National Toxicology Program

Board of Scientific Counselors Meeting

April 7-8, 1980

Summary Minutes

The National Toxicology Program (NTP) Board of Scientific Counselors met on April 7 in Conference Room 7, Building 31, National Institutes of Health, Bethesda, Maryland. (Attachment 1: Federal Register Meeting Announcement; Attachment 2: Agenda).

After a welcome to attendees by Dr. David P. Rall, Director of NTP and NIEHS, Dr. Norton Nelson, Board Chairperson, reviewed the status of the three Board subcommittees established at the first meeting of the Board, January 14-15, 1980. He indicated that the Chemical Nomination and Selection Subcommittee chaired by Dr. Marjorie Horning had met on March 13, 1980. The Report Review Subcommittee chaired by Dr. Nelson and the Automated Data Processing Subcommittee chaired by Dr. Mortimer Mendelsohn had been given their charge but had not met.

Dr. Richard Griesemer, Associate Director for the Carcinogenesis Testing Program (CTP), introduced the program to be reviewed at this meeting of the Board. It included a discussion of the final four phases of the chronic carcinogenesis bioassay process (Phases IV to VII), (Attachment 3). Phase I (Pretesting), Phase II (Initial Toxicology Characterization), and Phase III (Chronic Bioassay) had been reviewed at the previous meeting of the Board. Members of the CTP staff then discussed the bioassay analysis and reporting activities of the Program.

Mr. Dalton Tidwell, Expert, Technical Information Resources Branch, described the bioassay process commencing with the last animal-kill date by the contractor lab through internal peer review of the final technical report, i.e., Phases IV and V. The process involves 14 steps and an average 282 days to complete (Attachment 4: Time Line-Last Kill Date Through DEG First Draft Delivered). The first step, 90 days, is required for the contractor pathologist to study and diagnose the findings in the animal tissues. It then requires 23 days for the Individual Animal Data System (CBDS), (Attachment 5: CBDS Reports). A Systematized Nomenclature Pathology number (SNOP code) is assigned to each individual animal pathology table entered into the system. The attachment illustrates the types of data in the CBDS.

Dr. Jerrold Ward, Veterinary Pathologist, Tumor Pathology Branch, described the various aspects of pathology review and quality assessment. All of the animal pathology data, slides and tissue blocks are sent by the prime contractor, Tracor-Jitco, to Dr. Ward's group for review and quality assessment. The Pathology Working Group (PWG) then receives the findings and materials. The PWG is composed of government and/or contractor employees along with veterinary pathologists from the Washington, D.C., area. The PWG is supplemented with subgroups of pathologists with expertise specific to certain organs. These groups give input for accepting, modifying or rejecting the original report. The PWG sends a letter with slides to the original pathologist for review and the opportunity to change his opinion. If he agrees with the PWG's diagnosis, he files an updated IADR. If he disagrees, he details his reasons in a letter to Dr. Ward's group. As part of quality assessment, NCI pathology personnel make quarterly site visits, sometimes timing the visit to coincide with animal kills. Monthly reports from the contractor are also required. Dr. Ward discussed various problems such as missing tumors, difficulties in diagnosing primary tumor site, and error in diagnosis, especially where non-neoplastic lesions are diagnosed as tumors or tumors are diagnosed as non-neoplastic lesions.

Dr. William V. Hartwell, Toxicology Branch, described the types of information that must be pulled together during the various phases of the bioassay to be used as background and for inclusion in the technical report, the final product of the carcinogenesis bioassay. In addition to pathology reports on both neoplastic and non-neoplastic lesions, this includes toxicology data; chemistry (purity and analysis of the test chemical); background information on human exposure, uses and reasons for it being a hazard; protocols with animals used, animal handling, doses used and information developed for setting doses for the chronic phase, and statistical procedures used; results and analysis on the lifetime study including pathologic interpretation as to adequacy and validity of the testing; and conclusions, which are the 'bottom line.' Dr. Hartwell then described the usual sequence in the development of the technical report. Initially, a preliminary report is developed by the prime contractor with the draft going through review by an internal interdisciplinary group. The revised draft goes to NCI for preliminary review coordinated by the chemical manager, and then is sent back to the prime contractor for corrections. The corrected draft is submitted to the NCI Data Evaluation Group which reviews it with prime contractor representatives present as resource persons. Subsequently, a camera ready draft is given final internal review by the Associate Director, CTP. After further revisions and inclusions of additional data in some cases, the report is submitted to the Cancer Clearinghouse for peer review by non-government scientists.

