National Toxicology Program

Board of Scientific Counselor's Meeting

January 15 and 16, 1981

Summary Minutes

The National Toxicology Program (NTP) Board of Scientific Counselors met on January 15 and 16, 1981, in the Conference Room, Building 18, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina (Attachment 1: Federal Register Meeting Announcement; Attachment 2: Agenda).

The minutes of the October 16 and 17, 1980 Board of Scientific Counselor's meeting were approved.

Status Report on Implementation of Modifications in the NTP Chemical Nomination and Chemical Selection Process: Dr. D. Canter distributed copies of a memorandum describing changes in the chemical evaluation process (Attachment 3: January 21, 1981 Meeting of the Chemical Nomination and Selection Committee).

The memorandum indicates that primary and secondary reviewers will be assigned for each nominated chemical with the aim being to provide more indepth review of chemicals to aid in recommending types of testing needed and priority setting. The attached table gives the numbers of workers potentially exposed (from the National Occupational Hazard Survey), where available. The attached data summary form is being used on a trial basis as a means for aiding the NTP Technical Information Section in tracking nominated chemicals. Dr. Canter said that over the next four months a new list of 28 chemicals along with Executive Summaries would be moving through the chemical selection process. In keeping with the changes in the process approved at the October 1980 Board meeting, a Federal Register notice would be posted soliciting advice and comment on the chemicals, and letters requesting information or comment would be mailed to interested groups and individuals. Yet to be determined was the specific mechanism by which the Board will effect peer review and priority setting for the nominated chemicals prior to final Executive Committee review and action.

There was a discussion about the sources of nominations. Dr. Canter said that despite our efforts to broaden the sources, most of the nominations of chemicals were made by a few agencies, with NCI responsible for the largest number. Dr. Rall said that the large amount of data requested with a nomination may have discouraged some from submitting nominations. Dr. L. Hart, NTP, noted that NTP is trying to stress in various media that these many data elements are not required, only

desirable. Dr. Horning suggested that NTP consider other publications in which to solicit nominations, e.g., Science. Dr. Shepard reported that an editorial authored by him, which requested nominations for teratologic and reproductive toxicology testing, would appear in an upcoming issue of Teratology.

Action Item: NTP staff will consider other publications in which to solicit nominations of chemicals for testing.

Report and Recommendations on Warning Statements Concerning Hazard to Humans Based on Animal Bioassay Results: Dr. Harper distributed copies of a paper drafted by an ad hoc Subcommittee of the Board for which he was chairman (Attachment 4: Recommendations Based on Carcinogenesis Bioassay Results for Categorizing Experimental Results and for Establishing Warning (Cautionary) Statements for Potential Human Health Hazards).

Dr. Harper briefly described the paper including the subcommittee's recommendation that NTP adopt the definitions used by IARC for categorizing animal bioassay results (part b) of the paper). Based on these definitions, the Subcommittee recommended that the summary and discussion/conclusion sections of the bioassay report contain a standard and limited statement patterned after those defined by the IARC (statements (i) to (iv) under part d) of the paper).

Considerable discussion followed Dr. Harper's presentation. Dr. Rall said that NTP would use the IARC definitions for now and begin a dialogue with IARC and others to improve them. Dr. Nelson agreed and felt that such qualitative hazard statements were as far as we could go at present. Support was expressed for inclusion of data from other studies in bioassay reports to enable a more comprehensive assessment of risk. Dr. Moore said that, ideally, NTP would incorporate the bioassay data along with other data into a monograph. Dr. Shepard stated that the Subcommittee should consider other toxic endpoints (teratogenic and reproductive assessments) in recommending statements of hazard/risk. Drs. V. Frankos (FDA) and S. Johnson (EPA) noted that the regulatory agencies look at the results of other studies beside the bioassays in making regulatory decisions.

Dr. Nelson said that the sense of the Board seemed to be that NTP must consider all relevent information including epidemiologic data in assessing potential hazards of chemicals to humans. Some undefined new apparatus in the NTP may be needed, and he asked the Subcommittee to consider this as well as the issue of including endpoints other than cancer in qualitative hazard estimation. He requested also that the Technical Reports Review Subcommittee work on modifying the four proposed statements under d) in the paper if needed.

