

NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS
August 16-17, 1984

SUMMARY MINUTES

National Toxicology Program
Board of Scientific Counselors' Meeting
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Summary Minutes

The National Toxicology Program (NTP) Board of Scientific Counselors met on August 16 and 17, 1984, in the Conference Center, Building 101, South Campus, National Institute of Environmental Health Sciences, 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. Mortimer Mendelsohn (Chairperson), Norman Breslow, Leila Diamond, Curtis Harper, Jerry Hook, Jeanne Manson, Henry Pitot, and James Swenberg. Dr. Pitot was unable to attend the meeting.

The minutes of the Board of Scientific Counselors' meeting of March 27 and 28, 1984, were approved unanimously.

1. Peer Review and Priority Ranking of Chemicals Nominated for NTP Testing: (Attachment 3) There were 27 chemical nominations to be considered by the Board. All had been reviewed previously by the NTP Chemical Evaluation Committee (CEC). Dr. Mendelsohn chaired the review and Drs. Dorothy Canter, NIEHS, Barry Johnson, NIOSH, and Marilyn Wind, CPSC, members of the CEC, as well as Dr. Victor Fung, NTP Chemical Selection Coordinator, served as resource persons. Each Board member had been asked to serve as principal reviewer for three or four chemicals except Dr. Swenberg who was asked to lead the review of six nitropyrenes. Following oral presentation of each review and discussion, a motion was made and voted on by the Board members.

The group of six nitropyrene compounds, reviewed by the CEC on November 17, 1982, had been reviewed by the Board on September 27, 1983, and deferred for future consideration so that information could be provided on ongoing and completed studies by other organizations. Ms. Alice Freund, AFL-CIO, gave a presentation in which she commented on the greatly increased uses of diesel engines and the broad groups of workers being exposed to nitropyrenes. She said there had been little animal testing done although the need for studies was supported by the finding of potent effects by some nitropyrenes on unscheduled DNA synthesis. Dr. Jane Warren, Health Effects Institute (HEI), then addressed the Panel about studies the HEI was supporting on biological effects of nitropyrenes in several university and private laboratories. The studies were funded half by the EPA and half by the automotive industry and focused primarily on carcinogenic and mutagenic effects either in vitro in a variety of systems or in vivo by the inhalation route of exposure. Dr. Steven Nesnow, EPA, discussed that agency's findings, noting that most completed studies had been done with complex mixtures such as diesel exhaust. More studies needed to be done with individual nitropyrenes. He supported evaluation of the nitropyrenes in a battery of short term tests and chronic testing of 1-nitropyrene and 1,8-dinitropyrene in rodents by the gavage route. Dr. Swenberg, as principal reviewer, agreed with Dr. Nesnow's recommendations and added that reproductive and general toxicity studies also were needed. Further, since short-term tests were being or had been performed by others including HEI, all class members would not need to be evaluated in a complete test battery.

Of the remaining 21 chemical nominations to be evaluated, 11 had been reviewed by the CEC on May 31, 1983 (Attachment 3, Table I), while 10, including a group of substances (black newsprint inks), had been reviewed by the CEC on November 8, 1983 (Attachment 3, Table II). From this latter group of nominations, the Board made testing recommendations on five nominations. However, the Board recommended unanimously that action be deferred until the next meeting on five azo and nitro dyes (C.I. Direct Yellow 4, C.I. Disperse Brown 1, C.I. Basic Red 18, C.I. Acid Yellow 151, and C.I. Direct Red 80) to allow for a presentation on the rationale for the nomination of these dyes as representative of the azo and nitro dyes class.

The Board's recommendations, priority for testing, and additional remarks and/or caveats for the twenty-seven nominations are summarized in Attachment 4.

REVIEW OF NIEHS/NTP SYSTEMIC TOXICOLOGY BRANCH PROGRAMS

II. Overview: (Attachments 5 and 6) Dr. Bernard Schwetz, Branch Chief, described the organizational structure of the Toxicology Research and Testing Program (TRTP), the NIEHS component of the NTP, and the organization of the Systemic Toxicology Branch (STB) which is composed of five sections: biochemical toxicology, chemical disposition, immunotoxicology, fertility and reproduction, and inhalation toxicology. Dr. Schwetz explained how the programs to be reviewed fit into the toxicology evaluation process. He said the major scientific objectives of the STB were to help improve methods for toxicological evaluation, and to better understand mechanisms of toxicity of selected chemicals. In addition to a focus on applied research and methods development and validation along with some basic research on mechanisms, STB staff serve as chemical managers, as members of the Toxicology Design Committee, as consultants to other Institute programs and the interagency Chemical Evaluation Committee, and actively collaborate with professional staff in the intramural research program, other programs in TRTP, and where appropriate, with other government agencies. Dr. Schwetz handed out information on the research and development contracts and division of staff time among research and administrative or support activities for the three Branch programs to be reviewed (Attachment 6). He noted that time would not allow description of all activities, just selected ones.

III. Chemical Disposition Section: (Attachment 7) Dr. H.B. Matthews, Section Head, described the growth of his program since its formation in 1979 and the Section's last review by the Board in 1981. He said the early objectives of the Section were focused on characterizing the chemical disposition and pharmacokinetics of chemicals with strong potential for bioaccumulation. More recently emphasis has been placed on supporting NTP experimental designs for most chemicals through measuring rates of absorption, metabolism, clearance and dose-related effects prior to initiation of long-term toxicology and carcinogenesis studies. There is also increased participation in more in-depth toxicological characterization studies as required by the results of long-term tests. The long-term objectives of the Section are to investigate structure-activity relationships, determine mechanisms of toxicity as related to chemical disposition, and develop data which can be used in cross-species extrapolation. Dr. Matthews commented that not all chemicals coming into the program are studied, especially when adequate studies have been done by others or they are endogenous chemicals or complex mixtures. However, the disposition of over 100 chemicals has been evaluated since 1979 (Attachment 7, Table 1) with 17 of these chemicals evaluated to address specific questions raised in the long-term study.

Emphasis has been given where possible to examining structure-activity relationships (chemical class studies). He listed the personnel resources of the section and the extramural support, currently three contracts and one inter-agency agreement (Attachments 5 and 6). He also pointed out that the junior staff members devote most of their time to research while the senior staff divides their time among research, contract monitoring, chemical management and support activities.

Dr. Matthews discussed his own research projects over the last three years, including: (1) the disposition of four aniline derivatives; (2) blood transport of halogenated biphenyls; (3) disposition of furan in response to hepatotoxicity arising during testing; (4) disposition of benzyl acetate to assess the relationship between toxicity observed in two-year studies and disposition (route and dose dependency); and (5) disposition of 2,3-dibromopropanol by dermal and oral routes. The latter study led to a detailed investigation of how various factors in chemical dosing can affect the degree of chemical absorption and toxicity.

Discussion: Dr. Lech asked whether a chemical disposition study performed after chronic testing has been completed may provide answers which make repeat of the chronic study unnecessary. Dr. Matthews said this was so citing the study with benzyl acetate.

A. Studies by Dr. Y. M. Ioannou: Allyl isothiocyanate (AITC) was shown in an NTP chronic study to produce transitional cell tumors of the urinary bladder in male rats but not in female rats or mice of either sex. Dr. Ioannou described experiments on the metabolic fate of AITC in both sexes/species. These studies showed differences in metabolism between rats and mice, and sex differences in rats. These results indicate that toxicity may have been due to smaller urine volumes and decreased urinary frequency in male rats resulting in greater association of AITC and metabolites with bladder tissue thereby resulting in greater chronic stimulation and tumor formation. Other disposition studies by Dr. Ioannou are described in Attachment 7.

