

National Toxicology Program
Board of Scientific Counselors' Meeting

June 28, 1980

Summary Minutes

The National Toxicology Program (NTP) Board of Scientific Counselors met on June 28 in Conference Room 6, Building 31, National Institutes of Health, Bethesda, Maryland. (Attachment 1: Federal Register Meeting Announcement; Attachment 2: Agenda).

The first item on the agenda was a discussion of the mechanism for external peer review of NTP technical reports. Drs. Nelson and Hitchcock talked about the carcinogenesis bioassay report review of the previous day (June 27). Dr. Hitchcock reported that of the ten reports reviewed, eight had been accepted, some with moderate revisions, one had been returned to the authors for corrections, and one had been deferred due to serious discrepancies within the report. This report on the bioassay of C.I. Acid Orange 10 will be reviewed again at the next report review meeting. There was consensus that the report review meeting went quite well. Summary minutes of the reviews will be available at a later date.

Dr. Hitchcock stated there were three recommendations that needed to be considered. They are:

1. State of the art methodology for statistical analyses should be used. This is to include a review of experimental design and techniques to analyze data on compounds which may both suppress and stimulate tumor formation. As a first step, Dr. Whittemore will meet with Drs. Hoel and Haseman in August to discuss current statistical analyses procedures used in the technical reports. She will also seek input from Drs. N. Breslow and R. Shore, members of the Panel of Experts associated with the Technical Report Review Subcommittee, and from Dr. J. J. Gart (NCI). She will then draft a short report to NTP concerning their evaluation and recommendations which will be discussed at the next Board meeting.
2. Quality assurance of pathology review. A statement identifying discrepancies in pathologic evaluation should be given in the report together with statistical analyses based on the different conclusions. The members of the Board concurred with this recommendation.
3. Development of a set of guidelines concerning the type of human risk statement that can be made based on the animal data in the report. This recommendation will be discussed at the next Board meeting.

With regard to #3, it was suggested that we might be able to modify the statements in the foreward (p. iii) of each report.

Dr. Douglas said there are nine different possibilities postulated by Drs. Griesemer and Cueto in a chapter in an IARC book published this year. Dr. Huff said that he would see that copies of this chapter and also the IARC preamble are sent to Board members and the Panel of Experts for review and later discussion.

Dr. Rall talked about proposed agenda items for the next Board meeting to include: (1) review of quality assurance or assessment, especially pathology but other areas as well; (2) a review of experimental design and statistical analysis; (3) a discussion of how meaningful are animal and other laboratory studies for estimation of human risk; (4) further review and recommendations concerning the chemical nomination and selection process; and, (5) a status report on the Automatic Data Processing Study.

Dr. Whittemore asked whether in the future there would still be a single carcinogenesis bioassay report which would include short-term test results. Dr. Moore replied that, for recently started bioassays at least, NTP would publish a report following the prechronic studies which would include results of short-term tests, genetic toxicology studies, standard 90 day toxicology studies; chemical disposition data, etc. Then the long-term bioassay results would be published as they are now but in a broader format to include an update of short-term testing and what else is known about the chemical. Thus, there would be two documents. Production and use patterns for the chemical should be included in both. Dr. Whittemore then inquired as to how the technical reports are used. Dr. Nelson commented on the various legislative acts and the balance of risks-benefits and costs. He said the regulatory agency takes the technical reports and uses them within the framework of their mission, e.g., air, water, food, workplace, etc.

Dr. Shepard stated that quality assurance in studies on reproductive and teratogenic effects needs to be examined as there are problems in interpreting minor anatomic changes, effects of resorption.

Action Item: Dr. Rall proposed setting up a Statistical Analysis and Experimental Design Subcommittee of the Board. However, because of the ceiling on consultant services, formation of this new subcommittee will have to be deferred until the next fiscal year.

Dr. Mendelsohn said the issue of total tumors needs to be assessed even though it is difficult to interpret. Dr. Hitchcock said that we need to look at other toxicity which may develop in the chronic studies but which may not show up in prechronic testing, e.g., massive hemorrhaging associated with chronic bioassay of butylbenzyl phthalate. Dr. Grieshaber indicated that the bioassay program is including a complete hematologic workup in prechronic studies where hematotoxic effects are likely or suspected. Dr. Shepard said this profile should include prothrombin times and tests for Vitamin K deficiency. He also stated that teratologists approach quality assurance and risk estimation differently than do oncologists and would like these different approaches considered by the Subcommittee.

Action Item: Dr. Nelson made a motion that NTP continue technical report peer review with the present mechanism using the Technical Report Review Subcommittee and Panel of Experts. Dr. Mendelsohn seconded the motion and it passed unanimously.

