTP seeks to broaden public input while strengthening the scientific basis for listing in the BRC, and will ask the Board to assist initially in a review of the criteria for listing.

— Communications: are attempting to enhance the dialogue between the Program and the public, and establishment of an NTP Liaison Office will help.

II. Report of the Director, NTP: Dr. Kenneth Olden, Director, NTP and NIEHS, commented on the recent announcement that NIEHS scientists in the Environmental Carcinogenesis Program (ECP) were co-discoverers of the breast cancer gene (BRAC1)

and on the awarding of the Nobel prize for physiology or medicine to NIEHS Scientist Emeritus, Dr. Martin Rodbell. In discussing ways to better pay senior scientists, Dr. Olden noted passage of a bill that should help in recruiting and retaining outstanding scientists. He announced the upcoming departure of Dr. John McLachlan, Scientific Director, to take a position at Tulane University, and appointment of Dr. J. Carl Barrett, Director, ECP, as Acting Scientific Director.

Dr. Olden briefly reviewed the proposed role of the Board in the review of the criteria for inclusion of substances in the *Biennial Report on Carcinogens* (BRC) as approved by the Assistant Secretary for Health, Dr. Philip Lee. An *ad hoc* working group of about 40 persons will meet for two days in January in Washington, D.C., to review and make recommendations about the criteria. Besides Board members, the working group will include representatives from the NTP Executive Committee member agencies, from State health departments, environmental and public interest groups, labor, industry, academia, and the lay public. The report of the working group will be reviewed by the Board in February. The criteria and the Board's recommendations will then be reviewed in March by an NIEHS review group, in April by the NTP Executive Committee's Working Group on the BRC as well as by the PHS' Environmental Health Policy Committee chaired by Dr. Lee. After Executive Committee review, their recommendations will be given to the NTP Director, who will submit them to the Secretary, DHHS. Discussion: Dr. Mirer expressed concern that publication of the 8th and even 9th editions might be delayed due to this review process. Dr. Olden said this would not be the case, noting that the 7th had only recently been published.

III. Update on Activities of the Technical Reports Review Subcommittee: Dr. Michael Elwell, NIEHS, reported that the Subcommittee had met on June 21, 1994, and had reviewed five more-or-less standard two-year studies along with a comparative initiation-promotion study with three mouse strains. On November 29, the Subcommittee will review six long-term studies as well as a short-term toxicity study of 1-nitropyrene that is the first NTP short-term report where the conclusion was drawn that the chemical is a likely carcinogen in the absence of neoplasms in an NTP study. The Board was given a printout detailing the conclusions for the draft Reports peer reviewed in June, and summary information for the Reports to be reviewed in November.

IV. NTP Grants - Developmental Gene Expression RFA Progress Report and Alternative Methods RFA Preliminary Report: Dr. Jerrold Heindel, Division of Extramural Research and Training, NIEHS, updated the Board on the status of the first NTP-sponsored RFA on "Toxic Substance Effects on Developmental Gene Expression" which had resulted in 33 applications. Following approval by the National Advisory Environmental Health Sciences Council, six grants were awarded — all to investigators new to NIEHS funding and encompassing broad subject areas, including apoptosis, dioxins, neurotoxins, environmental estrogens, *hox* genes, and *pax* genes. Dr. Heindel moved on to a new RFA, issued October 7, on "Mechanistically-Based Alternative Methods in Toxicology" which derived in part from the mandates of the 1993 NIH Revitalization Act as well as from the slow progress and general need for good methods and models in this area. The allocation of \$1.5 million should fund eight to ten grants. Research objectives are to develop mechanistically-based models and methods in reproductive/developmental toxicology, carcinogenesis and neurotoxicity and using genetically engineered cell lines, transgenic animals, nonmammalian models, improved species extrapolation, computer-based systems, and ways to enhance well-being or reduce numbers of test animals. A further objective is to prevalidate model/method with emphasis on extrapolation of results to humans. Dr.