Dr. Williams said that these statements generate considerable discussion at IARC working group meetings. Dr. J. Ward (NTP) indicated that the statement relating to limited evidence (part d), (ii) was not current with respect to the validated value of mouse liver reliability. Dr. Nelson replied that the statements have stood the test of time even though they are not accepted by all. Drs. Nelson and Rall suggested that, as a trial exercise, the Technical Reports Review Subcommittee and its associated

Review Panel apply the recommended hazard statements to the carcinogenesis bioassay reports to be reviewed February 18.

Action Item: The ad hoc Subcommittee chaired by Dr. Harper should consider how NTP could use other carcinogenesis data as well as other toxic endpoints in assessment of human hazard.

Action Item: The Technical Reports Review Subcommittee should study possible qualifiers and other modifications which might improve the proposed hazard warning statements.

Action Item: The Technical Reports Review Subcommittee and associated Review Panel was asked to apply the four hazard statements to the carcinogenesis bioassay reports to be reviewed February 18. [The Subcommittee and Review Panel did this on a trial basis. However, there was a lack of consensus as to whether these statements or others should be adopted by NTP.]

Conceptual Review of the Animal Bioassay Process: Dr. Moore distributed a paper listing the concepts for which the NTP requested Board approval (Attachment 5: NTP Animal Bioassay Program). He described also the differences between technical peer review and concept peer review. Technical peer review serves to evaluate the scope of the work proposed including the technical soundness and scientific validity, and then may proceed to review and rank contract proposals in relation to these parameters. Concept review focuses on the feasibility and appropriateness of a proposed concept, e.g., 'Is it appropriate to use rats/mice in the animal bioassay to define toxic endpoints other than cancer for a chemical?' Both types of peer review require that at least 75% of the review group be non-government people. Dr. Nelson noted that concept review precedes technical review, and if NTP is to continue using the bioassay, it must have concept review of new guidelines.

The ensuing review by the Board indicated general approval of the concepts for the NTP animal bioassay program. Changes were recommended primarily to broaden or make less restrictive some of the statements. Attachment 4 includes these changes. Dr. Nelson moved that the resultant concept statements be approved. Dr. Horning seconded the motion, and the motion was unanimously passed.

Dr. Moore then said that the concept reviews for proposed NTP initiatives in Cellular and Genetic Toxicology (six concepts) and Reproductive and Developmental Toxicology (three concepts) would be conducted in separate but concurrent open sessions in the afternoon. Following these sessions. the entire Board would reconvene to discuss and vote on the concepts presented.

Automated Data Processing Study -- Final Report on the Review of the Toxicology Data Management System (TDMS): The final report of a three person team of expert consultants (Dr. Raymond K. Neff, Harvard University; Dr. C. Frank Starmer, Duke University; and Mr. Frederic B. Walsh, Hewlett-Packard) was received by NTP prior to this meeting. The report, Review and Evaluation of the Toxicology Data Management System for the National

Toxicology Program, is available on request. Contact Dr. L. G. Hart, National Toxicology Program, P. O. Box 12233, Research Triangle Park, NC 27709; telephone (919) 541-3971, fts 629-3971.

Dr. Neff described the evolution of the study. He stated that the consultants' recommendation to NTP was to use TDMS for meeting the automated data processing (ADP) needs of the animal bioassay programs, even though there were some problems with the system. The consultants' on-site review was performed in July 1980, and some of the problems have been resolved in the interim. He emphasized that NTP needed to better define its performance goals for TDMS.

Dr. Mendelsohn, Chairperson of the ADP Subcommittee, complimented the consultants. Dr. Nelson said that the future role of the Board would be to monitor progress in implementation of TDMS with regard to meeting NTP needs. Dr. Moore said NTP would accept the recommendation and proceed to evaluate TDMS in bioassay laboratories when "intelligent" terminals were available. The first terminals would be installed at Southern Research in February. Data would be captured both with the TDMS terminals and as previously captured for comparison. Terminals would also be installed at Research Triangle Park to allow users and staff to gain experience. Further, terminals and a total data system would be installed into one or more bioassay contractor laboratories later in the year. In the latter, the system would be evaluated by entering the two-year pathology results. Dr. Moore and Dr. R. Hart, Director of NCTR, agreed to meet and plan a course of action for implementation and evaluation of TDMS in the bioassay program. It was recommended that a followup peer review be held within the next year to evaluate improvements and any problems with implementation of TDMS in the bioassay program.

