NATIONAL TOXICOLOGY PROGRAM

BOARD OF SCIENTIFIC COUNSELORS

April 17, 1996

Summary Minutes

National Toxicology Program
Board of Scientific Counselors
April 17, 1996
Summary Minutes

Contents Page Numbers

SUMMARY MINUTES
NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS' MEETING

April 17, 1996

The National Toxicology Program (NTP) Board of Scientific Counselors (the Board) met on April 17, 1996, 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. Kenneth Reuhl (Chairman), Eula Bingham, Elaine Faustman, George Friedman-Jimenez, Carol Henry, David Hoel, Meryl Karol, Claudia Miller, Franklin Mirer, John Mulvihill, and John Stegeman. Expert Consultant to the Board is Dr. Hiroshi Yamasaki. All were present except Drs. Bingham and Hoel.

I. Report of the Director, NTP: Dr. Kenneth Olden, Director, NTP, and NIEHS, said that he was pleased to report an NIEHS budget for FY 1996 with a 6.2% increase over the previous year. The overall NIH budget showed a 5.7% increase. He said we expected to do well in FY 1997, perhaps exceeding the President's budget request. The largest portion of the increases were allocated to the extramural program, especially R01 grants. Contracts received the next largest increase, with most of this being NTP-related, while intramural research was held at 9-10% of the total budget. Dr. Olden said budget hearings were underway and he was scheduled to testify in the Senate on April 24. He said that the reauthorization hearings emphasized themes rather than specific institutes and this approach was well received. He had testified as part of a panel on cancer where the emphasis was on the genetic and environmental basis of cancer.

Dr. Olden noted that an external review of the Institute was to be conducted in 1996 patterned after the recent review of the National Cancer Institute (NCI) by a panel co-chaired by Drs. Michael Bishop and Paul Calabresi. Although not initiated by Dr. Harold Varmus, NIH Director, Dr. Olden had requested that Dr. Varmus endorse the members of the review committee and the issues to be considered. Dr. Philip Hanawalt will be the chair and Dr. Gail Cassell, who had co-chaired the recent review of NIH, will be the co-chair. Included among the issues to be examined are whether the collective intramural and extramural research efforts address the most critical issues in environmental health, whether the balance between basic and applied research is appropriate to meet critical needs, whether there is duplication of research efforts with other NIH institutes or academia, and how can the impact/effectiveness of the Institute's programs best be assessed on an ongoing basis. Dr. Olden said the review would begin in the fall and take 12 months.

In recent recruitments, Dr. Samuel Wilson, University of Texas/Galveston, has accepted the position of Deputy Director and will begin on August 1. He was approved under the new program for Senior Biomedical Research Scientists (SBRS). Dr. Sheila Newton, NIEHS, who has been on detail working with the Assistant Secretary for Health, will replace Mr. Dan Vandermeer, who retired, as Director, Office of Program Planning and Evaluation. Dr. Olden announced that a retreat of the leadership and scientists of the Environmental Toxicology Program would take place in the near future.

During the meeting, Dr. Olden presented certificates and acknowledged the contributions of retiring members of the Board: Dr. Faustman, Dr. Miller, and Dr. Reuhl.

II. Report of the Scientific Director, NIEHS: Dr. Carl Barrett, Scientific Director, pointed out that the NIEHS contributes to the NTP through awarding of extramural grants, through contracts and interagency agreements, and through intramural research. He said a restructuring of the intramural program was in progress with the aim of emphasizing three areas of excellence being developed. One area, fundamental basic biology, is concerned with how environmental agents perturb biological systems leading to disease and dysfunction. Two primary mechanisms are through effects on gene expression or on signal transduction pathways, mechanisms for which there is considerable expertise within the Institute. The four primary types of environmental diseases of interest are cancer, pulmonary disorders, reproductive and developmental abnormalities, and neurological diseases. The other areas of excellence are environmental medicine and pathobiology, and environmental toxicology. Dr. Barrett thought this restructuring would result in better integration toward meeting the needs of both the NIEHS and the NTP.

III. Report of the Director, Environmental Toxicology Program (ETP), NIEHS: Dr. George Lucier, ETP Director, commented that the restructuring should help create better links among basic research, applied research, human studies, and research on risk assessment methodology. Using a flow chart, he described the various offices, laboratories, and branches under the restructuring. Under the Deputy Director, Dr. John Bucher are offices for General Toxicology, which is responsible for monitoring and conducting short and long-term toxicology studies, Program Operations, which manages ETP contract activities, Alternative Models, which in response to the NIH Revitalization Act is responsible for coordinating the development, validation and regulatory acceptance of alternative models, the *Biennial Report on Carcinogens* (BRC) which has been involved in a lengthy process of review of the criteria for inclusion of substances in the BRC with proposed revised criteria awaiting approval by the Secretary, DHHS, and Information Systems and Central Files, which is responsible for handling the large volumes of data generated by the Program. Dr. Lucier described the functions of ETP laboratories and branches. The Experimental Pathology Laboratory is responsible for all pathology and laboratory animal medicine activities associated with the NTP including pathology research on neoplastic and nonneoplastic lesions. The Laboratory of Pharmacology and Chemistry represents a melding of efforts in chemistry, disposition and toxicokinetics, free radical toxicology, and photobiology and toxicology. The Systems Toxicology Laboratory encompasses efforts in organ systems toxicology including reproductive and developmental, immunological, neurobehavioral, and respiratory toxicology. The Laboratory of Computational Biology and Risk Analysis is concerned with developing biologically based mathematical models which can be used in predictions of dose-response, ligand-receptor interactions, species comparisons, and other similar efforts. Dr. Lucier described other activities under the ETP, including NTP Liaison and Scientific Review, which is responsible for organizing and coordinating Board of Scientific Counselors and Board Subcommittee meetings as well as meetings of the NTP Executive Committee, comprised of heads of major health research and regulatory agencies which provide policy oversight. This office is the main communications center for the Program and is responsible for various mailings and other interactions with our constituents including more recently the facilitating of partnership meetings with stakeholders. The office of Research Coordination has responsibilities with Congressional mandates, especially at present the collaborative studies on electromagnetic fields (EMF), and working with the EPA on meeting their priority chemical needs such as needs for studies on water disinfection byproducts. Finally, Dr. Lucier talked about activities in risk assessment research which includes considerable interaction with the EPA in advising them in their development of draft risk assessment guidelines for

carcinogenesis, neurobehavioral toxicology, and reproductive and developmental toxicity, as well as in evaluation of the EPA dioxin guidelines.

Discussion: Dr. Faustman inquired as to the distribution of resources among the three areas of excellence. Dr. Lucier said there was an approximately equal allocation among the three areas, although most of the contract dollars are administered by the ETP. Dr. Karol asked about coordination across the areas. Dr. Lucier responded that the various faculties had members from the different areas and served to facilitate crosstalk. He referred to faculties on Alternatives and Ecotoxicology, Functional Toxicology, Molecular Oncology, Toxicokinetics, and Chemical Nomination. Dr. Barrett commented on intramural grants which have as one purpose that of fostering crosscutting research and collaboration.