Heindel concluded by describing a new initiative, pegged to be available in 1996, called the RO3 grant, funded at \$50,000/year for two years, and intended to help newer investigators with hypothesis development leading the way to the more traditional RO1 grants. By dovetailing an RFA with NTP announcements of chemicals and endpoints to be studied, successful applicants could have access to animals and tissues and the NTP could benefit indirectly from the use of these animals and tissues in more mechanistically-based studies.

V. Alternative Methods - Status and Plans - Interagency Committee on Validation of Alternative Methods: Dr. William Stokes, NIEHS, briefly reviewed the directives of Section 1301 of the NIH Revitalization Act of 1993 (Public Law No. 103-43) including establishment of the Applied Toxicological Research and Testing Program within the NIEHS. Among the mandated activities was one 'to establish criteria for the validation and regulatory acceptance of alternative testing and to recommend a process through which scientifically validated alternative methods can be accepted for regulatory use.' The NIEHS considered it essential that staff from Federal agencies that generate or use toxicity testing data participate in development of these criteria and recommendations, and thus, established an *ad hoc* Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). Twelve other Federal regulatory and research agencies were invited and have agreed to participate, being the Agency for Toxic Substances and Disease Registry, Consumer Product Safety Commission, Environmental Protection Agency, Food and Drug Administration, National Cancer Institute, National Institute for Occupational Safety and Health, Occupational Safety and Health Administration, and the Departments of Agriculture, Defense, Energy, Interior, and Transportation. Additionally, input was to be sought from non-government sources including industry, academia, public interest groups, and the international community. The first meeting was held September 22 and the second meeting will be October 21.

The goals of ICCVAM are to establish uniform processes and consistent criteria within the Federal government that will: 1) encourage development of improved testing methods that will generate data more useful for risk assessment; 2) lead to scientific evaluation/validation of new and revised test methods; 3) increase likelihood of acceptance of scientifically valid new and revised test methods; and 4) encourage refinement and reduction of animal use in testing, and replacement of animals with non-animal methods and/or phylogenetically lower species, when scientifically feasible. Dr. Stokes outlined the draft implementation plan leading to an ICCVAM report Discussion: Dr. Mirer offered two suggestions, one being to evaluate the systems with chemicals for which there are bioassay, and if possible, epidemiological data, and secondly to test agents of cross-media importance. Dr. Reuhl cautioned that mechanistic or molecular studies be relevant to humans. Dr. William Allaben, FDA/NCTR, reported that the FDA Science Council was holding an open meeting on Friday (October 21) in Bethesda to discuss how to incorporate alternative test systems into the regulatory arena.

VI. Biennial Report on Carcinogens (BRC) and Role of the Board - Update: Dr. C. W. Jameson, NIEHS, commented that he would be reiterating some points made earlier by Dr. Olden as well as providing additional background information, emphasizing the importance that the Program placed on the BRC review process. He reviewed the historical context for the BRC (formerly *Annual Report on Carcinogens* or ARC), the degrees of evidence required for inclusion of substances in the BRC, and the current review process used. Dr. Jameson reminded the Board that an in-house NIEHS committee chaired by Dr. Barrett had examined the current process and framed the issues leading to defining three overall objectives for possible revisions in the process, being: 1) a need to broaden the input at all

stages of the process; 2) a need to broaden the scope of scientific review; and 3) provision for a review of the criteria used for inclusion of substances in the BRC. This led to approval by the Board at their meeting on April 6 of a resolution agreeing to involvement through creation of a new subcommittee to review the BRC, including convening of an *ad hoc* working group to review the criteria for listing. Dr. Jameson reported that there had been subsequent review and discussion by the NTP Executive Committee on May 24, by the Committee's Working Group for the BRC on July 29, and by the PHS Environmental Health Policy Committee on October 13. He briefly discussed the proposed chemical nomination review process noting that the review of nominations by the new Board subcommittee would follow review by the Executive Committee Working Group and prior to final review by the Executive Committee. Dr. Jameson then outlined the timetable for the criteria review process as follows:

- mid-January 1995 - a two-day public meeting in Washington, D.C., of an *ad hoc* working group of the Board to review and make recommendations on the criteria;
- mid-February - a public meeting of the Board to review the report of the working group and make recommendations to the NTP;
- March 1995 - NIEHS Review Group meeting to review criteria and NTP Board recommendations;
- April 1995 - NTP Executive Committee Working Group for the BRC meeting to review criteria and NTP Board recommendations;
- April 20, 1995 - PHS' Environmental Health Policy Committee meeting to review criteria recommendations;
- May 1995 - NTP Executive Committee meeting to review criteria recommendations; and
- June 1995 - Submission of final report by the Director, NTP, to the Secretary, DHHS.

Dr. Jameson asked that the Board comment and make recommendations on the criteria review process he had outlined and by November 1 submit to him nominations for the *ad hoc* working group, noting that we were looking for a balance of participants to include members from academia, industry, labor, public interest groups, and government. (ED NOTE: The deadline for receiving nominations was extended to November 14. The meeting of the *ad hoc* working group will be held on January 25 and 26.)

Discussion: Dr. Brown urged that some of these review steps go on simultaneously. Dr. Lucier said the process was already 'fast track,' and Dr. Jameson noted that each group in the review process finds it most useful to have access to a previous group's recommendations. Dr. Brown wondered whether congressional action would be required to make any changes in the criteria effective. Dr. Jameson said he didn't know but we will be consulting with the NIH legal counsel's office about such matters. Dr. Hoel raised the possibility of having to review all the previous entries in the ARCs should there be significant changes in the criteria. Dr. Mirer asked what would be provided to the working group, and opined that it would be desirable for the NTP to provide a document that members could react to. Dr. Jameson said that comments and suggestions about changing the criteria would be provided along with current NTP thinking. Dr. Mirer thought the soft spot in the process remained the epidemiological data and its interpretation. Dr. Allaben asked about the format and length of the January meeting, and hoped that the working group would discuss what constitutes an adequate cancer bioassay. Dr. Lucier said that two days would be needed, adequate background material would be provided, and he hoped that the meeting would identify not only areas of consensus but also areas where consensus did not exist. Dr. Olden commented that our approach would be similar to that used in the Board's Advisory Review of April 1992 in that we would present the group

issues but would not limit the discussion to just those issues. Dr. Harold Zenick, EPA, pointed out that there is a need to have consistency in cancer risk assessment guideline, e.g., in evaluating "weight of the evidence" considerations. Dr. Lucier agreed.

