

Blackpepper

NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS

March 30 and 31, 1987

Summary Minutes

National Toxicology Program
Board of Scientific Counselors Meeting

March 30-31, 1987

Summary Minutes

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NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS MEETING

March 30 and 31, 1987

SUMMARY MINUTES

The National Toxicology Program (NTP) Board of Scientific Counselors met on March 30 and 31, 1987, 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 and Expert Consultants.) Members of the Board are Drs. Henry Pitot (Chairman), Norman Breslow, Michael Gallo, Donald Mattison, Mortimer Mendelsohn, Frederica Perera, Adrienne Rogers, and Robert Scala. Dr. Breslow was unable to attend the meeting. Drs. Breslow, Mendelsohn and Pitot retired from the Board after this meeting.

I. Report of the Director, NTP: Dr. David Rall reported that: (1) Dr. Robert Goyer, NIEHS Deputy Director, left the Institute in February to become Professor and Chairman, Department of Pathology, University of Western Ontario; (2) the Congressional appropriations hearings for the FY 1988 NIEHS budget went well and the current services budget would allow for modest growth; and (3) the Biometry and Risk Assessment Program (BRAP), NIEHS, organized a Symposium on Basic Research in Risk Assessment which was held at NIEHS on March 9 to 12. Dr. David Hoel, BRAP Director, briefly described the scientific topics covered in the various sessions. He said the papers from the symposium would be published in a late 1987 or early 1988 volume of Environmental Health Perspectives.

II. Overview of the NIEHS Biometry and Risk Assessment Program: Dr. Hoel, Program Director, said there were four branches: Computer Technology Branch (CTB); Epidemiology Branch (EB); Statistics and Biomathematics Branch (SBB) and Biochemical Risk Analysis Branch (BRAB) (Attachment 3). A major emphasis of the Program is on issues of methodology for risk assessment. Also important is collaboration with and support to the Intramural Research and Toxicology Research and Testing Programs.

The Computer Technology Branch (CTB) is responsible for the NIEHS's computing and data processing. Computer expertise and capabilities are being utilized in studies on molecular imaging and certain kinds of sophisticated pharmacokinetics.

The Epidemiology Branch links laboratory studies to the field studies with a primary focus on the effects of environmental factors on reproductive outcomes, including studies on the effects of organochlorine chemicals in breast milk on development, studies on the effects of chemicals on placental enzymes, studies on the effects of "passive" smoking on children as expressed in terms of cancer risk in their adulthood, and an evaluation of the association between human maternal chorionic gonadotropin levels and early fetal loss.

The Statistics and Biomathematics Branch is concerned with: development and use of statistical methodology in the analysis of data from toxicology and carcinogenesis studies in rodents; the development and use of methodology for short-term genetic toxicology assays; the development and use of statistical methods in epidemiological studies; and the application of biomathematical approaches to population genetics and pharmacokinetic modelling.

The Biochemical Risk Analysis Branch is concerned with developing and applying laboratory methodology in quantitative risk assessment. Current areas of activity include studies on oncogene activation, the dosimetry of DNA adduct formation and metabolism, and development of data for risk assessment on chemicals of public health importance such as benzene and methylene chloride.

III. Review of Chemicals Nominated for "NTP Studies": Dr. Dorothy Canter, NIEHS, discussed some additions to the Executive Summaries. She noted the inclusion of a one-page overview for two of the chemicals to be reviewed, cholestyramine and sodium nitrite, and asked for Board feedback on the usefulness of these overviews and on whether they should be incorporated into all future Executive Summaries. She reported that in response to a suggestion by Dr. Scala, caveats on information on occupational exposure retrieved from NIOSH data bases were being added.

There were six chemical nominations to be considered by the Board. All had been reviewed previously by the NTP Chemical Evaluation Committee (CEC). Dr. Pitot chaired the review and Dr. Canter, also a member of the CEC, and Dr. Victor Fung, NIEHS, NTP Chemical Selection Coordinator, served as resource persons. Each Board member present had been asked to serve as principal reviewer for one chemical. Following oral presentation of each chemical review and discussion, a motion was made and voted on by the members.

The Board's recommendations, priority for testing, and additional remarks and/or caveats for the six chemicals reviewed are summarized in Attachment 4.

IV. NIEHS Carcinogenesis and Toxicology Evaluation Branch (CTEB) - Management of the Evaluation Process:

A. Introduction - Dr. James K. Selkirk, Chief, CTEB stated that while all Branches of the NIEHS Toxicology Research and Testing Program (TRTP) have significant roles in the evaluation of chemicals for toxicity, the stewardship for the overall process remains the major programmatic responsibility of the CTEB. The afternoon's presentations were aimed at describing in detail the steps involved in planning and carrying out a complete study on any chemical selected for toxicology evaluation. Dr. Selkirk emphasized that a number of staff scientists maintained research projects. Although this effort is secondary to the major programmatic responsibilities of the Branch, it represents an important avenue for professional growth as well as a means to extend results from contracted toxicology studies, develop new methods and probe new hypotheses and ideas. He noted that selected research projects would be peer reviewed by the Board and ad hoc reviewers the next morning.

Dr. Selkirk described the organizational structure of the Branch, the functions of the staff, and the time allocations among the various functions.

