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NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS
APRIL 30 AND MAY 1, 1985

SUMMARY MINUTES

National Toxicology Program
Board of Scientific Counselors Meeting
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Contents — Page Numbers

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Summary Minutes

The National Toxicology Program (NTP) Board of Scientific Counselors met on April 30 and May 1, 1985, in the Conference Center, Building 101, South Campus, 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). Continuing members of the Board are Drs. Mortimer Mendelsohn (Chairperson), Norman Breslow, Jerry Hook, Jeanne Manson, Henry Pitot, and James Swenberg. Dr. Mendelsohn and Dr. David Rall, NTP Director, thanked retiring members, Drs. Leila Diamond and Curtis Harper, for their contributions, and welcomed new members, Drs. Michael Gallo and Frederica Perera. All continuing, retiring and new members were in attendance.

National Toxicology Program (NTP) Response to Recommendations in the Report of the NTP Board of Scientific Counselors' Ad Hoc Panel on Chemical Carcinogenesis Testing and Evaluation (Attachments 3, 4 and 5)

I. Introduction: Dr. Rall welcomed Dr. John Doull, University of Kansas, Chairman of the Ad Hoc Panel, and the Subpanel Chairpersons, Dr. Perera; Dr. Robert Scala, Exxon Corporation; and Dr. Andrew Sivak, Arthur D. Little, Inc. Also present was Dr. Norton Nelson, NTP Board Chairman when the Ad Hoc Panel was commissioned. Dr. Rall noted that the NTP had or was in the process of implementing more than 95% of the specific recommendations. He said the discussion would focus on the few issues where the NTP staff have some differences of opinion with the report or where there are recommendations needing further discussion. Dr. Rall asked Dr. Ernest McConnell, Acting Director, Toxicology Research and Testing Program (TRTP), NIEHS, to chair the session. Dr. McConnell said each of the three chapters in the Report would be addressed separately. For each there would be a presentation by a TRTP/NIEHS staff scientist, followed by an opportunity for representatives from NCTR and NIOSH to make comments, and concluding with any public comment.

Copies of the Report of the NTP Ad Hoc Panel on Chemical Carcinogenesis Testing and Evaluation are available without charge from: NTP Public Information Office, Box 12233, Research Triangle Park, N. C. 27709. Telephone: (919) 541-3991, FTS: 629-3991.

II. Short-Term Tests: (Attachment 3) Dr. Raymond Tennant, NIEHS, said he would present the eleven general summary conclusions and recommendations included at the end of Chapter 1, and comment briefly on each, especially where recommendations have been implemented or where there is disagreement. Written responses to these summary recommendations (as well as others within the Chapter) were provided to the Board prior to the meeting (pages 7 to 12, Attachment 3).

Selected specific comments are as follows:

(1) Recommendations 2 and 3 - These have in large part to do with developing and validating a short term in vivo assay in rodents which may be applicable to parallel studies in humans or with human tissues or fluids (the "parallelogram" approach). Application could take place through cooperative studies with NIEHS and the National Institute for Occupational Safety and Health (NIOSH). Dr. Tennant said the NTP is concerned with the reliability of currently available short-term test systems to predict carcinogenesis and believes that effort is needed to develop and improve these systems before placing great emphasis on the parallelogram approach. Thus, most of current resources are focused on evaluating the interface between in vitro tests and short-term and long-term in vivo tests in rodents.

(2) Recommendations 4, 5 and 6 - These have to do with biological sampling and storage of biological fluids and tissues for parallel studies and retrospective analysis. Since many of these samples would be stored in a frozen state, the NTP has concerns as to the number of endpoints which could be reliably measured on samples that have been frozen.

Dr. Tennant said the NTP was in general agreement with the other recommendations, and was using, developing or considering development of most of the assay systems recommended.

Discussion: Dr. Perera, Chairperson of the Short-Term Tests Subpanel, commented that the use of the "parallelogram" approach would be a long-term goal. She agreed that the collection and storage of biological samples needed to be well defined and not just "shotgun". Dr. Swenberg stressed the biggest concern of the Subpanel was about the lack of good tests for promotion; this should be given high priority. Dr. Doull said the Panel wanted to emphasize the need for entering the earlier NCI/NTP bioassay chemicals into the genetic toxicology testing scheme including both known carcinogens and non-carcinogens. Dr. Tennant agreed but thought it better with limited resources to focus first on those chemicals evaluated in the more recent NTP long-term studies.