VII. NTP FY 1995 Research and Testing Plans: Dr. John Bucher, NIEHS, stated that this was the second year that the NTP had brought its annual plans early in the Fiscal Year for comment and said that comments both on specific research items and overall direction would be welcomed. Two changes of note since FY 1994 were in the way we group projects and the philosophy behind that, and in the House Appropriations Committee directives that there be increases in chronic study starts. He read the wording: "The Committee is concerned by the reduced number of carcinogenicity test starts for long term chronic diseases ... the Committee urges that substantially more than 15 new chemicals, or substances, or combination of substances, studies be started in 1995 for identifying potential carcinogenicity using the current standard NTP experimental two-year design protocol." **carcinogenesis** — Because of the numbers of people needed to manage chronic studies and the costs, this represents a considerable challenge to the Program. He noted the 22 chemicals or combinations planned for two-year study contract awards in FY 1995. Dr. Bucher discussed three complementary assay systems under development or in use that related to identification of carcinogens or mechanisms of carcinogenesis: transgenic mouse models, screens for genetic alterations in the NTP bioassay, and cellular proliferation studies. He mentioned several ongoing projects of note: inhalation carcinogenesis studies of three nickel salts; toxicity and carcinogenicity studies of fumonisin B<sub>1</sub> at NCTR; carcinogenesis studies of silica at NIOSH; a multiagency study of potential carcinogenicity and toxicity of electromagnetic fields; a peroxisome proliferators class study; effects of diet restriction on sensitivity of the bioassay; and induction of transformation in SHE cells by nongenotoxic carcinogens. Discussion: Dr. Brown asked if NIEHS plays a role in design of NCTR or NIOSH studies listed. Dr. Bucher said he along with scientists from other agencies served on the design committee for NCTR studies under the current interagency agreement. Dr. Reuhl commented as to funding if NTP has to effect 10-15 starts yearly. Dr. Lucier responded that the problem lies in the out-year costs and that at current budget levels up to 10 starts yearly might be feasible, while maintaining our emphasis on mechanistic and other kinds of studies, such as those evaluating alternative systems. A problem lies in gaining acceptance by the regulatory agencies, indicating a need to work through regulatory and scientific issues in parallel. Dr. Hoel inquired as to what gain was expected from studies on tamoxifen. Dr. Lucier said a good study of the agonist actions of tamoxifen and reported beneficial effects as in osteoporosis may be helpful in dealing with public health issues. Dr. Mirer thought the projected chemical starts lacked chemicals of importance in the workplace. Dr. Bucher disagreed and cited a number with large potential occupational exposures.

**Genetic Toxicology** — Dr. Bucher reported that there was a continuing deemphasis on routinely looking at large numbers of chemicals in a variety of *in vitro* genetic toxicology tests while integrating the *Salmonella* assay and *in vivo* cytogenetics assays within the short-term testing program. There are ongoing retrospective evaluations regarding the relationship of potency in genotoxicity assays to carcinogenicity. He noted workplace mutagen monitoring studies at NIOSH and continuing development of hepatocyte DNA repair/unscheduled DNA synthesis assays using flow cytometry at NCTR. **Toxicology** — Dr. Bucher pointed out several agent specific studies including those on allyl acetate and metabolites, chloral hydrate, methylene blue trihydrate, several photovoltaic and semiconductor chemicals, and 2-butoxyethanol. He briefly described methods development activities, among them being DNA-adduct measurement using capillary electrophoresis,

evaluation of the utility of expired breath analysis for cytochrome P450 phenotyping, and analysis of gene expression in human tissues following dioxin exposure at "environmental" concentrations. **Systems Toxicology** — Dr. Bucher commented on agent-specific screens for immunosuppression and hypersensitivity and studies on the role of inflammatory cytokines in tissue injury at NIEHS, studies on analysis of immuno-globulins in saliva and field studies of a comprehensive immunologic test panel at NIOSH, and studies developing antibody-based assay systems for biomarkers of exposure at NCTR. With regard to neurotoxicology, he said this was a small in-house program at NIEHS and is an area where we would like to put more resources. Functional Observational Batteries are utilized in short-term toxicity studies where neurobehavioral effects are anticipated and neurobehavioral measures are included in long-term assays when indicated. There is an in-house research program on cellular indicators of neuronal toxicity. At NIOSH, neurobehavioral assessment methods are being developed and applied to farm workers and pesticide applicators. With regard to respiratory toxicology, ongoing agent-specific studies at NIEHS include those on styrene, alpha-methylstyrene, divinylbenzene, tetranitromethane and carbon disulfide. There are in-house research projects on macrophage growth factors in particle-induced pulmonary disease, and on use of human and rat cultured airway epithelium for measuring responses to inhaled toxicants. There are biochemical and pathology studies of effects of inhaled freshly fractured vs. aged silica ongoing at NIOSH. In the area of reproductive and developmental toxicology, all chemicals undergoing short-term toxicity assays at NIEHS are evaluated for effects on sperm morphology and vaginal cytology, while there are beginning issue-driven studies of perinatal pesticide exposures and effects of environmental estrogens on reproduction and cancer. An extensive program of germ cell studies include projects on the mechanisms of aneuploidy formation and validation of the fluorescent *in situ* hybridization assay, on use of the dominant lethal test for germ cell mutagens, on evaluation of the sensitivity of the zygote and early embryo to chemical exposure, and on specific locus mutations in mouse germ cells. Methods development projects are ongoing in evaluation of whole embryo culture at NCTR and the rabbit model for reproductive toxicants at NIOSH. **Mechanism-Based Toxicology and Risk Assessment** — Dr. Bucher stated that this was new classification covering a diverse collection of new as well as long-standing projects grouped under five main headings, all areas developing information that can help move hazard identification into risk assessment. He briefly described projects under the headings of: quantitative dose-response relationships, human exposure assessment, animal models for human risk, biological variation, and mechanistically-based mathematical models, noting these were the areas where Board input would be most helpful.