Discussion: In response to Dr. Swenberg, Dr. Ioannou said the metabolites were carried in the urine and not formed in the bladder per se. Dr. Hook stated the sex differences in urinary volumes were an important observation in a good study. He cautioned against reference to tissue levels of a chemical as resulting from increased binding affinity without further evidence for such a mechanism.

B. Studies by Dr. B. I. Ghanayem: The basis for this research was the observation that there were increased incidences of forestomach tumors in several long-term rodent tests where a reactive chemical was given by gavage. Dr. Ghanayem described results obtained with one such chemical, ethyl acrylate, and structural analogs, methyl and n-butyl acrylates, using oil and water gavage as well as differing concentrations of chemical in the vehicle. The principal acute effect seen was edema of the forestomach which progressed with time to scarring and hyperkeratosis. This study showed the toxic effects of ethyl acrylate to be dose, time, and concentration dependent. Further, structure-activity studies demonstrated that acute toxicity decreased with increasing chain length of the alcohol moiety (methyl>ethyl>butyl acrylate).

Discussion: Dr. Swenberg commented that the results of this study show the usefulness of using this type of study in dose level and dose concentration setting for a long-term bioassay.

C. Studies by Dr. Linda S. Birnbaum: Her research programs focus on chemical disposition, particularly of halogenated aromatic chemicals, mechanisms of toxicity as related to chemical disposition, and aging as a modifying factor in chemical disposition and toxicity. Specific projects described included: (1) investigation of species, strain and sex differences in toxicity of 2,3,7,8-tetrachlorodibenzofuran (TCDF) and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) as affected by metabolism, body fat content, and differences at the Ah locus. Body fat composition seemed to be the most important determinant of toxicity; (2) a study of the disposition of Santonox (4,4'-thio-bis[6-t-butyl-m-cresol]) which showed that delayed absorption after oral dosing was due to increased retention in the stomach and severe irritation by the chemical. Linear absorption occurred in the small intestine followed by hepatic metabolism primarily to a glucuronide conjugate; (3) disposition of benzo(f)quinoline with rapid metabolism in the rat and about equal excretion in urine and feces; and (4) studies on the mechanisms of nephrotoxicity and liver enlargement caused by o-benzyl-p-chlorophenol which focused on the effects of the chemical on changes in xenobiotic metabolizing enzyme systems in liver and kidneys.

Dr. Birnbaum discussed her laboratories' investigations of the effects of aging on chemical metabolism, disposition and/or toxicity in rats, including: (1) studies of the disposition of two hexachlorobiphenyls (HCB) suggesting increased body fat in older animals as a major factor in decreased metabolism and excretion of chemicals; (2) studies of age-related changes in intestinal absorption of chemicals using glucose analogs. These studies suggest passive absorption is much less affected by senescence than active transport; and (3) studies on the balance between glucuronyl transferase and β -glucuronidase enzymes and how the balance in liver and kidney is affected by aging. She reported on studies looking at interactive effects of TCDD and TCDF (which were only additive) and of TCDD and a planar HCB (which were synergistic) in induction of cleft palate, and also of interactive studies with thyroid hormones. Finally, Dr. Birnbaum described studies of the chemical disposition and toxicity of two isomers of hexabromonaphthalene both contaminants of the polybrominated biphenyl mixture, Firemaster BP-6, involved in the major environmental contamination episodes in Michigan.

Discussion: Dr. Lech asked whether they had studied the relationship between changes in body fat levels and the area under the plasma level curve in chronic feeding studies. Dr. Birnbaum agreed this was important to do but had not been done in her studies although others had examined this relationship with more water soluble chemicals.

D. Studies by Dr. L. T. Burka: His major research interests are in (1) the metabolism of xenobiotics including identification of metabolites and products of the reaction of parent compounds or metabolites with tissue components, and (2) investigating the chemical mechanisms of mixed function oxidase metabolism. He commented on the use of physical organic chemistry techniques to evaluate changes in rates of metabolism from different substituents on the molecule. He described studies using these techniques to investigate the mechanisms of cytochrome P-450 catalyzed hydroxylation of monohalobenzenes and demethylation of p-substituted dimethylanilines. He observed that the problem for the future lay in how to expand results obtained *in vitro* to the more complex environment found in biological systems. Dr. Burka reported on the identification of metabolites for several chemicals carried out in collaboration with other members of the section.

E. Extramural Program - Research Contracts and Interagency Agreements:

Dr. Matthews said the current short and long-term objectives of the extramural program paralleled those for the intramural. He briefly discussed the accomplishments of two very productive contracts which have expired. One at the University of Oregon was primarily concerned with detailed disposition studies of benzidine and benzidine congener based dyes. The second expired contract at the University of Arizona examined the disposition of a number of diverse chemicals which have been or are currently in NTP long-term toxicology and carcinogenesis studies. These studies addressed more than 20 chemicals, including dermal absorption of a number of phthalates and in vitro metabolism studies of polychlorinated biphenyls. The latter studies were carried out to provide cross-species comparisons with human, monkey and dog liver microsomes.

New contracts include one at the Research Triangle Institute through which we are studying the disposition of a variety of chemicals including those that are volatile (cyclohexane), sparingly soluble in biological media (1-amino-2,4-dibromoanthraquinone, CI Vat Blue 1) and reactive (ethyl acrylate, toluene 2,6-diisocyanate, crotonaldehyde, and t-butyl perbenzoate). A second contract at Southern Research Institute brings a strength in development of analytical methodology useful in designing sensitive assays for use with non-radiolabelled compounds and in measuring gastrointestinal absorption of sparingly soluble chemicals. Third, the contract at the University of Arizona was reinitiated with the focus being placed on studying chemical disposition of binary combinations of eight Superfund chemicals in an effort to detect additive or synergistic toxicity.

Dr. Birnbaum described the activities at the Lovelace Biomedical and Environmental Research Institute under an interagency agreement with the Department of Energy. The major strength of this agreement is that the capability exists for doing disposition studies using inhalation exposure. Aims are to determine for a chemical by the inhalation route half lives to steady state, equilibrium concentrations in target tissues, and major routes of excretion. Data will be compared with that obtained by other routes such as intraperitoneal, oral or intratracheal. Dr. Birnbaum discussed disposition studies with 2,3-dichloropropene and methyl bromide. Methodology has been developed with azodicarbonamide for its administration as a dust and disposition of the chemical after inhalation exposure is being compared with that by oral and intratracheal administration. The agreement was expanded to allow repeated dose studies in more than one species with 1,3-butadiene and benzene, both to include DNA-binding assays and the latter to include various measures of genetic toxicity.

Discussion: Dr. Harper inquired whether there were significant stress effects on the animals from use of nose-only exposures. Dr. Birnbaum replied that there did not seem to be.

The ultimate goal of most studies in toxicology is to provide information which will facilitate extrapolation of laboratory data to humans. Dr. Burka reported that NTP was soliciting proposals for up to three contracts to develop methodology which will allow comparison of the metabolism of foreign chemicals by human tissues to metabolism by laboratory species. It is expected that most of the methods will use liver tissue but one contract may focus on extrahepatic

tissues, e.g. kidney. Standard substances will be used to develop a data base and evaluate interspecies variability.