IV. Research Partnerships:

Transgenic Models — Dr. Raymond Tennant, NIEHS, said he would describe a partnership in the evaluation of transgenic models for identifying carcinogens, and noted that the NIEHS had put considerable effort over the past 15 years into developing assays to complement or supplant the rodent bioassay. Why transgenics? He gave four reasons: (1) the metabolism and disposition of chemicals seen *in vivo* can be mimicked; (2) the transgenic mice can provide specific genotypic targets and phenotypic responses; (3) the endpoint of interest - tumor induction - can be measured directly; and (4) the influence of strain specific effects can be minimized. He thought the last reason to be the most important in that inbreeding of laboratory rodents amplifies strain-specific responses to chemicals and results in a high frequency of spontaneous tumors. Expectations for transgenic models are that they will primarily identify transpecies carcinogens, i.e., chemicals that induce tumors in both mice and rats in two-year bioassays, that they will not identify chemicals not carcinogenic in two-year bioassays, and they will not identify chemicals that produce strain-specific responses. Dr. Tennant emphasized again that evaluation of transgenic models has been a long-term project at NIEHS. The prototypic lines are the p53 deficient (a knockout mouse) and the TG.AC mouse with a regulated *ras* gene. Both have a very low spontaneous frequency of tumors. He compared chemical effects on $p53^{def}$ for six chemicals with varying (from noncarcinogenic to multisite and multispecies carcinogens) tumor responses in $B6C3F_1$ mice bioassays, noting that the $p53^{def}$ preferentially responds to genotoxic carcinogens. The TG.AC produces skin tumors and can be looked on as a reporter phenotype analogous to using the histidine locus in the *Salmonella* mutagenesis assay. This line carries a mutated *ras* gene which is inducible. Thus, this model is very appropriate for evaluating chemicals for which human exposure is via the skin. A big advantage is that there is a zero to very low spontaneous papilloma incidence. Dr. Tennant showed results with the TG.AC for three chemicals which were nonmutagenic carcinogens in NTP bioassays. For two, *o*-benzyl-*p*-chlorophenol and Mirex, positive results were obtained with TG.AC, while for the third, ethyl acrylate, a route-specific carcinogen (forestomach tumors after gavage exposure), there was not concordance. He also displayed a listing of noncarcinogens in bioassays for which there was complete agreement in TG.AC. Dr. Tennant said that in this initiative we would use weight of evidence, including information on structural alerts, mutagenicity, toxicity, etc., and in conjunction with the $p53^{def}$ line to identify transspecies carcinogens. Chemicals negative in both p53 and TG.AC lines would be candidates as potential noncarcinogens. He said that the important issue regards use of our findings in the regulatory arena where there must be a reasonable confidence of no harm for safety evaluation to be effective. Dr. Tennant noted concerns, one being that transgenic models are artificial, being products of modern gene manipulation. However, he said the two-species inbred rodent bioassay is

also artificial. The other major concern is that transgenics are too sensitive. He said their data did not support this criticism, and besides it is better to err on the side of safety. The bottom line is that these and other transgenic systems need to be validated, and this is the principal impetus for a partnership. The problem is how many assays will have to be done to achieve consensus within the scientific community that the transgenics represent reasonable alternatives to the bioassay. Dr. Tennant reported that the NIEHS/NTP is currently testing 15 chemicals in both lines, including carcinogens and noncarcinogens and mutagens and nonmutagens. As a result of an open meeting at NIEHS on February 9, 1996, partnerships were established for the evaluation and validation of transgenic carcinogenicity models. Four models are currently at the forefront; at the NIEHS, both the $p53^{def}$ and the TG.AC; at the Japanese Central Institute for Experimental Animals and the Japanese National Institute of Hygenic Sciences, the *ras* H2 line as well as at NIEHS; at the Netherlands National Institute of Public Health and Environmental Protection, the xpa repair deficient mouse; and at Boehringer-Ingelheim Pharmaceuticals, the TG.AC. The strategy is to obtain quantitative and qualitative reproducibility of results for a few chemicals among the organizations that will provide a database for comparisons with results from future models. He said that within about two years we will have a very objective basis for evaluating the uses and limitations of these models.

Discussion: Dr. Henry asked about relevance of doses to those that were used in the bioassays. Dr. Tennant said that where possible the same doses have been used and in some cases an expanded dose range was used. With the $p53^{def}$, the same routes were used as in the bioassays. Dr. Miller noted the time savings but wondered about cost savings versus the bioassay. Dr. Lucier said estimates would range from 1/10th to 1/3rd the cost of a bioassay. Dr. Mulvihill asked why these genes were selected out of all the thousands one could choose from. Dr. Barrett pointed out that these were not genes randomly chosen but are the two most commonly altered genes in human cancer. Dr. Reuhl saw the possible propensity for developing many different models which could become prohibitively expensive. His other concern was with whether attention was being paid to linking with normal metabolic profiles and physiologic responses as well of genes such as p53. Dr. Tennant said patterns of toxicity and later in life spontaneous neoplasms were similar to that seen in regular wild type inbred mice. Dr. Lucier commented that forthcoming studies would incorporate measures of metabolic capacities.

Proposed Center for the Evaluation of Risks to Human Reproduction — Dr. Michael Shelby, NIEHS, reported that the purpose of this proposed center was to provide timely, unbiased, scientifically sound assessments of reproductive health hazards associated with human exposures to environmental agents. There presently is no national center that does this. It is envisioned that the Center would be co-funded by Federal environmental health agencies, individual industries or trade organizations, and, possibly, international health organizations. A central office, away from the NIEHS, would be established and permanently staffed by toxicologists and support personnel. Also, a registry of experts representing all relevant areas of scientific expertise would be established, maintained, and regularly updated. From this registry, expert panels would be drawn to deal with each specific exposure assessment. Chemicals or chemical exposures for assessment would be selected by an oversight committee made up of representatives of the funding sources. Literature would be collected and distributed to the expert panel and working meetings organized. The expected product would be a report that would be generated for distribution and publication in the peer reviewed literature. This report would provide a consensus judgment on the potential human reproductive toxicity of the agent or exposure situation under consideration. An important component of the report

will be the specification of research or testing needs that could improve the assessment of reproductive risk. Dr. Shelby concluded that the Center would provide a valuable environmental health service and meet a long-standing public health need for information.

Discussion: Dr. Faustman strongly endorsed this overdue and very important initiative. In response to questions by Drs. Karol and Stegeman, Dr. Shelby stated that the Center could be operational within a year, the proposed budget would range from $400 - 800,000/year with more than half being staff costs, and on average two chemicals or exposure situations could be evaluated per year. Dr. Mirer pointed out what he thought to be a key area for a coordinated evaluation, that being low level occupational exposure to mixed solvents. Dr. Miller asked for examples of likely chemicals or groups of chemicals that might be candidates for review, and how priorities would be made. Dr. Shelby said that among chemicals that might be initial candidates would be bendectin, individual glycol ethers, heavy metals, individual pesticides, and endocrine disruptors. Both public concern and existence of a breadth and depth of reproductive toxicity data would be considered. Drs. Lucier and Olden saw a role for the Board. Dr. Mulvihill said the Center might aid in identifying available data bases, and urged that physical agents also be considered for review. He suggested relevant national, e.g., Teratology Society, and international professional societies as possible funding sources. Dr. Henry commented that since causative agents often could not be identified and etiologic factors such as nutrition could be involved more consideration might be given to disease driven evaluations. Dr. Reuhl asked that the Board be kept abreast of the activity, expressed concern about the stability of multiple funding sources, and hoped that the document developed would be in some sense, 'cutting edge.' Dr. Shelby saw public education as an important component. Dr. Barrett emphasized that the proposed Center was only one 'window' of the NIEHS and NTP's dealing with reproductive toxicity issues.

