

999-94-3

NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS

May 2 and 3, 1991

Summary Minutes

NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS

May 2 and 3, 1991

Summary Minutes

National Toxicology Program
Board of Scientific Counselors

May 2-3, 1991

Summary Minutes

<u>Contents</u>	<u>Page Numbers</u>
<u>Program Review of the Developmental and Reproductive Toxicology Group (DART), Systems Toxicity Branch (STB), DTRT, NIEHS</u>	1
I. <u>Overview of NTP Reproductive and Developmental Toxicology Program</u>	1
II. <u>Site and Mechanisms of Action of Tri-o-cresylphosphate</u>	2
III. <u>Mechanistic Studies on Phthalate Ester Toxicity to Sertoli Cells and Granulosa Cells</u>	2
IV. <u>Developmental Immunotoxicity of TCDD and DES</u>	2
V. <u>Neonatal Toxicity of Nitrofurantoin</u>	2
VI. <u>Developmental Neurotoxicity of Tellurium</u>	2
VII. <u>Possible Role of Altered Energy Metabolism in Developmental Toxicity</u>	3
VIII. <u>In Vitro Teratology: NTP Role in Directing the Field</u>	3
IX. <u>Summary of Future Directions</u>	3
<u>Program Review of the Immunotoxicology Group, STB, DTRT, NIEHS</u>	4
X. <u>Overview - Immunotoxicity</u>	4
XI. <u>Inhalation Immunotoxicology - Pentamidine and Asbestos</u>	4
XII. <u>Neuroimmunomodulation - Methods Development</u>	4
XIII. <u>Skin Immunity</u>	4
XIV. <u>In-house Research and Risk Quantification</u>	4
XV. <u>Future Directions</u>	5

XVI.	<u>Concept Review: Immunotoxicology of Workplace Xenobiotics in Humans</u>	5
END OF PROGRAM REVIEW		
XVII.	<u>Report of the Acting Director, NTP</u>	6
<u>Subcommittee Reports</u>		
XVIII.	<u>Technical Reports Review Subcommittee</u>	6
XIX.	<u>Reproductive and Developmental Toxicology Program Review Subcommittee</u>	6
XX.	<u>Review of Chemicals Nominated for NTP Studies</u>	7
<u>Scientific Presentations</u>		
XXI.	<u>Variability in Tumor Rates Among Control F344 Rats in NTP Studies</u>	7
XXII.	<u>Mononuclear Cell Leukemia in the F344 Rat - Research Approaches</u>	7
XXIII.	<u>Evaluation of the Usefulness of Interim Sacrifices in NTP Studies</u>	8

Attachments 1-6

SUMMARY MINUTES
NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS MEETING
May 2 and 3, 1991

The National Toxicology Program (NTP) Board of Scientific Counselors (the Board) met on May 2 and 3, 1991, at the 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. Arthur Upton (Chairman), Paul Bailey, Jay Goodman, John Little, Lawrence Loeb, Daniel Longnecker, Richard Miller, and Ellen Silbergeld. Dr. Loeb was unable to attend the meeting.

Program Review of the Developmental and Reproductive Toxicology Group (DART),
Systems Toxicity Branch (STB), Division of Toxicology Research and Testing
(DTRT), NIEHS

I. Overview of NTP Reproductive and Developmental Toxicology Program: Dr. Bernard Schwetz, Chief, STB, described the components of the NTP and the major objectives of the Program. He noted the good interactions among the participating agencies (NIEHS, NCTR, NIOSH) in this program area. Dr. Jerry Heindel, Group Leader, provided an overview of the DART group, describing its mandate, contract activities, research areas, and personnel. He said the group was charged to: (1) test industrial and environmental chemicals/agents/conditions for their reproductive and developmental toxicity; (2) develop new "markers" for detecting and modeling systems for testing potential reproductive and developmental toxicants; (3) develop a comprehensive state-of-the-art research program to determine the site of action and cellular, biochemical and molecular mechanisms of action of reproductive and developmental toxicants; (4) improve the toxicological basis for extrapolating animal data to human risk; and (5) act as consultants to other components of the NTP in matters relating to reproductive and developmental toxicology.

Dr. Heindel noted the growth of the group, especially during the past year with the addition of three new investigators, and the broad spectrum of research activities including animal and human (usually in collaboration with NIOSH) studies, and in vivo descriptive as well as in vitro mechanistic studies. Consistent with the needs and goals of the NTP, for many studies a vertically integrated approach is used for assessing an agent's toxicity. He discussed the primary screen for reproductive toxicity, the reproductive assessment by continuous breeding protocol (RACB), which was developed in collaboration with the Laboratory of Reproductive and Developmental Toxicology, Division of Intramural Research. The primary screen for developmental toxicity is still the FDA segment II protocol. Information developed on toxicity in these primary assays feeds into site and mechanism studies. Dr. Heindel concluded by noting the valuable advice and review provided by the Board's Reproductive and Developmental Toxicology Program Review Subcommittee, not only to the DART group but also to NTP activities at NIOSH and NCTR. He said the following presentations would be by the principal investigators in the group describing a representative portion of their research aimed at showing the approaches used and the questions asked.