Discussion: Dr. Lech asked whether there would be a provision for studying the time course for stability of isolated tissues. Dr. Matthews said this was an important aspect of methods development.

F. Future Plans: Dr. Matthews said that in addition to continuing primary support of the toxicity testing process from beginning to end, attention would be given to chemical dispositions mechanisms and their relationship to toxicity, development of pharmacokinetic models for data from NTP chronic studies, disposition studies of metals and metallic complexes, and use of in vitro systems.

IV. Biochemical Toxicology Section: (Attachment 8) Dr. Joyce Goldstein, Section Head, noted that her responsibilities as a Chemical Manager and as a member of the Toxicology Design Committee required about 40% of her time. She said the primary objective of her laboratory work over the past four years had been to examine the regulation of hepatic cytochrome P-450 in the rat, to contribute to understanding of the role this microsomal enzyme system plays in activation and deactivation of chemicals, and to examine how this system responds to influences such as age, sex and administration of foreign chemicals.

Dr. Goldstein proceeded to describe several of the major projects completed or in progress in her laboratory. (1) Recent emphasis has been on isolating a major isozyme of P-450 induced by a hexachlorobiphenyl (3,4,5,3',4',5'-HCB), characterizing its substrate specificity and comparing it with other induced isozymes. (2) A radioimmunoassay (RIA) using rabbit antisera was developed in collaboration with Dr. Michael Luster, STB, to detect the P-450 isozymes -- P-448MC, P-448-HCB, and P-450-PB. The procedure is much more sensitive than other techniques, such as radial immunodiffusion (RID), used in the past to measure P-450 isozymes. (3) The ability of the P-450 isozymes to generate mutagenic metabolites from premutagens was measured using a Salmonella assay. The P-448-MC isozyme was shown to be more effective than the P-448-HCB form in converting benzo(a)pyrene and its 7,8-dihydrodiol to mutagenic metabolites, while the P-448-HCB was more effective in producing the N-hydroxylated metabolite of 2-acetylaminofluorene (2-AAF). (4) An indepth study was done on the metabolism by in vitro liver systems of 2-AAF to both the ring hydroxylated form (inactive metabolite) and the N-hydroxylated form believed to be a step in activation to the mutagenic metabolite. Antibodies to the isozymes were made and used to assess the contribution of the isozymes in metabolism of 2-AAF. The P-448-HCB form was again more active in N-hydroxylation. (5) The induction by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) of P-448-MC and P-448-HCB in extrahepatic tissues was studied. The P-448-MC was induced in all tissues studied while P-448-HCB was induced only in liver. (6) A study was done to determine whether cytochromes P-448-MC and P-448-HCB were induced coordinately in liver. The data obtained suggested that the two isozymes are induced coordinately, probably via a common mechanism.

Dr. Goldstein discussed some of the specific NTP chemicals that the Section had worked with over the past few years including the PCBs. An objective is to explore effects of exposure to various chemicals or classes of chemicals on

P-450 isozyme regulation in the rat and define the consequence of changes observed. Chemicals are not being screened per se but are looked at as prototypes and are examined for their ability to induce the P-450 isozymes in hepatic and extrahepatic tissues. Specifically, she discussed induction of isozymes and formation of antibodies with clofibrate and diethylhexylphthalate.

Dr. Goldstein discussed studies being done by other workers in the Section. Dr. Heather Yeowell is investigating metabolism of prostaglandins by the P-450 isozymes and trying to relate toxicity to changes in metabolism, and in collaboration with Dr. Ernest Hodgson at North Carolina State University, she is studying interactions of certain methylene dioxyphenyl compounds and 3-MC in inhibition of isozyme induction. With Ms. Patricia McClelland-Green, Dr. Goldstein has begun isolating and characterizing various constitutive isozymes of P-450. In her concluding remarks, Dr. Goldstein stated that her laboratory could further contribute to NTP programs by preparing monoclonal antibodies to the various isozymes, and from their experience with prototype chemicals, they could classify and characterize NTP chemicals as to their potential for induction of chemical metabolizing enzymes.

Discussion: Dr. Gasiewicz inquired as to whether there was cross reactivity of the antibodies for rat isozymes with those for other species. Dr. Goldstein said there was wide cross species homology with the exception of the chicken and they would be examining human tissue (skin cells). Dr. Swenberg asked how these studies with isolated systems applied to the whole animal. Dr. Goldstein acknowledged the much greater complexity in vivo and said they hoped to do some in vivo adduct studies and would try to relate adduct formation to isozyme induction.

V. Immunological Toxicology Section: (Attachment 9) Dr. Michael Luster, Section Head, described the background, history and need for the program in immunotoxicology. He noted that he and Dr. Jack Dean had organized a consensus conference in 1979, sponsored by the NTP, bringing together primarily immunologists and toxicologists to define the critical issues in this scientific area. At the conference, the types of assays needed to measure immunotoxicity were defined and given a priority order.

A. Extramural Program: Dr. Luster said the NTP immunotoxicology efforts were carried out through the in-house research groups and two research and development contracts. In describing the extramural efforts, he noted three primary objectives of the contracts: (1) to develop methodology for measuring host resistance to infectious agents and transplantable tumor cells; (2) to establish a standard set of immunologic assays; and (3) to integrate and validate these assays using chemicals of interest to the NTP. The first two phases have been completed. Chemicals that were used in the developmental and validation phases included known immunosuppressants -- cyclophosphamide, diethylstilbestrol, dimethylnitrosamine, and cadmium. All chemicals examined following the validation phase have been from those tested in NTP prechronic and long-term toxicology and carcinogenesis studies. Dr. Luster reviewed the assays comprising the immunological and host resistance screening panel. Included are measures of immunopathology, host resistance, cell-mediated and humoral immunity, and macrophage function. Most recently added was hypersensitivity skin testing in

mice as many industrial chemicals and NTP chemicals are allergens. Dr. Luster described in more detail several of these assays, the types of data that can be obtained, and their biological relevance. Dr. Luster noted that the dose levels used in these studies were comparable to those used in the 14-day repeat or two-year chronic studies. He discussed some of the infectivity models chosen with a focus on the tumor susceptibility and mouse malaria models. The primary effort remaining on the two contracts is completion of the testing phase followed by data reduction and analysis.

Discussion: Dr. Swenberg asked whether there was an adaptive response of the immune system to chemical effects after chronic administration. Dr. Luster said that studies with tetrahydrocannabinol and cadmium chloride using different dosing regimens are presently being performed to start answering such questions.

B. Intramural Program: To introduce discussion of the in-house programs, Dr. Luster reviewed the genesis of the different cell types comprising the immune system and the functions of each type. He listed known or potential immunotoxins of NTP interest including estrogens, polycyclic aromatics, polyhalogenated aromatics, thiazoles, and mycotoxins. Selected chemicals examined in depth in-house over the past three years include benzidine, diphenylhydantoin, diethylstilbestrol and TCDD.

Dr. Anne Tucker described studies with diphenylhydantoin (DPH). Up to 60% of humans taking DPH exhibit clinical signs characteristic of humoral immunodeficiency. In mice, indicators of humoral immunity were depressed as was host resistance to infection with Plasmodium yoelii. The most sensitive site was the bone marrow where there was loss of the multipotent stem cells after one week. Concurrent administration of folic acid protected against the loss, indicating that DPH operates via an antifolate mechanism to alter stem cell kinetics in the mouse.

