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National Toxicology Program
Board of Scientific Counselors' Meeting
September 27, 1983

Summary Minutes

The National Toxicology Program (NTP) Board of Scientific Counselors met on September 27, 1983, 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 Board Members).

The minutes of the March 14 and 15, 1983 Board of Scientific Counselors' meeting were approved unanimously.

I. Briefing on the Auditing of Data From NTP Long-Term Toxicology and Carcinogenesis Studies: Dr. D. P. Rall, NTP Director, said that subsequent to transfer of the Carcinogenesis Bioassay Program from the National Cancer Institute to the NIEHS in 1981, NTP staff became aware of significant data quality problems at a contractor laboratory, Gulf South Research Institute (GSRI). Dr. E. E. McConnell, NIEHS/NTP, reported that after attempts at correcting the problems all pathology was removed from GSRI in March 1983. He said all completed studies from GSRI will be audited and recommendations made as to the adequacy of the data from each study. Dr. B. A. Schwetz, NIEHS/NTP manager for the audits, described the procedures used in auditing the following major aspects of a chronic study: (1) administrative information; (2) pretest animal data; (3) chemistry information; (4) dose preparation and administration; (5) environmental conditions (temperature, relative humidity, lighting, air changes); (6) in-life observations; (7) pathology; and (8) reports (Attachment 3). Major goals are to comply with Good Laboratory Practice (GLP) requirements and assure the quality of the science. Also, initial priority will be given to auditing completed studies for which the draft technical reports are ready for peer review; eventually all in-life studies -- prechronic and chronic -- will be audited.

Discussion: In response to a question by Dr. Hook, Dr. Schwetz said some auditing had been done in the past but, in general, the assumption has been that the laboratories are doing a good job. Dr. Rall noted that GSRI has been in compliance with GLP requirements. Dr. Manson inquired as to additional costs and personnel demands created by the need to audit. Dr. Schwetz replied that on the average a current audit committed four persons for one week. Dr. McConnell said the proposed in-life audits would not add significantly in time as they would be extensions of regular site visits. Dr. Swenberg asked about the audit policy with completed studies. Dr. Rall replied that studies to be audited would include all NTP studies not yet published, those done by GSRI, previously reported studies given high priority by Executive Committee agencies, and, over the next four to five years, select studies completed by the NTP giving first priority to those positive for carcinogenicity. All studies would be published, with appropriate caveats to explain any limitations of the studies, and all published reports would contain a summary report of the audit findings.

Dr. Rall said NTP staff would be meeting with representatives of the American Industrial Health Council to discuss methods for evaluating the scope of the problem in long-term studies being done outside of the NTP.

II. Overview of NTP Programs: (Attachments 4 and 5) Dr. Rall described the establishment of the NTP, origins of its funding and the mix of chemical testing, test validation and test method development, noting the largest allocation of resources to testing but with increasing recent emphasis in method development. He talked of the oversight roles of the Executive Committee and the Board. He said that the Board was expected to review science for all of NTP while also reviewing the scientists themselves for the NIEHS component. The NCTR and NIOSH components have other mechanisms for personnel review. Dr. Rall also mentioned the role of the Board in reviewing concepts for proposed contracts and interagency agreements. He said the Board is asked to review areas such as the toxicology data management system (TDMS) and major modifications in pathology requirements for long-term studies. The whole Board is involved on an ongoing basis in the chemical nomination and selection process while a subcommittee carries out peer review of the reports of long-term toxicology and carcinogenesis studies.

Discussion: As a means of getting more indepth and continuing involvement of Board members with specific programs, Dr. Manson proposed that an advisory committee be formed of Board members and ad hoc experts to provide continuity of peer review for the NTP Reproductive and Developmental Toxicology programs at the three agencies. She stated that the new method development initiatives, especially the effort to devise new methods in teratology, would benefit. The proposed committee would need to meet only once or twice a year and could effect review of reports by mail. Dr. Mendelsohn said the Board was encouraged to get more involved other than just at Board meetings so this would be one way to do that. Dr. Hook moved that an ad hoc advisory committee be formed. Dr. Diamond seconded the motion and it was approved unanimously by the Board. ACTION: Dr. Mendelsohn and Dr. Manson should provide NTP with names of proposed members so the committee can be formed.