Concept Review of NTP Contract Initiatives in Cellular and Genetic Toxicology: Dr. R. Tennant, Chief, Cellular and Genetic Toxicology Branch, presented the program for this concept review. Dr. M. Mendelsohn, NTP Board, was chairperson. Other Board members were Drs. Harper, Horning and Nelson. Expert consultants who served as peer reviewers were Dr. E. Chu, University of Michigan; Dr. R.J.M. Fry, Oak Ridge National Laboratory; Dr. L. Siminovitch, The Hospital for Sick Children, Toronto; and Dr. G. Williams, American Health Foundation.

Dr. Tennant described the five-year objectives of the program: (1) continued use of the primary screen - the Salmonella assay, and other tests for carcinogenicity; (2) establish contracts for measuring germ cell toxicity, i.e., the Drosophila test system, the mouse heritable translocation assay, and the mouse morphological specific locus assay; (3) establish contracts to estimate background levels of spontaneous human gene mutations, and cytogenetic damage; (4) training programs; and (5) provide support for grants in developmental areas related to the program's mission. A continuing principal goal is to develop and validate test systems using information from emerging research. Dr. Siminovitch said that NTP should be putting some effort into evaluating systems using human cells. Dr. Tennant replied that what he had presented was just our first course of activity, and he briefly described some of the in vitro transformation systems being evaluated.

Dr. E. Zeiger, NTP, then described the ongoing program in genetic toxicology testing. He noted that the mutagenesis testing program had begun as a result of a Congressional mandate. Contracts for microbial screening systems have been in place for about two years. More recently, an in vitro mammalian system, Chinese hamster ovary (CHO) cells, has been validated and is being used to measure chromosomal aberrations and sister chromatid exchanges. A 'second level' system has been established in Drosophila melanogaster. The in vitro microbial and mammalian systems are done in parallel, with all chemicals first being tested in Salmonella. In FY 1981, there will be about 300 test starts in Salmonella, 60 in Drosophila, and 50 in the mammalian cell system. Contract initiatives have been started for the development and validation of rapid screening tests for induction of aneuploidy, using Drosophila and yeast.

Concept Review: The first proposed project reviewed for concept--Development and Validation of a Multiple Endpoint Mutation System in Cultured Mammalian Cells--was presented by Dr. Zeiger. The objectives of the project are to: (1) Develop and test a protocol that can be used to determine the frequencies of both gene and chromosome mutations in a cell line; (2) determine the possibility of detecting other endpoints such as sister chromatid exchange, aneuploidy, and DNA damage/ repair in the same cell line, and (3) test a series of chemicals using the protocol developed.

Dr. Siminovitch said that all of the proposed endpoints could be measured in peripheral lymphocytes. Dr. Williams noted that lymphocytes lacked capacity for metabolic activation. There was considerable discussion and consensus among the reviewers as to the need for a broad RFP in the sense of not restricting the types of cell systems which will be considered, and should include both somatic and germinal cells. It was agreed that there were really two concepts: (1) Is it reasonable to determine the multiple endpoints proposed in cultured somatic cells?, and (2) the RFP should be broadened such that are no limitations on the cell types which will be considered. The peer reviewers unanimously recommended to the Board approval of these concepts.

The second proposed project presented for concept review--Testing of Dyes and Their Metabolites for Mutagenicity in Salmonella--was presented by Dr. Zeiger. The objectives are to: (1) Develop a protocol or series of protocols which will provide reductive metabolism in a Salmonella mutagenesis test system; (2) test a series of chemicals that are known to undergo reductive metabolism in vivo using the protocol(s) developed; and (3) test a series of chemicals using standard oxidative as well as reductive metabolic activation procedures. Dr. Zeiger said that there was a pressing need for a system which can provide metabolic activation for azo-containing dyes which may be metabolized to active mutagens only by reductive/anaerobic pathways.

After some discussion, it was indicated that the proposal should be broadened to apply to any chemical that requires reductive metabolism. Dr. Horning suggested it be retitled to read--Modification of the Salmonella Test for Chemicals that May Be Metabolized to Mutagens Under Reductive Conditions. With this modification, the peer reviewers recommended approval of the concepts by the Board, there being one negative vote.

The third proposed project presented for concept review--Carcinogen Metabolism Monitoring Resource/Reference Laboratory--was presented by Dr. W. Caspary, NCI/NTP. The objectives are:

(1) To establish a resource laboratory capable of monitoring the metabolizing capacity of subcellular fractions (such as S9) and other metabolizing systems;

(2) to determine the variability of the exogenous, metabolizing preparations with respect to enzyme concentration or metabolic profile;

(3) to explore the range of chemical classes that can be metabolized by these exogenous, metabolizing systems; and

(4) to explore the possibility of incorporating these monitoring systems into the laboratories performing the bioassays.