Dr. Tucker discussed studies with benzidine as a prototype aromatic amine. She summarized immune system effects of the chemical as being depressions of lymphocyte activation, cell-mediated immunity, and host resistance. Experiments were performed to determine whether biotransformation of benzidine was involved in its immunosuppressive effects. Acetylated or hydroxylated metabolites formed in the liver were shown not to be active. However, benzidine or methylated derivatives serve as a co-oxidation substrate for arachadonic acid metabolism. She said they postulated that the benzidine effects were mediated by the high levels of hydroxy fatty acids generated through the lipoxigenase pathway.

Dr. Luster described studies on the effects of TCDD on the immune system. He contrasted the long-lasting suppression of T-cell function in animals exposed perinatally vs. exposure of adult animals which produces suppression of B-cell and bone marrow functions. He discussed the role of the Ah receptor in the toxic effects of TCDD and noted that mouse strains with high levels of or high affinity of the TCDD receptor showed marked immunosuppression while there was little suppression in strains with low levels or low affinity of the receptor. Detailed studies in which antibody development was monitored indicated that TCDD directly affects B-cell maturation by affecting their ability to respond to growth factors. Dr. Luster also commented on a hematopoietic stem cell model for studying TCDD toxicity, in which altered stem cell differentiation occurred in Ah-responsive mice. Dr. Luster described an Ah receptor antagonist for TCDD, 1-amino-3,7,8-trichlorodibenzo-p-dioxin, which in in vitro studies abolishes certain immune suppressive effects of TCDD.

C. Future Plans: Dr. Luster concluded by reviewing the levels of effort for various aspects of the program over the last four years and future plans. He said the thrust of methods development and validation phases were completed although a small effort would continue to test the utility of new assays for possible incorporation into the screening panel. Screening of NTP chemicals for immunotoxic effects will continue to be a significant effort through contracts while the in-house effort will continue in examining mechanisms of toxic effects. There will be increased activity in (1) developing target organ site-specific models with relevance to humans, and (2) supporting studies of exposed human populations and correlations of data from these studies with animal studies. New approaches for detection and quantification of a chemical's potential for producing hypersensitivity will be given high priority.

VI. NIEHS/NTP Systemic Toxicology Branch Programs - Concept Reviews:

A. Effect of the Ah Locus on Lifespan and Pathology of Congenic Mice: (Attachment 10) Dr. Birnbaum said the objective of the proposal was to examine the effect of a single gene, the Ah locus, on lifespan, general health, tumor incidence and non-tumor pathology in female congenic mice which differ either in having the Ah receptor (Ah responsive) or lacking the receptor (Ah nonresponsive). To confirm genetic homogeneity about 35 to 50 other gene loci will be examined in the different strains of C57BL/6J mice. The experimental design proposed should provide a high power of resolving genotypic differences in lifespan, tumor incidence, and non-tumor pathology. Time points for sacrifice will allow comparison to data obtained with the B6C3F₁ mouse strain customarily used in NTP long-term toxicology and carcinogenesis studies. Dr. Swenberg commented that if a long-term objective of the study is to provide a different mouse strain to replace or complement the B6C3F₁ mouse in long-term testing then male mice should be included in the design. Dr. Birnbaum replied that this would be too costly in terms of the current objective of the concept, and further there had been no sex differences shown for the Ah locus. Chemicals likely to be chosen for study would be members of classes whose metabolism is modulated by the Ah locus. Dr. Lech said it was important to examine differences in chemical metabolism among the three strains. Dr. Birnbaum agreed and said these types of studies would be done by intramural investigators and not on the contract. Considerable discussion ensued as to whether the design should focus on background incidences of tumor and non-tumor pathology and perhaps include both sexes or whether the design should remain as presented to include treatment with chemical carcinogens. Dr. Mendelsohn said to include both sexes and carcinogen groups along with studies on induction and binding would make a very complicated design. Dr. Swenberg moved that the concept as originally presented be approved but with the modification that the design include both sexes. Dr. Harper seconded the motion and the concept proposal was approved unanimously by the Board. Dr. Rall pointed out that the Board should understand that the modification would markedly increase the cost.

B. Development of Ovarian Toxicity Screening Methods: Studies on the Classification of Ovarian Follicles as an Indication of Ovarian Toxicity: (Attachment 11) Dr. James C. Lamb said the objective of this proposal was to evaluate ovarian follicle classification as a method of screening chemicals for potential ovarian toxicity. In discussing current measurements of reproductive toxicity, he noted there was a need for an established procedure for measuring ovarian toxicity which could be incorporated into the 90-day prechronic studies. The method would be evaluated using tissues from animals in the NTP continuous breeding studies of 16 chemicals, thus making fertility data available. Except for one study in rats, mice will be the test animals as this is the species used

in the continuous breeding studies. The data generated will provide a much needed baseline. Dr. Manson reported that the concept proposal had received review by the NTP Board Subcommittee on Reproductive and Developmental Toxicology. Dr. Swenberg suggested applying stereologic techniques to gain quantitative information on the follicles. Dr. Manson moved that the concept be approved. Dr. Swenberg seconded the motion and it was approved unanimously by the Board.

VII. Report of the Director, NTP: Dr. David P. Rall reported that:

- (a) Mr. Ruckelshaus as Chairman of the NTP Executive Committee has initiated special evaluations of benzene, 1,3-butadiene, glycol ethers and halogenated solvents. He noted that the next Executive Committee meeting would be August 31. At this meeting, Dr. Robert Scala was to discuss the final report of the NTP Ad Hoc Panel Report on Chemical Carcinogenesis Testing and Evaluation while Dr. Mendelsohn was to discuss the recent activities of the NTP Board of Scientific Counselors;
- (b) Dr. Frank Young, former Dean of the Medical School at the University of Rochester, has begun his tenure as Commissioner, FDA;
- (c) the FY 1985 NIEHS budget was still awaiting Congressional passage.
- (d) upcoming meetings sponsored or cosponsored by the NIEHS and to be held in the Conference Center, Building 101 included:
 - (1) 'Brain Tumors in Man and Animals', September 5 and 6, 1984;
 - (2) 'DNA Adducts: Dosimeters to Monitor Human Exposure to Environmental Mutagens and Carcinogens', September 24-26, 1984; and
 - (3) 'Health Effects of Acid Precipitation', November 15 and 16, 1984, which was prompted by a request for a workshop on the subject from the Appropriations Committee, House of Representatives;
- (e) the NIEHS has several ongoing international activities. Among these are extensive interactions with the World Health Organization and its International Program on Chemical Safety (IPCS). An inter-regional research unit of the IPCS headed by Dr. George Becking, a Canadian toxicologist, is located at the NIEHS. The NIEHS has eleven bilateral agreements including major ones with Japan (two), Australia, and the USSR;
- (f) the third task force on environmental health and research needs (Task Force III), composed of distinguished scientists, met at the NIEHS for two weeks in June. Their final report will be presented to the Congress early in 1985;
- (g) the first draft of the FY 1985 NTP Annual Plan would be sent to the Executive Committee in late August for review while work on the FY 1985 Review of Current DHHS, DOE and EPA Research Related to Toxicology was in progress;
- (h) the Technical Reports Review Subcommittee of the Board met at the NIEHS July 26 to review the carcinogenicity data on D & C Red No. 33 for the FDA's Center for Food Safety and Applied Nutrition, and on July 27 to review and approve the technical reports for NTP toxicology and carcinogenesis studies of benzene, chrysotile asbestos, 1,3-dichloropropene (Telone II[®]), 2-chloroethanol, HC Blue No. 2, and dimethyl hydrogen phosphite. The next meeting will be held at the NIEHS on November 2; and
- (i) the next meeting of the Board will be on October 31 and November 1 at the NIEHS.