B. Designing A Study - Dr. Rajendra S. Chhabra, Manager, Study Design, CTEB, stated that study design is a major responsibility of staff scientists (called Chemical Managers) as well as monitoring and evaluating the resulting studies, and reporting of the results. He described each of the general considerations for designing toxicity studies including use of a multidisciplinary approach, selection and optimal use of laboratory animals, health and safety, and factors considered in selection of dose levels for chronic studies. He noted that all NTP prechronic and chronic study proposals are reviewed by the Toxicology Design Review Committee. Dr. Chhabra commented on the inclusion of three dose levels plus controls in most recent two-year studies as well as interim sacrifices for many and "stop" studies for some. He concluded by emphasizing that the 90-day studies may stand independent of the two-year studies and frequently include measures of genetic toxicity, chemical disposition, immunotoxicity, and reproductive and developmental toxicity.

C. Chemistry, Health and Safety - Dr. C.W. Jameson, Manager, Collaborative Resources, CTEB, said this chemistry program serves as a central resource for all study and research activities of the NTP in assuring chemical quality. The chemistry needs of the Program are facilitated via integrated contracts, an active in-house laboratory, and cooperation and interaction with other NTP programs. The chemistry capabilities provide for procurement of chemicals, chemical analysis, analytical methods development, purification and/or synthesis of test chemicals, and tissue residue analysis. Dr. Thomas J. Goehl, CTEB, provided a more detailed discussion of these capabilities and how and where they fit into the toxicology and carcinogenesis studies process.

Dr. Douglas B. Walters, CTEB, reported that the chemical health and safety office monitors each study laboratory and each study within a facility for factors which may adversely affect the proper research and study environment. Involved are initial laboratory evaluation, follow-up site visits, program reviews, report monitoring, recommended changes in procedures and facilities design, as well as response to problem emergency situations and concerns with eventual waste disposal and record archiving. Chemical health and safety also maintains the NTP chemical repository including the receipt, storage, shipment and handling of test chemicals as well as formulation of chemical specific safety documents. The repository contains over 1100 chemicals which are or have been studied by the NTP.

D. Contracting a Study - Dr. M.L. Vernon, Head, Collaborative Services Staff, CTEB, noted that all prechronic and long-term toxicology and carcinogenesis studies are under direct NTP management, and most are awarded through a master agreement contracting mechanism whereby laboratories and their staff are qualified for standard protocols and in each of various special study areas. Dr. Vernon discussed the many steps in the master agreement award process.

E. Monitoring a Study - Dr. Joseph H. Roycroft, Manager, Study Performance, CTEB, discussed the responsibilities of Chemical Managers and Project Officers during the contracting and performance phases of a study. Project officers are NTP staff scientists who are responsible for monitoring and evaluating overall operation of the contract laboratories. To establish that the studies are well conducted (scientifically, cost-efficiently, and timely,)

these scientists initiate: (1) annual program reviews by peer groups of scientists; (2) quarterly site visits; (3) ad hoc visits by Chemical Managers and experts in various scientific disciplines as needed; (4) communication with the laboratory principal investigator and relevant NTP personnel; and (5) interaction with NTP contract specialists. Dr. Roycroft detailed the various laboratory-specific reports and deliverables and chemical-specific deliverables required.

F. Reporting a Study - Dr. John H. Mennear, Manager, Study Reporting, CTEB, pointed out the central role of the Chemical Manager in the genesis of the "final product" - the Technical Report. He said the preliminary draft report began with generation of the final pathology tables, and is followed by the staff review draft wherein anomalies are noted and disagreements among staff are resolved, leading to the peer review draft where consensus is reached concerning the conclusions of the study. After review and approval by the NTP Peer Review Panel, a galley draft is generated which incorporates comments and revisions from the peer review, leading to the camera-ready draft from which the final Technical Report or "Blue Book" is produced and distributed.

G. Final Remarks - Dr. Selkirk concluded by providing information on the costs of taking selected chemicals through the toxicology and carcinogenesis studies process. He pointed out that about 90% of the costs in FY 1987 had been committed previously due to the multiyear nature of the process. He showed the wide range of costs for performing prechronic and chronic studies. The route of administration and inclusion of special studies in the design contributed most to the width of the range. Dr. Selkirk contrasted the total starts (prechronic and chronic) - 342 - between 1981 and 1987 with the total number of completions (again prechronic plus chronic) - 349, noting that 1981 was when the Carcinogenesis Bioassay Program was transferred from the NCI to the NIEHS.

V. NIEHS Quality Assurance Program: Dr. McConnell introduced the topic by commenting that a three-day conference on "Managing Conduct and Data Quality of Toxicology Studies" co-sponsored by the NIEHS/NTP and industry and trade groups was held in November 1985. The proceedings of this conference were published as a book. He said the presentation on the NIEHS Quality Assurance Program would describe how the NTP obtains an independent objective assessment of the quality of its studies.

Dr. Douglas W. Bristol, Director, TRTP Quality Assurance (QA) Group, stated the broad QA program goals: (1) to independently assess study conduct compliance with Good Laboratory Practice (GLP) regulations and standards; (2) to validate data and results presented in NTP Technical Reports; and (3) to provide feedback to help improve overall quality and cost effectiveness of NTP studies. He said the major activities of the Group had to do with the studies done at contract laboratories under the Master Agreement. There are essentially two levels of QA activity: (1) prospective - which includes auditing the laboratory QA Unit and auditing studies in progress; and (2) retrospective - which includes audits of materials at the archives from completed studies and validation of NTP Technical Reports.

Dr. Carrie E. Whitmire, QA Group Toxicologist, who has responsibility for overseeing the prospective activities, described the GLP requirements and the purposes of QA monitoring at the laboratories emphasizing that GLP compliance is only the baseline for QA. To carry out complete QA evaluations in the master agreement and support service laboratories has required the use of service contracts. Currently there are three QA/GLP contractors with disciplinary capabilities for toxicology and animal care, analytical chemistry, histo- and clinical pathology, and other expertise. Dr. Whitmire discussed her role in the annual program review at a laboratory, and, when necessary, followup visits. She concluded by listing some of the problems most commonly uncovered by prospective QA activities. Many of these problems could be avoided or resolved through improved communication.