Dr. Horning commented that the S9 (9000 x g) subcellular tissue fraction is an incomplete metabolizing system, and certain reactions involved in metabolic activation of chemicals may be missed. Drs. Harper and Siminovitch said there was lack of clarity in the proposal as to the functions of a resource laboratory. Dr. Williams said it was unclear as to what kind of variability the contract would be looking for. He also stated that a positive control chemical must come from the same chemical class as the unknowns, i.e., one cannot use a limited number of positive controls. Dr. Tennant recommended that the proposal be tabled.

The fourth proposed project presented for concept review--The Potential Hazard from Chemically Induced Transmitted Gene Mutations Using the Morphological Specific Locus Method in Mice--was presented by Dr. M. Shelby, NIEHS/NTP. The objectives are:

(1) To test five (5) environmentally significant chemicals for mutagenicity using the mouse morphological specific locus assay. Data from these tests will be used in the determination of human genetic risk estimations; and

(2) to conduct an in depth study of chemically induced mutation processes in mammalian germ cells. N-Ethyl-N-nitrosourea (ENU), extremely effective at inducing mutations in mammalian germ cells, will be used to investigate a number of variables including dose-response, germ cell stage sensitivity, sex differences, and age effects. Molecular dosimetry studies will be conducted using radioactively labeled ENU.

Dr. Shelby reviewed the background and needs to be met by this project. Dr. Mendelsohn said we very much need to know whether or not chemicals cause heritable mutations. Dr. Shelby said that the project calls for the testing of five chemicals (yet to be selected) over the next three years. Data from the tests will not only provide information on which genetic risk estimations can be made for the five chemicals but will also

serve as a means to evaluate, more thoroughly, the utility of the mouse morphological specific locus assay in assessing chemical risks. Dr. Siminovitch commented that the project could add significantly to an area where there is a paucity of information. The peer reviewers unanimously recommended approval of this concept to the Board.

The fifth proposed project presented for concept review--Determination of Background Levels of Chromosome Aberrations and Sister Chromatid Exchanges in Peripheral Lymphocytes of Humans--was presented by Dr. Shelby. He noted that monitoring of peripheral lymphocytes was the only system which had extensive application in humans for detection of genotoxicity; primarily as a dosimeter for radiation exposure. However, protocols which had been used for lymphocyte monitoring were widely varied precluding comparisons of results, inadequate information was obtained on spontaneous frequencies, a good system for scoring aberrations was lacking, and interpretation of cytogenetic damage in terms of human health effects is limited. Therefore the objectives of this proposal are:

(1) To develop and validate a protocol by which the frequency of the chromosome aberrations and sister-chromatid exchanges (SCE) can be accurately and reproducibly determined in the lymphocytes of humans;

(2) to use the protocol developed to determine the spontaneous frequencies of chromosome aberrations and SCE's in a normal unexposed population of humans; and

(3) to determine the variability in such spontaneous frequencies and, where possible, to define factors affecting variability.

With regard to the determination of spontaneous frequencies and their endogenous variability for chromosome aberrations and SCE's, Dr. Mendelsohn noted that smokers have a frequency of SCEs, up to 25% higher than non-smokers. Dr. Williams questioned the role of the NTP in human monitoring studies. The peer reviewers recommended to the Board approval of this concept, there being one negative vote.

The sixth proposed project presented for concept review--Evaluation of Mouse (In Vivo) Cytogenetic and Sister Chromatid Exchange Endpoints for Identification of Carcinogens and Mutagens--was presented by Dr. Tennant. The objectives are:

(1) To develop an experimental protocol for the determination of the frequency of chromosome aberrations and SCE's in the bone marrow of laboratory rodents, and

(2) to determine the utility of the protocol developed for detecting carcinogens and mutagens by testing a group of coded chemicals, selected by the NTP, in two independent laboratories.

Dr. Williams said that NTP needs a battery of tests to reduce dependence on the carcinogenesis bioassay. There ensued a discussion of which types of tests systems are needed in a battery.

The peer reviewers unanimously recommended to the Board approval of this sixth concept.

Concept Review of NTP Programs in Reproductive and Developmental Toxicology: Dr. Shepard was chairperson for this review. Other Board members were Drs. Dunbar, Hitchcock and Whittemore. Ad hoc consultants were Drs. J. Clark, Baylor College of Medicine, and J. Thomas, University of West Virginia School of Medicine. Drs. C. Kimmel, NCTR, J. Lamb, NIEHS/NTP, and B. Hardin, NIOHS, reviewed ongoing NTP research in reproductive and developmental toxicology at their agencies.