II. Site and Mechanism of Action of Tri-o-cresylphosphate: Dr. Robert Chapin said this project provided a good illustration of the vertically integrated approach to assessing toxicity of a chemical. Tri-o-cresylphosphate (TOCP) was identified as a male reproductive toxicant through the RACB protocol. TOCP is a testicular toxicant which affects the Sertoli cells. Through use of an in vitro model testis system it was shown that toxicity was effected by conversion of TOCP by P450 enzymes in Leydig cells to an active metabolite, saligenin, which inhibits nonspecific esterases in Sertoli cells.

III. Mechanistic Studies on Phthalate Ester Toxicity to Sertoli Cells and Granulosa Cells: Dr. Heindel said the phthalate esters had been shown by RACB to be reproductive toxicants. Among the most active esters is di-2-ethylhexyl phthalate (DEHP) which was studied in Sertoli cell cultures. The active species is the mono-ethylhexyl metabolite (MEHP) which appears to act by blocking the receptor for follicle stimulating hormone (FSH) thereby inhibiting FSH stimulation of the synthesis and accumulation of cyclic-AMP. Further studies with cultured rat ovarian granulosa cells showed that MEHP, similar to its effect in Sertoli cells, inhibited cAMP accumulation in granulosa cells also through an effect on the FSH receptor. Additional investigation indicated that the inhibitory effects of MEHP on cell function were independent of phorbol ester-sensitive protein kinase C activation.

IV. Developmental Immunotoxicity of TCDD and DES: Dr. Steven Holladay said the aims of his research were to characterize the effects of chemical treatment during gestation on development of the immune system with the overall goal of developing markers for detection of developmental immunotoxicants. This was a joint effort between DART and the Immunotoxicology Group, STB. The development of surface markers on B and T cells in fetal rodent spleen and thymus were evaluated with immunochemical and flow cytometric methods and the markers (primarily T-lymphocyte) were used to examine the mechanism of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and diethylstilbestrol (DES) developmental immunotoxicity. Results indicated the chemicals inhibited maturation of T-cells possibly through alteration of the expression of cell surface markers and this effect was manifested for up to 8-weeks postnatally as demonstrated through a decreased cytotoxic T-lymphocyte response.

V. Neonatal Toxicity of Nitrofurantoin: Dr. Frank Kari reported on studies concerned with neonatal toxicity of chemicals with special focus on toxicant-induced lactation disorders. Nitrofurantoin (NF) was chosen because of its potential for exposure of human neonates and because it was shown in the RACB protocol to be a reproductive toxicant. In experiments where nursing dams were fed NF in their food, rat pups were shown to have impaired growth. In other studies, NF was shown to reach a milk/plasma concentration of 40, an unexpected and as yet unexplained finding. Conclusions were that decreased growth in suckling pups was not due to direct toxicity of NF but rather to a decreased ability of the dam to synthesize milk, probably as a result of decreased food intake.

VI. Developmental Neurotoxicity of Tellurium: Dr. Jean Harry discussed plans to explore the differential sensitivity of the developing nervous system to chemicals and drugs. Using a model of tellurium (TE)-induced peripheral nerve demyelination, perturbations of the developing rat nervous system were to be examined. She described experimental evidence for biochemical alterations

during TE exposure including decreases in lipid synthesis, especially myelin specific lipids and cholesterol, and protein synthesis. There were also alterations in gene expression of nerve growth factor. Dr. Harry said they hoped to extend this model of demyelination with these biochemical markers to the central nervous system and also evaluate other demyelinating agents, e.g., lead.

VII. Possible Role of Altered Energy Metabolism in Developmental Toxicity: Dr. E. Sidney Hunter III stated that one potential mechanism for teratogenic effects of many xenobiotics is an alteration in embryonic metabolism, and especially on energy production. He said the focus of the project would be to assess normal patterns of embryonic metabolism, evaluate the developmental toxicity of agents which specifically inhibit energy production from glucose metabolism and determine how this metabolic perturbation results in dysmorphogenesis. Among likely toxic outcomes in the conceptuses are neural tube defects and heart effects.

VIII. In Vitro Teratology: NTP Role in Directing the Field: Dr. Schwetz described NTP efforts to develop and validate in vitro assays which would be predictive for Segment II developmental toxicity studies. While no in vitro screen is considered fully validated, the NTP evaluation of the mouse ovarian tumor and human palate cell assays is considered the only multi-laboratory evaluation using a large number of chemicals tested "blind." These assays are perhaps 70-80% predictive while the use of Drosophila as a screen evaluated by NIOSH may be somewhat more predictive. A conference held in 1989 agreed that in vitro models were needed as well as a reference list of chemicals for validation purposes including clear positives and negatives. A workshop was to be held at NIEHS in June 1991 to discuss the criteria for interpretation of the results of developmental toxicity studies. Dr. Schwetz discussed needs and plans for developing in vitro target cell systems for male and female reproductive toxicity. Other consensus initiatives have to do with lactation-mediated toxicity and a NIEHS-NIOSH collaborative effort in ways to use newer automated means of measuring sperm motility.