Dr. Bristol discussed the two types of retrospective audits: the data audit which reviews all archival study records including pathology specimens; and the report audit. He gave the priority order established by the NTP for doing retrospective audits, with Technical Reports in preparation for peer review given the highest priority.

Dr. Bristol related what he felt were accomplishments by the QA program including development of good procedures for doing audits, establishing a balance between prospective and retrospective audits, documentation of quality of individual studies, validation of Technical Reports, and timely identification of problems so corrective or even preventive actions can be taken. He cited the general and specific improvements in all aspects of the toxicology and carcinogenesis studies process which have resulted since establishment of the QA program. Dr. Bristol said their primary direction was to shift more toward prospective QA monitoring.

VI. NIEHS Carcinogenesis and Toxicology Evaluation Branch (CTEB) - Research Review:

A. Introduction - Dr. Selkirk stated again that the major programmatic responsibility of the CTEB is management of the process for evaluation of chemicals for toxicity as described in detail the previous day. Nonetheless, a number of staff scientists maintain research projects, and it was a selected number of these projects that were to be peer reviewed. To give perspective, he said the Experimental Toxicology Unit and other units conducting research were established in 1983 and have had their own laboratory space only since 1984. Research is conducted: (1) within CTEB; (2) through collaboration with other branches or laboratories within the Institute; or (3) through the contract mechanism. Dr. Selkirk said the projects represent all three approaches with the majority being conducted inhouse. The main purposes of CTEB research are: (1) to characterize the toxicologic potential of NTP priority chemicals; (2) to respond quickly to current toxicological issues concerning human health; e.g., evaluation of the toxicity of methyl isocyanate; and (3) to address major issues relevant to NTP studies, e.g., alternatives to gavage dosing. Dr. Selkirk concluded his introduction by discussing how research projects are identified and how they are then developed, evaluated and reported.

Studies with Program-Wide Application

B. Evaluation of Microencapsulation as a Means to Administer Chemicals in Feed - Dr. C.W. Jameson, CTEB, said microencapsulation for feed studies was being evaluated as an alternative to gavage for chemicals that were either volatile, unpalatable, reactive or otherwise unstable. Until recently, a centrifugal extrusion technique has been used for encapsulating chemicals and continues to be used to evaluate bioequivalence, stability, shelf life and other factors with several volatile liquid chemicals given in microencapsulated form in the feed compared with the same chemicals given by gavage in oil. Also being evaluated currently is a microencapsulation technique involving micelle formation which may be preferable with certain chemicals, e.g., cinnamaldehyde, where a chemical reaction may occur to some extent during the centrifugal extrusion process.

C. Application of Microencapsulation in Toxicology Studies: Toxicity of Microencapsulated Trichloroethylene (TCE) - Dr. Ronald L. Melnick, CTEB, said the objective was to evaluate giving microencapsulated chemicals in the diet as an alternative to gavage for studying the toxicology of trichloroethylene by the oral route of administration. The encapsulated form in the feed of rats was shown to be stable and did not deteriorate, and similar toxicity was observed between the two routes including dose-related increases in liver weight/body weight ratios, individual liver cell necrosis, and activities of several hepatic enzymes. Other priority chemicals were to be evaluated in future studies.

D. Evaluation of Chemical Leukemogenesis and Myelotoxicity Using the In Vivo Leukemia Transplant Model - Part I - Dr. John E. French, CTEB, reported that a Fischer 344 rat leukemia transplant model was developed, and has been characterized morphologically and biochemically to aid in better discrimination between age-induced and chemically-enhanced leukemia. Measured are spleen and body weights and their ratio, hematologic parameters and three marker enzymes for mononuclear cell leukemia (MNCL). Accuracy of the model was validated with 2-ethoxyethanol and pyridine, chemicals that respectively decreased and increased the incidences of MNCL in two-year carcinogenicity studies. Future in vitro studies include searching for protooncogenes and developing cell culture lines and monoclonal antibodies.

E. Evaluation of Chemical Leukemogenesis and Myelotoxicity Using the In Vivo Leukemia Transplant Model - Part II - Dr. Michael P. Dieter, CTEB, said the primary objective was to further identify and characterize tumor cell markers for F344 rat leukemia which would be sensitive and early appearing while correlating later with severity of the disease. Seven enzymes were evaluated with malate dehydrogenase and acetylcholinesterase appearing to be the most useful as biochemical markers for MNCL. Dr. Dieter described preliminary results from the studies with 2-ethoxyethanol and pyridine. Additional enzymes will be evaluated for their sensitivity as markers.

F. Initiation/Promotion Dermal Study to Compare Susceptibility of B6C3F₁ Mice with Swiss CD-1 and Sencar Mice - Dr. William C. Eastin, Jr., CTEB, noted that the impetus for these studies derived from a recommendation by the NTP Ad Hoc Panel on Chemical Carcinogenesis Testing and Evaluation that the absence of tests for promotion represents a major gap. Thus, the objectives of

the current studies were: to compare sensitivity of the B6C3F₁ mouse used in NTP studies with two established responsive mouse strains, and to compare the sensitivity of the three strains to different combinations of initiators and promoters. Dr. Eastin said that in-life studies had been completed and micropathologic data were being reviewed.