Discussion: Dr. Brown asked whether information developed under mechanism-based toxicology might lead to being able to measure 'thresholds.' Dr. Lucier said the existence of a threshold is almost impossible to prove, and we would rather use measurements in the low dose region along with mechanistic information developed to more accurately define the shape of the dose-response curve helping us to move away from use of default assumptions in risk estimation. Dr. Hoel inquired about inclusion of epidemiology studies and whether the NTP Board would be reviewing them. Dr. Lucier explained that our aim is to describe in the *Annual Plan* projects that are related to the mission of the NTP, although primary peer review of NIEHS Epidemiology Branch projects including concept proposals are performed by the Division of Intramural Research Board of Scientific Counselors. Dr. Reuhl commented that the NTP research plans do not include information on projects that have failed and why and suggested that such information would be of interest to other scientists because it might save them effort in not trying to duplicate failed experiments.

VIII. Chemicals Nominated for FY 1995: Dr. H. B. Matthews, NIEHS, reported on the September 22 meeting of the Interagency Committee for Chemical Evaluation and Coordination (ICCEC) at which six chemicals nominated to the NTP for extensive toxicological characterization were considered. Three of the chemicals - dimethyl adipate, 2,3-butanedione, and methyl styryl ketone - were recommended by the ICCEC for study, while the other three - 2,2-dipyridyl, *n*-bromosuccinimide, and 5-nitroindazole - were recommended for no testing. Dr. Matthews discussed the chemicals, ICCEC recommendations and supporting information (Attachment 3).

Public Comments: Dr. Matthew S. Bogdanffy, DuPont Central Research and Development, spoke to the nomination of dimethyl adipate (DMA) noting that he had done much of the mechanistic research on nasal lesions induced by dibasic esters (DBEs) of which DMA is a member. He said DuPont has an extensive data base on the DBEs and human exposure assessment data which they will be happy to share with the NTP, and he has already provided Dr. Errol Zeiger, NIEHS, with information on their mechanistic studies. Dr. Bogdanffy said DuPont was supportive of the NTP doing studies and would cooperate in any way they can. In response to a query from Dr. Klaassen, Dr. Bogdanffy said the longest term study they had done was 90-days in rats and nasal lesions were induced.

Plans for Chemical Nomination and Selection: Dr. Matthews stated that the NTP was committed to broadening public input into the chemical nomination and selection process and welcomed any thoughts Board members might have. He said that 8,000 letters had been sent to a very diverse mailing list requesting nominations and there also had been ads in journals such as *Environmental Health Perspectives*. He displayed the listing of nominations received in FY 1994. Dr. Matthews said the Program has examined 86 exposure-related data bases in which there were 8,613 entries and 6,636 unique substances. The NTP is in the process of preparing to try to rank these substances using appropriate computer programs by level of production, by level of exposure, by environmental release and other measures, and will try to identify chemicals most in need of study. Findings and rankings will be shared with the Board, other agencies, etc. The input of experts in the area of structure activity relationships will also be sought.