VIII. Final Report of the Ad Hoc Panel on Chemical Carcinogenesis Testing and Evaluation: Dr. John Doull, Panel Chairperson, gave an overview and background

of the Panel and its Subgroup's review processes and noted some cross cutting issues and recommendations. He said the final Panel report was a reasonable first step and recommended that the Board convene interactive workshops. He concluded that the NTP was already implementing many of the recommendations in the report.

Dr. Swenberg (filling in for Dr. Frederica Perera, Subpanel Chairperson) summarized some of the recommendations of the Subpanel on Short Term Tests. He said the current NTP program was making good use of the available assays. The Subpanel focused in their review on tests which might be amenable to human and animal testing and comparisons. The Subpanel gave emphasis to two areas needing special effort: (1) developing better methods for detecting promoters, and (2) developing a good series of non-carcinogens for test validation.

Dr. Andrew Sivak, Subpanel Chairperson, summarized the major issues identified by the Subpanel on Subchronic Studies and Related Issues, and recommendations thereon. These had to do with (1) the chemical selection process, (2) a suitability of the F344 rat and B6C3F₁ mouse as test species, and (3) factors affecting dose - range, numbers, route and vehicle.

Dr. Robert Scala, Subpanel Chairperson, summarized the issues and recommendations from the Subpanel on the Design of Chronic Studies. The specific areas covered were: (1) general experimental design considerations; (2) selection of species and doses; (3) selection of route of administration; (4) selection of dose vehicle; (5) duration of study; (6) use of an in utero exposure system; (7) husbandry requirements and quality control; (8) pathology requirements; (9) statistical issues in the interpretation of data from NTP whole animal bioassays; (10) errors and error rates; (11) combining benign and malignant neoplasms in evaluating carcinogenicity; and (12) evidence of carcinogenicity.

Dr. Mendelsohn responded for the Board. He praised the Ad Hoc Panel and thanked them for an extraordinarily important and well done task. He was particularly impressed by the enormous volume of written responses from the public, and the very constructive and interactive public meetings that were held. He said the Ad Hoc Panel process had served to enhance an image of openness of the NTP. He stated there were four recommendations for which the Board should play a role: (1) having the responsibility to see that the process continues; (2) evaluating the full data base of short-term tests - but not now; (3) examining the issue of input from outside the NTP into the interface between prechronic and chronic testing; and (4) advising on whether both rats and mice are needed, and, if so, which mouse strain. With regard to the other recommendations, he said the Board receives them and gives them to the NTP with the charge that the NTP respond at the next meeting or two.

There was agreement that the NTP should set aside time at upcoming Board meetings to discuss and respond to the recommendations in the Ad Hoc Panel report. Dr. Rall asked the Board to set up two or three person subcommittees from its membership to assist the NTP in planning workshops dealing with issues raised by the report.

Copies of the Report of the Ad Hoc Panel on Chemical Carcinogenesis Testing and Evaluation are available without charge from: NTP Public Information Office, MD B2-03, Box 12233, Research Triangle Park, NC 27709, Telephone (919) 541-3991, FTS: 629-3991.

The meeting was adjourned.

NOTICE OF MEETING
NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS

Pursuant to Public Law 92-463, notice is hereby given of the meeting of the National Toxicology Program (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 August 16 and 17, 1984.

The meeting will be open to the public from 8:30 a.m. to adjournment on August 16.

The preliminary agenda with approximate times are as follows:

8:30 a.m. - 11:30 a.m. Peer Review and Priority Ranking of Chemicals Nominated for NTP Testing. (Six nitropyrenes considered and deferred by the Board on September 27, 1983 will be reviewed and are listed in the Federal Register, Volume 48, No. 44, pp. 9379-9380, March 4, 1983. Additionally, 26 new chemical nominations will be reviewed and are listed in the Federal Register, Volume 48, No. 143, pp. 33747-33748, July 25, 1983, and Volume 49, No. 5, pp. 1139-1140, January 9, 1984.)

Review of NIEHS/NTP Systemic Toxicology Branch Programs

12:30 p.m. - 4:00 p.m. Introduction and Review of Chemical Disposition Program

4:00 p.m. - 5:00 p.m. NIEHS/NTP Concept Reviews:

- a. Effect of the Ah Locus on Lifespan and Pathology of Congenic Mice
- b. Development of Ovarian Toxicity Screening Methods: Studies on the Classification of Ovarian Follicles as an Indication of Ovarian Toxicity

The meeting on August 17 will be open to the public from 8:30 a.m. to 3:00 p.m.

The preliminary agenda with approximate times are as follows:

Review of NIEHS/NTP Systemic Toxicology Branch Programs (continued)

8:30 a.m. - 10:00 a.m. Review of Biochemical Toxicology Program

10:15 a.m. - 12:15 p.m. Review of Immunotoxicology Program

1:00 p.m. - 1:15 p.m. Report of the Director, NTP

1:15 p.m. - 3:00 p.m. Final Report to the Board of the Ad Hoc Panel
On Chemical Carcinogenesis Testing and Evaluation

In accordance with the provisions set forth in Section 552b(c)(6) Title 5 U.S. Code and Section 10(d) of Public Law 92-463, the meeting will be closed to the public on August 17 from approximately 3:00 p.m. to adjournment for further evaluation of NIEHS/NTP programs in chemical disposition, biochemical toxicology, and immunotoxicology, 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 furnish a roster of Board members and expert consultants and other program information prior to the meeting, and summary minutes subsequent to the meeting.

Date

David P. Rall, M.D. Ph.D.
Director
National Toxicology Program

AGENDA

Board of Scientific Counselors
National Toxicology Program
August 16-17, 1984

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

Thursday, August 16, 1984

OPEN

8:30 a.m. - 11:30 a.m. Peer Review and Priority
Ranking of Chemicals
Nominated for NTP Testing Board
Dr. Dorothy Canter,
NIEHS

REVIEW OF NIEHS/NTP SYSTEMIC TOXICOLOGY BRANCH PROGRAMS:

12:30 p.m. - 12:45 p.m. Introduction Dr. Bernard Schwetz,
NIEHS

12:45 p.m. - 4:00 p.m. Chemical Disposition Program Dr. H.B. Matthews and
Staff, NIEHS

4:00 p.m. - 5:00 p.m. Concept Reviews:
(1) Effect of the Ah Locus on
Lifespan and Pathology of
Congenic Mice Dr. Linda Birnbaum,
NIEHS

(2) Development of Ovarian
Toxicity Screening Methods:
Studies on the Classification
of Ovarian Follicles as an
Indication of Ovarian Toxicity Dr. James Lamb, NIEHS

Friday, August 17, 1984

OPEN

REVIEW OF NIEHS/NTP SYSTEMIC TOXICOLOGY BRANCH PROGRAMS (Continued):

8:30 a.m. - 10:00 a.m. Biochemical Toxicology Program Dr. Joyce Goldstein and
Staff, NIEHS

10:15 a.m. - 12:15 p.m. Immunological Toxicology
Program Dr. Michael Luster and
Staff, NIEHS