Quick Responses to Current Toxicological Issues

G. Acute and Short-Term Inhalation Toxicity Studies of Methyl Isocyanate (MIC) in Rats and Mice - Dr. John R. Bucher, CTEB, said that the NIEHS/NTP undertook a large scale collaborative toxicology study on the toxicity of MIC following the Bhopal tragedy. He described the generation of MIC vapors and protocols for acute and short-term animal inhalation exposures. The studies confirmed MIC to be a potent respiratory toxicant with a steep dose-response for injury resulting in persistent chronic obstructive lung disease. There were also alterations in immune function, genetic effects, and decreased fetal and neonatal survival. The findings have led to a two-year study in rodents exposed once to sublethal doses of MIC. Dr. Bucher underlined the NIEHS's unique capability to handle this type of public health problem.

H. Chemical Detection and Short-Term Toxicity Studies of 5-(4-Nitrophenyl)-2,4-Pentadien-1-al (NPPD) - Dr. Jameson commented that NPPD was referred to as "spy dust" as it was believed to have been used to track U.S. Embassy personnel in the Soviet Union. The State Department requested that the NIEHS/NTP investigate the toxicity of NPPD. He described the development of a colorimetric assay for detection of NPPD in the field and problems that arose due to binding of the chemical to cotton. Subchronic toxicity studies in F344 rats and B6C3F₁ mice exposed dermally and orally indicated there was no observable toxicity of NPPD.

Extensions of NTP Chemical Toxicology Studies

I. Mechanism of Di(2-Ethylhexyl) Phthalate (DEHP) - Induced Hepatotoxicity: Involvement of Peroxisome Proliferation - Dr. Konrad Tomaszewski, CTEB, said that DEHP had been shown to be hepatocarcinogenic in both rats and mice in NTP two-year studies. Since DEHP does not bind covalently to DNA nor is it mutagenic, hepatotoxicity is believed to be related to induction of peroxisomal proliferation. Examined were the induction of two peroxisomal enzymes by DEHP and their role in degradation of H₂O₂. Increases in steady state in vitro hepatic levels of H₂O₂ in animals treated with DEHP, di(2-ethylhexyl) adipate, and nafenopin correlated well with carcinogenic potential of these chemicals. The findings support the hypothesis that peroxisomal proliferation leads to cellular oxidative stress resulting in hepatotoxicity/carcinogenicity. The information developed may be used in predicting the hepatocarcinogenic potential of other chemicals. Future work will include generating more in vivo data.

J. A Biochemical Basis for 1,2-Dibromo-3-Chloropropane (DBCP) - Induced Male Infertility: Inhibition of Sperm Mitochondrial Electron Transport Chain Activity - Dr. Ronald L. Melnick, CTEB, reported that DBCP, a carcinogen in both rats and mice in NTP long-term studies, was also toxic to the testis and epidymis while in humans, exposure to the chemical has been causally associated

with lowered sperm counts, atrophy of the seminiferous tubular epithelium, and infertility. The objective of this study was to investigate the mechanisms of DBCP-induced infertility in rats. It was shown that DBCP inhibits glucose metabolism by epidymis and post-testicular sperm, in vivo and in vitro. Further studies demonstrated that the site of inhibition of glucose metabolism in sperm is the NADH dehydrogenase step of the mitochondrial electron transport chain. Future studies will examine the nature of the inhibition, determine the degree of tissue/species specificity for the effect, and possible structure-activity relationships for related compounds.

K. Toxicological Studies of Metallic Compounds - Dr. Dieter stated that studying the toxicology of inorganic or organic metals and metal complexes is of particular interest to the NTP because of their prevalence in drinking water and industrial processes, their use as constituents in anticancer drugs, and their diverse target organ toxicities. Metals studied or under study include mercury, titanium, nickel, antimony, chromium, and iron. Described were studies on mercuric chloride and nickel sulfate done in conjunction with prechronic and chronic studies with these salts. Mercuric chloride was shown to be immunotoxic with effects on T-cell function in the thymus. Urinary enzyme responses associated with nephrotoxic chemical insult were evaluated to develop a predictive model for renal toxicity in long-term studies. Studies with nickel sulfate revealed no immunotoxic effects, at least at low doses, but showed a major effect on myelopoiesis which is being further investigated. Future research will include other metals or metallics of priority to the NTP. Dr. Dieter briefly discussed a planned study to examine toxic effects of three chromate salts on the bone marrow of mice.

L. The Benzidine Dye Initiative - Dr. John H. Mennear, CTEB, explained that this initiative had resulted from regulatory concern, especially EPA, CPSC and OSHA, over the human health and environmental effects of benzidine, benzidine congeners, and derived dyes, and became a collaborative research effort among NIEHS, NIOSH, and NCTR. This was an integrated investigation into the metabolism, genetic toxicity and carcinogenicity of benzidine, 3,3'-dimethyl- and 3,3'-dimethoxybenzidine, and 12 dyes derived from the three parent amines. Begun in 1981, most of the studies have been completed with the exception of the final reporting on the long-term toxicology and carcinogenesis studies on the two benzidine congeners and two derived dyes. As designed, the initiative has provided scientific information required for making regulatory decisions and served as a model for other chemical class studies.

Alternatives to Animal Studies: In Vitro Models

M. Development and Use of An In Vitro System for the Study of Toxicity in Renal Tubules from Several Mammalian Species - Dr. Elmer Rauckman, CTEB, reported that the goals included developing viable and stable cultures of isolated renal tubules from several mammalian species, including humans, for comparative studies. Once developed, the system will be used to study events (and their progression) in chemically-induced nephropathy at the molecular, sub-cellular and cellular levels. The project is being conducted in four sequential phases: (1) tissue isolation; (2) developing culture techniques; (3) experimental studies with animal tissues; and (4) human tissue studies. Dr. Rauckman

described the in situ renal perfusion technique used. A modified collagenase perfusion technique works best to give tubules that can be maintained in culture for a minimum of four hours with less than 25% loss of viability.