NCTR Comments: Dr. Angelo Turturro supported the recommendation calling for more interagency cooperative efforts. He suggested there be more interaction of NTP with the NCTR biomarkers program. He said there should be more interaction of NTP with federal agencies having ongoing programs in biochemical epidemiology.

NIOSH Comments: Dr. Robert Mason stressed the need for more studies on complex mixtures. An area for useful interagency interaction was in male reproductive studies. Further, this was a good area for parallel studies, e.g., genetic changes in sperm from chemically exposed animals and humans.

Discussion: Dr. Diamond noted that the Panel had not provided any good suggestions for in vivo/in vitro promoter assays. Dr. Hooper said there needed to be better data on what mutagenic materials in human urine means to the individual. Dr. Frederick deSerres, NIEHS, commented on the high incidence of false positives in in vitro tests for chemicals shown to be non-carcinogens in rodent biossays. He said there was a growing data base showing

a good correlation between chemicals negative in in vivo short-term genetic tests and in long-term bioassays. Dr. Swenberg said improvements had been made in the ability to distinguish between "real" carcinogens and non-carcinogens.

III. Subchronic studies: (Attachment 4) Dr. Bernard Schwetz, NIEHS, said there were no recommendations in Chapter 2 with which the NTP could take serious issue or not effect. Written responses to all the specific recommendations are included in Attachment 4. He chose to focus his discussion on four of the recommendations that were of considerable interest to the toxicology community:

(1) Public input at the subchronic/chronic interface (ref - recommendation B.3., page 111): Dr. Schwetz noted that the NTP now announces selected chemicals in the Federal Register (FR) and asks for public comments and information on other tests. This could be expanded by asking interested parties to identify themselves to the chemical manager so there could be ongoing information exchange. Further, he proposed that a FR announcement be made near the end of the subchronic studies on a chemical, inviting interested parties to respond.

Discussion: Dr. Scala said peer review of decisions made after the subchronic studies appropriately could be done by the NTP Peer Review Panel. Dr. Nelson agreed with the need for peer review but disagreed with using the Panel as such a role could preempt their being able to serve impartially in review of the final report of a study. Dr. Swenberg suggested there be a group similar to a pathology working group. Dr. Rall stated that the NTP now tries hard to keep the public informed during the selection process and before publication of the findings; a formal step in between would not be useful. He said persons from the outside are and would continue to be invited to comment at the toxicology design step and there are informal interactions by the chemical manager with these persons and others. Dr. Sivak observed that the Report has suggested development and application of a matrix of criteria based on the best available data (weight gain, organ specific toxicity, clinical chemistry, pharmacokinetics). Judicious application of the matrix along with better information on dose setting would meet the concerns of those external to the Program. Dr. Rall replied that, perhaps, the minutes of the Toxicology Design Committee meeting for a chemical could be made available at a Peer Review Panel meeting.

Dr. Swenberg said that just a FR notice announcing chemicals scheduled for chronic studies would be helpful. Dr. Rall agreed but thought such an announcement prior to the prechronic study would be preferable since approximate time tables are measurable from this point, and not all chemicals go on to the chronic study phase.

(2) Use of alternate strains/species (ref - recommendation C.3., page 116): Dr. Schwetz reported on a recent NTP workshop focused on determining whether there was a better strain of mouse for toxicology testing than the B6C3F$_1$ strain. The conclusion was that there was not a sufficient data base to identify a better strain. With regard to alternate species, a recent NTP workshop was held to assess the usefulness of the hamster for carcinogenesis studies.

(3) Use of pharmacokinetics/chemical disposition data (ref - Recommendation D.3., page 125): Dr. Schwetz indicated that the NTP was following the recommendation, and illustrated this by discussing the acquisition of such data or the reason for not acquiring it with the upcoming studies scheduled for peer review. He described the approaches used for obtaining chemical disposition data.

(4) Route of exposure (ref - Recommendations E.I., 2., 3., page 140): Dr. Schwetz said the NTP was using the predominant route of human exposure, where possible; and where multiple routes are typical for humans have employed multiple routes in early subchronic studies. Chemical disposition data and sensitivity to toxicity help determine which route to use in the 90-day and chronic studies.