V. New Research Initiatives:

Effects of Endocrine Disrupting Chemicals on Fertility and Reproductive Tract Cancers — Ms. Retha Newbold, NIEHS, reported that this project had been developed by Dr. Suzanne Snedeker, a former staff scientist, and the concept previously had been approved by the Board. In its present form, the project has been broadened from environmental estrogens to look also at environmental anti-estrogens, androgens, anti-androgens, and progestins. As background, Ms. Newbold cited reports globally with effects of PCBs on wildlife as well as regionally as seen with feminization of alligators in Lake Apopka, Florida, and briefly summarized the extensive studies at NIEHS on the effects of diethylstilbestrol (DES) on the reproductive tracts of female and male mice exposed perinatally. She noted the recent book "Our Stolen Future" which has served to revitalize the 'Sea of Estrogen Controversy.' Ms. Newbold said these various reports have led to the NIEHS asking the question: "Do Environmental Endocrine Disrupting Chemicals Affect Reproduction and Increase Reproductive Tract Cancers?" Thus, the objectives of this initiative are to assess the effects of exposure to environmental endocrine disruptors on reproductive endpoints and the incidence of reproductive cancers in male and female rats over multiple generations. The Sprague Dawley rat will be the animal model because of its low spontaneous incidence of testicular cancer and available data on the effects of DES, methoxychlor, and vinclozolin. The test chemicals will include persistent and currently used environmental estrogens — endosulfan, methoxychlor, and *p*-nonylphenol — an anti-androgen, vinclozolin, and a naturally occurring plant estrogen, genistein. Endosulfan and vinclozolin were chosen for the chronic carcinogenesis study. The chemicals will be administered at effective high doses and at low doses commonly found in the environment as well as a mid-range dose, in the feed to F0, F1, and F2 generations; if effects are

observed, F3 and F4 generations will be evaluated for recovery or persistence of effects. Reproductive effects will be assessed using a variety of outcomes — functional, structural, behavioral, immunologic, and tumorigenic. Ms. Newbold concluded by stating that these studies offer to (1) address the perceived public health problem of the effect of environmental estrogens and endocrine disruptors on reproduction, (2) more accurately assess dose-response relationships of such chemicals on a variety of reproductive and developmental endpoints, and (3) further elucidate the relationship between environmental estrogens and endocrine disruptors and the incidence of reproductive cancers. She said that consideration was being given to conducting these studies through an Interagency Agreement with the NCTR.

Discussion: Dr. Mirer questioned whether the low doses would be likely to show effects. Ms. Newbold agreed but noted that since these are persistent chemicals there was the possibility of seeing effects in subsequent generations. Dr. Lucier said receptor binding might be seen which could help in establishing the shape of the dose-response curve. Dr. Stegeman noting the expense and complexity of this project wondered what was next. Dr. Lucier said that we hoped to obtain a sense of the estrogenicity required to cause toxicity and hoped the research would lead to development of better biomarkers and ultimately to better dose-response models. Dr. Olden pointed out that this was not the only research on endocrine disruptors being supported by the NIEHS. He said there was $7.8 million in grants and with awarding of eight new grants on endocrine disruptor research this total would rise to $10 million.

Health Hazards of EMF (Electric and Magnetic Fields) — Dr. Gary Boorman, NIEHS, said that an association between proximity of homes to high-voltage power lines and childhood leukemia was reported in a 1979 Colorado study; however, flaws in the study resulted in little scientific acceptance. Another study in Colorado in 1988, this by David Savitz, produced similar results and received more scientific attention and acceptance. Over 40 human studies have been completed to date, either residential studies in children or occupational studies with the primary disease endpoints reported being cancer, reproductive toxicity, and neurobehavioral toxicity. Of 15 residential studies on children, three were reported positive for leukemia, two for brain cancer, and the rest as negative. There were similar findings reported in the occupational studies. The lack of clear associations between EMF exposure and human cancer led to the beginning of a study in 1992 by the NIEHS to evaluate the toxic and carcinogenic potential of magnetic fields in laboratory animals. After this study was designed, the National Energy Policy Act was signed into law in October 1992, and provides for a five-year accelerated program with the Department of Energy (DOE) and NIEHS as the lead agencies to explore mechanisms by which electric and magnetic fields might cause human disease or dysfunction. Funds first became available in September 1994. About 80% of the funds have been allocated to 27 NIEHS grants with a focus on cellular and animal studies. The remainder of the funds have been for animal studies on contract and replication studies through Interagency Agreements with FDA and NIOSH at DOE regional facilities. Dr. Boorman summarized the NTP animal studies, noting that the eight week toxicity study was negative, developmental and reproductive toxicity studies had been completed, and the two-year carcinogenicity study was in progress with the in-life phase to end in September. To enhance sensitivity for a weak effect, the two-year study began with 100 animals/group. Independently, the Electric Power Research Institute (EPRI) has a large mouse leukemia study in progress, and the University of Quebec has a magnetic field study beginning with *in utero* exposures in F344 rats with exposures continuing post-natally for two years. This study is nearing completion. He mentioned NIEHS intramural research studies concerned

with melatonin and cancer cell growth, free radicals and magnetic fields, calcium and cell signaling, kinases and magnetic fields, and melatonin, light and breast cancer. Dr. Boorman said the Energy Policy Act requires that the NIEHS Director submit a report to Congress by March 1997 with conclusions on the issue of whether EMF are a human health hazard. The report should be a milestone of Federal research and state where we are, what risks, if any, do EMF pose, and what are future research needs, and also serve as an opportunity for public education. Scientific meetings are planned for 1997 with a focus on hazard assessment to include NIEHS risk assessment staff, the public, and policy makers. Dr. Boorman stated that based on the scientific evidence to date, EMF exposures are unlikely to be a major human health risk but the possibility of a minor health risk can not be ruled out.

Discussion: Dr. Mirer asked whether the findings from the EPRI and Quebec studies would undergo the same peer review process as the NTP bioassays on chemicals. Dr. Boorman said the Quebec studies would and we had offered quality assurance (QA) support for the EPRI studies. Dr. Friedman-Jimenez said that both laboratory and epidemiological studies are needed. Dr. Boorman agreed and noted that NCI child leukemia studies and breast cancer studies in Seattle and Los Angeles are in progress. He commented that better definition and measurement of exposure parameters were needed for epidemiologic studies. Dr. Olden praised Dr. Boorman's efforts in coordination of such diverse efforts within the required time frames.

VI. Validation and Regulatory Acceptance of Alternative Testing Methods - Report of the ICCVAM and OECD Workshops - Future Directions: Dr. William Stokes, NIEHS, said the 1993 NIH Revitalization Act directed the NIEHS to: — develop and validate alternative methods for acute and chronic safety testing, and — establish criteria and processes for the validation and regulatory acceptance of alternative testing methods. He said he would be talking about the latter of these. In 1994, the NIEHS established an *ad hoc* Interagency Coordinating Committee on Validation of Alternative Methods (ICCVAM) comprised of representatives from all Federal research and regulatory agencies involved in developing or using toxicological test methods. The ICCVAM process culminated with development of a draft report in October 1995. Considerations in development of this report were that: the scope of the report should be applicable to all toxicological testing methods; there should be flexibility in the criteria to meet diverse future needs; the broad scientific principles of validation and acceptance should be emphasized; advances in science and technology will increase development of greater numbers of new methods; and there are no established agency criteria or processes. The report was reviewed at an international NTP workshop in Arlington, Virginia, in December 1995, and subsequently, at an Organization of Economic Cooperation and Development (OECD) workshop in Solna, Sweden in January 1996. There were 130 participants from nine countries at the ICCVAM workshop and three breakout groups on validation criteria, regulatory acceptance criteria, and proposals for future directions. A workshop report was published in March. The OECD workshop, comprised of 60 participants from 13 countries, also had three breakout groups on principles and criteria for validation and acceptance, practical approaches to validation, and testing strategies. A workshop report is expected mid-1996.