Discussion: Dr. Mirer provided copies of two recent letters from the UAW to the ETP Office of Chemical Nomination and Selection regarding specific nominations for testing and comments concerning the process. Among specific nominations, he requested that the NTP revisit 1,1,1-trichloroethane with a bioassay by inhalation since an earlier NTP chronic study was found to be inadequate, and trichloroethylene in rats since there is only good carcinogenicity data in mice. Dr. Mirer thought more priority should be given to particulate studies. A policy issue he said had to do with who pays for testing drugs, food additives, pesticides, and other use groups where perhaps industry should be involved. Dr. Mirer provided specific suggestions concerning ways to help the public track status of nominated chemicals including their progress through the toxicology studies process.

IX. Report from an NTP Advisory Group — Toxicokinetics Faculty: Dr. Christopher Portier, NIEHS, said his group, the Laboratory of Quantitative and Computational Biology, DIR, performed most of the mathematical and computational modeling at the NIEHS. He defined toxicokinetics as the science that deals with the rates of absorption, distribution, metabolism and excretion of harmful substances, and major factors considered were age of the animals, doses given and duration and route of exposure. The faculty is composed of scientists from multiple disciplines, primarily within the DIR, whose purpose is to aid the ETP and the NTP in design, analysis, and interpretation of toxicokinetic studies. Their

activities are to review specific protocols as to adequacy to address toxicokinetic questions, to provide general guidance for study design and conduct as well as use in design and interpretation of toxicity studies, and to recommend formal toxicokinetic modeling for certain compounds. Dr. Portier described specific examples of studies done under these activities, and described toxicokinetic protocols for preliminary, single administration and two-year studies. Discussion: Dr. Stegeman asked how toxicokinetics deals with the problems of low dose effects and low dose extrapolation. With regard to the former, Dr. Portier responded that looking at saturation of metabolic activity would be an example. Dr. Lucier said the Faculty was not charged with looking at low dose extrapolation but within the larger purview of the ETP and NTP to provide information useful for risk assessment. He said we want to develop models that extend from the typical pharmaco- or toxicokinetic models with an example being the low dose dioxin model described in the *Annual Plan*, which is really a gene expression model layered over a physiological model.

X. Interagency Collaborative Studies — Interagency Agreement with NCTR: Dr. William Allaben, NCTR, briefly reviewed the nature of the Interagency Agreement between NIEHS and FDA, and the use of review teams for each chemical that are comprised of FDA and NIEHS scientists complemented by *ad hoc* members chosen specifically for each chemical. Two chemicals are currently under study and he updated the Board on progress of the studies. Dr. Allaben reported that with the first chemical, chloral hydrate, metabolism/pharmacokinetic studies had been completed in F344 rats and B6C3F<sub>1</sub> mice, a newborn mouse assay was being used to look at the chemical and its two major metabolites, trichloroacetic acid and trichloroethanol, and chronic study protocols had been approved for mice with females to be fed *ad lib* and males under both *ad lib* and caloric control. Continuing mechanistic studies include *in vitro* metabolism by microsomes/isozymes from rodent and human liver, mutagenesis in transgenic human CYP lymphoblastoid cell systems, and macromolecular binding studies. Dr. Allaben reported that studies with fumonisin B<sub>1</sub> (FB1) were well underway with the initial problem being to obtain enough FB1 of sufficient purity. Scientists from the FDA Center for Food Safety and Applied Nutrition have supplied 500 grams of purified FB1; about 850 grams of FB1 will be needed for all studies. To date, rangefinding studies have been completed, pharmacokinetic/metabolism studies have been started in non-human primates and rodents, developmental studies have begun in rabbits and rats, and protocols have been approved for chronic studies in rats and mice and for initiation-promotion studies. Additionally, a number of mechanistic studies have been initiated or are planned. Discussion: Dr. Klaassen asked why there were no long-term studies planned with chloral hydrate in rats. Dr. Allaben said that adequate negative studies had been conducted by the EPA.

