

**NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS**

October 27, 1992

Summary Minutes

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SUMMARY MINUTES
NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS MEETING
October 27, 1992

The National Toxicology Program (NTP) Board of Scientific Counselors (the Board) met on October 27, 1992, at the National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina. (Attachment 1: Federal Register Meeting Announcement; Attachment 2: Agency and Roster of Members.) Members of the Board are Drs. Daniel Longnecker (Chairman), Paul Bailey, Arnold Brown, Elaine Faustman, Barbara Hansen, Claude Hughes, Curtis Klaassen, Lawrence Loeb, Fumio Matsumura, Kenneth Reuhl, Ellen Silbergeld, and Peter Working. All members were present except Drs. Faustman and Loeb. Dr. Longnecker acknowledged the new members, Drs. Brown, Faustman, Hansen, Reuhl, and Working.

I. Welcome and Introductory Comments: Dr. Kenneth Olden, Director, NTP and NIEHS, thanked the Board for their efforts in the Advisory Review of the NTP. He noted that the resultant report was published in the Federal Register in July for public comment, and that an open meeting was held in Washington, D.C., on September 11 at which a broad spectrum of comments was received on the report. A majority of the speakers thought that the NTP needed to do both toxicity testing and mechanistic studies. Dr. Olden said he was pleased that most speakers supported the need for both testing and mechanistic research. There were 19 speakers at the meeting and about twice that many written statements received by the Program. He emphasized the openness of the process and the desire for all to be heard who wished to comment on the report and the Program. He said the Program response to the Advisory Review report would be published in the Federal Register to allow for public comment and then presented to the NTP Executive Committee. The final report and Program response then would be recommended to the Assistant Secretary for Health. Dr. Olden concluded by stating again that he was 100 % committed to the NTP and to continued testing as well to going beyond that as the resources permit. New assays are needed and should derive from increased emphasis on science.

II. NTP Response to the Advisory Review Report of the Board: Dr. B.A. Schwetz, Acting Director, Environmental Toxicology Program (ETP), NIEHS, began by noting that the Program in fashioning its response to the Report had also taken into consideration comments received from the public and other agencies. A written copy of the response had been sent to all of the expert reviewers who participated in the Advisory Review and their comments requested by November 10. A revised draft of the Program response would be published for public comment in the Federal Register in late November or December. Dr. Schwetz said that rather than just reiterate what was in the response, he had framed 10 questions he thought the Board would like to discuss after reading the response. As follows:

1) **How will the nomination and selection process be changed?** Dr. Schwetz said there was agreement that the NTP needed to broaden the sources of input as well as seek more nominations for non-cancer endpoints while reevaluating the criteria for these endpoints. Nominations of concepts, issues and hypotheses also would be welcome. Dr. Errol Zeiger, ETP, NIEHS, listed major points raised by the Board, including improving the quality of nominations, more emphasis on non-cancer endpoints, better justifications supporting nominations, and increasing public awareness of the process, while noting that some of these points were already being addressed. Dr. Zeiger said the current avenues of seeking public input on chemicals considered for study would be enhanced to reach academia, labor and public interest groups and the public in an improved manner. Dr.

Zeiger discussed the proposed three levels of review of the nomination. Discussion: Dr. Hughes emphasized the need to reach out to groups or organizations that are not aware of the nomination process.

2) How will we achieve greater emphasis on mechanistic work? -- Dr. Schwetz said the recent NIEHS reorganization would enhance interactions among scientists within the intramural program. He pointed out that a number of NIEHS/NTP studies recently completed, in progress or just underway incorporated mechanistic considerations, e.g., those on methylene chloride, oxazepam, boric acid, and low-frequency electromagnetic fields. "Toxicology Review Teams," including both NIEHS and outside scientists, will be formed to design the research program for new chemicals and issues, to review progress of studies from start to finish, and suggest further studies if needed. Care must be taken in incorporating mechanistic designs not to compromise overall study quality.

3) What impact will this have on the testing program? -- Dr. Schwetz cautioned that an increase in mechanistic work in the absence of an increase in resources would lead to a decrease in chemical test starts. Further, the Board had advised studying fewer agents more completely rather than more chemicals in less detail, a recommendation with which the Program agreed. An important point was that mechanistic studies may not have to be at the expense of testing if intramural scientists at NIEHS, NIOSH and NCTR can be more involved. Discussion: In response to a question from Dr. Reuhl citing lengthy studies of chemicals such as 'dioxin' as to "when is enough enough?", Dr. Schwetz said we need to look to other mechanisms such as grants, and the proposed "Toxicology Review Teams" should be able to aid in making such decisions. Dr. Klaassen questioned the reality of getting intramural scientists involved to any significant extent, and inquired as to how extramural scientists could become more involved in NTP studies. Dr. Schwetz said a number of intramural scientists within the three NTP agencies have expressed interest and this should set an example for others. With regard to extramural scientists, Dr. Schwetz stated that through membership on the "Toxicology Review Teams" extramural scientists could not only provide advice but also have the opportunity to collaborate.

4) How will we get more intramural scientists involved in NTP studies? -- Dr. Schwetz said intramural scientists would be invited to serve on the "Toxicology Review Teams". Another approach, when resources become available, will be awarding of internal competitive grants. Resources will be made available to NIEHS scientists who develop collaborative research projects at the interface between toxicological observations and mechanistic research. Dr. Olden affirmed the intent to encourage submission of applications for internal grants. Discussion: Dr. Hansen asked whether the U.S. has a backlog of untested chemicals. Dr. Schwetz said the NTP was not the mechanism for addressing a long backlog of untested chemicals, but rather the Program needed to choose carefully agents to study that had important public health significance and/or scientific interest that would allow us to test concepts. Dr. Silbergeld inquired as to what extent the NTP had to do 'gap-filling' as opposed to forward-looking and 'inspirational' science, noting the tension between the two goals. Dr. Olden replied that we need to both fill gaps and provide leadership while trying to get industry and other government agencies to do their part.