AGENDA

BOARD OF SCIENTIFIC COUNSELORS

NATIONAL TOXICOLOGY PROGRAM

March 30 and 31, 1987

CONFERENCE CENTER, BUILDING 101, SOUTH CAMPUS
 NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES
 RESEARCH TRIANGLE PARK, NORTH CAROLINA

Monday, March 30, 1987CLOSED MEETING

8:30 a.m. - 9:00 a.m.	Evaluation of Personnel in NIEHS Carcinogenesis and Toxicology Evaluation Branch	Board and Consultants
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OPEN MEETING

9:00 a.m. - 9:30 a.m.	Report of the Director, NTP	Dr. D.P. Rall, NIEHS
9:30 a.m. - 10:00 a.m.	Overview of the NIEHS Biometry and Risk Assessment Program	Dr. D.E. Hoel, NIEHS
10:15 a.m. - 11:30 a.m.	Review of Chemicals Nominated for NTP Studies	Board Dr. D.A. Canter, NIEHS
12:30 p.m. - 4:00 p.m.	NIEHS Carcinogenesis and Toxicology Evaluation Branch - Management of the Evaluation Process	
	I. Introduction	Dr. J.K. Selkirk
	II. Designing a Study	Dr. R.S. Chhabra
	III. Chemistry, Health and Safety	Dr. C.W. Jameson Dr. T.J. Goehl Dr. D.B. Walters
	IV. Contracting a Study	Dr. M.L. Vernon
	V. Monitoring a Study	Dr. J.H. Roycroft
	VI. Reporting a Study	Dr. J.H. Mennear
	VII. Final Remarks and Discussion	Dr. J.K. Selkirk
4:00 p.m. - 5:00 p.m.	NIEHS Quality Assurance Program	Dr. D.W. Bristol Dr. C.E. Whitmire

Tuesday, March 31, 1987

OPEN MEETING

8:30 a.m. - 1:00 p.m.

NIEHS Carcinogenesis and
Toxicology Evaluation Branch -
Research Review

- I. Introduction Dr. J.K. Selkirk
Studies with Program Wide Application
- II. Evaluation of Micro- Dr. C.W. Jameson
encapsulation as a Means
to Administer Chemicals
in Feed
- III. Application of Micro- Dr. R.L. Melnick
encapsulation in Toxicology
Studies: Toxicity of
Microencapsulated Trichloro-
ethylene
- IV. Evaluation of Chemical Dr. J.E. French
Leukemogenesis and Myelo-
toxicity Using the in vivo
Leukemia Transplant Model:
Part 1
- V. Evaluation of Chemical Dr. M.P. Dieter
Leukemogenesis and Myelo-
toxicity Using the in vivo
Leukemia Transplant Model:
Part 2
- VI. Initiation/Promotion Dr. W.C. Eastin, Jr.
Dermal Study to Compare
Susceptibility of B6C3F1
Mice With Swiss CD-1 and
Sencar Mice
- Quick Responses to Current Toxicological Issues
- VII. Acute and Short-Term In- Dr. J.R. Bucher
halation Toxicity Studies
of Methyl Isocyanate in
Rats and Mice
- VIII. Chemical Detection and Dr. C.W. Jameson
Short-Term Toxicity Studies
of 5-(4-Nitrophenyl)-2,
4-Pentadien-1-al (NPPD)
- Extensions of NTP Chemical Toxicology Studies
- IX. Mechanism of Di(2-Ethyl- Dr. K. Tomaszewski
hexyl)Phthalate Induced
Hepatotoxicity: Involvement of Peroxisome
Proliferation
- X. A Biochemical Basis for Dr. R.L. Melnick
1,2-Dibromo-3-Chloropropane
(DBCP)-Induced Male Infertility: Inhibition of Sperm
Mitochondrial Electron
Transport Chain Activity

- XI. Toxicological Studies of Metallic Compounds Dr. M.P. Dieter
XII. The Benzidine Dye Initiative Dr. J.H. Mennear
Alternatives to Animal Studies: In Vitro Models
XIII. Development and Use of an in vitro System for the Study of Toxicity in Renal Tubules from Several Mammalian Species Dr. E.J. Rauckman

CLOSED MEETING

1:15 p.m. - 2:45 p.m. Evaluation of Programs and Personnel in the Carcinogenesis and Toxicology Evaluation Branch Board and Consultants

Adjourn

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS

March 30-31, 1987

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AD HOC REVIEWERS FOR NTP BOARD OF SCIENTIFIC
COUNSELORS REVIEW OF
CARCINOGENESIS AND TOXICOLOGY EVALUATION BRANCH