Dr. Stokes said ICCVAM is now revising the draft report from comments received at both workshops and in response to *Federal Register* announcements. The final report should be ready by this summer and will be sent to the agencies for comment and concurrence. There was consensus reached on criteria for test method validation and for test method acceptance, and Dr. Stokes enumerated these. He described recommendations regarding

the regulatory acceptance process: (1) acceptance of new test methods will be facilitated by a consistent coordinated process of involvement and communication between all stakeholders; (2) acceptance of new test methods will be facilitated by regulatory agency involvement in all stages of development and validation; (3) a Federal interagency committee should be established to serve as a forum for exchange of information and coordination; (4) agencies should develop internal central clearing systems for evaluation of new or revised test methods; and (5) test method guidelines should be harmonized among interagency, international, and cross-international organizations. The NTP workshop participants recommended that the current *ad hoc* ICCVAM or its equivalent should be sustained by establishment of a standing permanent interagency Federal coordinating committee through the NIEHS/NTP, which would serve as an interagency clearinghouse to coordinate review of new methods and as a vital communication link to all stakeholders. It was further recommended that this committee should include representation from Federal research and regulatory agencies, that it should be established within two months after the ICCVAM final report, and that it should receive adequate resources. Dr. Stokes concluded by stating that the overall goal of the ICCVAM is to facilitate validation and regulatory acceptance of new test methods that will provide for improved protection of human health and the environment, and contribute to improved animal welfare through refinement, reduction, and replacement.

Discussion: Dr. Stegeman asked as to how the current initiative to validate transgenic models fit within the recommendations. Dr. Stokes said that when a permanent interagency committee was formed, it would be appropriate for the new ICCVAM to conduct an interagency review of the proposed use of the transgenic models. Dr. Lucier said the NTP efforts in evaluation of transgenics would be consistent with the more broad-based recommendations of the ICCVAM report. Dr. Karol asked whether reduction of animal use was the driving force for ICCVAM. Dr. Stokes said there is a legal requirement that we work toward refinement, reduction and replacement of animal use wherever scientifically feasible. In practical terms, the NTP tries in experimental design to maximize data obtained from each animal used, thereby reducing the total number of animals used. Dr. Bucher commented that a program such as ICCVAM provides a government response to offset the demands of animal rights groups, but ensures a rational approach.

VII. *Biennial Report on Carcinogens* (BRC) - Criteria Review Status - Upcoming BRC Subcommittee Meeting: Dr. Bill Jameson, NIEHS, cited the 1978 legislative authority for publishing the *Annual Report on Carcinogens* (ARC), which was amended in 1993 to the *Biennial Report on Carcinogens* (BRC). He went over the new process through which substances may be approved for listing or delisting in the BRC, noting that initial review by an NIEHS Review Group (RG1), and subsequent review by the NTP Executive Committee Working Group for the BRC (RG2) was the same as before while external peer review by an NTP Board BRC Subcommittee (RG3) was a new addition. The BRC Subcommittee was scheduled to meet for the first time on May 8, 1996. Dr. Jameson said the criteria review process began with review by an *ad hoc* Working Group of the Board in April 1995 followed by review by the Board in June 1995. The Working Group considered two issues: (1) the adequacy of existing criteria for listing substances in future Reports, and (2) the incorporation of mechanistic data as part of the criteria for listing substances in future Reports. Comments received from the members and the public ranged from - retention of current criteria with no change - to - minor revision of existing criteria to incorporate mechanistic information - to - major revision of existing criteria to incorporate all available mechanistic data. During the *ad hoc* Working Group meeting, three breakout groups met to consider these issues. Dr. Jameson reported that the main discussion in the breakout

groups was concerned with the degree of prescription. A majority of the members of the groups felt the criteria: (1) should be revised; (2) should include mechanistic information; (3) should not be overly prescriptive; (4) should not add additional categories; and (5) should not substitute for expert judgment. The Board, at its meeting in June, passed the following resolutions: (1) current criteria should be revised; (2) mechanistic information should be used; (:3) the number of categories should remain the same; (4) there should be a formal mechanism for delisting; (5) the proposed explanatory paragraph should be revised; and (6) there was an awareness that incorporation of mechanistic information will require an expansion of resources. Further reviews were conducted by the NTP Executive Committee Working Group for the BRC, the Public Health Service's Environmental Health Policy Committee, and the NTP Executive Committee. A report of the criteria review and the final recommendations for the BRC criteria for listing or delisting were submitted to the Secretary, DHHS, in February. Final approval is pending.

Dr. Jameson then went over the final proposed revised BRC criteria, comparing them side-by-side with the current or existing criteria. He pointed out modest revisions to category 1 ("Known to Be Human Carcinogens"), these being to add clarifying words (shown in bold face) as follows: "There is sufficient evidence of carcinogenicity from studies in humans which indicates a causal relationship between **exposure to** the agent, **substance or mixture** and human cancer." With regard to category 2 ("Reasonably Anticipated to Be Human Carcinogens"), in 2.a., there were no changes between current and revised criteria, except to remove the 'a.' reflecting Executive Committee discussion that 'a' and 'b' inferred a ranking or prioritization. With regard to category 2.b., the 'b' was removed. A number of changes in this subcategory were made by the Board on June 29, 1995, and the Executive Committee on July 27, 1995. Words, phrases, or sentences removed are shown in bold face in the current criteria as follows: "There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates that there is an increased incidence of malignant tumors: (a) in multiple species **or strains**, or **(b) in multiple experiments (preferably with different routes of administration or using different dose levels), or** (c) to an unusual degree with regard to incidence, site or type of tumor, or age at onset. **Additional evidence may be provided by data concerning dose-response effects, as well as information on mutagenicity or chemical structure.** In the proposed revised BRC criteria, wording added is shown in bold face: "There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates that there is an increased incidence of malignant **and/or combined benign and malignant** tumors: (a) in multiple species **or at multiple tissue sites,** or **(b) by multiple routes or exposures, or** (c) to an unusual degree with regard to incidence, site or type of tumor, or age at onset; **or**". Dr. Jameson reported that reflecting discussion at the Executive Committee meeting on July 27, 1995, a third paragraph or subcategory was added to cover agents supported with mechanistic data (shown in bold face): "**There is less than sufficient evidence of carcinogenicity in humans or laboratory animals; however, the agent, substance or mixture belongs to a well defined, structurally-related class of substances whose members are listed in a previous *Annual* or *Biennial Report on Carcinogens* as either a known to be human carcinogen, or reasonably anticipated to be a human carcinogen or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans."** Dr. Jameson then read a final paragraph which applies to all the criteria and discusses the role of scientific judgment, and other relevant information: "**Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant**

information includes, but is not limited to dose-response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore reasonably be anticipated not to cause cancer in humans."

Dr. Jameson concluded by noting again that the first meeting of the Board's new Biennial Report on Carcinogens Subcommittee was scheduled for May 8 and the purpose was not to review chemicals but to consider process. The Subcommittee will hear from representatives of the intergovernmental review groups, RG1 and RG2, as to how they carry out their reviews of petitions to the BRC. Hopefully, the Subcommittee will come to agreement as to how they plan to conduct reviews of petitions for listing or delisting of substances.

Discussion: Dr. Mulvihill opined that the final phrase of the new third paragraph or subcategory, i.e., "there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.", would produce endless contentious discussion. Drs. Henry and Reuhl commented about additions to the proposed revised criteria unfamiliar to them. Dr. Lucier explained that the third subcategory under "Reasonably Anticipated To Be Human Carcinogens" was added to better define uses of mechanistic information in review of a petition, and the last paragraph was added to better define the role of scientific judgment and uses of other relevant information. Both were added in response to recommendations from the NTP Executive Committee on July 27, 1995. Dr. Mirer was supportive of the paragraphs which he thought demonstrated that mechanism data can be used to support listing or delisting. Dr. Janet Haartz, NIOSH, asked for clarification on any further action on petitions deferred by RG1. Dr. Jameson said the nominator would be notified, deferred petitions would be listed in an appendix in subsequent editions of the BRC, and nomination packages along with reasons for deferral would be provided to RG2 and the BRC Subcommittee. Either committee could request a reconsideration.