IX. Summary of Future Directions: Dr. Heindel stated that major areas which would have the highest priority for the DART group over the next five years included continuation of: (1) routine testing for reproductive and developmental toxicants using whole animal functional tests; (2) development of short-term in vivo screens and alternatives to rodent testing such as the use of Drosophila for teratology screening; (3) involvement in the design and validation of in vitro reproductive and developmental toxicology screens; (4) broadening the base of interests and expertise to include human occupational and epidemiological studies through closer interaction and collaboration with NIOSH, the NIEHS epidemiology group, and other government agencies; (5) extrapolation of animal data to human risk is one of the most important areas of concentration; and (6) site and mechanism studies of reproductive and developmental toxicants with an emphasis on techniques of cellular and molecular biology.

General discussion touched on how to select chemicals for site and mechanism studies, how to incorporate data into risk models while avoiding duplication with such efforts at other agencies, and how to put more emphasis on noncancer endpoints.

Program Review of the Immunotoxicology Group, STB, DTRT, NIEHS

X. Overview - Immunotoxicity: Dr. Michael Luster, Head, Immunotoxicology Group, defined immunotoxicology as the study of the adverse effects of chemicals, drugs or biologics on the immune system. These effects are manifest as changes in immunoregulation (primarily suppression), hypersensitivity, or less often, autoimmunity. He discussed Program goals at the time of the last Board review (1987) as well as additional goals presently being pursued. In describing management of current contracts and interagency agreements, he noted the commitment to evaluating the general as well as neuro- and immunotoxicity of various AIDS therapeutic agents, especially in combinations. Whereas chemical/drug evaluation is a large part of extramural effort, it constitutes only 15 % of intramural research, while methods development is about 30 % and mechanistic studies come to 55 %. Dr. Luster described projects ongoing in the three areas.

XI. Inhalation Immunotoxicology - Pentamidine and Asbestos: Dr. Gary Rosenthal said the focus of pulmonary immunotoxicology was three-fold: (1) to conduct an immunotoxicology screen for inhaled chemicals; (2) investigating mechanisms of lung diseases with an apparent immunologic pathogenesis; and (3) investigating mechanisms of chemical activity. He discussed the differences between fibrosis-inducing and non-fibrosis-inducing fibers on responses of immune system cells in the lungs with special emphasis on the role of T cells in protecting against asbestos-induced fibrosis. Dr. Rosenthal described studies on the immunotoxicity of pentamidine isethionate, an agent used to treat patients with AIDS-related P. carinii pneumonia. Pentamidine was found to inhibit release of inflammatory cytokines from alveolar macrophages, an effect associated with inhibition of post-translational processing of a key membrane protein.

XII. Neuroimmunomodulation - Methods Development: Dr. Virginia Sanders said the aim of this project was to determine if a xenobiotic exerts an immunotoxic effect on antibody production through a direct or indirect action. She focused her discussion on indirect mechanisms of immune modulation concerned with the interaction of xenobiotics with neurotransmitters in nervous tissue that innervates lymphoid tissue. Dr. Sanders reported on studies attempting to use human-reconstituted SCID mice as a model for dissecting nervous system-immune targetting by selected chemicals.

XIII. Skin Immunity: Dr. Benny Blaylock described the skin immune system, noting the Langerhan's cell as the primary antigen-presenting cell in the skin, and discussed experiments which showed that topically applied pentamidine (used as a model compound) reduced ear swelling in the contact hypersensitivity reaction to oxazolone in B6C3F1 mice. The mechanism of pentamidine inhibition of the contact hypersensitivity reaction appeared to be through a reduction in antigen presentation by decreasing the active Langerhan's cell population. Dr. Blaylock described the effects of chemicals on keratinocytes and reported on methods being developed to evaluate chemical-medicated toxicity on skin immunity.

XIV. In-house Research and Risk Quantification: Dr. Luster reported on a symposium on risk quantification held in 1988 which dealt with issues such as - what were the most predictive immune tests? - and - what were the qualitative

and quantitative relationships between immune function changes and clinical disease? He discussed how data derived from extensive studies on 50 compounds examined with the NTP immunotoxicology screening battery is being used to statistically address three general questions: (1) what is the simplest testing configuration that can accurately identify potential immunotoxicants? - It appears that only a few are required - (2) how do these immune endpoints relate to other endpoints, e.g., carcinogenicity? - Compounds which are immunotoxicants are also likely to be carcinogens - and (3) how do the immune tests relate to host resistance assays? - there appears to be a linear correlation between depressions in certain immune parameters and an increase in susceptibility to infection or tumor cell growth.