XI. Concept Reviews, ETP, DIR, NIEHS:

(1) **Quantitative Relationship Between Immune Function Changes and Host Resistance** — (Attachment 4, pp. 2-3) Dr. Michael Luster, NIEHS, introduced the concept, and Dr. Kenneth Reuhl, Board member, served as principal reviewer. Dr. Luster said that in immunology there was an ongoing debate about the relationship between immune function changes and clinical disease. The objectives of the proposed project are to gain qualitative and quantitative insight between slight to moderate decreases in immune responses (~10-50%) and development of clinical diseases. Immune functions will be assessed and infectious disease diaries maintained in kidney transplant patients on long-term immunosuppressant (cyclosporin A) therapy. Dr. Reuhl noted that transplant



patients often have residual pathology and unpredictable immune responses. Thus, the inherent variability would make establishing the relationship where there were only slight alterations in immune function very difficult. He wondered why not do it first in an animal model. Dr. Luster said they had considered the problems mentioned. He said they had done the studies in animals so the issue was how translatable were the animal studies into humans. Dr. Larry Hart, NIEHS, read a written review submitted by Dr. Meryl Karol, University of Pittsburgh, who said technologies are available to undertake the immune function studies. She commented that adequacy of patient diaries to provide meaningful data on incidence of infection must be evaluated and in selecting patients, concern must be given to the nature of the underlying disease.

Dr. Brown asked how confident they were of their ability to detect 10-15% reductions in immune function. Dr. Luster said colleagues at NIOSH had been able to detect such alterations in a cohort of about 100, which would be the size population he anticipated using. Dr. Brown moved that the concept be approved, while at the same time expressing his concern about the ability of the study to answer the questions posed. Dr. Faustman seconded the motion. Dr. Reuhl suggested redesigning the patient self-assessment tool in consultation with a psychologist to provide evaluation of home life influences, especially presence of young children, on incidence of infection. The motion was defeated by five no votes with two abstentions (Hughes, Mirer). Dr. Klaassen asked if the two abstainers would comment on their vote. Dr. Hughes said the goals were laudable but there were too many clinical problems likely in the test population such that explicit results would not be obtained. Dr. Mirer said he lacked sufficient background and experience to judge the proposal. Dr. Lucier asked if the Board would entertain another proposal in the future. Dr. Brown said the Program needed to bring back one where there could be more confidence of a successful outcome. Dr. Hoel said there needed to be more input in design from clinicians and epidemiologists.

**(2) Chemical Induction of Transmissible Genetic Damage in Mammalian Germ Cells** — (Attachment 4, pp. 4-5) Dr. Michael Shelby, NIEHS, introduced the concept, and Dr. Elaine Faustman, Board member, served as principal reviewer. Dr. Shelby said this was a continuation in which they planned to continue investigations into the genetic effects of mutagenic agents upon mammalian germ cells, increase numbers of chemicals tested, broaden the spectrum of mutational events measured, and increase understanding of the mechanisms of germ cell mutagenesis. Dr. Shelby reported that there were two projects, one using the specific locus assay in mice to measure and characterize spontaneous and chemically-induced germ cell mutations, while the second project used the dominant lethal and heritable translocation assays to measure and characterize chromosomal aberrations in mice. He described recent accomplishments and proposed activities under both projects.

Dr. Faustman said she was quite enthusiastic about the goals and the productivity of these projects and noted specifically the identification of six female specific germ cell mutagenic agents as an important observation. She said the technology was readily available. She said potential clinical applications could be related to the important observations on the susceptibility of the early embryo to chemical insult and the identification of several female specific germ cell mutagens. Dr. Faustman said the methodology was more than adequate and innovative in use of molecular biological techniques. Dr. Brown moved that the concept be approved. Dr. Reuhl seconded the motion which was approved unanimously by the Board.

