National Toxicology Program
Board of Scientific Counselors' Meeting
May 27 and 28, 1981

SUMMARY MINUTES

Contents

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Summary Minutes

The National Toxicology Program (NTP) Board of Scientific Counselors met on May 27 and 28, 1981, in the Auditorium, Building 101, South Campus, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina (Attachment 1: Federal Register Meeting Announcement; Attachment 2: Agenda).

The minutes of the January 15 and 16, 1981 Board of Scientific Counselors' meeting were approved. Dr. M. Mendelsohn served as Chairman on May 27 in Dr. N. Nelson's absence. Dr. Nelson resumed the Chairmanship on May 28.

Review of NIH/NTP Program in Chemical Disposition: (Attachment 3: Chemical Disposition Program - NTP). Expert consultants who supplemented the Board members as peer reviewers were Dr. J. J. Lech, University of Wisconsin and Dr. R. A. Neal, Chemical Industry Institute of Toxicology. Dr. H. B. Matthews, Program Leader, briefly described the objectives of the chemical disposition program, experimental design, and the rationale for doses used and for the chemicals or chemical classes chosen for study. He said that the General Protocols (Attachment 3) serve as a guide for any study. He said that in dose setting the highest dose used would be below that which would saturate disposition processes. The high dose used usually does not exceed one-tenth of the LD 50 dose.

Dr. Matthews outlined the history at NIEHS of chemical disposition studies on polyhalogenated aromatic compounds. He pointed out how the position of chlorine substituents was a major determinant of whether or not the chemical was persistent in the body. He discussed recent studies with certain aromatic amines, especially p-nitroaniline, 4-chloro-2-nitroaniline, and 1,3-diphenylguanidine. He said that chemical disposition studies were about to start on 2,4-dinitroaniline and 2-bromo-4,6-dinitroaniline.

Dr. Matthews described contract studies at the University of Arizona under the direction of Dr. I. G. Sipes. Ongoing or completed studies included: 1) comparative studies of *in vitro* vs. *in vivo* metabolism of three polychlorinated biphenyls (PCBs) (4,4'-dichloro-, 2,2',3,3',6,6'-hexachloro, and 2,2',4,4',5,5'-hexachlorobiphenyl). In some cases, hepatocytes are being used *in vitro* in an attempt to avoid problems of non-specific sequestration of chemical in liver homogenates. The goal is to refine techniques which will permit an *in vitro* to *in vivo* extrapolation for laboratory animals and ultimately to humans; 2) he described disposition studies of chlorpheniramine maleate; 3) disposition studies with p-chloroaniline and the formation of a persistent metabolite, the N-acetyl derivative; 4) disposition studies of p-chlorotoluene, and 5) disposition studies with acrylamide which has a short half-life in most tissues, spinal cord, skin and testes being exceptions.

Planned studies included: 1) disposition studies of 1,2,3-trichloropropane with interest due to its similarity to dibromochloropropane, and 2) comparative

studies with the ortho-, meta-, and para- tricresylphosphates to determine if the metabolism and disposition of the meta and para isomers are similar to that for the neurotoxic ortho isomer.

Dr. Matthews described contract studies at the University of Oregon under the direction of Dr. R. K. Lynn. This contract is almost exclusively concerned with the metabolism, excretion and synthesis of radio labeled bisazobiphenyl (benzidine-based) dyes. Newer studies were carbon-14 labeled Direct Blue 6 will provide more quantitative information on dye disposition, and will also look at the possible role of gut flora in metabolism.

The data from the chemical disposition studies are provided to the chemical manager for use in the design of bioassays, and also may be used for structure-activity comparisons, and for purposes of extrapolation across species.

Following Dr. Matthews' presentation, there was considerable discussion about the choice of species for chemical disposition studies. Routinely, the male rat is used; however, in some cases, mice, dogs and monkeys are also used. Dr. Moore asked whether NTP should routinely use both rats and mice, in which case chemical disposition studies could be done on only half as many chemicals. Dr. Neal commented that the dog is a better species to use for the dye studies since it is more sensitive to bladder carcinogenesis. Dr. Moore said that we will use rats and mice in the bioassay unless chemical disposition studies show them to be inappropriate species. Dr. Rall stated that the NTP intends to make the bioassay more flexible or custom designed for each chemical.