III. Status Report on the Ad Hoc Panel on Chemical Carcinogenesis Testing and Evaluation: (Attachment 6) Dr. Rall reported on the progress of the Panel since its authorization at the last Board meeting. He said the full Panel had met twice, May 17 and August 23, 1983, and each of the four subgroups also had met once, all in public sessions. A final integrated report of the Panel to the Board is projected for the spring of 1984. Ample time will be allowed for public comment on a preliminary draft report. Dr. Schwetz, NTP representative for the Subgroup on Data Required from Prechronic Studies, gave an overview of questions raised and issues discussed at the Subgroup's meeting on July 15. Dr. McConnell, NTP representative for the Subgroup on Design of Chronic Studies, discussed the major issues raised at the Subgroup's meeting on September 15. Dr. R. Tennant, NTP representative for the Subgroup on Techniques to Supplement or Foreshorten Cancer Tests, reported on the Subgroup's meeting held on September 21. Dr. Swenberg, a Subgroup member, said a major focus was on evaluating test systems which could be used to obtain 'parallel' data from animals and humans or human fluids or tissues. Dr. Mendelsohn pointed out short-term tests could contribute prior to a bioassay by aiding in chemical, dose, and

route selection; during the bioassay to monitor for toxicity and genetic effects; and after the bioassay to aid in interpreting the results and for purposes of cross validation. Dr. Swenberg noted that the area of tumor promotion systems was least well studied and a recommendation would be to give the area more emphasis. Dr. Rall, NTP representative for the Subgroup on Regulatory Aspects, commented on the Subgroup's meeting held on September 14. Summary minutes and other program information from meetings of the Panel and its Subgroups may be obtained by contacting Ms. Janet Riley, Secretary to the Panel, P. O. Box 12233, Research Triangle Park, N.C. 27709; telephone (919) 541-7621 or FTS 629-7621.

IV. NIH/NTP Concept Reviews - Contracts: Two concepts were reviewed for support services to be effected through contracts in the areas of chemistry support and inhalation toxicology.

(1) Chemistry Support for Toxicity Testing at NIEHS: (Attachment 7) The proposal was presented by Dr. C. W. Jameson, NIEHS, who said the objective is to provide routine chemistry support for all in-house (Toxicology Research and Testing Program) toxicity studies. Preference would be given to a contractor within a one hour drive of the NIEHS. Included would be chemical procurement and analyses, dose preparation, routine analysis of tissue and body fluids, and development of analytical methods where needed. The move into the new laboratories at NIEHS will enable considerable increases in in-house toxicity studies making necessary more chemistry support than is available in existing contracts. Dr. Hook stated that the best way would be to provide the chemistry support in-house, and asked why this could not be done. Dr. Rall said that with budgetary restraints and personnel ceilings, developing a large chemistry support group in-house is not the best way to use these limited resources. Dr. Swenberg moved that the concept be approved. Dr. Manson seconded the motion and it was approved unanimously by the Board.

(2) Animal Research on the Inhalation Toxicology of Environmental Chemicals: (Attachment 8) Dr. McConnell said the inhalation toxicology program and support contract historically had been part of the NIEHS intramural research program, and only recently had been transferred to the NTP component, the TRTP. Thus, a review for concept was deemed necessary prior to recompeting the contract. Dr. E. Van Stee, NIEHS, gave additional background information and described the exposure facilities and types of studies (on gases and particulates) which have been done or are in progress. The contract is carried out in the NIEHS exposure facility with a smaller part of the facility being operated by NIEHS staff under Dr. Van Stee. He said the objectives of the contract were to improve inhalation technology for gases and the use of computerized monitoring systems. The contractor part of the facility is best suited to long-term studies (3 months to 2 years) while the in-house part is used primarily for short-term studies and research. Dr. Hook inquired as to why a cooperative agreement might not be preferable to a contract. Mr. A. Benton, NIEHS, replied that the collaborative nature of the studies made the contract mechanism more appropriate. Dr. Swenberg urged continuation and more effort with inhalation studies using time-varying concentrations of gases. Dr. Van

Stee said most of the contract costs would be personnel-related since most of the major equipment was in place. Dr. Manson moved for approval of the concept proposal. Dr. Hook seconded the motion and it was approved unanimously.