XV. Future Directions: Dr. Luster listed research needs in immunotoxicology where his group could make a contribution: (1) establishment of predictive models for suppression; (2) development of quantitative models for hypersensitivity; (3) a clinical studies program; (4) local immunity, e.g., lung, skin, gastrointestinal tract; (5) the role of chemicals in autoimmune disease; (6) animal models for occupational immunologic lung disease; and (6) multiple chemical sensitivities. He concluded with a discussion of future directions. Among these were: (1) development of more predictive models, including use of immune cells or cell lines of human origin, use of genetically altered mice, and in vitro antigen-stimulated immune responses; (2) studies on local immunity, with emphasis on the skin and particularly the lung, and inclusion of the cytokine network using keratinocytes and type II epithelial cells; and (3) screening through contract mechanisms, especially on AIDS therapeutics - (for suppression and myelotoxicity) and environmental chemicals (for suppression and hypersensitivity).

XVI. Concept Review: Immunotoxicology of Workplace Xenobiotics in Humans: (Attachment 3) (This was a concept for a new project which had been first reviewed by the Board on October 15, 1990, and deferred for revision and future consideration.) NOTE: Dr. Silbergeld asked that the meeting be closed to the public so that details of proposed methodology could be discussed in evaluation of the concept, and this was done. The Board was reminded that by doing so, they and their families, close professional associates, business partners, and their organizations would be ineligible to receive a contract based on a subsequent request for proposal (RFP). Dr. Luster introduced the concept and Dr. Silbergeld, Board member, served as principal reviewer. Dr. Luster said that although an extensive data base had been established and validated on the toxic effects of xenobiotics in animals, whether these effects occur in humans has not been determined. He said the goals of the agreement were to: (1) establish efficiency of selected immune function tests using human peripheral blood lymphocytes; (2) work with NIOSH to apply these tests to selected xenobiotic-exposed worker populations; and (3) determine if a specific immune parameter is altered by xenobiotic exposure so that it can be used as a biomarker of exposure. These goals will be accomplished through a cooperative effort between NIEHS and NIOSH.

Dr. Silbergeld was concerned about the issue of confounding variables. She also asked for clarification as to whether there was still an intent to extend the concept to diagnosis of clinical status or disease in humans. Dr. Luster responded that they hoped to identify a large enough population so the problem of confounding variables could be overcome, and the project will not be extended

to diagnosis of clinical disease at this point. The development of laboratory studies will be done at NIEHS, avoiding interlaboratory variability. Dr. Goodman expressed concerns about the difficulty of finding worker populations for study with well-defined exposures to single immunotoxic chemicals and suggested looking at persons receiving therapeutic agents. Dr. Luster said that such persons might have the confounding factor of a disease state, and further, the aim of the proposal was to identify the immunotoxicity of workplace chemicals. Dr. Gerry Henningsen, NIOSH, discussed an example of a well-defined exposure in the workplace.

Dr. Silbergeld moved that the concept be approved. Dr. Longnecker seconded the motion which was approved unanimously by the Board.

END OF PROGRAM REVIEW

XVII. Report of the Acting Director, NTP: Dr. David Hoel reported that: (1) Dr. Bernadine Healy was sworn in as Director, NIH, on April 9; (2) the search committee evaluating candidates for Director, NIEHS, had not yet submitted a short list to Dr. Healy; (3) during the Congressional appropriations hearings in March and April there had been discussions about funding for additions to the NIEHS permanent facility so that the North campus leased facilities could be vacated; (4) Dr. Healy will have her first meeting with the NIEHS Advisory Council this month; and (5) recent conferences co-organized and held at NIEHS included a conference on manganese toxicity in March and a symposium on the uses of transgenic mice in biology and toxicology in April, while upcoming were (a) Dioxin 91. The 11th International Symposium on Chlorinated Dioxins and Related Compounds, September 23-27, RTP, (b) an international conference on Molecular Mechanisms of Carcinogens in Humans and Rodents at NIEHS, September 8-12, and (c) a symposium on Cell Proliferation and Chemical Carcinogenesis at NIEHS, January 14-16, 1992.

Subcommittee Reports

XVIII. Technical Reports Review Subcommittee: Dr. Scot Eustis, NIEHS, gave the Board a progress report on recent and upcoming meetings of the Subcommittee. He provided the Board written summary information noting that seven two-year toxicology and carcinogenesis study reports and four short-term toxicity study reports had been reviewed on November 19-20, 1990, while seven more two-year and three short-term study reports were peer reviewed on March 11-12, 1991, and nine two-year and four short-term study reports are scheduled for peer review by the Subcommittee on July 9-10. About 10 two-year reports are projected for review at the meeting on November 21-22. Looking ahead, Dr. Eustis estimated about 30 long-term studies reaching the report review phase in 1992, and about the same number in 1993. Dr. Longnecker, Subcommittee Chairman, commented on the large effort needed to bring all these studies to peer review and on the quality control involved.

XIX. Reproductive and Developmental Toxicology Program Review Subcommittee: Dr. Miller, Subcommittee Chairman, said the Board members had received a copy of the report prepared by the Subcommittee following their meeting with NTP program staff on November 8-9, 1990, in Cincinnati, and would be happy to respond to any questions or comments. Dr. Richard Griesemer, NIEHS, thanked Dr. Miller and the Subcommittee for this very helpful report.