5) What will be the future role of the NTP in development and evaluation of alternative test systems? -- Dr. Schwetz said the Program agreed with the report that the NTP should foster development of alternative systems. Two considerations are that we would give major emphasis to assays of endpoints where we have good in vivo experience and alternative systems would be preferred that would have mechanistic

applications and not just usefulness as a screen. With limited resources, the NTP has to be selective in what it chooses to study. He cited a useful role of the NTP as bringing together somewhat disparate groups to attack a problem, e.g., developmental biologists and developmental toxicologists to look at a new species and new approaches for evaluating developmental toxicity.

6) How will the broadened range of NTP studies be done? -- Dr. Schwetz commented that contracts and interagency agreements were already in place. To obtain better understanding of animal models, requests for applications (RFAs) and grant mechanisms would be promoted. As a shorter-term bridge between applied and basic science, the use of cooperative agreements would be pursued. And, of course, more intramural involvement with scientists at NIEHS, NIOSH, and NCTR would be sought. Discussion: Dr. Silbergeld expressed concern that all of this implies that fewer chemicals will be entering two-year test starts. Dr. Schwetz responded that NTP-allocated funds cannot be used for other purposes, and further, our intent is not to drop below 10 two-year starts annually. Dr. Olden agreed and said he was working to make the case to policy makers and the Congress that the NIEHS needed a sufficient increase in funding to enable doing more testing and mechanistic studies. Dr. William Allaben, NCTR, described their experience in negotiating cooperative research agreements with industry. Dr. Schwetz said such agreements would be considered as long as potential conflicts of interest can be resolved.

7) Issues surrounding the concept of the MTD. -- Dr. Schwetz stated that the NTP is currently operating closer to a "minimally toxic dose" concept than to the traditional Maximum Tolerated Dose (MTD) in its animal studies. He said the MTD was not solely a problem of the NTP, but hoped that NTP data would help solve the problem of abuse of the MTD. We are trying to have negative studies of value while minimizing confounding toxicological variables. Turning to default assumptions, Dr. Schwetz said we were working to lessen the dependence on them. Hopefully, the proposed toxicology review teams will design research programs that minimize the need for default assumptions.

8) What mechanisms will be used for peer review of NTP reports? -- Dr. Schwetz commented that one of the strengths of the NTP was that its data already receive more public scrutiny than any other program. We will continue to use the Technical Reports Review Subcommittee of the Board to peer review in public sessions the findings from long-term toxicology and carcinogenesis studies with votes taken as in the past. He proposed that short-term toxicity studies be peer reviewed by mail in the future using Board or Subcommittee members as well as ad hoc reviewers with expertise selected on the basis of relevant toxic endpoints. Discussion: Drs. Longnecker and Klaassen suggested a compromise whereby controversial issues arising in a mail review also could be brought to a Subcommittee meeting. Dr. Schwetz agreed.

9) The NTP as the focus for the national toxicology strategy. -- Dr. Schwetz stated that we (the NTP) think we are already a focus, if not overtly, at least by example, and have an impact on national toxicology issues. If we make our work subservient to a formal strategy, we'll have to defend the strategy rather than focus on our work. Discussion: Dr. Klaassen commented that his workgroup at the Advisory Review had viewed a national strategy as a good idea whether or not it was undertaken by the NTP, NIEHS, or some other group. Such a strategy would involve assessing what is being done in the U.S. and defining the gaps. He acknowledged that there may be too many expectations of the NTP in view of their limited resources but said that the NTP does have a lot of influence in the toxicology community, disproportionate to the size of its budget. Dr. Olden called the strategy proposal an excellent suggestion and said the NTP should help in developing a sense of leadership and be involved in long-term planning.

10) **Summary--what will be different?** -- Dr. Schwetz said the Program would continue a) to maintain a balance between testing work and mechanistic studies, b) to develop, evaluate and validate alternative systems, c) to look to more innovative approaches to evaluating toxicity, d) to put more emphasis on noncancer endpoints including more mechanistic considerations, and e) to involve more scientists from the NIEHS intramural program and from other laboratories in design and execution of research. We are committed to a more extensive program of work on as many chemicals as can be handled within the system. Discussion: In replying to a question from Dr. Longnecker, Dr. Schwetz said the Program response to the report reflects input from all three agencies. Dr. Janet Haartz, NIOSH, stated that the extent of the interactions and collaborations among the three agencies was much more extensive than was generally recognized by scientists outside of the NTP, and that this review was only one example of the collaborations.

III. Summary of Public Comments on the Report: Dr. Larry Hart, ETP, NIEHS, reported that, as agreed, the final report of the Advisory Review of the NTP was published in the Federal Register on July 17, 1992, and public comments were requested on the report as well as suggestions of other activities to improve the NTP. Additionally, a public meeting attended by about 100 persons was held in Washington, D.C., on September 11, 1992, at which time comments were received from 19 speakers. Of these, eleven were from industry or representing industrial trade associations, while there were two speakers representing labor, two from public interest groups, two Federal scientists representing themselves, a representative for an animal protection group, and a private citizen. Without exception, the industrial speakers expressed general support for the recommendations in the report, especially the call for more mechanistic research in study design, while being in less agreement on whether there should be less testing, the same as now, or more. These speakers thought the use of the MTD should be reevaluated. Other speakers encouraged more studies of mechanisms but not at the expense of doing bioassays, with two noting that there was no current alternative to the bioassay for predicting human cancer risk. There was general support for an NTP role in development and validation of alternative test systems to replace the use of whole animals. With regard to improving chemical nomination and selection, there was some support expressed for selection of natural substances as well as opposition to selecting and testing pharmaceuticals and chemicals that should be tested by industry. One subject not treated specifically in the report that drew comments from several speakers was the Annual Report on Carcinogens (ARC) with several stating that the criteria for inclusion of substances needed to be reevaluated to include the use of mechanistic information. Others said the ARC was an important public health tool and there should be no delays in its release.