March 30-31, 1987

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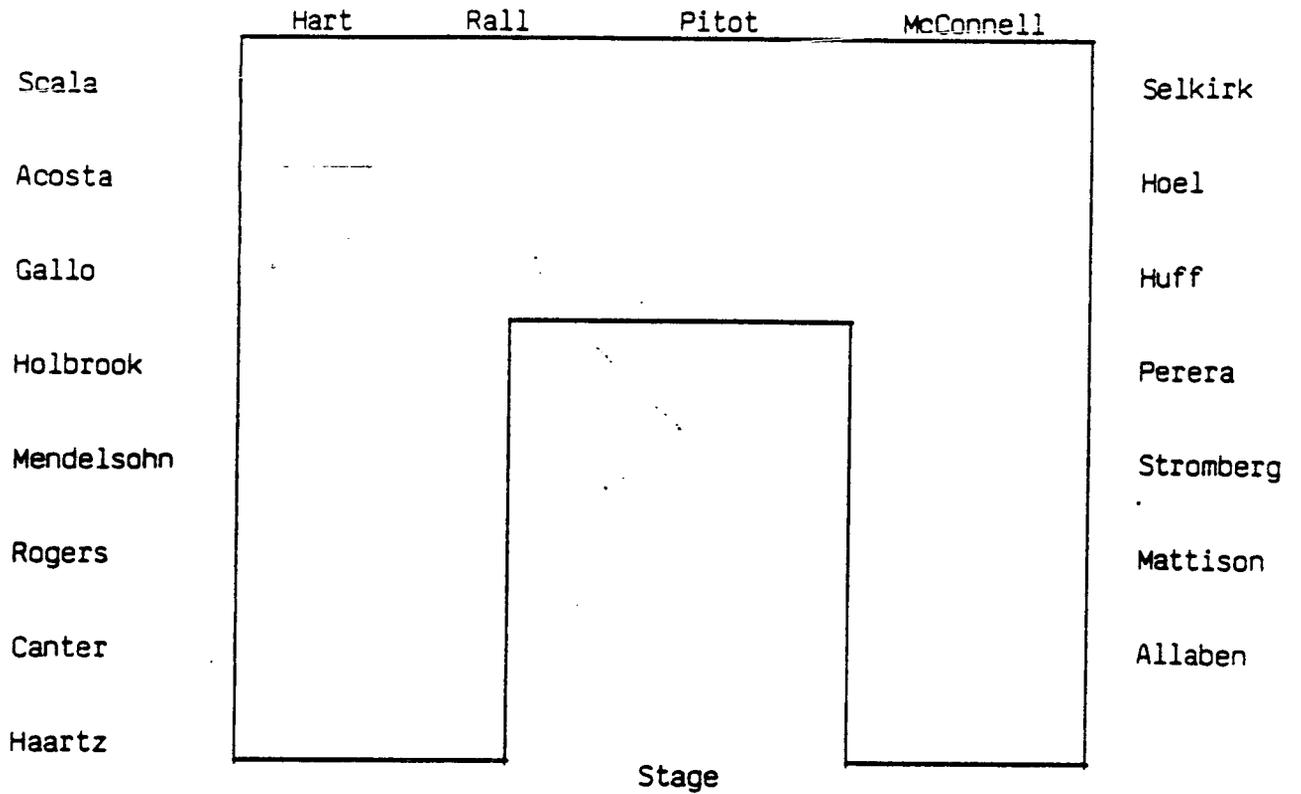
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Columbus, Ohio 43210

NTP BOARD OF SCIENTIFIC COUNSELORS MEETING

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

March 30 and 31, 1987



assessments are based on the most current knowledge concerning the safety and clinical effectiveness of a technology. Based on these assessments, a PHS recommendation will be formulated to assist the Health Care Financing Administration (HCFA) in establishing Medicare coverage policy. Any person or group wishing to provide OHTA with information relevant to this assessment should do so in writing no later than June 1, 1987 (or within 90 days from the date of publication of this notice).

The information being sought is a review and assessment of past, current, and planned research related to this technology, a bibliography of published controlled clinical trials and other well-designed clinical studies, information related to the clinical acceptability and effectiveness of this technology, and a characterization of the patient population most likely to benefit from this technology in the diagnosis of cardiovascular disease. Proprietary information is not being sought.

Written material should be submitted to: Richard S. Bodaness, M.D., Ph.D., Office of Health Technology Assessment, 5600 Fishers Lane, Room 18A-27, Rockville, MD 20857, (301) 443-4990.

Dated: March 5, 1987.

Enrique D. Carter, M.D.,

Director, National Center for Health Services Research and Health Care Technology Assessment.

[FR Doc. 87-5419 Filed 3-12-87; 8:45 am]

BILLING CODE 4160-17-M

National Center for Health Services Research and Health Care Technology Assessment; Fourth Notice of Assessment of Medical Technology, 1987

The Public Health Service (PHS), through the Office of Health Technology Assessment (OHTA), announces that it is coordinating a reassessment of what is known of the safety, effectiveness, appropriateness and use (indication) of gating devices and surface coils in conjunction with magnetic resonance imaging (MRI) procedures. Specifically, we are interested in: (1) The areas of clinical imaging where the use of cardiac or respiratory gating has provided clinically useful information and is considered an effective diagnostic imaging technique, (2) the areas of clinical imaging where the use of surface coils has provided clinically useful information and is considered an effective diagnostic imaging technique, (3) specific indications for use of gated MRI procedures and MRI procedures

that employ surface coils, (4) a comparison of gated and surface coil NMR imaging with the more conventional diagnostic procedures, and (5) whether these techniques assist with diagnosis or have an effect on the treatment of the patient.

The PHS, through the OHTA, has previously announced that it was conducting an assessment of what is known of the safety, clinical effectiveness, and indications for the use of MRI. (*Federal Register* 49(85):18624, 1984. *Federal Register* (49(215):44244, 1984. *Federal Register* 49(246):49515, 1984).

The PHS assessment consists of a synthesis of information obtained from appropriate organizations in the private sector and from PHS agencies and others in the Federal Government. PHS assessments are based on the most current knowledge concerning the safety and clinical effectiveness of a technology. Based on this assessment, a PHS recommendation will be formulated to assist the Health Care Financing Administration in establishing Medicare coverage policy. Any person or group wishing to provide OHTA with information relevant to this assessment should do so in writing no later than June 1, 1987, or within 90 days from the date of publication of this notice.

The information being sought is a review and assessment of past, current, and planned research related to this technology, a bibliography of published, controlled clinical trials and other well-designed clinical studies. Information related to the characterization of the patient population most likely to benefit, the clinical acceptability, and the effectiveness of this technology is also being sought.