Dr. L. Birnbaum described her work with the halogenated furans, dioxins, biphenyls and naphthalenes. She made a few general observations including: (1) bromine confers a molecule with more toxicity than chlorine, (2) there is often a direct correlation between increased numbers of halogen atoms and increased toxicity, and (3) appreciable metabolism occurs only when there are two adjacent unsubstituted carbon atoms.

Dr. Birnbaum devoted most of her time to a discussion of chemical disposition studies on 2,3,7,8-tetrachlorodibenzofuran (TCDF). She showed there was a direct correlation among species between increases in biological half life ($T_{\frac{1}{2}}$) and increases in toxicity of TCDF. The $T_{\frac{1}{2}}$'s were: rat, < 2 days; monkey, 8 days; and guinea pig, > 20 days. The major route of excretion in all three species was fecal, and almost all of the products excreted in urine and feces were metabolites. Recent studies in two inbred mouse strains have shown that DBA mice which have fat content almost double that of C57 Black mice also have much higher fat levels of TCDF. Based on previous studies with 2,3,7,8-tetrachlorodibenzodioxin, high fat content may protect against toxicity of these polyhalogenated hydrocarbons. Other recent studies with a hexachlorodibenzofuran (1,2,4,6,8,9-) have shown that only about one-third of an oral dose is absorbed. Of the metabolites excreted, most are believed to be derived from pentachlorodibenzofuran contaminants. Another hexachloro isomer (2,3,4,6,7,8-) is currently under study.

Report on the NTP Benzidine Initiative: (Attachment 4: The Benzidine Congener Dye Initiative). Dr. J. Mennear, NIEHS/NTP, reviewed the background of this initiative which includes involvement by OSHA, EPA, CPSC, NCTR, NIOSH, and NIH/NTP as well as an industry trade group, the Dyes Environmental and Toxicology Organization (DETO). He said there were more than 2,000 dyes commercially available. The NTP initiative will focus on the large class of bisazobiphenyl dyes.

The objective will be to develop an integrated body of scientific information about the: A. Pharmacokinetics, B. Genetic toxicology, and C. In vivo toxicity and carcinogenicity of the benzidine congeners and prototypical dyes. The congeners include benzidine, dimethyl benzidine (di-o-tolidine) and dimethoxy benzidine (di-o-anisidine). The prototypical dyes are representative of the large class of dyes derived from the congeners. Dose-carcinogenic response information obtained will be used in development of a screen which should have predictive value for potential carcinogenicity of other dyes tested in the screen. Dr. Mennear discussed the prototype dyes chosen, and the current status of the major testing aspects of the program.

Review of NTP Program in Immunotoxicology: (Attachment 5: Review of the Immunological Toxicology Program - National Toxicology Program - National Institute of Environmental Health Sciences, May 27, 1981). Expert consultants who supplemented the Board Members as peer reviewers were Dr. Q. N. Myrvik, Wake Forest University, and Dr. C. C. Stewart, Los Alamos National Laboratory. Dr. J. Dean, Program Leader, described the background of the immunotoxicology program (Table B., p.5 of the attachment), detailed staffing and research responsibilities (Table II., pp. 14-15), and current contract and interagency initiatives (p.10).

Dr. Dean explained why the immune system is studied as a target organ: it is a sensitive organ system for describing cellular injury since methods are available for measuring alterations both in vivo and in vitro. Alterations include hypersensitivity, allergy, autoimmune disease and supression. He outlined the organization of the immune system, discussed cell-mediated and humoral immunity, explained what is known about the mechanisms of immune system alteration, and listed the drugs and chemicals which have been reported to alter immune response.