XX. Review of Chemicals Nominated for NTP Studies: Nominations of seven chemicals were considered by the Board. All had been reviewed previously by the NTP Chemical Evaluation Committee (CEC), and one, p,p'-dichlorodiphenyl sulfone, had been reviewed by the Board on October 15, 1990, and deferred. (Summary data on the chemicals including CEC recommendations are provided in Attachment 4.) Dr. Little chaired the review. Dr. William Allaben, NCTR, and Dr. Janet Haartz, NIOSH, CEC Members, and Dr. Victor Fung, NTP Chemical Selection Coordinator, served as resource persons. Board members served as principal reviewers for one or two chemicals each, and following the presentation and discussion of each chemical, motions were made and voted upon. The Board's recommendations for the seven chemicals are summarized in Attachment 5.

Scientific Presentations

XXI. Variability in Tumor Rates Among Control F344 Rats in NTP Studies: Dr. Joseph Haseman, NIEHS, began by stating that concurrent control tumor rates are preferred but historical control rates can be useful, especially with rare tumors and studies where there may be a marginal increase in tumors in a treated group compared with concurrent controls. He listed important potential sources of variability in control tumor rates (Attachment 6, p.2) noting that these factors may result in inter-laboratory variability and time-related trends in tumor occurrence. Dr. Haseman summarized the results from 88 studies in F344 rats which supported earlier findings that showed corn oil gavage increased pancreatic acinar cell tumor rates and decreased incidences of mononuclear cell leukemias in male rats relative to untreated or water gavage controls while having no effect in female rats (Attachment 6, pp.4-5). He then discussed the increases in tumor rates over time, from the early 1970s to the early 1980s, for leukemias and several other tumors, primarily of endocrine origin, in both sexes (Attachment 6, pp.6-7). Dr. Haseman further discussed trends in leukemia rates, and presented individual study rates to illustrate the variability in this tumor across control groups and the determination of a "normal" control range. (Attachment 6, pp. 9-10). He concluded his presentation with an example of inter-laboratory variability in control tumor rates (Attachment 6, p. 11).

XXII. Mononuclear Cell Leukemia in the F344 Rat- Research Approaches: Dr. Richard Irwin, NIEHS, described the characteristics of mononuclear cell leukemia (MCL) in F344 rats, noting that MCL originates in the spleen, and the MCL cell which is a large granular lymphocyte. Although labeled a 'rat' disease, humans have large granular lymphocytes, and recently there have been about 50 cases cited in the literature of a chronic proliferative disease of these cells. He reiterated concerns expressed by Dr. Haseman about the reduced survival and high and variable incidences in controls which complicate interpretation of the effects of chemical exposure. Dr. Irwin discussed some research approaches by the NTP including: (1) evaluating the influence of diet composition; (2) the effects of chemical exposure, doing a retrospective examination of the NTP data base of studies employing the NIH-07 diet; (3) attempting to correlate structural/or metabolic properties of a chemical with pattern of leukemic response; and (4) examining the influence of toxic or neoplastic responses at other sites on the incidence of MCL. Goals of NTP studies are to: (1) reduce the incidence of MCL in F344 rats; (2) gain some insights into the mechanism of development of MCL; and (3) obtain a better understanding of changes in the incidence associated with chemical exposure.

XXIII. Evaluation of the Usefulness of Interim Sacrifices in NTP Studies:
Dr. Scot Eustis, NIEHS, stated that interim evaluations have been a standard part of NTP two-year studies, usually at 15 months with 10 animals per group, and including measurements of body and organ weights, hematology, clinical chemistry, and histopathology. Interim evaluations constitute about 10% of the cost of a feed study so as part of an analysis of the cost-effectiveness of two-year studies, an examination was made of their usefulness. He presented data from the first 13 studies with interim evaluations that had been peer reviewed by the Subcommittee. Conclusions drawn from this analysis were: (1) interim evaluations have not contributed to carcinogenicity determination; (2) they have not contributed substantively to clarifying or identifying chronic toxicity; (3) they have not contributed substantively to characterizing progression of lesions; (4) routine inclusion of interim evaluations in 2-year carcinogenicity studies is not cost effective; (5) they may be warranted when testing specific hypotheses in carcinogenicity studies; and (6) interim evaluations may be warranted in studies designed more specifically to determine chronic toxicity.