1:00 p.m. - 1:15 p.m. Report of the Director, NTP Dr. David Rall, NIEHS

1:15 p.m. - 3:00 p.m. Final Report of the Ad Hoc
Panel on Chemical Carcino-
genesis Testing and Evaluation Dr. John Doull,
Dr. Robert Scala,
Dr. Andrew Sivak

CLOSED

3:00 p.m. - Adjournment Evaluation of Programs and
Personnel in Chemical Disposi-
tion, Biochemical Toxicology,
and Immunological Toxicology Board and Consultants

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS

Dr. Norman Breslow
Professor, Department of
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Dr. Henry Pitot
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Professor of Oncology and Pathology
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Dr. James A. Swenberg
Chief, Pathology Department
Chemical Industry Institute of
Toxicology
P. O. Box 12137
Research Triangle Park, NC 27709

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
MEETING OF AUGUST 16 and 17, 1984

EXPERT CONSULTANTS FOR REVIEW OF
NIEHS/NTP SYSTEMIC TOXICOLOGY BRANCH PROGRAMS

Biochemical Toxicology

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Chemical Disposition

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Dept. of Pharmacology and Toxicology
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Milwaukee, Wisconsin 53226

Immunological Toxicology

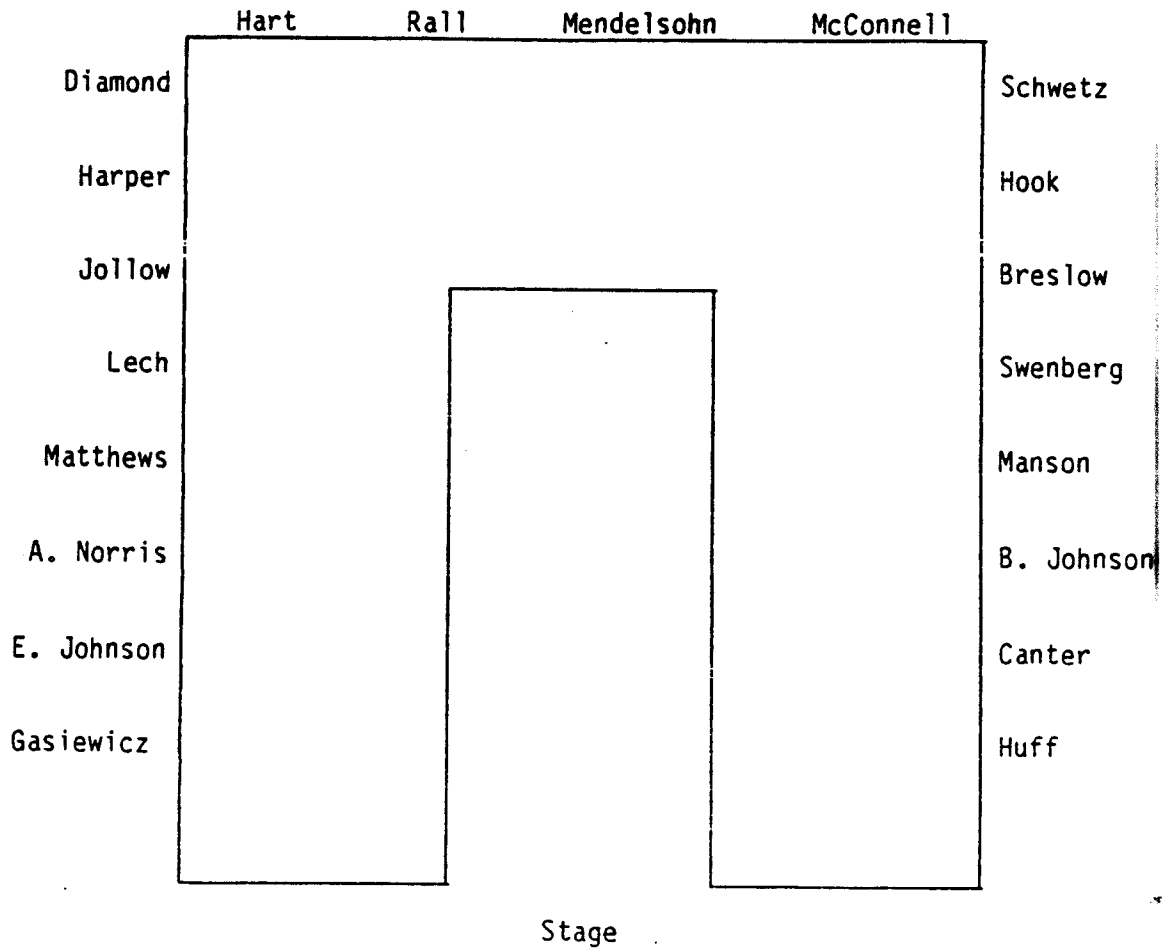
Dr. Dolph Adams
Professor, Dept. of Pathology
Duke University
Durham, North Carolina 27710

Dr. James Folds, Director
Clinical Microbiology-Immunology
Laboratories
Memorial Hospital
University of North Carolina
Chapel Hill, North Carolina 27514