VIII. Interagency Collaborative Studies - Status Reports:

Immunotoxicology Interagency Agreement (IAG) Between NIOSH and the NIEHS — Dr. Dori Germolec, NIEHS, said the IAG titled, "Validation Studies in Occupational Immunotoxicology," was established in 1991 to cooperatively determine the immunotoxicity of workplace chemicals in humans, with the goal being to establish an improved database for humans exposed to chemicals known to be immunotoxic in animals. She introduced Dr. Raymond Biagini, NIOSH Project Officer. Dr. Germolec stated the objectives of the IAG were to: (1) establish and validate a sensitive panel of immune tests that would give information on the immune status of individuals exposed in the workplace, and conduct *in vitro* exposure studies with known immunotoxicants to validate these methodologies; (2) conduct field studies designed to determine if there was a relationship between selected chemical exposures and specific alterations in immune function in humans; and (3) evaluate the results of the field studies to determine if immunotoxic changes in animal models predict immune responses in exposed workers. She noted that the testing panel had been validated. The strategy for the field studies has been to examine a panel of endpoints appropriate for the potential immune effects to give a profile of the immunologic status of the individual. Dr. Germolec reported that 400 to 500 people

have been observed to date in the field studies. Completed studies include evaluation of effects of mycotoxin exposure on employees at an underground art museum (immunosuppression of T-cells), lead exposure among smelter workers (negligible immunosuppression related to lead exposure agreeing with animal studies), and egg protein hypersensitivity of workers in an egg processing facility (a potent allergen as demonstrated by positive skin tests and antibodies agreeing with animal studies). For each study, she presented information on the exposed populations, control populations, endpoints measured, selected results and conclusions. Dr. Germolec described a proposed study with latex, noting that about 5,500,000 health care workers are exposed to latex with as many as 500,000 having the potential to become sensitized. At present it appears that it is a small number of soluble protein allergens which are important in latex glove allergy. The proposed study would be a cross-sectional study of health-care workers exposed to latex using incoming nursing students as the cross-sectional control. Along with the usual endpoints, skin biopsies will be taken to measure cytokine profiles. Corresponding animal studies including irritancy studies, the mouse ear swelling test, and the local lymph node assay, will be conducted at the Medical College of Virginia as part of the immunotoxicology testing contract.

Discussion: Dr. Karol asked whether any of the findings were predictive of a clinical outcome. Dr. Germolec said they were in the egg protein study but not the lead study. Dr. Henry inquired as to how NIOSH would use these findings. Dr. Haartz said that if the animal data were predictive it could be used as a basis for developing biological monitoring approaches. Dr. Friedman-Jimenez said these kinds of studies could be very valuable to physicians working in occupational and environmental medicine.

Preliminary Toxicity Evaluations of Complex Industrial Exposures - Proposed IAG Between NIOSH and NIEHS — Dr. Bucher said he saw this proposed agreement helping the NTP decide which of a list of complex substances and mixtures to select for study as well as which aspects of these occupational exposures are most important to study. The listing includes: asphalt fumes, biogenic silica fibers, carbon/graphite fiber composites, cellulose insulation, flour dust, graphite (pitch-based) fibers, machining fluid constituents, mineral particulates, paint dust/paint mist dust, phenol-formaldehyde resin dust, polyester-polystyrene dust, synthetic polymer process emissions, thermoplastic pyrolysis products, welding fumes, and wood dust. He said that NIOSH could provide some of their biomarkers so comparisons could be made between our animal studies and their human studies. Dr. Bucher noted that NIOSH has inhalation exposure capabilities for particulates and fibers that could be utilized in short-term or "Phase 1 Studies" on some of the materials listed. Finally, he commented on the possibility of conducting inhalation toxicokinetics studies under this agreement.

Discussion: Dr. Mirer was pleased to see the NTP moving ahead to design studies on these difficult to study materials. Dr. Henry was supportive and thought this to be an opportunity to make real advances in the toxicology of complex mixtures and substances.

Comprehensive Toxicological Assessment Through the Interagency Agreement Between NCTR/FDA and NIEHS — Dr. William Allaben, NCTR, said that the IAG had been signed in January 1992 and the purpose was to conduct, at the NCTR, comprehensive toxicological assessments on FDA priority chemicals/agents nominated to the NTP. He reported on four chemicals currently being studied under the IAG. The first to be studied is chloral hydrate, a hypnotic in long-time use and the agent of choice in pediatric medicine, for which reports of genotoxicity and increased incidence of liver

tumors in mice led to FDA's nominating it. Dr. Allaben said that two-year bioassays are in progress in mice with the male mice studies including a caloric restriction component. Fumonisin B_1 (FB1) is a mycotoxin contaminating corn products and subsequently processed foods for which there have been reports of association with human cancer. Dr. Allaben said that among mechanistic studies with FB1 were those looking at its possible role in turning on apoptosis and as a tumor promoter. Developmental toxicity studies were completed and two-year bioassays in rats and mice were in progress. Malachite Green is an unapproved drug which has been used in animal medicine and aquaculture as an effective antifungal agent. Dr. Allaben said there had been some problems with bioavailability for one of the two forms of the chemical. When this problem was resolved, 28 and 90-day studies in rats and mice would be initiated. Most recently included under the IAG is urethane, ethanol and combinations of the two, urethane being a known carcinogen and fermentation byproduct of ethanol. An aim is to determine whether ethanol potentiates the carcinogenic activity of urethane. Dr. Allaben said studies in mice were anticipated to begin in mid-summer.

IX. Concept Reviews, ETP, DIR, NIEHS:

Assessment of Chemically-Induced Reproductive and Developmental Toxicity — (Attachment 3) Dr. Robert Chapin, NIEHS, presented the concept, and Dr. Elaine Faustman, Board member, served as principal reviewer. Dr. Chapin stated that the proposal was to continue to perform reproductive and developmental toxicity testing on contract, and to pursue mechanistic and special studies in-house. To highlight the need, he noted that infertility continues to affect about 20% of married couples, and reproductive and developmental toxicity continues to be perceived by the public as important, particularly in view of the recent issues around endocrine disruptor chemicals. Dr. Chapin reviewed accomplishments on this initiative. He noted that definitive hazard identification data had been generated for more than 100 compounds and special studies were ongoing on tamoxifen, nonylphenol, drinking water disinfection byproducts, and pesticides in juveniles. Dr. Chapin related a number of accomplishments in development and evaluation of new methods, cross species toxicity comparisons, studies on mechanisms of testicular toxicity, and activities in risk assessment.

Dr. Faustman said this program represented a unique national resource for which staff and other resources were insufficient to carry out most of the studies in-house and thus the need for a contract. She said there were multiple users of the data developed including public agencies, occupational and industrial groups, clinicians, and public health officials. The methodology being used is current. Some discussion ensued with the Board as to why resources for this area have not increased in view of the need for more data as part of a general discussion about how research priorities are established. Dr. Faustman moved that the concept be approved. Dr. Karol seconded the motion, which was approved unanimously by the Board.

Studies of Chemical Disposition in Mammals — (Attachment 3) Dr. H. B. Matthews, NIEHS, presented the concept, and Dr. John Stegeman, Board member, served as principal reviewer. Dr. Matthews said this represents an ongoing contract operation for which no significant changes have been proposed and is being reviewed as it has been a number of years since the last concept review. The objectives of the project are to conduct investigations into the mechanisms of toxicity, absorption, tissue distribution, metabolism, and clearance of chemicals studied by the NTP. Data obtained from studies of the fate of chemicals in intact animals also provide a foundation on which extrapolation of risks from laboratory animals to humans are based.