Written material should be submitted to: Office of Health Technology Assessment, Room 18A-27, 5600 Fishers Lane, Rockville, MD 20857.

Dated: March 5, 1987.

Enrique D. Carter,

Director, National Center for Health Services Research and Health Care Technology Assessment.

[FR Doc. 87-5420 Filed 3-12-87; 8:45 am]

BILLING CODE 4160-17-M

Public Health Service

National Toxicology Program Scientific Counselors Meeting

Pursuant to Pub. L. 92-463, notice is hereby given of a meeting of the National Toxicology Program (NTP) Board of Scientific Counselors, U.S. Public Health Service, in the Conference Center, Building 101, South Campus,

National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, on March 30 and 31, 1987.

The meeting will be open to the public from 9:00 a.m. until adjournment on March 30. The preliminary agenda with approximate times are as follows:

- 9:00 a.m.-9:30 a.m.—Report of the Director, NTP
- 9:30 a.m.-10:00 a.m.—Overview of the NIEHS Biometry and Risk Assessment Program
- 10:15 a.m.-11:30 a.m.—Review of Chemicals Nominated for NTP Studies. (Six chemicals will be reviewed. The chemicals were evaluated by the NTP Chemical Evaluation Committee on January 13, 1987, and are: (1) Black Pepper (*Piper Nigrum Linn*); (2) Cholestyramine; (3) 1,3-Diphenyl-guanidine; (4) Divinylbenzene; (5) Sodium Nitrite; and (6) 1,3,5-Trichloro-1,3,5-triazine-2,4,6-(1H, 3H, 5H)-trione.
- 12:15 p.m.-4:00 p.m.—Description of the NTP toxicology and carcinogenesis studies process.
- 4:00 p.m.-5:00 p.m.—Description of the NTP quality assurance program. The meeting on March 31 will be open to the public from 8:30 a.m. to 12:30 p.m. The preliminary agenda with approximate time is as follows:
- 8:30 a.m.-12:30 p.m.—Review of research in the Carcinogenesis and Toxicology Evaluation Branch, Toxicology Research and Testing Program, NIEHS.

In accordance with the provisions set forth in section 552b (c)(6) Title 5 U.S. Code and section 10 (d) of Pub. L. 92-463, the meeting will be closed to the public on March 30 from 8:30 a.m. to 9:00 a.m. and on March 31 from 1:30 p.m. to 3:00 p.m. for further evaluation of research activities in the Carcinogenesis and Toxicology Evaluation Branch, including the consideration of personnel qualifications and performance, the competence of individual investigators, and similar items, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

The Executive Secretary, Dr. Larry G. Hart, Office of the Director, National Toxicology Program, P.O. Box 12233, Research Triangle Park, North Carolina 27709, telephone (919) 541-3971, FTS 629-3971, will have available a roster of Board members and expert consultants and other program information prior to the meeting, and summary minutes subsequent to the meeting.

Dated: February 25, 1987.

David P. Rall,

Director, National Toxicology Program.

[FR Doc. 87-5369 Filed 3-12-87; 8:45 am]

BILLING CODE 4160-01-M

**BIOMETRY AND RISK ASSESSMENT PROGRAM
(BRAP)**

**OFFICE OF THE
PROGRAM DIRECTOR (OPD)**

**Dr. David G. Hoel,
Director**

**COMPUTER TECHNOLOGY
BRANCH (CTB)**

**Gerald J. Nehls,
Acting Chief**

**EPIDEMIOLOGY BRANCH
(EB)**

**Dr. Walter J. Rogan,
Chief**

**STATISTICS AND
BIOMATHEMATICS BR. (SBB)**

**Dr. Joseph K. Haseman,
Acting Chief**

**BIOCHEMICAL RISK
ANALYSIS BR. (BRAB)**

**Dr. George W. Lucier,
Chief**

Testing Recommendations for Chemicals Reviewed by Board of Scientific Counselors
on March 30, 1987

Chemical (CAS Number)	Nomination Source	Testing Recommendations (Priority)	Rationale/ Remarks
1. Black Pepper (Piper Nigrum Linn) (--)	NIEHS	Carcinogenicity (Low)	<ul style="list-style-type: none"> - No standard composition - Extensive exposure - Lack of chronic toxicity data - Potential difficulties in testing black pepper due to variation of constituents from one batch to another; may be difficult to obtain representative sample - Maximum tolerated dose may be difficult to reach because of significant irritative effects - If testing is feasible, the study protocol should be submitted to the Board for evaluation
2. Cholestyramine (11041-12-6)	NCI	<ul style="list-style-type: none"> - Carcinogenicity testing in mice and rats - Co-carcinogenicity studies with colon carcinogen (Low)	<ul style="list-style-type: none"> - Limitations in chronic studies in mice - Drug used more widely in past; new hypolipidemic drugs are being prescribed instead
3. Divinylbenzene (1321-74-0)	NCI	<ul style="list-style-type: none"> - Chemical disposition (Moderate-high) - Carcinogenicity (Moderate-low) 	<ul style="list-style-type: none"> - Structural relationship to styrene, ethylbenzene, and benzene - Lack of toxicology test data - May be difficult to obtain suitable material for testing since it is marketed as a mixture