There were 38 written statements received prior to the Board meeting with the sources being similar to those who spoke at the public meeting; many of the comments received mirrored those received in the public meeting. Two writers supported a call for more interaction, even collaboration, between NTP scientists and industrial scientists. Two proposed that, because of limited NTP resources, testing be shifted to industry where possible. Thirteen correspondents referred to the ARC, the comments primarily echoing those received at the public meeting. All of the oral and written comments received from the public were promptly provided to NTP staff at the three agencies for their review and consideration in the process of formulating the Program's response to the recommendations of the Advisory Review report. Discussion: Dr. Clay Frederick, Rohm and Haas Company, commented that he was unaware of any NTP mechanistic data being used in development of the ARC, and hoped that it would be in the future. Dr. James Fouts, NIEHS, said the Scientific Review Committee and the NTP Interagency Working Group had been grappling with this issue and had recently made a recommendation about inclusion of mechanistic data to the Director, NTP.

IV. Reorganization of the NIEHS Intramural Programs -- Impact on the NTP: Dr. John McLachlan, Director, Division of Intramural Research (DIR), NIEHS, discussed the proposed new organizational structure for intramural research within the NIEHS. The reorganization combines three existing divisions, Division of Intramural Research, Division of Biometry and Risk Assessment, and Division of Toxicology Research and Testing under a single Division of Intramural Research containing four major programs in Environmental Toxicology, Environmental Carcinogenesis, Environmental Biometry and Epidemiology, and Environmental Biology and Medicine. The new structure is consistent with efforts to improve the NIEHS contribution to the NTP by assuring that the latest basic research findings and advances in biotechnology are accessible for interface with toxicology studies. Dr. McLachlan said the reorganization would foster cross-cutting research citing a revolution in modern biology and chemical concepts that can be used to redefine toxicology. Formalized committees composed of senior scientists, branch/ lab chiefs and principal investigators from across programs have been formed to look at some cross-cutting issues, research on risk assessment being an example. He called attention to development of a clinical studies program, which he said would allow NIEHS scientists to proceed from hazard identification through basic biology to epidemiology and prevention. Discussion: Dr. Hughes observed that clinical scientists often don't talk to basic scientists and wondered how interactions could be assured. Dr. McLachlan responded that there would be incentives for interaction as well as pressure in terms of the priority-setting process and resource allocation. Dr. Reuhl expressed concern about there being too many committees which could take away from the spontaneity needed for effective collaboration. Dr. McLachlan acknowledged his concern while noting that there are not as many committees as it sounds, the aim is to return priorities to working scientists. Dr. Olden stated that he thought we had accomplished the most difficult task in creating a vehicle for interaction, i.e., the reorganization, and he didn't sense that this had been imposed on people; the structure came from the bottom up.

V. Procedure for Release of Preliminary Findings from NTP Studies: (Attachment 3) Dr. Schwetz said the early release of data is important both from the standpoint of public health and also from the standpoint of the Board's Technical Reports Review Subcommittee. In the past, two considerations for early release have been 1) that there were positive findings that were highly statistically significant, and 2) that large numbers of people were potentially being exposed to the chemical. This issue had been brought before the NTP Executive Committee several times in the past, and then, following Dr. Olden's request that it be reviewed again as part of the Advisory Review, a revised procedure was brought before the Committee at their May and September, 1992, meetings. The Committee endorsed the revised procedure and its publication in the Federal Register to allow public comment, which occurred on October 6. Dr. Schwetz discussed earlier NTP two-year studies where there was early release of data. Under the current proposal, the following criteria are important in deciding whether or not to consider early release: (1) nature of the toxic effect -- life threatening or irreversible effects would lend more urgency; (2) dose level relative to levels of human exposure; (3) the number of people potentially exposed; (4) length of time from identification of effect to draft study report -- if only a few months, such as for a short-term toxicity study, early notification might not make a difference while for a chronic carcinogenicity study, the two years between necropsy and the pathology working group (PWG) report could; and (5) pending regulatory activities. During the almost four years from time of final necropsy to publication of the final Technical Report, there are two points where early release is most likely with the first being after necropsy and receipt of the final laboratory report of chemicals for which there is such a substantial

tumor response that subsequent QA and pathology reviews are unlikely to impact the conclusions. The second is after the PWG review when the pathology data have been verified.

Discussion: In response to a question by Dr. Hansen as to whether the lengthy process associated with a long-term study can be shortened, Dr. Griesemer said the first eight months from necropsy to final laboratory report could not be shortened. In response to Dr. Bailey, Dr. Griesemer said where there was a significant incidence of early tumors or toxicity we would certainly consider reporting early. Dr. Bailey commented that under TSCA guidelines from EPA, industry is required to notify the Government of unusual toxicity within 15 days.

VI. Role and Responsibilities of the NTP Board and NTP Executive Committee: Dr. Schwetz stated that in view of the changes arising from the Advisory Review and the reorganization of the NIEHS intramural program there needed to be a clarification of the roles of the NTP's major oversight bodies, the Board of Scientific Counselors and the Executive Committee. He defined the Board and its responsibilities: The Board, composed of non-governmental scientists, reviews the Program for scientific adequacy and helps identify program needs, assisted on particular issues by ad hoc scientists with relevant expertise. He defined the Executive Committee and its responsibilities: The Executive Committee, composed of the heads of Federal health research and regulatory agencies, serves as NTP's major advisory group on research and testing needs, on selection and priority-setting for specific chemicals to be studied, and as a forum for discussion of science policy issues and information exchange among agency heads. The Committee also reviews and approves the NTP Annual Plan.