NTP BOARD OF SCIENTIFIC COUNSELORS MEETING

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

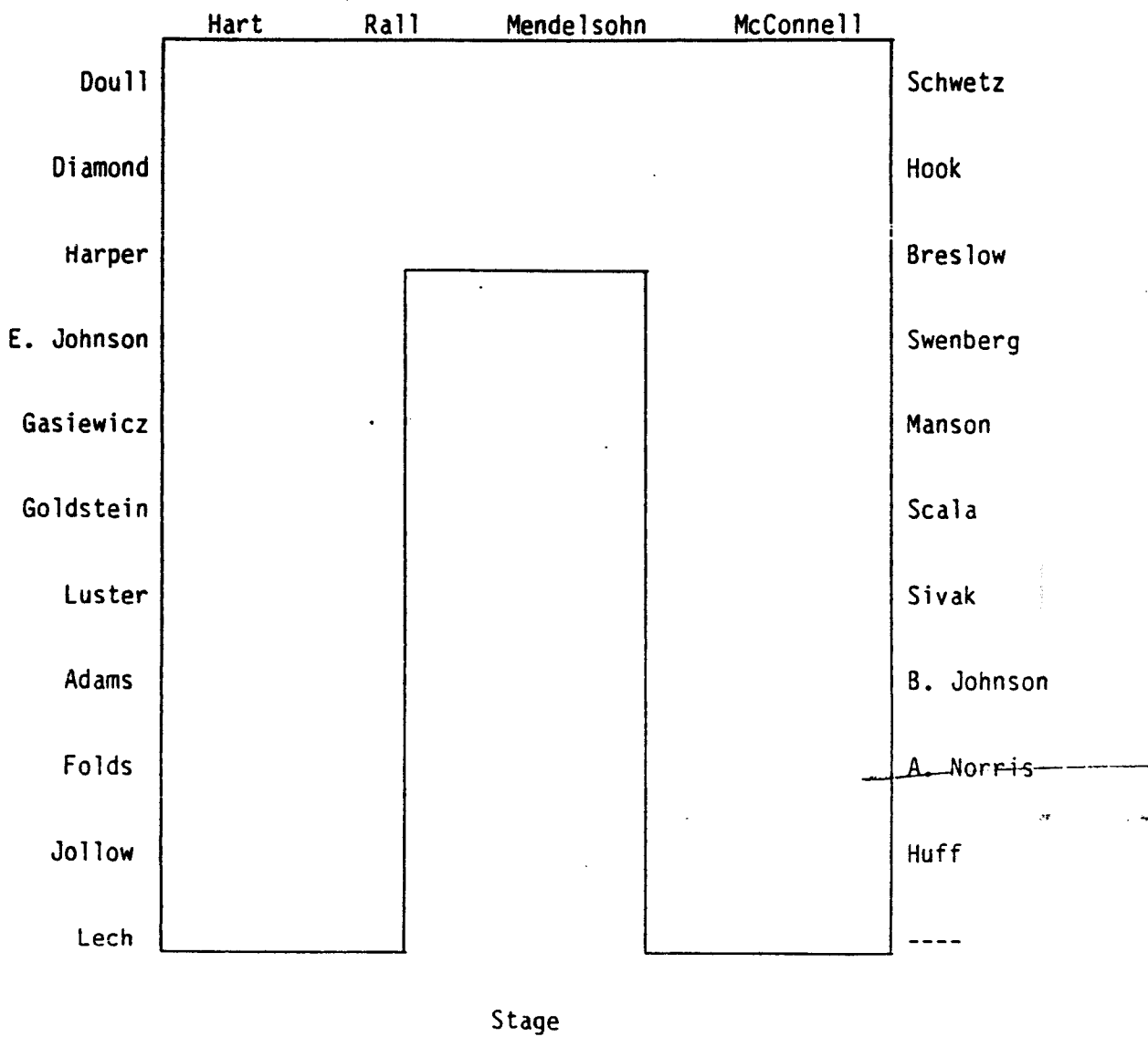
August 16, 1984



NTP BOARD OF SCIENTIFIC COUNSELORS MEETING

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

August 17, 1984





DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
National Institutes of Health

National Toxicology Program

Memorandum

Date July 30, 1984

From NTP Chemical Selection Coordinator

Subject Review of Twenty-six Chemicals and One Group of Substances
Nominated to the NTP for Toxicological Testing

To National Toxicology Program Board of Scientific Counselors

As part of the NTP chemical selection process, the Board of Scientific Counselors evaluates and makes recommendations on chemicals nominated to the NTP for toxicological testing. This assessment takes place following review of the chemicals by the NTP Chemical Evaluation Committee (CEC) and subsequent publication of that Committee's recommendations in the Federal Register with request for public comment.

The Board of Scientific Counselors will review twenty chemicals and one group of substances evaluated by the NTP Chemical Evaluation Committee at the May 31, 1983 and November 8, 1983 meetings, and six nitropyrene compounds previously reviewed and deferred by the Board on September 27, 1983.

On May 31, 1983, the CEC evaluated thirteen nominated chemicals. One of these chemicals, β -pinene was nominated only for tumor promotion studies. Another chemical, chromic acid, was nominated for short-term in vivo and in vitro mechanistic studies, and consideration for a chronic study pending the results of an ongoing sodium dichromate study. The remaining eleven compounds were nominated for carcinogenicity testing. Methyl isobutyl ketone and antimony potassium tartrate were nominated for other toxicological testing in addition to carcinogenicity. Two of the thirteen chemicals, p-chloro- α, α, α -trifluorotoluene and methyl isobutyl ketone, were deferred by the CEC to obtain more information on industry sponsored testing from EPA, and therefore, will be presented to the Board for review at a subsequent meeting.

A Federal Register notice was published on July 25, 1983, listing the thirteen chemicals and the type of testing recommended by the CEC, and soliciting public input. In response to the Federal Register notice, data on methylene bis(thiocyanate), 2-(2-butoxy-ethoxy)ethyl thiocyanate, formic acid and nitromethane were submitted to the NTP. This information has been incorporated into the revised Executive Summaries on these compounds.

Table 1 contains the chemicals, source of nomination, production, worker exposure, NTP testing status, and CEC recommendations and priority assigned.

On November 8, 1983, the CEC evaluated twelve nominated chemicals and one group of substances. One of these chemicals, malathion, was nominated only for reproductive studies. Six chemicals were nominated for chemical disposition studies, with subsequent consideration for carcinogenicity testing upon completion of these studies. The remaining five chemicals and the group of substances were nominated for carcinogenicity testing. C.I. Direct Red 80 and picloram were nominated for other toxicological testing in addition to carcinogenicity.

Two of the chemicals, malathion and picloram, were deferred by the CEC, pending receipt of data from the EPA Office of Pesticides, and will be submitted to the Board for review at a subsequent meeting. D&C Yellow No. 11 will not be reviewed by the Board since it was the FDA's Fiscal Year 1983 priority chemical for carcinogenicity testing. This chemical was referred directly to the NTP Executive Committee after CEC review in accordance with the NTP policy of rapid decision making for priority chemicals of NTP participating agencies.

A Federal Register notice was published on January 9, 1984, listing the twelve chemicals and one group of substances and the type of testing recommended by the CEC, and soliciting public input. In response to the Federal Register notice, data on C.I. Acid Yellow 151, C.I. Basic Red 18, C.I. Direct Red 80, C.I. Direct Yellow No. 4, C.I. Disperse Brown 1, D&C Yellow No. 11, and cinquasia red were submitted to the NTP. This information has been incorporated into the revised Executive Summaries of these compounds.

Table II contains the chemicals, source of nomination, production, worker exposure, NTP testing status and CEC recommendations and priority assigned.

On September 27, 1983, the Board of Scientific Counselors reviewed and deferred six nitropyrenes nominated for testing. The Board was interested in recommending testing but requested that further information on ongoing and completed studies of other organizations be assembled and that representatives of EPA and The Health Effects Institute be invited to discuss their studies at a future Board meeting. On August 16, 1984, Dr. Stephen Nesnow, EPA, and Dr. Jane Warren, The Health Effects Institute, will be making presentations on the nitropyrenes to the Board.

The Board will review the 26 chemicals and one group of substances from 8:30 a.m. to 11:30 a.m., on Thursday, August 16, 1984. The following material is enclosed in order to assist you in your review of these chemicals:

- 1) Set of 27 Executive Summaries.
- 2) Two Summary Data Tables on the chemicals discussed at the May and November 1983 CEC meetings.
- 3) July 25, 1983 and January 9, 1984 Federal Register notices.

As at past meetings, each of the Board members who will be in attendance has been assigned chemicals to review for the purpose of leading the Board's discussion and presenting testing recommendations. The list of assignments follows:

<u>Name</u>	<u>Chemicals</u>
Dr. Norman Breslow	Cinquasia red C.I. Direct Yellow 4 C.I. Disperse Brown 1
Dr. Leila Diamond	Antimony potassium tartrate 2-(2-Butoxyethoxy)ethyl thiocyanate Methylene bis(thiocyanate) -Pinene
Dr. Curtis Harper	Chromic acid Formic acid Linoleic acid Thiophene
Dr. Jerry Hook	Black newsprint inks 2,3-Dichloropropylene Nitromethane 1,2,4,5-Tetrachlorobenzene
Dr. Jeanne Manson	Arsine Luminol Stannous fluoride
Dr. Mortimer Mendelsohn	C.I. Acid Yellow 151 C.I. Basic Red 18 C.I. Direct Red 80
Dr. James Swenberg	1-Nitropyrene 1,3-Dinitropyrene 1,6-Dinitropyrene 1,8-Dinitropyrene 1,3,6-Trinitropyrene 1,3,6,8-Tetranitropyrene

If you wish to receive references for any of the chemicals, please contact me and we will send them by express mail.