V. NIH/NTP Concept Reviews - Cooperative Agreements: Three proposals for research to be performed through the cooperative agreement mechanism were reviewed for concept by the Board. A cooperative agreement is similar to a research grant yet differs in that it allows substantial involvement of agency staff with the awardee during the performance period and applications are generally received in response to a Request for Applications (RFA).

(1) Determine the Biological Nature of Proliferative Exocrine Pancreatic Lesions in F344 Rats and the Possible Role of Vegetable Oil in Promoting the Formation of These Lesions: (Attachment 9) Dr. G. Boorman, NIEHS, discussed the increased incidences of pancreatic acinar cell lesions observed in male rat vehicle controls from recent long-term corn oil gavage studies in NTP. He noted that 59 of long-term (usually two-year) studies in progress were by the gavage route. The mechanisms of the vegetable oil in causation of and the biological significance of the lesions are not known. Thus, there is a need for a basic understanding of the oil effects. Dr. Boorman said there are good reasons for doing the study through a cooperative agreement. First, there is not sufficient staff in-house to do the work especially in view of the repetitive gavage studies which will be required. Second, the cooperative agreement mechanism will allow for drawing on expertise not available in-house, e.g., performing hormone assays, yet in-house staff will retain control over direction of the study. As principal reviewer, Dr. Swenberg said there was definitely a need for such a study in view of the fact that one third of current bioassays were by the corn oil gavage route. In response to a question by Dr. Hook, Dr. McConnell said there is a definite but not consistent association between the increased incidence of the pancreatic lesions and the corn oil vehicle. The mechanism for this association remains to be established. Dr. Hook commented that NTP needed to more crisply define the objectives of the proposal so as to get the broadest possible response to the RFA. Dr. Swenberg moved for approval of the concept proposal. Dr. Hook seconded the motion and it was approved unanimously.

Dr. Schwetz provided introductory remarks for the final two concept proposals. He noted the approval at the March 1983 Board meeting of a concept entitled "Development of Human Cell Assay Systems for Genetic Toxicity" which, along with the concepts yet to be discussed, represented a NTP goal to perform studies in human cells where feasible.

(2) Development of an In Vitro System for the Co-Incubation or Co-Culture of Isolated Renal Tubules and Hepatocytes (Attachment 10) Dr. W. Kluwe, NIEHS, presented the proposal. He said a cooperative agreement was preferred because it obviated having to develop expertise in-house yet allowed for considerable staff input into design and conduct of the studies. He reported that about 25% of the chemicals studied by the

NTP cause nephrotoxicity in at least one species or sex, including nearly every compound with an amine moiety or halogenated carbon. An in vitro approach was chosen so that factors which modify toxicity, including metabolism of the chemical, could be studied. Dr. Hook stated the proposal was overly ambitious and not focused enough; the study should be confined to renal tubules. Dr. Swenberg said there needed to be more specificity as to which segment of the renal tubules were to be examined, and also agreed that the goals of the proposal needed to be more tightly focused. Dr. Manson said there needed to be better definition of the types of toxicity to be evaluated in the assay system. As principal reviewer, Dr. Diamond concluded that the Board wants the focus put on the renal tubule with exclusion of hepatocytes, and information should be included clearly defining the toxic endpoints to be studied in vitro. Dr. Kluwe pointed out that the probable end points were specified in the proposal. Further, the cooperative award recipient was to be allowed some latitude in proposing additional end points. Dr. Diamond then moved for approval of the concept proposal with the suggested modifications. Dr. Manson seconded the motion and it was approved unanimously.