Dr. Dean described the comprehensive screening panel for defining immune system alterations in response to chemical exposure. The panel was divided into two tiers. Tier 1 is a screening tier composed of five assays: 1) tumor challenge assay, 2) plaque forming cell response, 3) quantitation of phytomitogen responses, 4) quantitation of delayed hypersensitivity response, and 5) serum immunoglobulin quantitation. Tier 2 is a comprehensive tier which primarily focuses on characterizing effects seen in Tier 1.

Dr. Dean summarized studies with the carcinogen benzo(a)pyrene (BaP) and the noncarcinogen benzo(e)pyrene (BeP). Perhaps the most striking observation with BaP was its induction of severe depression in the primary antibody plaque forming cell (PFC) response to both T-dependent and independent antigen. Dr. Hitchcock asked whether they correlated aryl hydrocarbon hydroxylase induction with PFC response. Dr. Dean said they hadn't done

this but would. He noted a lack of effect by BaP on skin graft rejection or tumor susceptibility. BeP was without effect on any of the parameters measured. The data supported the contention that immune alterations induced by carcinogenic polycyclic aromatic hydrocarbons in general, and in particular BaP, are linked to their carcinogenic potential.

Dr. Dean then reported findings with phorbol esters, chemicals of immunological concern because of their tumor promoting potential. The most active phorbol tumor promoter, 12-O-tetradecanoyl phorbol 13-acetate (TPA), was used. He elaborated on several of the many immunotoxic effects of TPA. Among these, TPA suppresses lymphocyte blastogenesis, depresses lymphocyte T-cell surface markers, enhances susceptibility to tumor cell challenge, and decreases spontaneous cytolysis of tumor target cells in vitro (so called natural killer cells). In the discussion period, Dr. Stewart stated that NTP needs to be more concerned with chronic exposures and possible long-term effects on the immune system. Dr. Rall replied that we could do many of the assays at the end of a lifetime study, if indicated. Dr. Hitchcock commented that we need more 'model' compounds that don't show other types of toxicity and Dr. Dean responded that all of the studies described were conducted with non-overtly toxic dosage levels of chemicals.

Dr. Luster spoke in detail about the immunotoxicology group's studies with diethylstilbestrol (DES). While there were increases in peripheral leukocytes and various macrophage functions in female mice, there was severe depression of most other immune functions measured. These included depressed antibody plaque forming cell responses to sheep erythrocytes and lipopolysaccharide, decreased delayed hypersensitivity responses, and lymphoproliferative response to both mitogens and allogeneic cells in mixed leukocyte cultures. Coculture experiments revealed the presence of suppressor cell activity residing in the macrophage population. DES decreased resistance to tumor cell challenge and increased host susceptibility to Listeria. In response to questions from the reviewers, Dr. Luster agreed that the various effects of DES could be attributed to both the estrogenic and non-estrogenic properties of the chemical. He emphasized that the enhancement of tumor susceptibility was related to immune depression.

Dr. Boorman discussed the development and use of bone marrow progenitor cell assays as a valuable adjunct in an overall immune system assessment. He talked about the use of recently developed in vitro and in vivo culture techniques for examining the capacity of bone marrow cells to proliferate and produce colony forming units such as stem cells, cells which he stressed play key roles in immune function. In studies of over 12 chemicals of environmental concern most caused some alterations in bone marrow parameters; changes which correlated with host resistance assays and immunological studies.

Overview of NTP Programs, Staffing, Resources, and Projected Initiatives: (Attachment 6: NIH/National Toxicology Program). Dr. Moore described the NIH/NTP research and testing programs as being in four major areas or segments, i.e., mutagenesis, in vivo carcinogenesis, toxicologic characterization, and reproductive assessment and development toxicology. This last area (sometimes titled 'fertility and reproduction') as discussed also includes NTP programs at NCTR and NIOSH. He discussed and compared FY 1980-82 budget figures for the four areas in testing, methods development and validation (Attachment 6a), and noted that the percentage of the budget going into

testing has steadily if modestly decreased from 1980 to 1982 (FY 1980, 86%; FY 1981, 83%; and FY 1982, 78%). The dollar allocations, staffing and program descriptions for the four areas were broken out in Attachments 6b, 6c, 6d, 6e and 6f.