NIOSH Comments: Dr. Mason said the dermal route is the most common route of exposure in the workplace yet may not be the best or most feasible for long-term animal studies.

NCTR Comments: Dr. Turturro said peer review during the design and testing processes should be incorporated to the extent feasible. He was encouraged by the proposal to examine alternate species and not just rely on rats and mice, and by the focus on trying to use the predominant route of human exposure in experimental studies.

Discussion: Dr. Doull reported that many comments received by the Panel had to do with the issue of the MTD (maximum tolerated dose), and in view of its importance in toxicology testing, he wanted to know the NTP's plans to explore alternatives to the MTD. Dr. McConnell responded that the NTP would continue to use the estimated MTD as the highest dose as defined in the Report. Dr. Nelson said that historically the MTD was used to give the maximum sensitivity for picking up a qualitative effect. Dr. Scala added that the definition of MTD as given in the Report (page 126) also includes the qualifying statement that: "the MTD should not cause morphologic evidence of toxicity of a severity that would interfere with the interpretation of the study."

With regard to chemical selection, Dr. Sivak wondered whether less emphasis might be given to dealing with outside ad hoc nominations and more emphasis focused on selection by the Program to answer questions, e.g., to round out information on chemical classes, elucidate mechanisms, and, in general, expand the science base. Dr. Dorothy Canter, NIEHS, replied that among the tasks for a new support contract would be filling in toxicity data gaps by performing chemical class studies to identify additional candidates for testing. The data generated would be useful in ascertaining structure-activity relationships and in examining mechanisms of toxicity. Dr. Breslow asked what NTP was doing to strengthen the data base for human exposure and effects data. Dr. Canter said the data base at the regulatory agencies could be and were accessed. Telephone surveys with followup letters to obtain information on current production, worker exposure and the like, would be conducted under the new support contract, and interactions with industry and trade groups would be continued. Dr. Scala cautioned that much of the exposure data in industry are not very good both from the standpoint of specific chemicals and levels of exposure to workers.

Dr. Turturro warned that the NTP data were going to be used by others in quantitative risk assessment, like it or not. Dr. Breslow said the recommendation for one more dose level would improve the data for such uses. Dr. Donald Hughes, American Industrial Health Council, commended the NTP for development of the microencapsulation technique as an alternative to the gavage route.

IV. Chronic Studies: (Attachment 5) Dr. McConnell briefly discussed NTP initiatives to evaluate strain and species differences, to investigate effects of vegetable oil gavage, and long-term studies begun in utero. With regard to quality assurance, he discussed problems and discrepancies most commonly revealed at contract laboratories during audits of the data from two-year carcinogenesis studies.

Discussion: There was discussion on whether 24 months is an optimum duration for a long-term study, and on the rationale and pros and cons for beginning long-term studies in utero.

Dr. McConnell concluded with background and discussion of the five levels of evidence for carcinogenicity used by the NTP since June 1983 in interpreting the findings from the long-term rodent studies. He noted these descriptors may not work well with skin paint or promotion studies. He stated that the NTP will reexamine the levels as defined and report back to the next Board meeting with any proposed modifications.

Discussion: Dr. Swenberg said he supported using the levels but said there was one area of ambiguity that needed to be examined. This has to do with the distinction between clear evidence of carcinogenicity and some evidence of carcinogenicity in the situation where only benign tumors are increased. Dr. Nelson and Dr. Perera supported a reexamination. Dr. Nelson urged that the Peer Review Panel as primary users be asked for input. Dr. Scala praised the outstanding and detailed responses by NTP to the report and the rapid implementation of the recommendations. He commended the Program's emphasis on quality assurance and the in-life and post-life auditing of studies.