(3) Development of Methods to Assess Human Metabolism of Chemical Xenobiotics: (Attachment 11) Dr. H. B. Matthews, NIEHS, presented the proposal. He explained that the objective was to develop and evaluate methodology for assessing metabolism of xenobiotics by human tissues, particularly the liver. Data obtained would be used to determine whether the usual animal models handle a chemical in a similar manner to humans, and, if so, could they be valid extrapolation models. As principal reviewer, Dr. Hook asked why the study should be done since others were looking at human metabolism; why not use tissues other than liver; and how many subjects would be needed to establish baseline data and assess degree of inter-subject variability in metabolism. Dr. Matthews replied that others were not studying metabolism of environmental chemicals, and tissues other than liver would be used when available. Dr. Manson commented that based on knowledge that there is great variability in the human metabolism of xenobiotics she was concerned as to the interpretability of data obtained. Dr. Rall responded that the need for biostatistical involvement should be written into the proposal. Dr. Diamond suggested that information on the types as well as rate of metabolism would be useful. Dr. Hook moved for approval of the concept proposal. Dr. Swenberg seconded the motion and it was approved by the Board with one vote against (Dr. Manson).

VI. Peer Review and Priority Ranking of Chemicals Nominated for NTP Testing: (Attachment 12) There were 12 chemical nominations to be considered by the Board. All had been reviewed previously by the NTP Chemical Evaluation Committee (CEC) on November 17, 1982, and were listed in the Federal Register of March 4, 1983 along with CEC recommendations. Seven of the chemicals were nitroaromatic compounds nominated by the American Federation of State, County and Municipal Employees, AFL-CIO. Six were nitropyrenes and the seventh was 2,4,7-trinitrofluoren-9-one (TNF). The other five compounds were aliphatic aldehydes, namely formaldehyde, citral, butyralde hyde, crotonaldehyde and furfural, recommended to be tested for various reproductive toxicology endpoints. They were selected from a group of 12 aldehydes already under test by the NTP for other toxic endpoints.

Dr. Mendelsohn chaired the review and Dr. D. Canter, NIEHS, member of the CEC served as resource person. Each Board member had been asked to serve as principal reviewer for one or two chemicals prior to the meeting except Dr. Manson who was asked to review the testing proposal for the five aldehydes. Following oral presentation of the review and of the CEC testing recommendations for each chemical and discussion, a motion was made and voted on by the Board members. Since there were ongoing studies outside of NTP with the nitropyrene class, the decision was made to defer further consideration of the six nitropyrenes so that representatives of the testing groups could be invited to an upcoming Board meeting to discuss their studies. The Board's recommendations, priority for testing, and additional remarks and/or caveats are summarized in Attachment 13.

The meeting was adjourned.

TESTING RECOMMENDATIONS FOR CHEMICALS REVIEWED BY THE
NTP BOARD OF SCIENTIFIC COUNSELORS
ON SEPTEMBER 27, 1983

Chemical	Recommendation (Priority)	Remarks
2,4,7-Trinitrofluorenone	Carcinogenicity (Low)	Priority for testing would increase if evidence of substantial production and exposure
1-Nitropyrene) 1,3-Dinitropyrene) 1,6-Dinitropyrene) 1,8-Dinitropyrene) 1,3,6-Trinitropyrene) 1,3,6,8-Tetranitropyrene)	Deferred	-Assemble further information on ongoing studies -Invite representatives of EPA and The Health Effects Institute to discuss their studies at next Board meeting
Formaldehyde	Inhalation teratology and reproductive toxicology studies (High)	-High usage -Known carcinogen -Before undertaking studies, confirm that no such other research underway
Citral	Teratology (High)	-Vitamin A intermediate -If study positive, consider for additional reproductive toxicology testing
Butyraldehyde	Teratology (Moderate)	Potential occupational exposure
Crotonaldehyde	Teratology (Moderate)	Positive in several mutagenicity assays
Furfural	Teratology (Moderate)	Assess results from NTP carcinogenesis testing to determine if further reproductive studies advisable