Reproductive Assessment and Developmental Toxicology

Dr. Moore highlighted some of the reproductive assessment and developmental toxicology studies ongoing or planned at the three components (Attachment 6b). He termed the NIEHS efforts as primarily a broad characterization of reproductive effects of chemicals. Underscoring the lack of good in vitro teratologic test systems, he announced an NCTR-initiated workshop in August to explore future testing systems. NCTR continues under contract with Research Triangle Institute - conventional teratology testing of up to 12 chemicals/year. He noted that contracts awards are due in late FY 1981 or early 1982 to evaluate continuous breeding techniques for which concept approval had been given by the Board. The NCTR interlaboratory behavioral teratology initiative, with support from NIOSH, is underway. Finally, proposed for initiation in FY 1982 by the NIH component is an addition to the general toxicology screen. This would involve adding measures of reproductive dysfunction at the end of the 90-day subchronic phase--testicular pathology, epididymal weights and sperm counts in males, and vaginal cytology in female animals. Additionally, plasma may be stored for future determinations of sex hormones. A mating protocol has also been defined as a special study.

Mutagenesis

Dr. Moore said emphasis over the three years (1980-1982) has been on markedly increasing the efforts in cellular and genetic toxicologic methods development and validation while steadily increasing the numbers of chemicals which can be tested for genetic and related effects. (Attachment 6c).

He commented that the Salmonella/microsome validation is nearing completion. In mammalian cell transformation, primary activity has been to award contracts for development of methods (FY 1981) and validation of methods (FY 1982). Studies in in vitro mammalian cell mutagenesis are focused on showing correlations between mutagenic response and carcinogenic properties as derived from the bioassay. The concept has been approved by the Board for a study of spontaneous chromosome aberrations and sister chromatid exchanges in human lymphocytes. A contract has been in place since 1975 to support validation of the rat hepatocyte DNA repair assay and is now winding down. In the area of cytogenetics, the Chinese hamster ovary system is in place, and 200 chemical tests will be done in two laboratories over the next three years. The concept was approved by the Board for contracts to standardize and validate in vivo assays for induction of chromosomal aberrations and sister chromatid exchange.

With regard to heritable effects, the Drosophila assay is in the second year of actual testing. Dr. Nelson asked which chemicals are in which test groups to point up coordination. He said it would be useful to have a table listing chemicals which are being tested in more than one of these systems. The concept was previously approved by the Board for contracts to

further develop, validate and actually test using the specific locus tests. One contract was just awarded and a second is in process for development and validation of assays for the detection of aneuploidy.

Toxicologic Characterization

Dr. Moore reported that the major testing initiatives here are acute, 14 day and subchronic (90-day) experiments with chemicals originally selected for evaluation as to carcinogenic potential (Attachment 6d). With 79 starts in FY 1979, and 40 in FY 1980, there were large numbers of chemicals in the prechronic testing phases in FY 1980-81. Major new emphasis in these two years was the revision of protocols both to give more in depth toxicologic assessment as well as to give at least presumptive evidence of toxic effects other than carcinogenesis including information on chemical disposition. Efforts are being implemented to develop toxicity principles for chemical classes based on evaluation of a few carefully selected members; e.g., psoralens, chlorinated dibenzofurans, benzidine-derived dyes, phthalates.

In the area of chemical disposition, award of two contracts in FY 1981 to supplement the two ongoing contracts will enable conduct of 20-25 disposition studies a year.

The neurobehavioral toxicology program is an example of a strong link between a NIEHS intramural program and NTP through a common interest in development and validation of screening methods. A new initiative here will be an evaluation of home-cage behavioral alterations as a simple means to detect toxicity.