V. Concluding Discussion: Dr. Doull stressed the cooperation given the Panel from all sectors: Government, industry and others. He said a number of topics were nominated but not considered, usually because the state-of-the-art/science were insufficient or the topic did not fit within the mission of the NTP but had to do with regulatory issues. He commented that the Panel felt the Report was a substantial first step and hoped the NTP would take it from there and focus in depth on specific issues, perhaps through conferences and workshops, and examine the regulatory/scientific interface. He urged that the NTP build on their experience with data audits, and go back and audit older studies on which regulatory decisions have been based. He hoped the toxicology community will continue to give input to the Program. Dr. Mendelsohn seconded the compliments given by Dr. Doull, Dr. Scala and others. He envisioned at reasonable time intervals, perhaps, a series of independent panels examining problem issues associated with the bioassay process. Dr. Rall saw this as more of an ad hoc process dealing also with newer developments such as oncogene activation or early indicators of DNA damage as well as problem areas. Dr. Nelson said he had been concerned at the outset as to what would come out of the Panel in view of the quite diverse viewpoints in the field of carcinogenesis, but was pleasantly surprised to see affirmation of much of the existing program yet a little disappointed that there were no big breakthroughs in the Report.

Status Reports on NIEHS/NTP Research Projects

VI. Current Collaborative Studies on Oncogene Activation and Expression: Dr. Robert Maronpot, NIEHS, defined oncogene and proto-oncogene, their ubiquity in nature, their characteristics, and two mechanisms for oncogene activation and expression. He said that oncogenes are believed to act as regulators of cell growth, differentiation and proliferation. The benefit to the NTP programs can be in taking the Fischer rat and B6C3F$_1$ mouse and looking at the state of oncogene activation in an organ or tissue and relating this to tumor response as an aid in understanding mechanisms and in fine tuning diagnoses. Dr. Maronpot said they were collecting samples of both spontaneous and chemically-induced tumors from NTP two-year studies. In rats these were primarily subcutaneous tumors, leukemias and testicular tumors while in mice, liver tumors. Dr. Marshall Anderson, NIEHS, presented data and discussed two specific and ongoing studies. In one study, pulmonary tumors induced by tetranitromethane in rats and mice were assayed. Members of the ras family of genes were found, primarily the k-ras. In the other study, liver adenomas and carcinomas in untreated mice were tested. The pre-dominant oncogene was the h-ras although there could be other transforming genes. The standard NIH-3T3 transfection assay was used in these studies.

VII. Applications of Nuclear Magnetic Resonance (NMR) Imaging in Toxicologic Testing: Dr. Morrow Thompson, NIEHS, said this was a collaborative project with the Radiology Department at Duke University Medical Center. NMR techniques are being used to look at normal anatomic structures as well as spontaneous and chemically-induced lesions in rats. He described how the technique of NMR imaging takes advantage of the electronic charge of atoms and nuclei in tissues as well as their composition (lipid, protein, water) to produce "pictures." The NMR system at Duke has a large bore magnet which is primarily used with humans, and is modified for studies with rats. Dr. Thompson showed slides of transverse whole body sections of rats from an initiation/promotion study using diethylnitrosamine as the initiator and phenobarbital as the promoter, pointing out the types of lesions in the liver. He then demonstrated the detail available with imaging of other tissues including brain. Future experiments include: (1) carcinogenesis studies in which animals are treated with hepatocarcinogens and the development or regression of lesions are followed with imaging; (2) hepatic function studies with compounds taken up by the liver and execreted in the bile; and (3) continuation of ongoing studies with mononuclear cell leukemia and with pituitary neoplasms.

VIII. Report of the Director, NTP: Dr. David Rall reported that: (1) Dr. James Wyngaarden, Director of NIH, was elected Chairman of the NTP Executive Committee at the Committee meeting on February 17, 1985. He succeeds Mr. Ruckelshaus; (2) the NIEHS has begun various types of toxicology studies on methylisocyanate; (3) the Technical Reports Review Subcommittee (Peer Review Panel) met on March 29 to review the draft technical reports on the toxicology and carcinogenesis studies of C.I. Basic Red 9, Disperse Blue 1, HC Red No. 3, methylene chloride, o-phenylphenol, and 4-vinylcyclohexene. Four new members joined the Panel: Dr. John Crowley, the Fred Hutchinson Cancer Research Center, Seattle; Dr. Kim Hooper, California Department of Health Services, Berkeley; Dr. Frederica Perera, Columbia University School of Public Health; and Dr. Ian Purchase, Central Toxicology Laboratory, Imperial Chemical Industries. At the request of the Center for Food Safety and Applied Nutrition, FDA, the Panel on March 28 reviewed data on testicular tumors in mice fed irradiated chicken meat in lifetime studies; (4) Charles (Nick) Carter has retired as