TESTING RECOMMENDATIONS FOR CHEMICALS REVIEWED BY NTP BOARD OF SCIENTIFIC COUNSELORS
ON MAY 3, 1991

Chemical (CAS Number)	Nomination Source	Testing Recommendations (Priority)	Rationale/Remarks
1. ((o-Carboxyphenyl)thio) ethylmercury sodium salt (54-64-8)	NIEHS	No testing	-Acute toxicity of the chemical is well documented and exposure should be limited based on these data -Several chronic studies indicated no carcinogenic effects -Toxicity of the chemical is due to alkyl mercury
2. p,p'-Dichlorodiphenyl- sulfone (80-07-9)	NCI	-Subchronic studies -Mutagenicity (High)	-High production -Potential for accidental exposure -Lack of specific information on exposure -Prior to initiating studies, NTP should provide opportunity to producers to submit information on actual production volume, uses, and exposure
3. Hexamethyldisilazane (HMDS) (999-97-3)	Private Individual	-Neurotoxicity -Reproductive effects -Carcinogenicity (High)	-High production -Widely used in electronics industry -Potential for high occupational exposure -Many workers are in reproductive ages -Very little information available on toxicity and environmental fate of HMDS -NTP should look at breakdown products in water -Before initiating testing NTP should ensure that HMDS is the best representative of the organosilicon amines chemical class
4. Isoeugenol (97-54-1)	NCI	-Chemical disposition -Reproductive and developmental effects -Carcinogenicity (Low to moderate)	-Widespread use in consumer products -High human exposure -High percentage of workers are female -Naturally occurring product -Genotoxic effects observed in human cell lines -Structurally related to known or suspect carcinogens -Chemical disposition studies might provide information that is useful in determining the need for toxicity studies

TABLE (CONT'D)

Chemical (CAS Number)	Nomination Source	Testing Recommendations (Priority)	Rationale/Remarks
5. Sesamol (533-31-3)	NCI	No testing	-Minor component of sesame oil, a naturally occurring product -No commercial production or use reported -Sesamol should be re-evaluated if it is produced and used in high volume in the future
6. 3,3',4,4'-Tetrachloro- azobenzene (14047-09-7)	EPA	Carcinogenicity (High)	-Environmental contaminants , -Potential for human exposure -Lack of carcinogenicity data -EPA's interest in the testing of these compounds
7. 3,3',4,4'-Tetrachloro- azoxybenzene (21232-47-3)			-Data from carcinogenicity studies are needed to determine if regulation is necessary



Date: May 28, 1991

From: Chemical Selection Coordinator, NTP

Subject: Selection of NTP Fiscal Year 1991 Priority Chemicals
for In-Depth Toxicological Evaluation

To: Members, NTP Executive Committee and Agency Staff

During each fiscal year, the NTP Executive Committee selects priority chemicals for in-depth toxicological evaluation. These chemicals are chosen from among those chemicals nominated to the Program that have been reviewed by both the NTP Chemical Evaluation Committee (CEC) and the NTP Board of Scientific Counselors.

In addition they are selected from among those nominations which are NTP participating agency Fiscal Year priority chemicals for NTP carcinogenicity testing. Because of limited resources each participating agency is allowed one such nomination per fiscal year. The NTP participating agencies' Fiscal Year priority nominations are evaluated only by the CEC and then submitted directly to the Executive Committee in order to place them on a fast track for NTP decision-making.

At the upcoming July 11, 1991, meeting of the Executive Committee, there are five candidate chemicals for selection as NTP FY 1991 priority chemicals for in-depth toxicological evaluation. The chemicals are: p,p'-dichlorodiphenyl sulfone, hexamethyldisilazane, isoeugenol, 3,3',4,4'-tetrachloroazobenzene, and 3,3',4,4'-tetrachloroazoxybenzene.

A brief description of each of the five candidates, with the relevant CEC and Board of Scientific Counselors' recommendations, is contained below.

p,p'-Dichlorodiphenyl sulfone

p,p'-Dichlorodiphenyl sulfone was nominated by NCI for carcinogenicity studies. It is a starting material in the production of polysulfones, which are a subset of a general product group known as engineering plastics. These plastics are used in a wide variety of consumer products, including electrical equipment, auto components and appliances. There are no specific production volume data on p,p'-dichlorodiphenyl sulfone. However, the annual production of engineering plastics increased from 7.8 million pounds in 1985 to 1.5 billion pounds in 1988.

Page 2 - Executive Committee

There is also a lack of specific exposure information on the chemical.

Both the CEC and Board recommended subchronic and mutagenicity studies for p,p'-dichlorodiphenyl sulfone based on its high production and potential increased use, and the lack of toxicity data. Both the CEC and the Board were concerned about the lack of exposure information. For this reason, the CEC recommended only subchronic studies at this time, and the Board recommended that, prior to initiating toxicity studies, the NTP should offer the opportunity to the producers to provide information on actual production, use, and exposure.

Since the EPA has offered to obtain this type of information through TSCA authorities, NTP staff recommends that p,p','-dichlorodiphenyl sulfone be nominated to the EPA Interagency Testing Committee to obtain production, importation, and exposure data under TSCA 8(a) and non-public health and safety studies under TSCA 8(d). These data can be used by NTP in the future to evaluate the desirability of testing.