The immunological toxicology program continues to focus on developing and validating a series of procedures needed to define a battery of tests for determining which chemicals alter immunologic function. The biochemical toxicology program continues as a small in-house effort primarily concerned with characterizing biochemical changes in the liver caused by chemicals. The pulmonary toxicology effort continues to assess the value of pulmonary function indexes as a complement to standard pathologic evaluation of lung injury. A new initiative in FY 1982 will be to rigorously examine the usefulness of the clinical chemistry used in the rodent screen.

In Vivo Carcinogenesis

Dr. Moore stated that the predominant effort here is the two-year bioassay with a small percentage of dollars devoted to in vitro studies (second pie chart) (Attachment 6e). He pointed out that the continuing large numbers of dollars reflect, in large part, the 'out year' costs for bioassay starts initiated prior to NTP involvement. This investment will gradually scale down starting in FY 1983 with fewer bioassay starts and more funds being devoted to development of tests as alternatives to the bioassay. Dr. Nelson asked if this was part of a 'grand plan' for shifting resources from one area to another. Dr. Moore replied that it was for the area of carcinogenesis testing. He said we need much more method development and validation, other in vivo tests besides the mouse lung adenoma test, as for example in the area of initiation-promotion assays. NTP must keep a minimal level of bioassay

starts at 20-25 per year, and this would include model compounds, e.g. benzidine. He stated that the two-year bioassay was still the best test for assessing carcinogenic potential but we do need better prechronic phase protocols to allow us to be better informed toxicologically and thus more selective in choosing which chemicals will begin two-year studies, as well as to enable better experimental design of the chronic bioassay. This decision-point at the prechronic-chronic interface is an NTP initiative.

He briefly reviewed the status of method development and validation. Validation of the mouse lung adenoma is nearly completed in one laboratory and will be completed in the second laboratory this fall. A study to evaluate the possible influence of the Sendai virus on chemically-induced oncogenesis has been approved for concept (see below). A program to assess the utility of rat liver tumor assays for carcinogenesis effects via initiation/promotion will begin in FY 1982. A study with hybrid mice will begin in FY 1982 to determine whether there might be a strain(s) better than the B6C3F1 mouse for carcinogenesis studies. Dr. Mendelsohn asked whether NTP had considered development of repair defective mouse strains. Dr. Moore replied that we were not considering it at present. Dr. Nelson said we need to deal with the issue of repair altered strains. This could be a topic for discussion at a future Board meeting. Dr. Moore reviewed NIH/NTP staffing and staffing needs (Attachment 6f).

Action Item: NTP should schedule as an agenda item for a future Board meeting the issue of development and use of repair altered animal strains in toxicology studies.

Concept Review: Dr. Moore said that even though the Board had approved guidelines for the animal bioassay process at the January Board meeting, he was unsure as to whether the Board felt that it had approved data management procedures. Dr. Nelson suggested that an amendment be added to the concept proposal spelling out the procedures. An amendment was added to the concept proposal (Attachment 7).

There was further discussion by the Board of what is encompassed by a concept review. Dr. Moore said he thought it should include an assessment of whether the proposed work was in line with regard to scientific objectives, cost and whether it could cause an imbalance in relation to other program needs. The Board said it felt more comfortable with assessing scientific merit or feasibility. Three concept proposals were then reviewed by the Board.

1) Support Services: (Attachment 8) Concept approval was requested for a number of support service contracts which are listed in the attachment. The Board unanimously approved the concepts.

2) Influence of Sendai Virus on Chemically Induced Carcinogenesis Process: (Attachment 8) Dr. Moore said that barrier derived animals are not necessarily free of Sendai virus. Literature reports suggest that Sendai virus may have had effects on the course of chemical oncogenesis. The proposal will attempt to establish whether the virus influences chemical carcinogenesis processes in the life-time bioassay with B6C3F1 mice and in the strain A mouse lung adenoma model, then investigate possible underlying mechanisms if such altered responses are observed. Dr. Mendelsohn

inquired as to controls. Dr. Moore replied that controls would either be vaccinated against the virus or isolated. The Board agreed that vaccination of controls should be included in the concept. Dr. Nelson proposed that the Board give qualified approval, i.e., give overall approval of the concept but with the caveat that close scrutiny be given during technical review to ensure appropriate controls are included. The concept was then approved unanimously.