The Board will continue to meet twice a year. Prior to the first meeting of the fiscal year in the fall, the Program will have decided on its plan of work for the year, and this meeting will be to review plans and selected research results. Agenda items will include: a) plans for contracts or interagency agreements for the year; b) chemicals to be evaluated and for what endpoints; c) toxicological issues, hypotheses, and methods to be evaluated; d) formation of new toxicology review teams; e) updates on efforts of existing teams; f) plans to sponsor symposia, workshops or special-function committees; g) review of selected ongoing research programs; h) update on meetings of the Technical Reports Review Subcommittee; and i) other scientific issues as appropriate. The second meeting of the year to be held in the spring will be to review progress against the plan of work, i.e. results and accomplishments. Agenda items will include: a) summary of allocation of contract/agreement resources; b) summary of studies completed to the peer review stage and plans for additional studies; c) reports from toxicology review teams; d) outcomes of symposia, workshops, and special-function committees; e) review of selected ongoing research programs; f) update on meetings of the Technical Reports Review Subcommittee; and g) other scientific issues as appropriate.

Dr. Schwetz said the NTP Executive Committee meetings would follow the Board meetings in the fall and spring. Agenda for the fall meeting will include: a) a summary of the fall Board meeting and the NTP work plan including chemicals for evaluation, toxicology issues, and a review of toxicology review teams, with emphasis on interagency needs and participation; b) a discussion of the NTP Annual Plan with modification if necessary or recommendation of approval to the Secretary, DHHS; and c) other policy or scientific issues as appropriate. The agenda for the spring meeting includes: a) discussion of any significant changes to the plans as approved in the Annual Plan; b) highlights of the spring Board meeting, with emphasis on interagency participation; and c) other policy or scientific issues as appropriate.

Dr. McLachlan discussed the role and responsibilities of the DIR Board of Scientific Counselors. He said this board was analogous to that of boards of scientific counselors at the other NIH institutes and its sole function was to peer review the intramural scientists and their research. Dr. McLachlan commented on the National Advisory Environmental Health Sciences Council (NAEHSC) which reports to the Director, NIEHS, and advises on grants as well as on the overall health and directions of the Institute. The Chairs of the DIR and NTP Boards report to the Council yearly. He said the problem was to determine the best way to establish effective liaison between the two Boards.

Discussion. In response to a question from Dr. Silbergeld about scope of review, Dr. McLachlan said testing and methods development activities would be reviewed mainly by the NTP Board. Dr. Allaben noted that the NCTR had its own Science Advisory Board but NTP-related activities were also brought before the NTP Board. Dr. Haartz commented that collaborative activities that are both NTP-related and involve NIOSH intramural programs have been on occasion reviewed by the NIOSH Board of Scientific Counselors and the NTP Board. Drs. Olden and Mc Lachlan said they were still thinking about how to establish effective liaison between the two boards, which could involve having a member from one board sit in with the other board or there could be a merging of the boards for a particular review function. Dr. Olden said that one important objective in having a single intramural program was to establish uniform standards for quality. Dr. Klaassen cautioned against trying to apply the same evaluation criteria to a scientific staff with such diverse major responsibilities. Dr. Longnecker commented that this caution would be more relevant to internal promotion/tenure committees. Dr. Silbergeld stated that she thought it important that the Board maintain a role in assessing whether the goals of the NTP are being met.

Dr. Schwetz discussed proposed toxicology studies with styrene that would be appropriate for peer review by the NTP Board and toxicology studies with dibutylphthalate that could involve laboratories in several components of the intramural program and would be appropriate for review in part by the NTP Board and in part by the DIR Board.

VII. Update on Activities of the Technical Reports Review Subcommittee: Dr. Scot Eustis, ETP, NIEHS, gave the Board a progress report on the most recent (November 1991 and June 1992) and upcoming (December 1-2, 1992) meetings of the Subcommittee. He provided the Board written summary information noting that five two-year toxicology and carcinogenesis study reports and six short-term toxicity study reports were reviewed in November 1991 while eight two-year and five short-term reports were reviewed in June 1992. Dr. Eustis reported that for the 13 two-year study reports, a majority of the Subcommittee concurred with the levels of evidence for carcinogenic activity for all sex/species experiments in 12 and for three of four in the 13th study report. With regard to the upcoming meeting on December 1-2, he said six two-year and five short-term study reports were scheduled for peer review.

VIII. Concept Reviews, ETP, DIR, NIEHS: Dr. Schwetz commented that all four concepts were continuations of ongoing work.

(1) Developmental Toxicity Testing and Methods Development -- (Attachment 4, p. 2) Dr. Jerrold Heindel, ETP, NIEHS, introduced the concept, and Dr. Claude Hughes, Board member, served as principal reviewer. Dr. Heindel said the objective was to continue testing for developmental toxicity via conventional in vivo protocols, while at the same time developing and/or validating alternative model systems which may utilize alternative species and designs either in vivo or in vitro. As an example, he noted the collaborative effort with the Army to validate the FETAX system.

Dr. Hughes stated that this was an important concept worthy of support. Dr. Silbergeld asked whether there would be an integration of reproductive and developmental effects, and in both parents. Dr. Heindel said this would be done. Dr. Richard Griesemer, Deputy Director, NIEHS, noted that the NTP had a Congressional mandate to develop/validate alternative assay systems. Dr. Hughes moved that the concept be approved. Dr. Bailey seconded the motion which was approved unanimously by the Board.

(2) Pathology Archive -- (Attachment 4, p. 3) Dr. Scot Eustis, ETP, NIEHS, introduced the concept, and Dr. Daniel Longnecker, Board chair, served as principal reviewer. Dr. Eustis said the NIEHS has maintained the NTP archives since 1984 and the principal objective was to provide secure storage and retrieval for all documents, including pathology specimens, associated with toxicology and carcinogenesis studies conducted by the Program. The Archive coordinates and tracks data flow from study laboratories, inventories and files materials, reviews pathology data and specimens, and supports NTP and outside auditors in their reviews. Samples may be and are used for intramural research studies, e.g., studies on oncogenes and tumor suppressor genes.

Dr. Longnecker said it was obvious that this contract provides necessary services to a very meritorious part of the Program, and the more recent and increasing use of the archival materials for research only enhanced its value. Dr. Brown asked whether older materials were discarded to alleviate storage problems. Dr. Eustis said paper data was put on microfiche while older tissue samples and blocks were discarded if there was no indication of further need. Dr. Brown moved that the concept be approved. Dr. Longnecker seconded the motion which was approved unanimously by the Board.