Hexamethyldisilazane

Hexamethyldisilazane (HMDS) was nominated by a private individual for absorption, reproductive effects, and carcinogenicity studies. The nomination was supported by the NCI and another private individual. HMDS is a high production volume chemical which is widely used in the electronics industry. The Silicones Health Council reported that 300,000 to 900,000 pounds of HMDS are produced by its member companies each year. Both the CEC and Board recommended carcinogenicity and reproductive effects studies of HMDS based on its high production, widespread use in the electronics industry, potential for worker exposure, and the lack of toxicity data. The Board also recommended neurotoxicity studies.

Isoeugenol

Isoeugenol was nominated by the NCI for carcinogenicity studies. It is a naturally occurring product that is widely used in fragrances and as a flavoring agent. According to the TSCA Inventory, 21,000 to 212,000 pounds were produced in 1983. Both the CEC and Board recommended isoeugenol for chemical disposition, reproductive and developmental effects, and carcinogenicity studies based on its widespread use in consumer products, high human exposure, and its structural relationship to known or suspect carcinogens such as safrole and eugenol.

Page 3 - Executive Committee

3,3',4,4'-Tetrachloroazobenzene and 3,3',4,4'-Tetrachloroazoxybenzene (TCAB and TCAOB)

TCAB and TCAOB were nominated by EPA for reproductive and developmental effects, and carcinogenicity studies. TCAB and TCAOB are not produced commercially per se but are formed during the synthesis of 3,4-dichloroaniline (DCA) and pesticides derived from DCA. TCAB and TCAOB are environmental contaminants. The chemicals are isosteric to 2,3,7,8-tetrachlorodibenzodioxin (TCDD) and exhibit similar teratogenic effects as TCDD. The EPA Office of Drinking Water is concerned about exposures to TCAB and TCAOB in drinking water. The EPA is interested in data from toxicity studies to evaluate the need for regulating action. Both the CEC and Board recommended carcinogenicity studies for TCAB and TCAOB based on potential for human exposure, lack of carcinogenicity data, and the EPA's testing needs.

Summary

The CEC reviewed p,p'-dichlorodiphenyl sulfone on September 12, 1990, and the remaining four chemicals on March 13, 1991. The Board reviewed the five chemicals on May 3, 1991. However, p,p'-dichlorodiphenyl sulfone was previously reviewed by the Board on October 15, 1990. At that time, the Board deferred the chemical in order to retrieve more information on its chemical properties and toxicity.

A summary table of the CEC and Board of Scientific Counselors' recommendations is attached.

Please call me at FTS-496-3511, if you have any questions about the candidate chemicals.

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

Attachment

TABLE (CONT'D)

Chemical (CAS Number)	Source and Date of Nomina- tion	Chemical Evaluation Committee Review		Board of Scientific Counselors Review	
		Recommendations (Priority)	Rationale/Remarks	Recommendations (Priority)	Rationale/Remarks
4. 3,3',4,4'- Tetra- chloro- azobenzene (14047-09-7)	EPA	Carcinogenicity (Moderate)	<ul style="list-style-type: none"> -Potential for human exposure -TCAB and TCAOB are contaminants of dichloroaniline (DCA) and herbicides synthesized from DCA -TCAB and TCAOB are microbial transformation products of several 3,4-dichloroacylanilide herbicides, such as Diuron, Linuron, and Propanil, which are still registered and commercially available -EPA Office of Drinking Water (ODW) is concerned about exposures to TCAB and TCAOB in drinking water which is contaminated by these products from the use of 3,4-dichloroaniline-derived herbicides -EPA ODW will use NTP data to determine need for regulation and, if necessary, to set appropriate regulatory levels 	Carcinogenicity (High)	<ul style="list-style-type: none"> -Environmental contaminants -Potential for human exposure -Lack of carcinogenicity data -EPA's interest in the testing of these compounds -Data from carcinogenicity studies are needed to determine if regulation is necessary
5. 3,3',4,4'- Tetra- chloro- azoxy- benzene (21232-47-3)					

CANDIDATE CHEMICALS FOR FISCAL YEAR 1991 PRIORITY DESIGNATION

Chemical (CAS Number)	Source and Date of Nomina- tion	Chemical Evaluation Committee Review		Board of Scientific Counselors Review	
		Recommendations (Priority)	Rationale/Remarks	Recommendations (Priority)	Rationale/Remarks
1. p,p'-Di- chlorodi- phenyl- sulfone (80-07-9)	NCI	-Subchronic studies -Mutagenicity (High)	-High production -Potential for increased use -Lack of toxicological data -Lack of information on residues (if any) of the chemical in poly- meric products and whether the monomer is released from the polymers at high temperatures -ITC will recommend chemical to EPA for physical/chemical testing by industry	-Subchronic studies -Mutageni- city (High)	-High production -Potential for accidental exposure -Lack of specific information on exposure -Prior to initiating studies, NTP should provide opportunity to producers to submit information on actual production volume, uses, and exposure
2. Hexamethyl- disilazane (HMDS) (999-97-3)	Private Indivi- dual	-Reproductive effects -Carcinogenicity (High)	-Widespread use in electronics industry -Potential for high occupational exposure -Important member of organosilicon chemicals class -Limited toxicology data available -Chemical will be difficult to test because it is an irritant, and is expected to decompose in moist air -Route of administration should be selected by NTP toxicology design review group	-Neurotoxicity -Reproductive effects -Carcinogenicity (High)	-High production -Widely used in electronics industry -Potential for high occupational exposure -Many workers are in reproductive ages -Very little information available on toxicity and environmental fate of HMDS -NTP should look at breakdown products in water -Before initiating testing NTP should ensure that HMDS is the best representative of the organosilicon amines chemical class