Action Item: NTP staff and the project officer should better define the makeup of the control animals in the Sendai virus study.

3) Rapid In Vitro Test Capability: (Attachment 8) Dr. R. Tennant, NTP, said the intent of this proposal is to provide the cellular and genetic toxicology program with specific test information on selected chemicals in a timely manner. This does not endorse a specific battery but is rather an effort to give NTP a rapid test capability for five broad classes of in vitro short-term tests. The information would be used by experimental design groups and in the ranking process for establishing the priority of chemicals for entering two-year bioassays. Initially 25 chemicals/year would require such rapid test response. The project would involve more than one contract laboratory. Dr. Mendelsohn asked which kinds of DNA damage would be looked at, and Dr. Tennant replied that it would be effects on unscheduled DNA systhesis (UDS) in hepatocytes. Dr. Moore noted that in the cases of tests for gene mutations in bacteria and chromosome damages in mammalian cells we had ongoing contracts. The emphasis here would be to expand the capability of the existing contracts through supplemental appropriations. Dr. Whittemore asked whether there would be a linkage of chemicals chosen to the chemical disposition list, and the answer was yes. Dr. Mendelsohn said the proposed work was an important direction, and strongly approved the thrust of the concept. Dr. Nelson recommended approval and the concept was approved unanimously by the Board.

Recommendations For Categorizing Bioassay Results as to Strength of Evidence For Carcinogenicity in Animals: Dr. Harper, Chairperson of the Board subgroup studying the issue, reported that the Technical Reports Review Subcommittee and expert panel had discussed the recommendations from the January 15 Board meeting following the bioassay report review on February 18. He said there was considerable disagreement concerning not only the wording of some of the IARC categories for strength of evidence for carcinogenicity but also with respect to their applying these categories to formulation of human hazard statements for the bioassay reports. Dr. Harper said that following the February 18 meeting and recent discussions with Drs. L. Hart and J. Huff, NTP, he had proposed narrowing the focus to formulating acceptable strength of evidence statements for experimental animal results and leaving the formulation of human hazard statements as a separate issue to be dealt with at a later time. He met on May 27 with the other subgroup members, Drs. Hitchcock, Horning and Whittemore, and they agreed that a fifth category called 'equivocal evidence' would be appropriate. However, there was lack of agreement on the wording of some of the categories, especially the definitions for 'sufficient evidence' and 'limited evidence'. As a followup to this meeting, Drs. Mendelsohn and Whittemore suggested using a weighting scheme to aid in defining what each category should include. Dr. Horning said this could involve

an exercise in numerical weighting using as a data source carcinogenesis bioassay reports reviewed by the NTP peer review process over the past year. Dr. Nelson stated that he was very sensitive to trying to put numerical weights on the results of bioassays. After further discussion, the Board subgroup agreed to grapple further with the issue and report back at the next Board meeting.

Action Item: The Board subgroup is to report at the next meeting.

Additions to the Bioassay Technical Reports Peer Review Scheduled for June 23, 1981: Dr. Moore asked the Boards' consensus on resubmitting conclusions to the bioassay reports peer review group when the peer review comments have led to a significant alteration of the conclusions of a particular bioassay. He referred specifically to the bioassay report for butyl benzyl phthalate which had been approved at the peer review meeting on June 27, 1980. Dr. Hitchcock, chairperson of the Technical Reports Review Subcommittee, said NTP should bring the revised conclusion before the panel for review. If the panel does not concur, then the report might have to undergo a full rereview. [EDITOR'S NOTE: The revised conclusions were reviewed and approved by the panel on June 23, 1981.]

Dr. Moore said that two versions of the NCI technical report on the bioassay of dimethylterephthalate had been released in 1979. The two versions had different conclusions. The first version was that approved by the Cancer Clearinghouse on Environmental Carcinogens, while the second version resulted from a reanalysis of the data. In light of this and the fact that the second report was not peer reviewed, the NTP decided to re-examine the original pathology and statistical data and make an interpretation as to what the conclusions should be. They would then provide a full report to the NTP review panel. [EDITOR'S NOTE: The revised conclusions were reviewed and approved by the panel on June 23, 1981.]