Dr. Arnold Brown, Chairman, Cancer Clearinghouse on Environmental Carcinogens, reviewed the history, composition, and procedures of the Clearinghouse. The Clearinghouse was established in 1976. It was established to meet several needs, including: 1) the need for mechanism for channeling information developed by the CTP to potential users; 2) to provide independent peer review for the backlog of approximately 307 chemical bioassays for which reports had not been issued, this was a primary concern during the first few years of the Clearinghouse; 3) a means for reviewing data on controversial issues, e.g., the FDA-cyclamate issue; and 4) to bring broad representation into the review process, particularly industry, academic and consumer groups as well as government. There were about 25 to 26 members and four subgroups: I-Chemical Selection; II-Experimental Design; III-Risk Assessment; and IV-Data Analysis. The latter two groups were later combined. For each technical report, a primary and secondary reviewer were assigned. In their reviews, high emphasis was given to the findings of the Pathology Work Group, Table II of the report. The Clearinghouse referees rarely totally disagreed with the conclusions in a report. Further, the review meetings provided a forum for industry and others to bring in their data. There were problems in reviewing some of the early bioassays, e.g., 1968-69, in that much data were not available, certain parameters were missing, e.g., were there other chemicals on test in the same animal rooms? Of the 307 bioassays in the backlog, a number were not reported out because of limited or flawed experimental design.

Dr. Brown commented on limitations of the bioassay, such as with reference to the endpoint of carcinogenesis--essentially you got only a yes or no answer. For the large cost, he felt we should get more useful information, including information on other toxicologic endpoints. Further, the reports were primarily confined to tumor data. The data on non-tumor pathology was treated very cursorily, although data available but not in the report would be provided in response to query by Clearinghouse members. Further, with reference to non-tumor pathology, wet and block specimens are stored in the repository and can be retrieved if needed. He indicated two areas with which NTP should be concerned: 1) how best to define maximum tolerated dose (MTD); there should be a criteria better than weight loss, e.g., appropriate biochemical markers, and 2) how to use the data for reasonable risk assessment. He also stated that we need incorporated into the bioassay protocols more hematologic analysis, hepatorenal function tests, and more biochemical tests. Dr. Rall replied that a major purpose of the NTP is to broaden toxicologic characterization as resources allow. Dr. Joseph Rodricks, FDA, said we need a NTP review of experimental design, and Dr. Rall indicated we were considering forming a Board subcommittee in that area.

Ms. Harriett Kennedy, Office of Cancer Communications (OCC), NCI, talked about procedures involved in the release of reports and report data. She handed out two types of releases, press releases and pamphlets with more detailed background information on a technical report (Attachment 6: News Release - Bioassay of Malathion; and Attachment 7: Technical Background Information - Carcinogenesis Bioassay of Trichloroethylene). The background and full technical report including notes and discussion from the Clearinghouse review go to OCC. They set dates for Federal Register announcements and arrange with the National Technical Information Service to stock the report, both in hard copy and in microfiche. Twenty-five to thirty copies of the report are sent to key public or private individuals in advance. The news releases and backgrounders are sent to a mailing list including television, radio, newspapers, environmental groups, trade groups and labor unions. These initial mailings are meant to prevent 'leaks' and their attendant problems. Some problems mentioned included the fact that data which has not been completely reviewed or validated is accessible to the public under Freedom of Information. Also, there are four or five levels of clearance in the NCI. It is hoped that NTP can reduce the number of levels and, thus the total clearance time. In response to a question concerning inclusion of other toxicology results in the report, Dr. Rall said that NTP would release that sort of information as available, e.g., acute toxicity, organ toxicity, and mutagenicity, and not wait until the Bioassay is completed.

Ms. Joan Chase, Technical Information Resources Branch (TIRB), talked about the types of queries they receive, information requested, items that are disseminated in response, and who the requestors are (Attachment 8: Queries). Recent queries received concern chemicals found in waste dumps, water contaminants, and chemicals mentioned in news stories. The most frequent query is concerned with the status of a particular ongoing bioassay. Responses are given with the caveat that the bioassay is incomplete and the requestor must draw their own conclusions. To queries on carcinogens not under study, the TIRB uses standard manual sources in their reply. If the query refers to specific information of a scientific nature, the chemical manage is contacted. For requests from industry, the TIRB may ask the requester what studies they are doing and may even propose collaborative studies. Ms. Chase passed out a package illustrating internal information needs of the CTP to which the TIRB responds (Attachment 9: Information Needs of the Carcinogenesis Testing Program).

Ms. Dorothy Britton, Contracting Officer, Carcinogenesis Section, NCI, discussed concept review for proposed research and development contracts. Concept review involves evaluating the purpose, scope and objectives of a proposed project or program and should be done prior to issuance of an RFP. The review could follow the RFP issuance if determined to be in

the best interest of the government but must precede award of a contract. A peer group considers significance of the proposal, availability of resources and methodology, and the state of the art, then votes on the concept. The vote can be done by telephone. Dr. Griesemer said he would like to see the Board of Scientific Counselors serve as a peer group for concept review. The concept could relate to a new type of methodology or a specific type of toxicologic study and could result in several RFPs. The resulting RFP is then reviewed by an in-house group for scientific merit and further reviewed for merit by an advisory peer review group which must be composed of 75% or more non-government members. Participation on a concept review, as opposed to peer review of an RFP, would not necessarily constitute a conflict of interest which would preclude the participant's responding later to a specific RFP. Dr. Griesemer thought it would be alright for the NTP Executive Committee to serve as a concept review group but he would like the Board to look at a smaller part of the concept with reference to whether the concept was scientifically feasible. For the record, it was agreed that discussion of scientific issues by the Board would serve as a concept review for the purposes required by Ms. Britton, so that an RFP can be initiated at a later time without further concept review.