Dr. Kimmel discussed the coordination of NTP programs in reproductive and developmental toxicology at the three agencies: NIOSH, NCTR and NIEHS. Important to this coordination are quarterly meetings by professional staff from the agencies. She described the NCTR contract for conventional teratology testing, and the soon to be initiated collaborative studies in behavioral teratology which would involve up to six laboratories. Also discussed was the project--Reliability of Experimental studies for Predicting Hazards to Human Development. Preliminary results were presented at the Toxicology Forum, February 18, 1981.

Dr. Hardin described NIOSH studies, some of which are not under NTP, e.g., human studies. Studies that are under NTP include the use of Tier II mutagenesis tests for screening: Drosophila sex-linked recessive lethal, rat bone marrow cytology, mouse sperm head morphology, rat dominant lethal, and in vitro unscheduled DNA synthesis in human fibroblasts. A number of chemicals are being screened for teratologic effects by inhalation exposure of rodents. Current emphasis is on development and validation of methods which could be used in a test battery. He described an in vitro teratology test using larval Drosophila which was being evaluated.

Dr. Lamb described the recently completed NIEHS study in which the reproductive toxicologic and developmental effects of the components of the herbicide "Agent Orange" were assessed. He discussed ongoing studies with dibromochloropropane (sperm and dominant lethal effects), and kepone (female fertility and reproduction, subcellular localization).

Concept Review: The first proposed project reviewed for concept--Reproductive Toxicity of Glycol Ethers--was presented by Dr. Hardin. He reported that there were a number of glycol ethers and their alkyl derivatives to which large numbers of industrial workers are exposed. Further, there is a growing body of experimental evidence which indicates some of these glycol ethers are reproductive toxins. The research would have two objectives: 1) to screen chemicals in this family for evidence of reproductive toxicity; and 2) to evaluate results in terms of chemical structure-function relationships. In terms of structure-function, three questions would be addressed, those being the effects on reproductive toxicity of (1) increasing alkyl chain length, (2) end substitution on the glycol, and (3) type of glycol. Four screening tests were proposed which evaluate toxicity to both the male and female reproductive systems. Mutagenic and male reproductive effects would be screened in sex-linked recessive lethal, dominant lethal, and sperm head morphology assays. A rapid screening test recently developed by Chernoff and Kavlock would be employed to screen for teratogenic or other reproductive effects in pregnant females. After some discussion, it was determined that the primary concept for review had to do with evaluation of in vivo tests,

particularly the Chernoff screen, for measuring effects of chemicals on reproduction and development. The concept proposal was retitled--Assessment of In Vivo Developmental and Reproductive Prescreening Tests.

The second proposed project reviewed for concept--Fertility Testing Using a Forced Breeding Test System--was presented by Dr. Lamb. This test system will stress the first generation by studying a larger number of litters than do other in vivo test systems. The second generation will only be tested if no effects of chemical exposure have been noted in the first generation. This experimental design should tell whether or not a chemical can alter reproduction after two generations of chronic exposure. If an effect(s) is detected further studies will be done to determine which sex is affected and possibly which reproductive organ(s) may be a target organ for chemical toxicity.

The third proposed project reviewed for concept--The Research and Development of In Vitro Tests of Teratogenic Potential--was presented by Dr. Kimmel. The proposals derive from the premise that application of in vitro systems in developmental toxicology to chemical screening and risk assessment has not been well addressed. Further, work that has been done is for the most part relatively recent and suffers from the lack of a coordinated approach to methods development and validation. Therefore, three proposals were raised as part of the concept because they are considered important first steps in the development and assessment of in vitro systems as tests of teratogenicity: (1) Design and initiation of a workshop/symposium to include a review of the current state-of-the-art of specific test systems, and, then, evaluation of the applicability of in vitro screening to teratogenic risk assessment; (2) initial validation studies of the most promising systems to help in future standardization and to encourage other laboratories to begin addressing the applicability of their specific in vitro systems to teratogenicity screening; and (3) establishment of a literature review system to enable maintenance of current information on advances in in vitro teratogenesis testing. These three proposals are intended to serve as the initial approach to assessing the potential usefulness of in vitro testing in the area of developmental toxicology screening.