Other Business: The dates for the next Board of Scientific Counselors' meeting will be either October 19-20 or October 22-23, 1981. Tentative agenda items would include: 1) review of NTP neurobehavioral toxicology programs, 2) status report on test validation results in cellular and genetic toxicology, 3) a report on recommendations for categorizing bioassay results as to strength of evidence for carcinogenicity in animals, and 4) peer review of chemicals nominated for NTP testing. [EDITOR'S NOTE: The next Board meeting will be October 22-23, 1981 in Cincinnati, Ohio.]

Peer Review and Priority Ranking of Chemicals Nominated for NTP Testing: At the October 1980 meeting of the NTP Board of Scientific Counselors a number of changes in the chemical nomination and selection process were approved. One of these changes, which was aimed at increasing public input, was to have the Board peer review and recommend testing priorities for nominated chemicals prior to final Executive Committee review and action. This Board meeting was the first at which review and recommendation of priorities were implemented.

Dr. D. Canter, NTP, said that the chemical nominations to be considered by the Board had been previously reviewed by the NTP Chemical Evaluation Committee. The list with Committee recommendations had been published in the Federal Register with a request for public comments. (Attachment 9: Chemicals (20) Nominated For Toxicological Testing) Comments received on four of the chemicals were given to the Board as addenda, to the Executive Summaries and would be included in the final Executive Summaries. Dr. Canter announced that each Executive Summary was going to be revised. Executive Summaries prepared for chemicals nominated for testing, starting in FY 1981, will follow a new format, as follows:

I. Chemical
   - A. Synonyms
   - B. CAS #
   - C. NTP#
   - D. Properties - Physical & chemical

II. Surveillance Index
   - A. Production
     1. Mode(s)
     2. Volume
        - a) TSCA inventory data
        - b) Other
   - B. Uses
   - C. Exposure
     1. Occupational - NOHS data
        - TLV's (PEL's)
     2. Consumer
     3. Environmental

III. Toxicological Effects
   - A. Human data
     1. Acute
     2. Epidemiological evidence/case reports
     3. Chemical disposition
     4. Chronic
     5. Reproductive effects
   - B. Animal data
     1. Acute
     2. Chemical disposition
     3. Subchronic
     4. Chronic
     5. Reproductive
   - C. Mutagenicity
   - D. Structure activity relationships

IV. Nomination Source
   - A. Source
   - B. Recommended tests
   - C. Rationale
   - D. Priority

V. CEC Recommendations
   - A. Recommended tests
   - B. Priority
   - C. NTP chemical selection principle(s)
   - D. Remarks

VI. Board of Scientific Counselors Review
   A. Recommended tests
   B. Priority
   C. Remarks

VII. Public Input - Acknowledgement(s)

In discussion by the Board, the question was raised as to whether there could be an earlier public notice in the Federal Register of chemicals to be considered, i.e., prior to Chemical Evaluation Committee action. This would allow for public input earlier on in the process and, perhaps, result in submission of information which could be useful to the Committee in their review. The Board asked NTP to consider this addition to the selection process.

Dr. Horning, Chairperson of the Board Subcommittee on Chemical Nomination and Selection, chaired the review of the individual chemicals. There was agreement to use the Chemical Evaluation Committee's mode of ranking as to kinds of tests and priority (High, Medium and Low). The Chairman of the Chemical Evaluation Committee, Dr. L. Fishbein, NCTR, and four members of the Committee (Dr. C. Morris, EPA; Dr. V. Frankos, FDA; Dr. W. Piver, NIEHS; and Dr. Canter, NIEHS) were present in an advisory role to the Board.