Dr. Stegeman stated that this project is an important component in evaluating the toxicity of a chemical and thus an important component of the NTP. The relationship of chemical fate and residues in target and non-target tissues is crucial to interpretations regarding dose-response relationships and mechanisms of action of chemicals. He said the effort and resources required make it necessary to do most of these studies on contract. Scientific uses for the data are clear, although the possible clinical relevance needs to be explored. Dr. Stegeman moved that the concept proposal be approved. Dr. Karol seconded the motion, which was approved unanimously by the Board.

X. Technical Reports Review Subcommittee Activities: Dr. Rick Hailey, NIEHS, reported briefly on the Subcommittee meeting of December 5, 1995, in which the draft Technical Reports for six long-term toxicology and carcinogenesis studies were peer reviewed. He noted that three of the chemicals, nitromethane, phenolphthalein, and tetrafluoroethylene, demonstrated **clear evidence of carcinogenic activity**. Dr. Hailey previewed the 10 draft Reports tentatively scheduled for review at the next meeting of the Subcommittee on December 11-12, 1996. The reports are: 3'-azido-3'-deoxythymidine (AZT)/interferon (IFN), chloroprene, cobalt sulfate, ethylbenzene, isobutyraldehyde, oxazepam, polyvinyl alcohol, primaclone, tetrahydrofuran, and theophylline. He reported that in four of the studies there is evidence of *Helicobacter* infection in mice which may impact on interpretation of these studies in mice, although, nonetheless, he thought that accurate assessment of carcinogenic potential should be possible.

Discussion: Dr. Mirer said he was pleased to see the reports were now giving dose ranges. He commented that in reports where a Maximum Tolerated Dose (MTD) was not achieved there should be a clear statement indicating that a higher top dose could have been used, and in studies where the dose range between species was substantially different, this should be highlighted and an explanation attempted.

XI. Recent NTP Study Results/Accomplishments: Dr. Bucher noted that a document titled, "National Toxicology Program Study Starts and Completions Since March 1995", had been sent to the Board prior to this meeting. He asked whether Board members had questions or comments. Dr. Mirer observed that there were a number of industrially important chemicals with substantial human exposure that were not being studied.

Several Board members commented on the need to evaluate how chemicals are selected for study. Dr. Mirer asked that a discussion of the nomination/selection process be put on the agenda for the next meeting. Dr. Stegeman said emphasis needed to be put on endpoints of toxicity other than carcinogenesis. Dr. Friedman-Jimenez said there needed to be a better fit between what the NTP is studying and the chemicals that are actually harming people. He reported that in New York there is a network of about eight clinics around the state in which there are about 20,000 patient records which record chemicals the patient was exposed to and make an attempt to assess whether there was a possible relationship of chemical exposure to the medical problem. Thus, there are databases that are not being tapped. Dr. Henry agreed that there needs to be established a better linkage between chemical exposure and disease. Dr. Lucier stated that we need better input from all sources to help us set priorities for what we study. He said we would plan to make a comprehensive presentation on the nomination/selection process at the next Board meeting. Also, he asked for their input on specific program areas they would like to hear about, e. g., reproductive and developmental toxicology, and we could plan to have presentations by staff from the three agencies on what the Program is doing in a particular

area. Dr. Mulvihill asked whether this could include what is going on in the Extramural Program since such a large portion of the budget is allocated to extramural activities. Dr. Lucier said presentations would cover what was going on in grants, contracts, and in-house.

ATTACHMENT 1

[*Federal Register*: March 19, 1996, (Volume 51, Number 54, pp 11216-11217)]

[Billing Code 4140-01-P]
Public Health Service
National Toxicology Program
Board of Scientific Counselors' Meeting

Pursuant to Public Law 92-463, notice is hereby given of a meeting of the National Toxicology Program (NTP) Board of Scientific Counselors, U.S. Public Health Service, in the Conference Center, Building 101, South Campus, National Institute of Environmental Health Sciences (NIEHS), 111 Alexander Drive, Research Triangle Park, North Carolina, on April 17, 1996.

The meeting will be open to the public from 8:30 a.m. to adjournment with attendance limited only by space available. Preliminary agenda topics include: discussion of research partnerships on transgenic models; new research initiatives on environmental hormones, 'dioxin-like' chemicals, and health hazards of electromagnetic fields (EMF); activities in development and validation of alternative animal test methods; a final report on the review of the criteria for the *Biennial Report on Carcinogens*; status reports on interagency collaborative studies with NIOSH in immunotoxicity and with NCTR in comprehensive toxicological assessment of chemicals; and review by the Board of concept proposals in the areas of chemical disposition and reproductive and developmental toxicity.

The Executive Secretary, Dr. Larry G. Hart, National Toxicology Program, P.O. Box 12233, NIEHS, Research Triangle Park, North Carolina 27709, telephone (919) 541-3971, FAX (919) 541-0719, will have available a firm agenda with times and a roster of Board members prior to the meeting and summary minutes subsequent to the meeting.

Dated: March 8, 1996

Kenneth Olden, Ph.D.
Director
National Toxicology Program

ATTACHMENT 2

AGENDA
NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS

April 17, 1996

Conference Center, Building 101, Rooms A and B, South Campus
National Institute of Environmental Health Sciences (NIEHS)
Research Triangle Park, North Carolina

8:45 - 9:00 a.m.	Report of the Director, NIEHS	Dr. K. Olden, NIEHS
9:00 - 9:30 a.m.	Report of the Director, Environmental Toxicology Program (ETP) - NTP Executive Committee - Restructuring of the ETP	Dr. G. Lucier, NIEHS
9:30 - 10:15 a.m.	Research Partnerships - Transgenic Models - Proposed Center for the Evaluation of Risks to Human Reproduction	Dr. R. Tennant, NIEHS Dr. M. Shelby, NIEHS
10:15 -10:45 a.m.	*Coffee Break*	
10:45 -11:45 a.m.	New Research Initiatives - Environmental Hormones - TEFs of 'Dioxin-Like Chemicals' in Relation to Carcinogenic Potency - Health Hazards of EMF	Ms. R. Newbold, NIEHS Dr. G. Lucier, NIEHS Dr. G. Boorman, NIEHS
11:45 - 1:00 p.m.	*Lunch*	
1:00 - 1:30 p.m.	Validation and Regulatory Acceptance of Alternative Testing Methods - Report of the ICCVAM and OECD Workshops - Future Directions	Dr. W. Stokes, NIEHS
1:30 - 2:00 p.m.	*Biennial Report on Carcinogens* (BRC) - Criteria Review Status - Upcoming BRC Subcommittee Meeting	Dr. W. Jameson, NIEHS
2:00 - 2:45 p.m.	Interagency Collaborative Studies - Status Reports - Immunotoxicology Interagency Agreement (IAG) - NIOSH/NIEHS - Preliminary Toxicity Evaluations of Complex Industrial Exposures (proposed IAG) NIOSH/NIEHS	Dr. D. Germolec, NIEHS Dr. J. Haartz, NIOSH Dr. J. Bucher, NIEHS

	- Comprehensive Toxicological Assessment through IAG - NCTR/NIEHS	Dr. W. Allaben, NCTR
2:45 - 3:05 p.m.	*Break*	
3:05 - 3:45 p.m.	Concept Reviews	
	- Study of Chemical Disposition in Mammals	Dr. H. Matthews, NIEHS
	- Assessment of Chemically-Induced Reproductive and Developmental Toxicity	Dr. R. Chapin, NIEHS
3:45 - 4:00 p.m.	Technical Reports Review Subcommittee Activities	Dr. R. Hailey, NIEHS
4:00 - 4:15 p.m.	Recent NTP Study Results/Accomplishments	Dr. J. Bucher, NIEHS