(3) Pathology Support -- (Attachment 4, p.5) Dr. Eustis introduced the concept and Dr. Longnecker served as principal reviewer. Dr. Eustis said the objectives were a) to provide pathology support for NTP studies at contract laboratories and at NIEHS including necropsy, histology, histopathologic interpretation, evaluation of clinical pathology data and data entry, and preparation of samples and participation in pathology working group (PWG) reviews, b) to evaluate hematologic, clinical chemical, and urinalysis data from all prechronic and chronic animal studies, and c) pathology support in providing professional assistance for PWG reviews.

Dr. Longnecker said this contract provided an obvious contribution to quality control in the Program and he supported continuation. Dr. Brown moved that the concept be approved. Dr. Longnecker seconded the motion which was approved unanimously by the Board.

(4) Pathology Quality Assurance -- (Attachment 4, p. 4) Dr. Richard Hailey, ETP, NIEHS, introduced the concept, and Dr. Longnecker served as principal reviewer. Dr. Hailey stated the primary objective was to continue to provide pathology quality assurance for the NTP's short-term toxicity studies and long-term chemical evaluations in rodents by ensuring the accuracy and consistency of pathology diagnoses. He said the contract had served the NTP well and the need still existed. Dr. Hailey noted that with likely more emphasis on mechanistic studies, there is an even greater need to better characterize toxic lesions. The overall level of effort probably would be less since there are currently fewer NTP long-term studies being started.

Dr. Longnecker commented that this concept represented an important part of the quality control process which contributes to the Program's reputation for excellence. Dr. Griesemer noted that the excellent quality assurance aided in reducing the error rates in NTP studies to a most acceptable level. Dr. Brown moved that the concept be approved. Dr. Longnecker seconded the motion which was approved unanimously by the Board.

Meeting to Review Individual Grant Applications in the Areas of the Behavioral and Neurosciences:

Scientific Review Administrator: Dr. Teresa Leviton (301) 496-7025.

Date of Meeting: October 9, 1992.

Place of Meeting: Lowes New York Hotel, New York, NY.

Time of Meeting: 2 p.m.

Meeting to Review Individual Grant Applications in the Areas of the Behavioral and Neurosciences

Scientific Review Administrator: Dr. Robert Weller (301) 496-7906.

Date of Meeting: October 10, 1992.

Place of Meeting: Holiday Inn, Chevy Chase, MD.

Time of Meeting: 9 a.m.

Meeting to Review Individual Grant Applications in the Areas of the Behavioral and Neurosciences

Scientific Review Administrator: Dr. Robert Weller (301) 496-7906.

Date of Meeting: November 6, 1992.

Place of Meeting: Holiday Inn, Chevy Chase, MD.

Time of Meeting: 9 a.m.

(Catalog of Federal Domestic Assistance Program Nos. 93.306, 93.333, 93.337, 93.393-93.396, 93.837-93.844, 93.846-93.878, 93.882, 93.883, National Institutes of Health, HHS)

Dated: September 24, 1992.

Susan K. Feldman.

Committee Management Officer, NIH

[FR Doc. 92-24159 Filed 10-5-92; 8:45 am]

BILLING CODE 4140-01-M

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 October 27, 1992.

The meeting will be open to the public from 9 a.m. to adjournment with attendance limited only by space available. The preliminary agenda topics with approximate times are as follows:

9 a.m.-12 noon—The NTP staff will present responses to the recommendations in the Advisory Review Report of the Board (*Federal Register* 57, No. 138, pp. 31721-31730, July 17, 1992), and provide a summary of public comments received. There will be a discussion of the proposed procedure for release of preliminary findings from NTP studies including comments received by agencies on the NTP Executive Committee. The impact of the recent reorganization of the NIEHS

intramural programs and reordered research priorities on the NTP will be discussed.

1 p.m.-2 p.m.—Discussion of the role and responsibilities of the NTP Board within the context of the reorganized NIEHS Intramural Program.

2 p.m.-3 p.m.—(1) Update on Activities of the Technical Reports Review Subcommittee. (2) Concept Reviews.

Adjournment

The Executive Secretary, Dr. Larry G. Hart, National Toxicology Program, P.O. Box 12233, Research Triangle Park, North Carolina 27709, will have available a roster of Board members and other program information prior to the meeting and summary minutes subsequent to the meeting.

Dated: September 30, 1992.

Kenneth Olden.

Director, National Toxicology Program.

[FR Doc. 92-24160 Filed 10-5-92; 8:45 am]

BILLING CODE 4140-01-M

National Toxicology Program; Request for Comments on Proposed Procedures for Release of Preliminary Findings From National Toxicology Program (NTP) Studies**Background**

Dr. Kenneth Olden, Director of the NTP, has as one of his major goals to assure that the Program serves the public health by strengthening its role as the Nation's premier toxicology research and testing program. To accomplish this goal, Dr. Olden asked the NTP Board of Scientific Counselors, the primary scientific oversight body for the NTP, to review three specific issues of the operation and function of the NTP. Their findings and recommendations were published in the *Federal Register* 57, No. 138, 31721-31730, July 17, 1992.

A fourth issue, for which advice was sought, was concerned with how to improve the procedures for alerting regulatory agencies and the public about test results on chemicals (particularly data which suggest potential hazard to humans from chemicals of widespread importance). The NTP Executive Committee was asked to review this issue separately.

Action

To aid the Committee, Program staff drafted "Proposed Procedures for Release of Preliminary Findings from National Toxicology Program (NTP) Studies", which is attached to this announcement. The NTP seeks written comments and views on the proposed procedures and will consider those received by October 23, 1992. However,

comments will be accepted after this date and used if possible. Comments should be addressed to Dr. Larry G. Hart, NIEHS, P.O. Box 12233, Research Triangle Park, North Carolina 27709, FAX 919/541-2260.

Dated: September 30, 1992.

Kenneth Olden.

Director, National Toxicology Program.