Each Board member had been assigned two or three chemicals to review prior to the meeting. Following oral presentation of the review and testing recommendations for a chemical there was discussion; a motion was made and voted on by all of the Board. The approved recommendations, priority for testing, and additional remarks and/or caveats are summarized (Attachment 10: 20 Chemicals Evaluated by the Board of Scientific Counselors on May 28, 1981). The meeting was adjourned following the review.

AGENDA

Board of Scientific Counselors
National Toxicology Program

May 27-28, 1981

Auditorium, Bldg. 101, South Campus
National Institute of Environmental Health Sciences
Research Triangle Park, North Carolina

May 27, 1981		OPEN
8:45 am - 11:30 am	Review of NIH/NTP Program in Chemical Disposition	Drs. Matthews and Birnbaum
11:30 am - 12:30 pm	Report on the NTP Benzidine Initiative	Dr. Mennear
1:30 pm - 4:00 pm	Review of NTP Program in Immunotoxicology	Drs. Dean, Luster and Boorman
		CLOSED
4:00 pm - 5:00 pm	Evaluation of Programs and Personnel in Chemical Disposition and Immunotoxicology	Board and Consultants
May 28, 1981		OPEN
8:30 am - 10:30 am	Overview of Programs, Staffing, Resources, and Projected Initiatives	Dr. Moore and Staff
10:30 am - 11:30 am	Concept Review of NTP Contract Initiatives	NTP Staff
11:30 am - 12:00 pm	Report and Recommendations on Warning Statements Concerning Hazard to Humans Based on Animal Test Results	Drs. Harper, Hitchcock, Horning and Whittemore
12:00 pm - 12:30 pm	Other Business	Drs. Rall and Moore
1:30 pm - 5:00 pm	Peer Review and Priority Ranking of Chemicals Nominated for NTP Testing	Board

Department of Health and Human Services

U.S. Public Health Service

National Toxicology Program

Notice of Meeting

National Toxicology Program Board of Scientific Counselors

Pursuant to Public Law 92-463, notice is hereby given of the meeting of the National Toxicology Program (NTP) Board of Scientific Counselors, U.S. Public Health Service, in the auditorium of Building 101, South Campus, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, on May 27 and 28, 1981.

This meeting will be open to the public from 8:45 a.m. to 4:00 p.m. on May 27. The preliminary agenda is as follows:

8:45 a.m. - 11:30 a.m. Review of NIH/NTP Program in Chemical Disposition

11:30 a.m. - 12:30 p.m. Report on the NTP Benzidine Initiative

1:30 p.m. - 4:00 p.m. Review of NTP Program in Immunotoxicology

In accordance with the provisions set forth in Section 5526(c)(6) Title 5 U.S. Code and Section 10(d) of Public Law 92-463, the meeting will be closed to the public on May 27 from 4:00 p.m. to adjournment for further evaluation of NTP programs in chemical disposition, and immunotoxicology, including the consideration of personnel qualifications and performance, the competence of individual investigators, and similar items, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

The meeting on May 28 will be open to the public from 8:30 a.m. to adjournment. The preliminary agenda is as follows:

8:30 a.m. - 10:30 a.m.	Overview of Programs, Staffing, Resources, and Projected Initiatives
10:30 a.m. - 11:30 a.m.	Concept Review of NTP Contract Initiatives
11:30 a.m. - 12:00 noon	Report and Recommendations on Warning Statements Concerning Hazard to Humans Based on Animal Test Results
12:00 noon - 12:30 p.m.	Other Business
1:30 p.m. - 5:00 p.m.	Peer Review and Priority Ranking of Chemicals Nominated for NTP Testing (Twenty chemical nominations will be reviewed and are listed in the Federal Register Volume 46, page 21828, April 14, 1981)

The Executive Secretary, Dr. Larry G. Hart, Office of the Director, National Toxicology Program, P.O. Box 12233, Research Triangle Park, North Carolina 27709, telephone (919)541-3971, FTS 629-3971, will furnish summary minutes of the meeting, rosters of Board members, directions to the South Campus, and other program information.

4/17/81
Date

David P. Rall, M.D., Ph.D.
Director
National Toxicology Program