Chemical (CAS Number)	Nomination Source	Testing Recommendations (Priority)	Rationale/ Remarks
4. 1,3-Diphenylguanidine (102-06-7)	NCI	- Carcinogenicity - Examine reproductive endpoints in pre- chronic studies (Moderate)	- Potential for significant industrial exposure - Lack of adequate carcinogenicity data - Structural interest
5. Sodium nitrite (7632-00-0)	FDA	No testing	- Sufficient carcinogenicity studies already performed
6. 1,3,5-Trichloro-1,3,5- triazine-2,4,6-(1H,3H, 5H)-trione (TTT) (87-90-1)	NIEHS	No testing	- TTT readily hydrolyzes to hypochlorous acid and cyanuric acid upon contact with water - In chronic studies conducted by industry, sodium cyanurate was not carcinogenic in mice and rats - On basis of data from sodium cyanurate studies, not necessary to test TTT

Testing Recommendations for Chemicals Reviewed by Board of Scientific Counselors
on March 30, 1987

Chemical (CAS Number)	Nomination Source	Testing Recommendations (Priority)	Rationale/ Remarks
1. Black Pepper (Piper Nigrum Linn) (--)	NIEHS	Carcinogenicity (Low)	<ul style="list-style-type: none"> - No standard composition - Extensive exposure - Lack of chronic toxicity data - Potential difficulties in testing black pepper due to variation of constituents from one batch to another; may be difficult to obtain representative sample - Maximum tolerated dose may be difficult to reach because of significant irritative effects - If testing is feasible, the study protocol should be submitted to the Board for evaluation
2. Cholestyramine (11041-12-6)	NCI	<ul style="list-style-type: none"> - Carcinogenicity testing in mice and rats - Co-carcinogenicity studies with colon carcinogen (Low)	<ul style="list-style-type: none"> - Limitations in chronic studies in mice - Drug used more widely in past; new hypolipidemic drugs are being prescribed instead
3. Divinylbenzene (1321-74-0)	NCI	<ul style="list-style-type: none"> - Chemical disposition (Moderate-high) - Carcinogenicity (Moderate-low) 	<ul style="list-style-type: none"> - Structural relationship to styrene, ethylbenzene, and benzene - Lack of toxicology test data - May be difficult to obtain suitable material for testing since it is marketed as a mixture

Chemical (CAS Number)	Nomination Source	Testing Recommendations (Priority)	Rationale/ Remarks
4. 1,3-Diphenylguanidine (102-06-7)	NCI	<ul style="list-style-type: none">- Carcinogenicity- Examine reproductive endpoints in pre-chronic studies (Moderate)	<ul style="list-style-type: none">- Potential for significant industrial exposure- Lack of adequate carcinogenicity data- Structural interest
5. Sodium nitrite (7632-00-0)	FDA	No testing	<ul style="list-style-type: none">- Sufficient carcinogenicity studies already performed
6. 1,3,5-Trichloro-1,3,5-triazine-2,4,6-(1H,3H,5H)-trione (TTT) (87-90-1)	NIEHS	No testing	<ul style="list-style-type: none">- TTT readily hydrolyzes to hypochlorous acid and cyanuric acid upon contact with water- In chronic studies conducted by industry, sodium cyanurate was not carcinogenic in mice and rats- On basis of data from sodium cyanurate studies, not necessary to test TTT



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
National Institutes of Health

Memorandum

Date July 8, 1987
From Chemical Selection Coordinator
Subject Black Pepper

To The Director, NTP
Through the Assistant to the Director, NTP *DK*

This memo is in response to your request for information regarding the status of black pepper.

Black pepper was nominated by NIEHS for toxicity and carcinogenicity studies in May 1985.

The Chemical Evaluation Committee (CEC) reviewed the substance in January 1987. The CEC recommended the substance for toxicity and carcinogenicity testing with low priority based on the significant consumer exposure, and the potential for toxicity as indicated by preliminary studies. However, the CEC was concerned that it would not be possible to obtain a sample for testing that would be representative of the various types of black pepper. Therefore, the CEC added the caveat that testing should be subject to a preliminary study to determine the extent of variation of constituents from one sample to another.

The Board of Scientific Counselors evaluated black pepper in March 1987 and recommended the substance for carcinogenicity testing with a low priority based on the extensive exposure and lack of chronic toxicity data. The Board noted that black pepper has no standard composition and that there may be potential difficulties in testing the substance due to the variation of constituents from one batch to another. Thus, it might be difficult to obtain a representative sample. The Board opined that achieving a maximum tolerated dose in the testing would be problematic because the substance has significant irritative effects. Finally, the Board requested that if testing is feasible, the study protocol be submitted to them for evaluation.

After the Board's meeting, I received a letter from Mr. Thomas Burns (American Spice Trade Association) requesting that NTP remove black pepper from the list of potential candidates for NTP testing. Mr. Burns provided data on the production and exposure of black pepper, and quantitative data on the various types of black pepper, their constituents, and the variation of the constituents in various black pepper samples. Mutagenicity data and literature references were also submitted. Mr. Burns stated in his letter

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that black pepper by its very nature is self limiting in the human diet because it is unpalatable at levels in excess of its normal culinary usage. He cited a study in which no adverse effects were observed in animals fed 10 times the average human consumption for eight weeks. At levels higher than this 10 times factor, the animals refused to eat. Attached is a copy of the paper by Bhat and Chandrasekhara reporting this study.

I have retrieved the literature article "Pepper - Chemistry, Technology, and Quality Evaluation" by V. S. Govindarajan. From a cursory reading it appears that it would indeed be difficult to select a representative sample for testing because of the large number of varieties in use and the great variation of the constituents in these samples. Also attached is a copy of the paper by Govindarajan. I recommend that a group of NTP staff review the information that I have received since the Board meeting in order to determine the feasibility of testing black pepper. This should be done prior to submission of this nomination to the NTP Executive Committee.

Victor A. Fung
Victor A. Fung, Ph.D.

Attachments