Proposed Procedures for Release of Preliminary Findings From National Toxicology Program (NTP) Studies

Periodically, NTP studies yield results that are judged to have such a significant potential impact on public health that release of the results on a preliminary basis is warranted. These have most often occurred with the rodent cancer studies, and less frequently in studies with non-cancer endpoints. Although many NTP studies give results that are suggestive of a potential hazard associated with exposure to a chemical, the relative strength of the "signal" depends on a variety of factors including the consequence of exposure (death, cancer), the effective doses required in relation to the human exposure, the numbers of people potentially exposed, and other factors. It has been NTP policy to alert the nominator, various government regulating agencies and others as deemed appropriate, to findings that are not yet in a final peer review form, when the Director has deemed such an early release of data to be in the public interest. The purpose of this document is to propose for your consideration a more formal procedure for handling such events.

Issuing Official: Director, NTP.

Issued to:

1. Assistant Secretary for Health, DHHS
2. Director, NIH; Director, NIOSH; and Commissioner, FDA
3. NTP Executive Committee
4. Nominator of agent for study
5. Private sector individuals or organizations who have expressed an interest

Nature of Communication: Written summary of protocol including agent, test species, response of concern (tabulated summary of preliminary findings limited to the responding organ or tissue), and any possible study confounders.

Timing of Notification: Assistant Secretary of Health, DHHS, followed by Director, NIH; Director, NIOSH; and Commissioner, FDA, within 24 hours. Notification of NTP Executive Committee, study nominator and others as appropriate within 48 hours.

**AGENDA
BOARD OF SCIENTIFIC COUNSELORS
NATIONAL TOXICOLOGY PROGRAM**

October 27, 1992

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

9:00 a.m.-9:15 a.m.	Welcome and Introductory Comments	Dr. K. Olden, NIEHS Dr. D. Longnecker, Board Chair
9:15 a.m.-10:45 a.m.	NTP Response to the Advisory Review Report of the Board	Dr. B. Schwetz, NIEHS Dr. E. Zeiger, NIEHS
10:45 a.m.-11:00 a.m.	BREAK	
11:00 a.m.-11:15 a.m.	Summary of Public Comments on the Report	Dr. L. Hart, NIEHS
11:15 a.m.-11:30 a.m.	Public Comment and Discussion	
11:30 a.m.-12:00 noon	Reorganization of the NIEHS Intramural Programs -- Impact on the NTP	Dr. J. McLachlan, NIEHS
12:00 noon-1:00 p.m.	LUNCH	
1:00 p.m.-1:30 p.m.	Procedure for Release of Preliminary Findings from NTP Studies	Dr. B. Schwetz, NIEHS
1:30 p.m.-2:30 p.m.	Role and Responsibilities of the NTP Board and NTP Executive Committee	Dr. B. Schwetz, NIEHS
2:30 p.m.-2:45 p.m.	Update on Activities of the Technical Reports Review Subcommittee	Dr. S. Eustis, NIEHS
2:45 p.m.-3:00 p.m.	BREAK	
3:00 p.m.-4:00 p.m.	Concept Reviews, Program on Environmental Toxicology, Division of Intramural Research, NIEHS	Dr. B. Schwetz, NIEHS

Procedures and Principles

- I. Developmental Toxicity Testing
and Methods Development
- II. Pathology Archive
- III. Pathology Quality Assurance
- IV. Pathology Support

Dr. W. Johnston, NIEHS

Dr. J. Heindel, NIEHS

Dr. S. Eustis, NIEHS

Dr. R. Hailey, NIEHS

Dr. S. Eustis, NIEHS

4:00 p.m.-4:15 p.m.

Public Comments

Adjourn

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS

October 27, 1992

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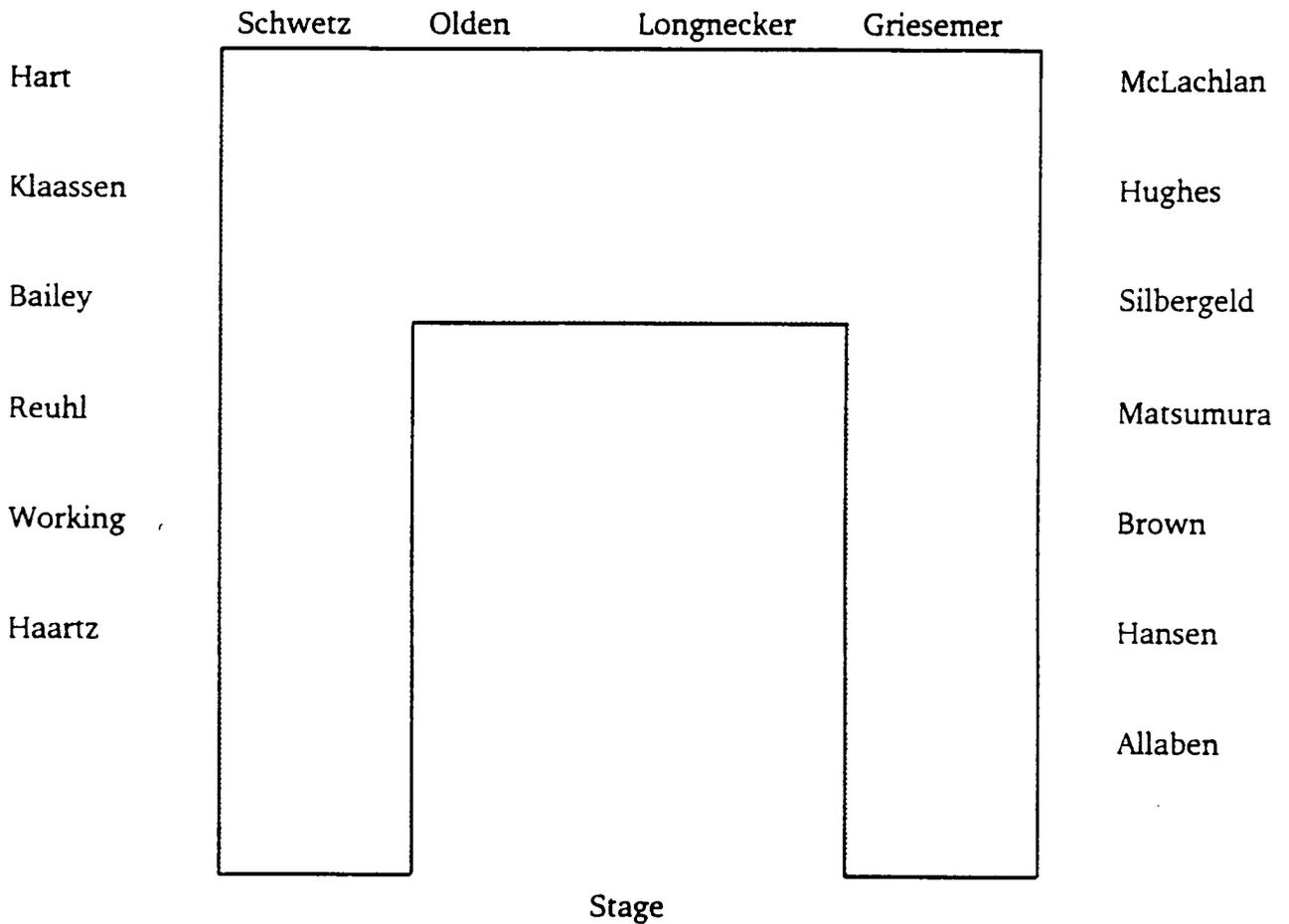
(Reproductive Toxicology, Genetics)