A general discussion ensued following the last NCI presentation. Dr. Nelson raised the question as to quality assessment procedures for toxic endpoints other than cancer and said that even though they may be shorter term studies, quality assessment is still critical. He commented that quality assessments for hematology and histopathology are fairly straightforward but quality assessments for organ function and neurobehavioral tests are not and, further, there is often not much background or baseline data to draw on. Dr. Griesemer indicated he would like to see review of hematology and clinical chemistry on a separate future agenda, followed by review of toxicology of the various key organ areas, one by one. Dr. Whittemore expressed concern about false negatives in bioassay studies. She wanted to know whether the vast body of data on incidence of tumors in control animals could be used in assessing the significance of rare tumors in treated groups.

Dr. James E. Huff, Senior Toxicologist, NTP, made a brief presentation on NTP technical report and manuscript generation and dissemination. He raised the question as to what mechanism NTP should use to replace the Clearinghouse for external peer review. One proposal would be to use the professional societies such as the Society of Toxicology (SOT) and the Federation of American Societies for Experimental Biology (FASEB). Preliminary inquiries to SOT and FASEB have received favorable responses. Dr. Nelson said that the proposal to work through the professional societies on a contractural basis was presented here only for information not action. Any comments on this proposal should be given to the Report Review Subcommittee. Initial review would be on technical reports resulting from tests started five years ago. Dr. Griesemer stated there would be about 20 bioassay reports coming up for review in the near

future and about 20 on other aspects of toxicity. Dr. Rall suggested a mixed option, i.e., routine reports would go for society review and more critical or controversial reports could be reviewed by the Board or a Subcommittee of the Board. Dr. Nelson proposed that the Board form a standing subcommittee to carry out external review until another mechanism can be effected since the Clearinghouse charter expires in May. The Board could form an ad hoc review body which would include at least one Board member. Dr. Shepard suggested that the President of the Teratology Society would be a good source for a nominee in the area of teratogenesis. Dr. Rall suggested that there be a panel of experts who could be assigned as primary and secondary reviewers, like the Clearinghouse. The reports could be mailed to them and then they would all meet to complete the review process. Dr. Griesemer would like to have such a meeting by the end of June to consider about ten Bioassay reports.

Dr. Harper made a motion that the Chairman of the Board be authorized to establish an ad hoc review panel to review technical reports. The motion was approved unanimously by the Board members present. It was decided that the panel would receive the reports by mail and then would convene with a Technical Report Review Subcommittee of the Board in late June to complete review. The meeting would be concurrent with the next regular Board meeting. As one of the agenda items, the Board will attempt to decide on a permanent report review mechanism.

Dr. Huff discussed consideration of scientific journal publication for the technical reports. Journal publication would require more peer review but would also give an archival status to the reports. It was proposed that the report data be rotated among a select list of journals. The Report Review Subcommittee will bring a draft proposal to the full Board for action. He said there is also a need for archival compilation in one location of all the backup documents and data. Dr. J.F. Douglas, Carcinogenesis Testing Program, stated that the Program has a 5000 sq. ft. archival respository for data books, raw data, background material, and hard copy. Also, there is a chemical repository with 150 sq. ft. of space at each of three temperatures for the storage of all chemicals that have ever been tested. A major problem to be resolved is how to dispose of chemicals.

Dr. Alice Whittemore commented on the Automated Data Processing Subcommittee in the absence of Dr. Mendelsohn. She stated that the Subcommittee needs ad hoc experts to advise them on a highly technical and complex task. The agency staff who prepared the document describing in detail the ADP needs of the NTP should attend the first meeting of the Subcommittee. It was decided that NTP staff should assist Dr. Mendelsohn in making arrangements for a meeting, either in the Washington, D.C., area or in Chicago. Dr. Whittemore suggested having ADP vendor representatives come and describe what their systems would do.

Dr. Harper gave a brief report of the first meeting of the Chemical Nomination and Selection Subcommittee. At this meeting, the Clearinghouse process was reviewed by NCI representatives. A proposal was made that the Subcommittee meet with appropriate NTP agency staff and representatives of labor, public interest groups, and trade associations to hear how they select chemicals for nomination. The information received would be used by the Subcommittee in preparing recommendations aimed at improving the nomination and selection process. The Subcommittee recommended that NTP strive to reach a wider audience for soliciation of nominations. Dr. Moore said that a letter had been drafted and would be sent out shortly which would attempt to do this. Dr Nelson suggested the Subcommittee should proceed to solicit information from the agencies and other groups mentioned by Dr. Harper and invite them to send representatives to a meeting with the Subcommittee. He said they also should invite Dr. Robert Harris, CEQ Toxic Chemicals Program, to come to the next meeting.

Dr. Rall proposed that there be a Board meeting in September or October at NIEHS to review the various NTP programs at NIEHS. He also recommended setting up a Subcommittee on Experimental Design and Protocol Development, probably at the time of that meeting. He also commented on the upcoming review of NTP by the Office of the Secretary, Department of Health and Human Services.

There being no further business, Dr. Nelson adjourned the meeting at 4:00 p.m.