TABLE (CONT'D)

Chemical (CAS Number)	Source and Date of Nomina- tion	Chemical Evaluation Committee Review		Board of Scientific Counselors Review	
		Recommendations (Priority)	Rationale/Remarks	Recommendations (Priority)	Rationale/Remarks
3. Isoeugenol (97-54-1)	NCI	<ul style="list-style-type: none"> -Chemical disposition -Reproductive and developmental effects -Carcinogenicity (Low to moderate) 	<ul style="list-style-type: none"> -High occupational and consumer exposure -Relatively high female industrial exposure -Widespread use in fragrances and as a flavoring agent -Naturally occurring product -Evidence of genotoxicity in human cells -Structurally related to compounds with known or suspect carcinogenic potential 	<ul style="list-style-type: none"> -Chemical disposition -Reproductive and developmental effects -Carcinogenicity (Low to Moderate) 	<ul style="list-style-type: none"> -Widespread use in consumer products -High human exposure -High percentage of workers are female -Naturally occurring product -Genotoxic effects observed in human cell lines -Structurally related to known or suspect carcinogens -Chemical disposition studies might provide information that is useful in determining the need for toxicity studies



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Toxicology Program
Bethesda, MD 20892

Date: May 31, 1991
From: Chemical Selection Coordinator
Subject: Board of Scientific Counselors' Testing Recommendations
May 3, 1991, Meeting
To: Dr. Larry Hart

The following chemicals were reviewed by the Board of Scientific Counselors on May 3, 1991:

- ((o-Carboxyphenyl)thio)ethylmercury sodium salt
- p,p'-Dichlorodiphenyl sulfone
- Hexamethyldisilazane
- Isoeugenol
- Sesamol
- 3,3',4,4'-Tetrachloroazobenzene
- 3,3',4,4'-Tetrachloroazoxybenzene

Attached is a summary table containing the names and CAS numbers of the chemicals, the nomination source, and the Board's testing recommendations, priority, and rationale/comments.

Please contact me if you have any questions.

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

Attachment

cc: Sharon Soward ✓

TESTING RECOMMENDATIONS FOR CHEMICALS REVIEWED BY NTP BOARD OF SCIENTIFIC COUNSELORS
ON MAY 3, 1991

Chemical (CAS Number)	Nomination Source	Testing Recommendations (Priority)	Rationale/Remarks
1. ((o-Carboxyphenyl)thio) ethylmercury sodium salt (54-64-8)	NIEHS	No testing	-Acute toxicity of the chemical is well documented and exposure should be limited based on these data -Several chronic studies indicated no carcinogenic effects -Toxicity of the chemical is due to alkyl mercury
2. p,p'-Dichlorodiphenyl- sulfone (80-07-9)	NCI	-Subchronic studies -Mutagenicity (High)	-High production -Potential for accidental exposure -Lack of specific information on exposure -Prior to initiating studies, NTP should provide opportunity to producers to submit information on actual production volume, uses, and exposure
3. Hexamethyldisilazane (HMDS) (999-97-3)	Private Individual	-Neurotoxicity -Reproductive effects -Carcinogenicity (High)	-High production -Widely used in electronics industry -Potential for high occupational exposure -Many workers are in reproductive ages -Very little information available on toxicity and environmental fate of HMDS -NTP should look at breakdown products in water -Before initiating testing NTP should ensure that HMDS is the best representative of the organosilicon amines chemical class
4. Isoeugenol (97-54-1)	NCI	-Chemical disposition -Reproductive and developmental effects -Carcinogenicity (Low to moderate)	-Widespread use in consumer products -High human exposure -High percentage of workers are female -Naturally occurring product -Genotoxic effects observed in human cell lines -Structurally related to known or suspect carcinogens -Chemical disposition studies might provide information that is useful in determining the need for toxicity studies

TABLE (CONT'D)

Chemical (CAS Number)	Nomination Source	Testing Recommendations (Priority)	Rationale/Remarks
5. Sesamol (533-31-3)	NCI	No testing	-Minor component of sesame oil, a naturally occurring product -No commercial production or use reported -Sesamol should be re-evaluated if it is produced and used in high volume in the future
6. 3,3',4,4'-Tetrachloro- azobenzene (14047-09-7)	EPA	Carcinogenicity (High)	-Environmental contaminants -Potential for human exposure -Lack of carcinogenicity data -EPA's interest in the testing of these compounds
7. 3,3',4,4'-Tetrachloro- azoxybenzene (21232-47-3)			-Data from carcinogenicity studies are needed to determine if regulation is necessary