* Not present

NTP BOARD OF SCIENTIFIC COUNSELORS

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

October 27, 1992



Proposed Procedures for Release of Preliminary Findings from National Toxicology Program (NTP) Studies

Periodically, NTP studies yield results that are judged to have such a significant potential impact on public health that release of the results on a preliminary basis is warranted. These have most often occurred with the rodent cancer studies, and less frequently in studies with non-cancer endpoints. Although many NTP studies give results that are suggestive of a potential hazard associated with exposure to a chemical, the relative strength of the "signal" depends on a variety of factors including the consequence of exposure (death, cancer), the effective doses required in relation to the human exposure, the numbers of people potentially exposed, and other factors. It has been NTP policy to alert the nominator, various government regulating agencies and others as deemed appropriate, to findings that are not yet in a final peer review form, when the Director has deemed such an early release of data to be in the public interest. The purpose of this document is to propose for your consideration a more formal procedure for handling such events.

Issuing Official:	Director, NTP
Issued to:	<ol style="list-style-type: none">1. Assistant Secretary DHHS2. Director, NIH, NIOSH and Commissioner of FDA3. NTP Executive Committee4. Nominator of agent for study5. Private sector individuals or organizations who have expressed an interest
Nature of Communication:	Written summary of protocol including agent, test species, response of concern (tabulated summary of preliminary findings limited to the responding organ or tissue), and any possible study confounders.
Timing of Notification:	Assistant Secretary DHHS, followed by Directors of NIH, NIOSH and Commissioner of FDA within 24 hours. Notification of NTP Executive Committee, study nominator and others as appropriate within 48 hours.

It is the NTP position to limit the release of preliminary pathology or other toxicology findings until the usual verification steps have been completed. It is however, recognized that special situations may arise which would require deviating from these procedures. These will be considered on a case by case basis.

BACKGROUND CONCEPT REVIEWS

There are currently 100 research and resource contracts and interagency agreements for toxicology research and testing. These contracts and agreements support a variety of activities -- toxicologic characterization, testing, methods development, and program resources (i.e., chemistry, occupational health and safety, animal production, pathology, quality assurance, archives, etc.).

Prior to issuance of a Request for Proposal (RFP), a project concept review is required by Public Health Service regulations. These project concepts in many instances consist of more than one contract or interagency agreement. Concept reviews are needed for new projects, for recompetitions with changes in statements of work, and for projects ongoing for 5 years or more since the last concept review. Twenty-nine concepts have been reviewed by the Board since March 1989.

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

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

- a. scientific, technical or program significance of the proposed activity;
- b. availability of the technology and other resources necessary to achieve required goals;
- c. extent to which there are identified, practical scientific or clinical uses for the anticipated results; and
- d. where pertinent, adequacy of the methodology to be used in performing the activity.

NATIONAL TOXICOLOGY PROGRAM CONCEPT PROPOSAL

Contract Title: Developmental Toxicity Testing and Methods Development

Project Officers: B.A. Schwetz, (919) 541-7992
G. Jean Harry, (919) 541-0927
E. Sidney Hunter (919) 541-2274

Objective: To test chemical or physical agents for developmental toxicity and develop new/alternative methods to aid in this process.

Concept Statement: The testing of chemical or physical agents or altered environmental conditions for developmental toxicity and the development of new, novel methods to enhance the sensitivity specificity and efficiency of these tests is an important part of the NTP mandate. We propose, therefore, to continue testing for developmental toxicity via conventional *in vivo* protocols, while at the same time to develop and/or validate alternative model systems which may utilize alternative species and designs either *in vivo* or *in vitro*. These alternative systems may allow us to more effectively screen chemicals for *in vivo* mammalian tests and to reduce the time and cost of testing. They may also be extremely useful in determining structure activity relationships and the site and mechanism of action of developmental toxicants.

NATIONAL TOXICOLOGY PROGRAM CONCEPT PROPOSAL

Contract Title: Pathology Archive

Project Officers: Scot Eustis, (919) 541-3231

Objective: To continue to provide storage and retrieval for all of the histological slides, paraffin blocks, formalin-fixed wet tissues, frozen tissues, paper data, microfiche and optical disks for the toxicity and carcinogenicity studies that have been conducted by the Program.

Concept Statement: The NTP Archive files and preserves the data and specimens from over 450 rodent toxicology and carcinogenicity studies. Materials from reproductive and teratology studies are also saved. The Archive coordinates and tracks data flow from study laboratories, inventories and files materials, reviews pathology data and specimens, and supports NTP and outside auditors in their review of these studies. The Archive periodically identifies older studies for disposal of selected materials.