Scientific Director for the Intramural Research Program, NIEHS, but will remain as Senior Scientific Advisor to Dr. Rall. Dr. Martin Rodbell, who comes from a long career at the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases is the new NIEHS Scientific Director. His research interests are focused primarily on chemical messengers and their action in regulating cell function. Dr. Rall said he would ask Dr. Rodbell and, Dr. David Hoel, Director, Biometry and Risk Assessment Program, to describe the NIEHS's other (than NTP) research activities at an upcoming Board meeting; (5) the FY 1985 NIEHS budget as passed was quite generous, $195 million, providing for 115 new and competing grants and four new centers. However, the budget resolution just passed by the Senate allows for less new and competing grants and centers in the overall NIH budget so the NIEHS's final figures probably will be less.

NIEHS/NTP Concept Review:

IX. In Vitro Transformation of Oncogene Primed Cells by Genotoxic Chemicals: (Attachment 6) Dr. Lawrence Boone, Cellular and Genetic Toxicology Branch, noted that a previous version of the concept had been reviewed at the last Board meeting (October 31 - November 1, 1984) and deferred to consider Board concerns and a change in scope. The objective then was to develop through the research contract mechanism mammalian target cell cultures (mouse embryo) with incorporated proto-oncogenes that would provide a more sensitive assay for chemically-induced transformation. Subsequently, the decision was made to emphasize the basic research aspect of the project rather than assay development. Thus, a cooperative agreement mechanism was recommended. This allows for substantial program involvement with the recipient of the award while also drawing on the recipient's creativity. Dr. Boone said the study would involve developing target cell cultures genetically engineered to express specific oncogenes. The culture system would mimic some of the stages in transformation but would require addition of genotoxic chemicals to complete the process. The first step will be to construct oncogene containing retrovirus rectors. The value of studying this system will be to increase basic understanding of the role of certain oncogenes and their interaction with other genetic targets in neoplastic transformation. Cell lines developed in this research may prove to be very useful targets in routine in vitro assay systems.

Discussion: Dr. Pitot said the current and improved proposal more correctly emphasized the research aspects of the problem which is more appropriate for a cooperative agreement than a contract. Dr. Diamond commented that there are other laboratories using this approach so some cell lines may be in place and could be available for use in the project. Dr. Mendelsohn moved that the concept proposal as now written for a cooperative agreement be approved. The Board voted unanimously to approve the concept.

X. Design for the Testing Phase of a Retrospective Study of PMN Health Hazard Predictions: (Attachment 7) Dr. Charles Auer, EPA, began with an overview of provisions of the Toxic Substances Control Act (TSCA), with particular emphasis on section 5 which requires that manufacturers and importers of new industrial chemicals must submit a premanufacture notification (PMN) to the EPA 90 days prior to commencing manufacture or import. TSCA does not require that submitters of PMNs conduct toxicity testing; thus, test data is available on fewer than half and then usually only acute lethality and local irritation studies. The yearly numbers of PMNs have increased such that there have been an average of 1250 annually in FY 1983 and 1984. To determine whether the PMN chemical may present an unreasonable risk of injury to human health or the environment, the

EPA relies on "structure activity relationships" (SAR) in its evaluations of potential hazards. This approach involves using a combination of: (1) review of submitted toxicity data (if available); (2) review of test data available on analogous substances; (3) use of quantitative SAR methods where available and applicable; and (4) professional judgments of the scientific assessors.

Dr. William Farland, EPA, stated that the purpose of the retrospective study is to obtain some measure of the accuracy of hazard predictions made by the EPA in its evaluation of new chemicals submitted by industry under the PMN requirement of section 5 of TSCA. In so doing, the study was to provide some measure of the validity of EPA's use of the SAR approach as a tool in hazard assessment of PMN chemicals.