Dr. Rall mentioned the New York Times' article on the dioxins and asked how we could avoid these leaks to the press in the future. It was thought that leaks probably could not be avoided so NTP should make the draft technical reports available to the press ahead of the review meeting and emphasize that they were DRAFT.

Dr. Horning reviewed the June 17-18, 1980, meeting of the Subcommittee on Chemical Nomination and Selection. Draft minutes for this meeting were distributed. (Attachment 3: Minutes--NTP Board of Scientific Counselors Subcommittee on Chemical Nomination and Selection, June 17-18, 1980) The meeting included presentations by staff from Executive Committee agencies, as well as by representatives from industry, labor and public interest groups. Presentations were also given by the Chairpersons of the NCI Chemical Selection Working Group (CSWG) and the Chemical Selection Subgroup (CSSG) of the Clearinghouse on Environmental Carcinogens and by a member of the Interagency Testing Committee. Dr. Horning discussed the current chemical nomination form and types of back-up information requested and the current chemical nomination and selection process.

She talked about several issues that had been raised by the Subcommittee at the end of the meeting, then further discussed two of these issues. One had to do with the quality of executive summaries. She asked for recommendations from the Board on improving the quality and depth of the summaries. Dr. Nelson said that NTP needs a "prescreen" to filter out chemicals that, unbeknownst to the nominator, may have been tested already. Dr. Rall agreed but said we must respond to any nominees. Dr. Shepard said that if there is a question relating to teratology, his lab has a computerized data base and that others at NIH and other agencies could be contacted, e.g., NICHHD. Dr. Nelson proposed that NTP get access to the system used by CSWG to get production and use patterns for our executive summaries. Dr. Mendelsohn said that such information search should be expanded to cover other toxicologic endpoints.

Action Item: Dr. Whittemore moved that NTP access an outside contractor or other source inside or outside government to provide information on toxic endpoints (besides cancer) and production and use patterns similar to that provided to NCI by Stanford Research Institute. Dr. Harper seconded the motion. After discussion about NTP using data bases of other NIH Institutes where appropriate, the motion was approved.

Dr. Horning then discussed the proposed inclusion of a public advisory group in the chemical selection process which could allow more public scrutiny and input into the process. This might be something like the CSSG which had good interactions with labor, public interest groups and industry. Dr. Harper suggested such a group might provide a point for inclusion of expertise not available on the Chemical Evaluation Committee. Dr. Nelson said that such a group would defuse criticism about chemical selection being a closed process. Dr. Moore asked whether it would have to be a formal group or rather could it be an open meeting where the public could give input. Dr. Horning

replied that it could be less formal than CSSG meetings. It was also agreed that chemicals nominated for an Ames test need not be included for such a meeting, but only those chemicals nominated for more extensive testing, such as chronic bioassay. Also discussed was the issue of where a public advisory group would fit into the process, i.e., sequential or parallel.

Action Item: Dr. Horning moved that NTP staff should come back to the next Board meeting with a proposal for a public advisory group; how constituted and in what time sequence in the chemical selection process; and, what chemicals should or should not be included. Dr. Shepard seconded the motion and it was approved. Dr. Rall commented that it would be best if a public advisory group meet after the Chemical Evaluation Committee had met.

Mr. Lovre (FDA/NCTR) said that the Chemical Review Group at NCTR was preparing a new proposal for the chemical nomination and selection process which they would like to discuss with NTP staff.

Dr. Horning said that Dr. Verne Ray, ad hoc member of the Chemical Nomination and Selection Subcommittee, was drafting a new format for the final executive summary which would be considered by the Subcommittee. There was some discussion about the format for data to be supplied with chemical nominations. It was noted that OSHA and FDA staff did not have the time to supply all the information asked for. It was stated that NTP would not reject a nomination if all the requested information is not supplied. It was suggested that we should indicate this on the nomination form or in a cover letter.

Another issue--the role of short-term testing in the chemical selection process--was discussed. Dr. Moore said that decisions on short-term testing and whether long-term testing should be done on the basis of short-term tests were the responsibility of NTP staff. Dr. Canter reported that the public interest group stated at the Subcommittee meeting that NTP should test in short-term mutagenesis screens chemicals recommended for testing by the Interagency Testing Committee (ITC). NTP should, however, avoid testing such chemicals for other recommended toxicologic endpoints. Other participants disagreed, stating that NTP should continue to test such chemicals for all nominated endpoints until TSCA is fully implemented. Dr. Rall noted that the interagency group under TSCA or EPA can ask NTP to do short-term testing.