Summary Data on Nitro Aromatic Compounds

Reviewed by the NTP Chemical Evaluation Committee on November 17, 1982

Chemical	CAS Number NTP Number	Nominating Source	Use	Production	NTP Status	Other	Testing Recommendation (Priority)	Chemical Selection Principles	Remarks
1) 2,4,7-Trinitrofluorenone	129-79-3 (11118-P)	-Am.Fed.of State, County & Municipal Employees, AFL-CIO; -NCI	-Previously base for photoconductor in IBM photocopying machines (Use discontinued by IBM,10/16/81) -In photosensitive organic semiconductors & videotape films	-Listed in TSCA Inventory, production range not given -Greater than or equal to 9.1×10^5 g (1975) -Greater than or equal to 2.3×10^6 g (1976;1977)	--	-Scored but not studied by ITC (1978) -Mut. in Salm. & mouse lymphoma assays with & w/o activation, induced SCE in CHO cells in vitro -Mammary carcinogen in SD rats -Two carcino. studies in mice - s.c. & dermal applications elicited fibrosarcomas, while dermal applications alone did not	90-Day subchronic skin painting study (H)	4	-Maintain animals for 18 mos. & evaluate for tumors -Concern about previous exposure when used in IBM photocopiers -Mutagenicity data -Structure activity relationships
2) Nitropyrene	5522-43-0 (11119-T)	Am.Fed.of State, County & Municipal Employees, AFL-CIO	In photocopying machine toners	Listed in TSCA Inventory, production range not given	--	-Mutagenic in Salm. -Mouse skin tumor initiation & promotion studies ongoing by EPA	-Mouse lymphoma assay -In vitro cytogenetics -Other appropriate short-term tests -Carcinogenicity (inh.) -Cocarcinogenesis study with benzo-(a)pyrene -Teratology study (inh.) (H)	1,3	-Concern as to environmental exposure -Consider nitropyrenes as a class study -Coordinate testing with EPA studies

Chemical	CAS Number NTP Number	Nominating Source	Use	Production	NTP Status	Other	Testing Recommendation (Priority)	Chemical Selection Principles	Remarks
3) 1,3-Dinitro-pyrene	75321-20-9 (11120-R)	Am.Fed.of State, County & Municipal Employees, AFL-CIO	In photo-copying machine toners	--		-Mutagenic in Salm. -EPA to conduct mouse skin tumor initiation & promotion studies of dinitro-pyrene mixtures	Test well-defined mixture of 3 dinitro-pyrenes: -Mouse lymphoma assay -In vitro cytogenetics -Other appropriate short-term tests -Carcinogenicity (inh.) -Cocarcinogenesis study with benzo(a)pyrene -Teratology study (inh.) (H)	7	-Concern about occupational & environmental exposures to the mixture -Consider nitropyrenes as a class study -Coordinate testing with EPA studies -Use same proportions of three dinitropyrenes in mixture as that utilized by EPA
4) 1,6-Dinitro pyrene	42397-64-8 (11121-V)	Am.Fed.of State, County & Municipal Employees, AFL-CIO	In photo-copying machine toners	--		-Mutagenic in Salm. -EPA to conduct mouse skin tumor initiation & promotion studies of dinitro-pyrene mixtures	Mutagenicity testing of individual dinitropyrenes: -Mouse lymphoma assay -In vitro cytogenetics -Other appropriate short-term tests (M-H)	1,3	
5) 1,8-Dinitro-pyrene	42397-65-9 (11122-Y)	Am.Fed.of State, County & Municipal Employees, AFL-CIO	In photo-copying machine toners	--		-Mutagenic in Salm. -EPA to conduct mouse skin tumor initiation & promotion studies of dinitro-pyrene mixtures			

Chemical	CAS Number NTP Number	Nominating Source	Use	Production	NTP Status	Other	Testing Recommendation (Priority)	Chemical Selection Principles	Remarks
6) 1,3,6-Trinitropyrene	75321-19-6 (11123-D)	Am.Fed.of State, County & Municipal Employees, AFL-CIO	In photocopying machine toners	--		Mutagenic in Salm.	-Mouse lymphoma assay -In vitro cytogenetics -Other appropriate short-term tests (M-H)	1,3	-Consider nitropyrenes as a class study -Testing contingent upon compound availability
7) 1,3,6,8-Tetranitropyrene	28767-61-5 (11124-G)	Am.Fed.of State, County & Municipal Employees, AFL-CIO	In photocopying machine toners	--		Mutagenic in Salm.	-Mouse lymphoma assay -In vitro cytogenetics -Other appropriate short-term tests (M-H)	1,3	-Consider nitropyrenes as a class study -Testing contingent upon compound availability