Dr. Farland said the general scheme of the Retrospective Study will involve conducting a core set of laboratory toxicity tests on a representative sample of 100 PMN chemicals. Test data obtained will be compared with EPA's previously generated hazard predictions on the sampled PMN chemicals to determine the concordance of those predictions with results obtained by testing. He described the process used to select a statistically valid sample of 100 chemicals from the over 4000 PMN chemicals received since 1979. After excluding high molecular weight, nonreactive, water-insoluble polymers, and chemicals for which manufacturing has not commenced, the remaining chemicals would be stratified on the basis of polymers/non-polymers, and on the basis of general level of toxicity concern, i.e., "low," "medium," or "high." Dr. Farland described a core set of laboratory toxicity tests: (1) three in vitro mutagenicity assays; (2) acute and 28-day repeated oral toxicity studies in rats; and (3) a dermal sensitization assay in the guinea pig (Attachment 7, page 2). Additionally, tests for other specific effects would be considered on a case-by-case basis. The core set would allow testing of 100 chemicals at a cost of about $50,000/chemical.

In concluding the presentation, Dr. McConnell stated the SAR techniques were necessary in view of the 90-day PMN limits, the NTP had the resources and the competence to manage the testing, and the study offered the NTP the chance to do more chemical class studies.

Discussion: This centered around criticism of the adequacy of the core set of tests and, to a lesser extent, on the sampling scheme to determine the 100 chemicals. On the other hand, there was general agreement on the need for a study. Dr. Nelson said there was no basis for the "low," "medium," and "high" classifications used to stratify chemicals for the sample, and, secondly, there was a need to examine the basis for the SAR itself as there are several techniques in use to evaluate SAR. Dr. Farland said a SAR team, including experts, would serve as advisors. Dr. Perera commented that the test set is too narrow, missing several endpoints, especially cell transformation. Dr. Hook observed that the study will not provide answers about hazard, and as proposed, it is set up to fail. Dr. Swenberg suggested applying the SAR techniques to existing data bases including those of the NTP which could supply answers about the validity of the techniques while conserving limited resources. To sum up, Dr. Mendelsohn stated: (1) He (the Board) applauded the need for validation of the SAR techniques; (2) he applauded the need for obtaining good test data; but (3) he was concerned with generating inadequate answers from an inadequate testing scheme.

Dr. Dorothy Canter, NIEHS, proposed that a subcommittee be formed to help EPA design an adequate validation test scheme. Dr. Rall said this could be a working group composed of NTP Board members, EPA Science Advisory Board members, and key agency staff. Dr. Hook moved that the Board fundamentally agrees with the concept of testing the SAR procedures used but would like more attention paid to creating better methods to do it. Rephrased, the Board agrees that there is an urgent need for studies but does not agree with or support the proposed concept. The Board would like to be involved in developing an improved concept. Dr. Swenberg seconded the motion which was approved unanimously.

XI. Peer Review and Priority Ranking of Chemicals Nominated for NTP Testing: There were 12 individual chemical nominations and a class study of three chemicals to be considered by the Board (Attachment 8). All had been reviewed previously by the NTP Chemical Evaluation Committee (CEC). Dr. Mendelsohn chaired the review and Dr. Canter, member of the CEC, and Dr. Victor Fung, NTP Chemical Selection Coordinator, served as resource persons. Each Board member had been asked to serve as principal reviewer for one to three chemicals. As before, following oral presentation of each review and discussion, a motion was made and voted on by the Board members.

Of the 12 individual chemical nominations, four (atrazine; p-chloro-alpha, alpha, alpha-trifluorotoluene; ordram; and 2,3,4,6-tetrachlorophenol) had been reviewed by the CEC on February 28, 1984. Eight (carbenoxolone, dimethylheptylpyran, emodin, malathion, 5-methoxypsoralen, phencyclidine hydrochloride, picloram, and 2,6-xylidine) had been reviewed by the CEC on October 25, 1984 (Attachment 8, Table 1).

The class study on three mononitrotoluenes (o-, m-, and p-isomers) was reviewed by the CEC on February 5, 1985 (Attachment 8, Table 1). Dr. Douglas Bristol, NIEHS, who had proposed the study presented the background. He said the literature led to a prediction that the o-isomer would be a hepatocarcinogen in male rats while the m-isomer and p-isomer would not be carcinogenic. In view of the apparent very specific differences in the isomers, he had proposed both prechronic and chronic toxicity studies for all three isomers. Dr. Swenberg discussed the carcinogenicity of the 2,4- and 2,6-dinitrotoluene isomers as studied by CIIT, and said DNA adduct studies were in progress. He recommended high priority for carcinogenicity studies in male and female rats and mice for all three isomers. The Board concurred unanimously.

The Board's recommendations, priority for testing, and additional remarks and/or caveats for the 15 chemicals reviewed are summarized in Attachment 9.