Drs. Mendelsohn and Moore gave a status report on the activities of the Automated Data Processing Subcommittee. Dr. Mendelsohn defined the initial charge to the Subcommittee and said that NTP staff was moving ahead with arranging for an expert assessment of the Toxicology Data Management System (TDMS) at NCTR for its potential utility in meeting the needs of NTP. Dr. Moore said that a list of qualified consultants had been submitted to Dr. R. Hart, Director, NCTR. A panel of three consultants had been chosen, being Dr. Frank Starmer, Duke University (Chairperson); Dr. Raymond Neff, Harvard University; and, Mr. Rick Walsh, Hewlett-Packard. The panel has met with and been briefed by NTP and NCTR staff and has scheduled a site visit to the TDMS facility at NCTR for late July. The panel will then submit a report on their findings and recommendations to NTP by late August

or September. NTP staff will evaluate the report and submit it along with supporting information to the Subcommittee for their evaluation and recommendations. Dr. Moore said that first priority for an ADP system is that it be able to capture and process laboratory data, while a lower priority would be assigned to a system used for meeting management informational needs.

Dr. Chandler (NIOSH) said that representatives of the regulatory agencies should be invited to be present as observers at Subcommittee meetings. Dr. Rall agreed.

Dr. Horning inquired as to the status of development of new tests for measuring toxicity. She said the Board should be kept informed and have a chance for input. It was recommended that NTP staff put together a short program for the next Board meeting. This would not be a definitive discussion but rather a briefing on NTP toxicology test development and validation activities.

The dates for the next meeting will be October 15, 16 and 17 at NIH. The October 15 meeting will involve the Technical Report Review Subcommittee and an ad hoc Panel of Experts in completing peer review on eight to ten technical reports of carcinogenesis bioassays. The agenda for the October 16 and 17 meeting of the full Board will include the agenda items listed by Dr. Rall earlier in the minutes as well as the briefing by NTP staff on toxicology test development activities.

Tentative dates were set for a subsequent meeting of the Board. These dates are January 14, 15, and 16, 1981. The primary agenda item would be a review by the Board of NTP short-term testing programs including presentations by staff from NTP components at NIOSH and NCTR.

The meeting was adjourned at 12:10 p.m.

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FEDERAL REGISTER

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Department of Health and Human Services
U.S. Public Health Service
National Toxicology Program

Notice of Meeting
National Toxicology Program Board of Scientific Counselors

Pursuant to Public Law 92-463, notice is hereby given of the meeting of the National Toxicology Program Board of Scientific Counselors, U.S. Public Health Service, June 27-28, 1980.

The meeting on June 27 will be held in Room 1331, Switzer Building (formerly HEW South Building), 330 C Street, S.W., Washington, D.C. This meeting will be open to the public from 9 a.m. until adjournment for the purpose of completing external peer review on technical reports of bioassays from the National Cancer Institute (NCI) Carcinogenesis Testing Program. Reviews will be conducted by the Technical Report Review Subcommittee of the Board in conjunction with an ad hoc panel of experts. Attendance by the public will be limited to space available.

The meeting on June 28 will be held in Building 31C, Conference Room 10, National Institutes of Health, Bethesda, Maryland. The meeting will be open to the public from 9 a.m. to adjournment for the purpose of discussing and making recommendations on a permanent mechanism for external peer review of National Toxicology Program (NTP) technical reports and for hearing progress reports by the Chemical Nomination and Selection Subcommittee, the Report Review Subcommittee, and the Automated Data Processing Subcommittee. Attendance by the public will be limited to space available.

The NTP Director, Dr. David P. Rall, P. O. Box 12233, Research Triangle Park, North Carolina 27709, telephone (919) 541-3201, or FTS 629-3201, will furnish summaries of the meeting, rosters of committee members, and substantive program information.

Regarding technical report peer review, reports will be reviewed June 27 on the following chemicals (and routes of administration):

<u>Chemical</u>	<u>Route</u>
2,3,7,8-Tetrachlorodibenzo-p-dioxin	Skin paint
2,3,7,8-Tetrachlorodibenzo-p-dioxin	Gavage
Dibromochloropropane (DBCP)	Inhalation
1,2-dibromoethane (EDB)	Inhalation
Cytembena	Intraperitoneal
Yellow 6	Dosed feed
Orange 10	Dosed feed
Butylbenzyl phthalate	Dosed feed
Di(2-ethylhexyl)adipate	Dosed feed
Caprolactam	Dosed feed

5/23/80
Date

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