**(3) Estrogenic and Anti-Androgenic Environmental Xenobiotics; Effect on Reproduction and Incidence of Reproductive Cancers in Rats** — (Attachment 4, pp. 6-9) Dr. Suzanne Snedeker, NIEHS, introduced the concept, and Dr. Claude Hughes, Board member, served as principal reviewer. Dr. Snedeker reviewed the evidence for the relationship between exposure to environmental estrogenic chemicals and adverse effects on reproduction in a variety of species including humans as discussed by researchers in the NIEHS-sponsored conference "Estrogens in the Environment III" in January 1994. She said the purpose of the proposed study is to assess the effects of environmental endocrine disrupting chemicals (estrogens and anti-androgens) on reproduction and cancer endpoints over multiple generations. Reproductive effects will be assessed using a variety of functional, structural, and behavioral endpoints. Dr. Hughes said that 48 letters had been sent out requesting input on the project and most recipients had replied with comments that were supportive. He said resources were available and this study would be scientifically and clinically valuable. He questioned whether the number of generations proposed was necessary. Dr. Snedeker responded that they had reduced the number by two. Dr. Hughes moved that the concept be approved. Dr. Reuhl seconded the motion which was approved unanimously by the Board.

**(4) Chemistry Support Services** — (Attachment 4, pp. 10-11) Dr. Thomas Goehl, NIEHS, introduced the concept, and Dr. Frank Mirer, Board member, served as principal reviewer. Dr. Goehl said the purpose of these contracts is to provide analytical chemistry support services for the toxicology and carcinogenesis studies conducted by the NTP as well as studies conducted in the DIR, NIEHS. The new contracts will require that toxicokinetic studies be conducted to establish basic kinetic parameters, dose proportionality, bioavailability, and internal dose. Dr. Mirer stated that he was impressed with the quality of the chemistry in the toxicology studies. He inquired as to why there were three contracts before while there will be four under the recompetition. Dr. Goehl clarified this by stating that a fourth contract is currently in place but is quite small. Three large contracts now will be required because the Program has been centralizing support so that most chemical analyses including the routine bulk chemical and dose analyses will be conducted by a contract laboratory, and because the number of chemicals to be analyzed is increasing. The fourth contract, currently with an 8A firm, will be competed separately at a somewhat increased size. Dr. Brown moved that the concept be approved. Dr. Mirer seconded the motion which was approved unanimously by the Board.

**(5) Research on the Inhalation Toxicology of Environmental Chemicals** — (Attachment 4, pp. 12-13) Mr. Michael Moorman and Dr. Daniel Morgan, NIEHS, introduced the concept, and Dr. Fumio Matsumura, Board member, served as principal reviewer. Mr. Moorman said the objective was to continue to provide support in inhalation toxicology for the NTP and for the other research components of the NIEHS in a contractor operated exposure facility that was accessible to NIEHS scientists. Dr. Morgan stressed the need for a local facility using as an example the neurobehavioral studies on carbon disulfide which involved complex design and multidisciplinary expertise. Such expertise was available in the local area. Dr. Matsumura said this type of facility was needed and the collaborative nature of some of the projects appeared to be important to their success. Dr. Mirer asked whether the current facility had the capability for doing particulate studies. Mr. Moorman said it did but by nose-only exposure. In response to a question about whether two-year studies could be performed, Dr. Morgan said they could but this would not be the most efficient way to use the contract's capabilities. Dr. Reuhl moved that the concept be approved. Dr. Matsumura seconded the motion which was approved unanimously by the Board.

Summary Minutes, NTP Board of Scientific Counselors' Meeting  
*October 18, 1994*

These Summary Minutes have been read and approved by the Chair of the National Toxicology Program Board of Scientific Counselors as certified below.

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Date

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Dr. Curtis D. Klaassen,  
Chair  
NTP Board of Scientific Counselors