Dr. Kimmel said that the three concept proposals and subproposals fit together in a complementary way. Results obtained should aid in setting priorities as to which chemicals should receive more detailed testing with currently available test systems. Dr. Shepard summarized the discussion, and the peer reviewers agreed to recommend the concepts presented for full Board approval.

Plenary Discussion: The Board of Scientific Counselors met to consider and vote on the concepts presented by the NTP programs in Cellular and Genetic Toxicology, and Reproductive and Developmental Toxicology.

Dr. Mendelsohn led the discussion on the six proposals presented for concept review in Cellular and Genetic Toxicology:

(1) The Potential Hazard from Chemically Induced Transmitted Gene Mutations Using the Morphological Specific Locus Method in Mice - He said that the test was able to score four to seven loci, required 100,000 offspring and cost about $150,000/test. The specific locus test is the

only well-validated method for measuring heritable mutations in mammals. There are very few environmental chemicals shown to be positive in this test, even though they may be mutagenic in other tests. The project proposes to (a) test five environmentally significant chemicals for mutagenicity, and (b) conduct an indepth study of chemically induced mutation processes in mammalian germ cells using N-Ethyl-N-nitrosourea (ENU). Dr. Mendelsohn moved that the concept be approved, Dr. Shepard seconded the motion, and it was passed unanimously.

(2) Modification of the Salmonella Test for Chemicals that May Be Metabolized to Mutagens Under Reductive Conditions - Dr. Mendelsohn moved for approval of the concept with its modified title, Dr. Horning seconded the motion, and it was passed unanimously.

(3) Development and Validation of a Multiple Endpoint Mutation System in Cultured Mammalian Cells - Dr. Mendelsohn said the aim of the proposal was to develop protocols to test for gene and chromosome effects in an in vitro cell line, determine the possibility of detecting other endpoints, and test a series of chemicals. There was consensus by the reviewers that the scope as to the types of cell systems considered should be broad, and there should be emphasis on human relevance. Dr. Mendelsohn moved for approval of the concept, Dr. Horning seconded the motion, and it was passed unanimously.

(4) Carcinogen Metabolism Monitoring Resource/Reference Laboratory - Dr. Mendelsohn said that the reviewers had reservations about this concept proposal in that the mandate was too broad, there was not a sharp enough focus to the concept, it may not be the right approach, and it was too specific for the S-9 fraction, i.e., other activating systems should be considered. The Board members agreed that the concept needed more thought, and recommended tabling at this time.

(5) Determination of Background Levels of Chromosome Aberrations and Sister Chromatid Exchanges in Peripheral Lymphocytes of Humans - Dr. Mendelsohn said this system was unique with regard to experience in monitoring humans for genotoxicity. Lacking is information on background levels of spontaneous frequencies of cytogenetic effects. The concept proposal will address this need. Although the reviewers felt this was not a really imaginative concept, it was important that it be done. Dr. Mendelsohn moved that the Board approve the concept. Dr. Shepard seconded the motion, and it was approved unanimously.

(6) Evaluation of Mouse (In Vivo) Cytogenetic and Sister Chromatid Exchange Endpoints for Identification of Carcinogens and Mutagens - This concept, related to the previous concept, would serve to provide a stronger underpinning of mouse data. Dr. Mendelsohn moved for approval by the Board. Dr. Horning seconded and the motion was approved unanimously.

Reproductive and Developmental Toxicology - Dr. Shepard summarized the concepts presented for review in this program area. The three concepts are prescreening procedures which will be developed to provide a more efficient way of setting priorities for further testing of chemicals. The first concept, Assessment of In Vivo Developmental and Reproductive Prescreening Tests, had to do with evaluating four screening tests for

measuring toxicity to male and female reproductive systems. Emphasis would be given to an in vivo teratology prescreen which involves a seven-day treatment of gravid rats followed by a four-day postnatal observational period. The second concept, Fertility Testing Using a Forced Breeding System, involves evaluating reproductive outcomes of a male-female cohabitation for 120 days. The third concept, The Research and Development of In Vitro Tests of Teratogenic Potential, had to do with a plan for the development, testing and validation of in vitro teratogenesis prescreening assays. Although several in vitro systems would be considered, whole rat embryos in culture appeared to be favored at this time.

Dr. Shepard said that the reviewers recommended approval of the three concepts. Because the in vitro concept was less well defined, he said the review group would like to have input into more specific proposals as they are developed. Dr. Shepard then moved that the three concepts be approved. Dr. Horning seconded and the motion was approved unanimously by the Board.