National Toxicology Program
Board of Scientific Counselors

April 17, 1996

Eula Bingham, Ph.D. (6/99)*
Professor
Department of Environmental Health, M.L. 056
University of Cincinnati
College of Medicine
Cincinnati, OH 45267
(Occupational and Environmental Health)

George Friedman-Jimenez, M.D., DrPH. (6/98)
Director, School of Public Health
HHC/Bellevue Occupational & Env. Medicine Clinic
Bellevue Hospital, Room CD349
First Avenue and 27th Street
New York, NY 10016
(Occupational Epidemiology, Environmental Justice)

David G. Hoel, Ph.D. (6/96)*
Professor and Chairman
Department of Biometry and Epidemiology
Medical University of South Carolina
171 Ashley Avenue
Charleston, SC 29426-2503
(Biostatistics, Risk Assessment)

Claudia S. Miller, M.D., M.S. (6/96)
Assistant Professor
University of Texas Health Sciences Center
7703 Floyd Curl Drive
San Antonio, TX 78284-7794
(Chemical Sensitivity, Occupational Medicine)

John J. Mulvihill, M.D. (6/98)
Professor of Human Genetics
University of Pittsburgh
Graduate School of Public Health
A 302 Crabtree Hall
Pittsburgh, PA 15261
(Genetic Epidemiology)

John J. Stegeman, Ph.D. (6/97)
Senior Scientist
Biology Department
Woods Hole Oceanographic Institution
Woods Hole, MA 02543
(Alternatives, Xenobiotic Metabolism)

Elaine M. Faustman, Ph.D. (6/96)
Professor and Associate Chair
Department of Environmental Health
University of Washington SC-34
F561, 1705 N. E. Pacific
Seattle, WA 98105
(Developmental Toxicology)

Carol J. Henry, Ph.D. (6/97)
U.S. Department of Energy
Room 5A031 (EM6)
1000 Independence Avenue, S.W.
Washington, DC 20585
(Toxicology, Risk Assessment)

Meryl H. Karol, Ph.D. (6/97)
Professor
Department of Environmental Occupational Health, RIDC Park
University of Pittsburgh
260 Kappa Drive
Pittsburgh, PA 15238
(General and Immunotoxicology)

Franklin E. Mirer, Ph.D. (6/96)
Director
Health and Safety Department
International Union, UAW
8000 East Jefferson Avenue
Detroit, MI 48214
(Toxicology, Occupational Health)

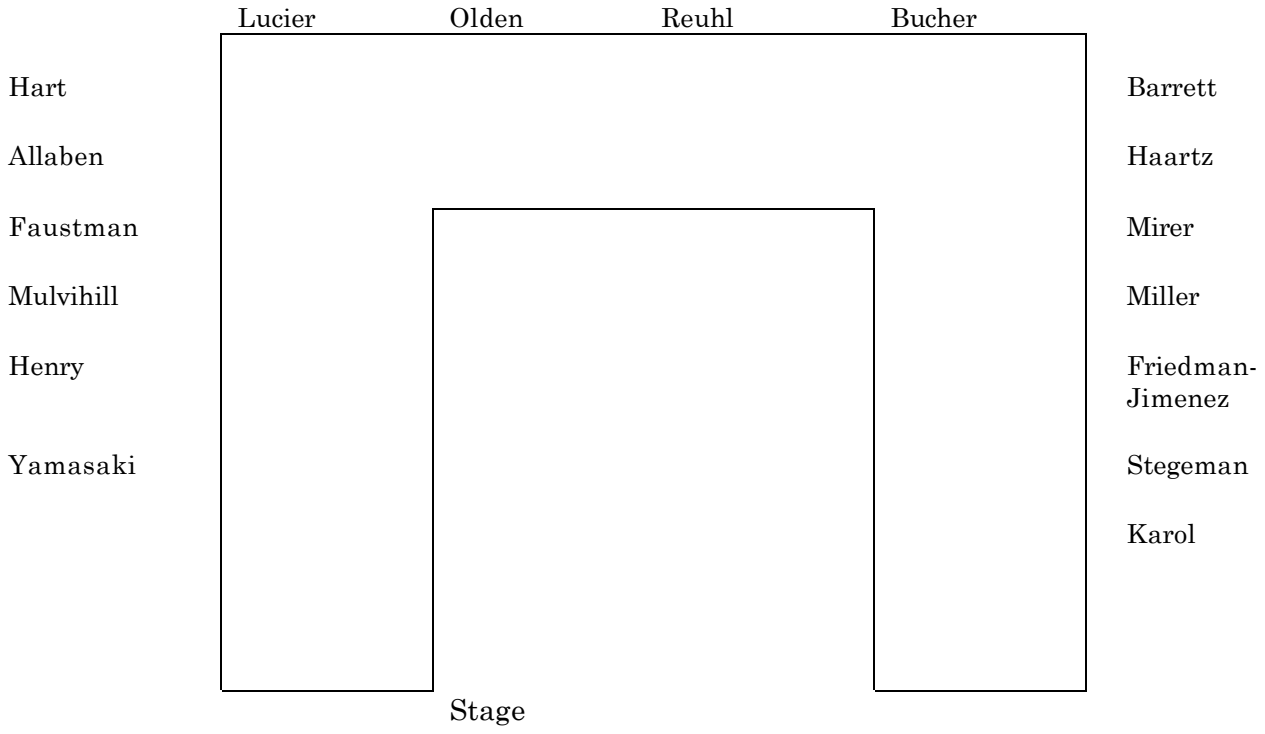
Kenneth R. Reuhl, Ph.D. (6/96) (Chair)
Professor
Department of Pharmacology and Toxicology
School of Pharmacy
Rutgers University
Piscataway, NJ 08855-0789
(Neurotoxicology)

Expert Consultant
Hiroshi Yamasaki, Ph.D. (6/98)
Chief, Unit of Multistage Carcinogenesis
International Agency for Research on Cancer
150 Cours Albert-Thomas
69372 Lyon Cedex 08, FRANCE
(Experimental Carcinogenesis)

National Toxicology Program
Board of Scientific Counselors' Meeting

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

April 17, 1996



ATTACHMENT 3

Environmental Toxicology Program

Division of Intramural Research

National Institute of Environmental Health Sciences

CONCEPT REVIEWS

Prepared for:

National Toxicology Program
Board of Scientific Counselors

April 17, 1996

CONCEPT REVIEWS

National Toxicology Program
Board of Scientific Counselors

April 17, 1996

Table of Contents

BACKGROUND ON CONCEPT REVIEWS

NTP contracts, interagency agreements, and grants support a variety of activities — toxicologic characterization, testing, methods development, and program resources (i.e., chemistry, occupational health and safety, animal production, pathology, quality assurance, archives, etc.).

Prior to issuance of a Request for Proposal (RFP) or a Request for Application (RFA), a project concept review is required. These project concepts in many instances may consist of more than one contract, interagency agreement, or grant. Concept reviews are needed for new projects, recompetitions with changes in statements of work, and projects ongoing for five years or more since the last concept review.

The project concept reviews are conducted by the NTP Board of Scientific Counselors and are open to the public so long as discussions are limited to review of the general project purposes, scopes, goals, and various optional approaches to pursue the overall program objectives. The meeting will be closed to the public, however, if the concept discussions turn to the development or selection of details of the projects or RFPs/RFAs, such as specific technical approaches, protocols, statements of work, data formats, or product specifications. Closing the session is intended to protect the free exchange of the advisory group members' opinions and to avoid premature release of details of proposed contract projects or RFPs/RFAs.