Since carcinogenicity studies are time consuming and expensive, access to pathology specimens from these studies is invaluable. The pathology specimens provide a unique resource for the analysis of chemical-related lesions using newer molecular biology techniques as they become available.

Proposed Changes To The Current Work Statement: The work to be performed under the recompetition is changed very little. Greater emphasis will be given to storage of data on optical disks, collecting frozen tissues for oncogene analysis, and using the materials for analysis using the latest molecular biology techniques.

NATIONAL TOXICOLOGY PROGRAM CONCEPT REVIEW

Contract Title: Pathology Quality Assurance

Project Officers: Rick Hailey, (919) 541-0294
Scot Eustis, (919) 541-3231

Objective: To continue to provide pathology quality assurance for the National Toxicology Program's (NTP) short-term toxicity studies and NTP long-term chemical evaluations in rodents.

Concept Statement: The NTP long-term and short-term rodent studies to evaluate chemicals for potential hazard and to characterize that hazard are often the pivotal data used by regulatory agents to set standards for human exposure. Therefore the NTP studies must be above reproach. This has been accomplished by having quality assurance pathologists review the diagnoses for all tumors in the studies and for all tissues for which a chemically-related effect is found. Discrepancies are resolved by a Pathology Working Group. This procedure has resulted in excellent creditability for the NTP studies.

Proposed Changes To The Current Work Statement: The work to be performed under the recompetition is changed very little. Since currently fewer NTP long-term studies are being started, the level of effort will be less than for the current contract.

NATIONAL TOXICOLOGY PROGRAM CONCEPT PROPOSAL

Contract Title: Pathology Support

Project Officers: Scot Eustis, (919) 541-3231

Objective: The objectives of this contract are 1) to provide pathology support including necropsy assistance, tissue section preparation, histopathological evaluation, and special quantitative morphological procedures such as morphometrics or cell proliferation for studies conducted in-house as well as for supplemental studies on pathology specimens generated through contracted studies, 2) to review and assess the pathology of toxicology and carcinogenicity studies performed by contractors by chairing and serving on NTP Pathology Working Group reviews, and 3) to provide technical support as needed for quality assessment of pathology evaluations and Pathology Working Group reviews.

Concept Statement: Studies designed to characterize the toxicity and carcinogenicity of chemicals or biological or physical agents are conducted through contracts or at NIEHS under the auspices of the NTP. A program of the magnitude and diversification of the NTP requires cooperation and collaboration of numerous testing facilities. For these studies, there is a need to assure uniformity, consistency, accuracy of diagnostic criteria and pathology procedures. This is accomplished through a variety of pathology tasks which are performed prior to, during, and after study completion. Further, as study results become available, there is often need for additional follow-up studies to further define the toxicity or carcinogenicity and mechanisms involved. This may include examination of additional sections or the application of special procedures such as histochemistry, electron microscopy, morphometrics, or the measurement of cell replication.

Proposed Changes To The Current Work Statement: The work to be performed under the proposed five-year recompetition is essentially the same as described above. Estimated workload for histology laboratory support is decreased but additional technical effort is required for new techniques such as quantitation of cell replication or using polymerase chain reaction (PCR) to detect molecular events in tissues and for the evaluation of clinical pathology data from prechronic studies.

LIST OF CONCEPTS APPROVED BY
NTP BOARD OF SCIENTIFIC COUNSELORS
March 1989 to October 1991

March 1989

Toxicity and Carcinogenicity Studies in Animals
Chemical Repository and Safety Support
Chemistry Support Services
Rodent Disease Diagnostic Laboratories
Genetic Monitoring on Inbred Rodents
Pathology Support
Pathology Archive
Statistical Analysis of Laboratory Studies
Expired Breath Analysis in Chemical Toxicity Assessment
Immunotoxicity of Environmental Chemicals and Therapeutics
Neurotoxicology Methods Validation
Mutagenicity Studies with Salmonella
In Vivo Cytogenetics
Mammalian Germ Cell Mutagenesis
Identification of Rodent Tumor Suppressor Genes

November 1989

In Vitro Methods to Assess Human Metabolism of Chemical Xenobiotics
Reproductive Toxicity Testing and Methods Development
Site and Mechanism Studies of Reproductive Toxicants
General Toxicity Testing and Research On-Site at the NIEHS

March 1990

Chemical Induction of Genetic Transposition
Chemical Induction of Chromosome Damage in Mouse Germ Cells
Investigation of Spontaneous and Induced Mutation in Mouse Germ Cells

October 1990

Investigation of Molecular Mechanisms of Chemical Carcinogenesis in Mammalian Cell Systems
Studies of Chemical Disposition in Mammals

May 1991

Immunotoxicity of Workplace Xenobiotics in Humans

October 1991

Environmental Neurotoxicology
Development and Evaluation of Rodent Strains with Inactivated Tumor Suppressor Genes for Studies Aimed at Discerning Mechanisms Involved in Carcinogenesis
Predictive Toxicology Methods Development
Quality Assurance (QA) Inspection and Auditing Support Resource Contracts

Experimental Toxicology:

Testing the Urine of Rats in the 14-Day Prechronic Test
for Mutagenic Activity
In Vitro Cytogenetics

Systems Toxicity:

Developmental Toxicity Testing:
Range Finding
Testing and Research

Mutagenesis and Experimental Carcinogenesis:

Mutagenesis Assays Using Transgenic Mice
Drosophila Mutagenesis Testing
Response of Centromeres to DNA Damaging Agents
Mammalian Cell (Mouse Lymphoma) Mutagenesis Assays
Transformation Assays
DNA Adducts and DNA Modifications
Development of Detection Methods for Non-Electrophilic Carcinogens
Validation of Chemicals in Drosophila and Yeast Aneuploidy
Detection Assays

Resources:

Pathology Quality Assurance
Health and Safety