Testing Recommendations for Chemicals Reviewed by the NTP Board of Scientific Counselors
on May 1, 1985

Chemical (CAS Number)	Nominating Source	Testing Recommendations (Priority)	Remarks
1. Atrazine (1912-24-9)	California Reg. Water Quality Control Board	Multigeneration and fertility studies (High)	-Concern about potential antifertility effects in both males and females -Prior to testing, check with EPA Office of Pesticide Programs to ascertain if multi-generation reproductive study has been done.
2. Carbenoxolone (5697-56-3)	Dr. W. Lewis	Defer	-Consult with FDA regarding current U.S. usage and toxicity studies submitted to date. -If drug is not used in U.S. then no testing is recommended.
3. p-Chloro-α,α,α-trifluorotoluene (98-56-6)	National Cancer Institute	Oral subchronic study in mice (Low)	-Low exposure -Chronic and reproductive studies not recommended because of low exposure to chemical.
4. Dimethylheptylpyran (32904-22-6)	National Academy of Sciences	Genotoxicity (Low)	-Testing dependent on commercial availability of the chemical -No current usage
5. Emodin (518-82-1)	Dr. W. Lewis	-Chemical disposition -Carcinogenicity -Teratogenicity (High) -Reproductive Toxicity (Moderate)	-Concern about exposure of pregnant women -Positive mutagenic results -Structure activity relationship to other anthraquinones -Chemical disposition study should precede carcinogenicity study -Consider carcinogenicity testing in connection with that of 1,8-dihydroxy-4,5-dinitroanthra-quinone

Chemical (CAS Number)	Nominating Source	Testing Recommendations (Priority)	Remarks
6. Malathion (121-75-5)	Dr. A. S. Whitmore	-Fertility assessment by continuous breeding (High)	-Wide exposure -Examine effects on both male and female fertility -Concern as to adequacy of past malathion carcinogenicity studies; although no reason to believe malathion is carcinogenic, there is need for state of art carcinogenesis study -Communicate strong concern of Board regarding carcinogenicity testing to EPA Office of Pesticide Programs
7. 5-Methoxypsoralen (484-20-8)	Food and Drug Administration (FDA)	Defer	-Toxic properties expected to be similar to that of 8-methoxypsoralen -Consult with FDA regarding occurrence of 5-MOP in current products other than natural products (foods), and regulatory concern of agency
8. Ordram (2212-67-1)	California Reg. Water Quality Control Board	Defer	-Ascertain status of industry chronic and genotoxicity studies
9. Phencyclidine hydrochloride (956-90-1)	National Academy of Sciences	No testing	-Seriousness of acutely toxic effects of this drug of abuse well documented in animal and human studies -Results of carcinogenicity study would probably not act as deterrent to potential users.
10. Picloram (1918-02-1)	1. Ms. E. Clark 2. Dr. L. Clark Hansbarger	No testing	-Industry conducting two-year feeding study in rats -EPA will require industry testing under registration standards expected to be issued in 1985
11. 2,3,4,6-Tetrachlorophenol (58-90-2)	California Reg. Water Quality Control Board	Defer	-Obtain status of current studies from EPA -Resubmit to Board after completion of pentachlorophenol study for comparison of effects of two chemicals

Chemical (CAS Number)	Nominating Source	Testing Recommendations (Priority)	Remarks
12. 2,6-Xylidine (87-62-7)	Occupational Safety and Health Administration	No testing	-No question as to carcinogenic potential based on results of feeding study in rats. -Low usage and exposure
Mononitrotoluene Class Study			
1. m-Nitrotoluene (99-08-1)	NIOSH/NIEHS*	Carcinogenicity testing in male and female rats and mice	-Considerable human exposure to mononitrotoluenes -Excellent class study which will yield data complementary to those obtained by Chemical Industry Institute of Toxicology -Good study in which to investigate structure activity effects with respect to methemoglobinemia
2. o-Nitrotoluene (88-72-2)	NIOSH/NIEHS*		
3. p-Nitrotoluene (99-99-0)	NIOSH*		

*In January 1979 NIOSH nominated mononitrotoluene for carcinogenicity testing but did not specify the isomer to be tested. NTP subsequently selected p-nitrotoluene as the representative isomer.