The Board members are asked to review the project concepts for overall value and scientific relevance as well as for fulfilling the program goal of protecting public health. Specific areas should include:

a. scientific, technical or program significance of the proposed activity;

b. availability of the technology and other resources necessary to achieve required goals;

c. extent to which there are identified, practical scientific or clinical uses for the anticipated results; and

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

NATIONAL TOXICOLOGY PROGRAM CONCEPT REVIEW

CONCEPT TITLE: Studies of Chemical Disposition in Mammals

PRESENTER: H. B. Matthews
Chemistry Branch, ETP

OBJECTIVES: Continued investigations into the mechanisms of toxicity, absorption, tissue distribution, metabolism and clearance of chemicals studied by the National Toxicology Program (NTP).

BACKGROUND: Exposure to chemicals encountered in the environment, work-place or food supply can have profoundly negative impacts on human health. The NTP seeks to assess risks associated with possible acute, repeated or chronic exposure to chemicals by investigating a variety of biological effects including carcinogenicity induced on chronic exposure. Studies of the mechanism(s) of toxicity and the fate of chemicals in intact animals are an integral part of the range of NTP studies designed to characterize the toxicity of chemicals. Data obtained from studies of the fate of chemicals in intact animals also provide the foundation on which extrapolations of risks from laboratory animals to humans are based. Knowledge of mechanisms of toxicity also facilitates extrapolation of risks among groups and/or classes of chemicals and thus extends the knowledge gained from individual studies.

Objectives of studies of individual chemicals under the proposed chemical disposition contracts are two fold. Each study is designed to address those physical and chemical properties unique to the compound studied as well as to provide data that will permit structural characterization of the respective chemical class. These studies may also be designed to address the impact of one or more factors such as dose, species, age, sex or route of exposure on the fate and/or toxicity of the chemical(s) studied and the significance of these data to assessments of human health risks.

Chemical disposition studies conducted in support of the NTP have been conducted by a group of in-house investigators, research contracts and an interagency agreement. The contracts have been distributed between university and private research laboratories. The interagency agreement was with a National Laboratory. The present capacity of the program allows approximately 13-15 studies per year. A single contract usually conducts 3-5 studies per year depending on the complexity of the respective studies. The present contract has studied 17 individual chemicals during the past 4.5 years. Some chemicals were subjects of multiple studies. All studies are selected and directed by NTP personnel located at the National Institute of Environmental Health Sciences (NIEHS). The contract(s) obtained under this solicitation will continue the work of a similar contract with an expected expiration date of February 1997.

PROPOSED CHANGES IN THE CURRENT STATEMENT OF WORK:
No significant changes are proposed in the current contract. Changes are not considered necessary, because the current contract incorporates sufficient flexibility to permit any anticipated variations from standard protocol. That is, to permit design of studies to most appropriately address the chemical/physical properties of chemicals studied, the current contract allows variation of the number and range of doses administered, species studied, tissues and biological samples taken, and enzymes assayed. Other biological effects may also be determined as the need arises.

NATIONAL TOXICOLOGY PROGRAM CONCEPT REVIEW

CONCEPT TITLE: Assessment of Chemically-Induced Reproductive and Developmental Toxicity

PRESENTER: Robert E. Chapin, Reproductive Toxicology Group
Toxicology Branch, ETP

OBJECTIVES: To test chemicals for their effects on reproduction and development, to further integrate the developmental and reproductive testing strategies, to increase our understanding of the interrelationships of the various endpoints measured in these studies, to use this understanding to develop improved test methods, and to define mechanisms of reproductive and developmental toxicity.

BACKGROUND: Unwanted infertility affects approximately 2 million U.S. couples. Miscarriages and developmental defects are thought to affect > 800,000 more families each year. While the contribution of environmental toxicants to this burden is unknown, experts polled by the GAO in 1990 estimate that between 10 and ≥ 25% of these health problems will be found to have an environmental cause. Since successful treatment of infertility and birth defects is at best costly, and at worst, impossible, society would benefit most from preventing these effects. Preventing problem exposures must start with knowing which exposures pose a real risk to the exposed individual or fetus. The goals of the Reproductive Toxicology Group are to identify those compounds that produce reproductive or developmental toxicity, to characterize that toxicity, to identify the site and mechanism of action of such toxicants, and to ensure that these data are generated and presented in such a way that they will be useful to risk assessors. These studies use rats, mice or rabbits, and are done both on contract, and in-house.

As a preliminary indicator, reproductive system endpoints are collected for compounds that are being tested for general toxicity during 90-day exposures. These preliminary data serve to identify those compounds that appear to target the reproductive system, and thus may deserve further evaluation. Further evaluation is most often obtained using the Reproductive Assessment by Continuous Breeding design. This generates a comprehensive data set for reproductive effects. Recently, special designs have been devised to address unique data needs for selected compounds that appear to be hormonally active during development. Similarly, for developmental toxicity, a conventional paradigm is followed for most compounds (gestational exposure followed by pre-term structural evaluation). However, the data needs for some compounds dictate either more limited exposures, or more extended evaluations (i.e., of post-natal growth, or performance in specific areas). Since their inception in the early 1980s, our reproductive and developmental toxicity testing programs have evaluated more than 120 chemicals or mixtures. These are the most comprehensive programs of their kind in the U.S., and they are part of the reason why the NTP is considered an 'authoritative body' by California's Environmental Protection Agency charged with evaluating toxicants under Proposition 65.

In-house research efforts, primarily in reproductive toxicology, explore mechanisms and modes of toxicity for specific compounds, investigate effects across species, and respond to specific high-profile needs. As examples, current projects involve identifying and characterizing the distribution of testicular enzymes involved in apoptosis, comparing the responses of rodent and human seminiferous tubules to glycol ether exposure and determining the involvement of unregulated calcium fluxes in that lesion, and

collaborating with EPA to generate neurotoxicity data, immunotoxicity data, and reproductive toxicity data on the adult effects of pre-/peri-natal exposure to pesticides.

In the past 7 years, the program has tested ≈ 60 chemicals for developmental and/or reproductive toxicity, has developed and used a short-term (28-day) test to help identify the most vulnerable sex and process (development, female reproduction, male reproduction), has more fully incorporated rats into the RACB studies, and has continued efforts to collaborate with other Government agencies in collecting additional data from these studies. In the previous contract, approximately 15 chemicals were identified as reproductive toxicants, a comprehensive dataset on boric acid toxicity was developed and utilized in a risk assessment process, an improved method for the *in vitro* evaluation of spermatogenic toxicity was adapted and is now used preferentially, the relationship between some sperm endpoints and fertility has been clarified, and we began to assess the ability of the highly-touted computer-assisted semen analyzers to accurately identify impaired sperm motion that correlates with decreased fertility. Over 30 peer-reviewed publications have resulted from this work in the past 5 years.

PROPOSED CHANGES TO THE CURRENT STATEMENT OF WORK: In the coming year, one award is anticipated: this will be for the reproductive toxicity studies. The estimated capacity for this contract will be 5-6 RACB studies/year, or 12-15 short-term studies/year. This contract represents ≈ 35% of the total testing effort for this Group. Since one priority is optimizing study design and resource use, this contract will: i) use more short-term studies, which are primarily used to help identify chemicals of highest concern for further investigation; ii) use an evolved RACB design to facilitate collection of data on dominant lethality and neuromuscular function, and iii) evaluate some of the pups in the RACB studies for structural defects, thus identifying compounds deserving of a fuller developmental toxicity investigation. Important scientific areas for this effort are likely to be the adult consequences of juvenile or pre-natal exposures, obtaining better dosimetry data concurrent with an adverse effect, optimizing the design of these studies to allow best use with benchmark dose techniques, and close collaboration with the germ cell mutagenesis program within ETP.