If you will be unable to assume the responsibility for discussing the assigned chemicals, please call me at (301) 496-3511 or FTS 496-3511 so that other arrangements can be made.

We look forward to seeing you on August 16-17.

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

Attachments

Addresses: Dr. Mortimer L. Mendelsohn, Chairman
Dr. Norman E. Breslow
Dr. Leila Diamond
Dr. Curtis Harper
Dr. Jerry B. Hook
Dr. Jeanne M. Manson
Dr. Henry C. Pitot
Dr. James A. Swenberg

cc: Dr. David Rall
Dr. Eugene McConnell
Dr. Larry Hart
Dr. James Huff
Dr. Lawrence Fishbein
Ms. Florence Jordan
Dr. Bernard Schwetz
Dr. Raymond Tennant
Dr. William Kluwe

Table 1

Summary Data on Chemicals Reviewed by the NTP Chemical Evaluation Committee on May 31, 1983

Chemical CAS No.	Nominating Source	Production (lbs)	Worker Exposure	NTP Status	Other	Testing Recommendation (Priority)	Chemical Selection Principles	Remarks
1) Antimony potassium tartrate 28300-74-5	NCI	10 ⁵ -10 ⁶ 3.1x10 ⁵ (imports) (1977)	3,554 workers potentially exposed (NOHS)	--	--	Subchronic study, with emphasis on identifying tar- get organs such as liver, bladder, and heart (Moderate)	6	-Past usage in U.S., present usage in other countries -Investigate in animal model pos- sible relationship between use of drug and higher rate of bladder cancer in Egypt
2) 2-(2-Butoxy- ethoxy)ethyl thiocyanate 112-56-1	NCI	2x10 ⁶ (1983)	88,167 workers potentially exposed (NOHS)	Sel. for <u>Salm.</u> assay	--	- <u>Salm.</u> assay [also perform <u>Salm.</u> assay on metabolite 2- (2-butoxyethoxy) ethyl mercaptan] -Subchronic study including sperm morphology and vaginal cytology assays -Short-term in vivo reproductive toxic- ity assay (Moderate)	3	-Potential for expos- ure from pesticidal use -Reproductive effects testing recommended because of struc- tural relationship to cellosolves -Evaluate for car- cinogenicity testing following receipt of all data
3) Methylene bis (thiocyanate) 6317-18-6	NCI	>10 ⁴ (1978)	1,807 workers potentially exposed (NOHS).	Sel. for <u>Salm.</u> assay	--	- <u>Salm.</u> assay -Chemical disposition study -Subchronic study (Moderate)	3	-Interest in structure -Potential for exposure

Chemical CAS No.	Nominating Source	Production (lbs)	Worker Exposure	NTP Status	Other	Testing Recommendation (Priority)	Chemical Selection Principles	Remarks
4) p-Chloro- α, α, α - trifluoro- toluene 98-56-5	NCI	10^7 - 5×10^7 1.5×10^6 (imports) (1977)	20 workers exposed (NOHS)	Neg. in Salm., as were 4- chloro-3-nitro- α, α, α -trifluoro- toluene and 4-chlor-3,5- dinitro- α, α, α - trifluoroto- luene	-Designated by ITC in 1981 for consider- ation for chronic ef- fects, chemi- cal fate and bioconcentra- tion testing -EPA accepted negotiated testing agree- ment with industry to include muta- genicity and subchronic studies -Found in dumps	Defer until next CEC meeting		Ascertain extent of negotiated testing undertaken by industry as result of designation by Interagency Testing Committee to EPA
5) Chromic acid 13530-68-2	United Auto Workers Union	2×10^7 - 10^8 (1977)	85,749	--	--	Comparative chemical disposition study of chromic acid and sodium dichromate (High)	3,4,8	-Industrial ex- posure -Because of in- creased incidence of pulmonary cancer in rats in study of sodium dichromate administered by intracheal instal- lation, useful to compare chemical disposition of two chemicals

Chemical CAS No.	Nominating Source	Production (lbs)	Worker Exposure	NTP Status	Other	Testing Recommendation (Priority)	Chemical Selection Principles	Remarks
6) 2,3-Dichloro- propylene 78-88-6	NCI	>5x10 ³ (1975-78)	--	-Sel. for <u>Salm.</u> assay, on test in <u>Drosophila</u> -Data on structu- rally related compound; -1,3-dichloro- propene in histopathology phase of gavage bioassay, also pos. in <u>Salm.</u> and selected for <u>Drosophila</u> testing	--	- <u>Salm.</u> assay -Mouse lymphoma assay -In vitro cytogenetics -Subchronic study, possibly for longer than 90 days, to identify target organ toxicities -Carcinogenicity to be performed in tandem with other commercially important chlorinated alkene (High)	3,4	-Pos. in <u>Salm.</u> assay -Structure activity considerations -Examine further toxicologic potential of chlorinated alkenes -Subchronic and carcinogenicity studies should be performed by in- halational or skin painting routes -Suggest NTP staff select other alkene for study
7) Formic acid 64-18-6	NCI	6.9x10 ⁷ 8.2x10 ⁴ (imports) (1979)	533,799 workers potentially exposed	Formaldehyde pos./ weakly pos. in <u>Salm.</u> ; pos., for chromosomal aber- rations and pos./ weakly pos. for sister chromatid exchanges in CHO cells; on test in <u>Drosophila</u> Formamide neg. in <u>Salm.</u>	--	-Inhalational carcino- genicity study -Reproductive effects study (Med.-High)	3,8	-High production -Widespread exposure -Structural rela- tionship to formaldehyde, a rodent carcinogen

Chemical CAS No.	Nominating Source	Production (lbs)	Worker Exposure	NTP Status	Other	Testing Recommendation (Priority)	Chemical Selection Principles	Remarks
8) Linoleic acid 506-21-8	NCI	--	--	Structurally related compound, linoleic acid neg. in <u>Salm.</u>	--	No testing	--	-Refer to NCI for possible entry into program investigat- ing relationship between nutrition and cancer
9) Methyl isobutyl ketone 108-10-1	NCI	1.9x10 ⁸ 2.4x10 ⁶ (imports) (1979)	1,433,813 workers potentially exposed (NOHS)	--	-Designated by EPC for consid- eration for mutagenicity, teratogenicity, chronic effects and epidemiology and testing by in- dustry -IPA accepted renegotiated testing agree- ment to be coordinated by CMA -Subject to TSCA Sections 8(a) and 8(d) report- ing rules -Found in dumps	-Defer until next CEC meeting -Refer to NTP Reproductive and Developmental Toxicology Program for evaluation of reproductive effects testing needs	--	Ascertain progress of industry spon- sored testing of chemical for geno- toxicity subchronic effects and tera- tology

Chemical CAS No.	Nominating Source	Production (lbs)	Worker Exposure	NTP Status	Other	Testing Recommendation (Priority)	Chemical Selection Principles	Remarks
10) Nitromethane 75-52-5	NCI	TSCA inventory data: Amount claimed as confidential, but $>5 \times 10^3$ (1977)	838,491 workers potentially exposed (NOHS)	Neg. in Salm., as were structurally related compounds nitroethane, 1- nitropropane, 1-nitrobutane; tetranitromethane, 2-nitropropane pos. in Salm. Tetranitromethane in chronic phase of inhal. bioassay	-Deferred in- definitely by ITC -Neg. in Salm., pos. in mouse lymphoma with- out activation (NCI)	Carcinogenicity with examination of thyroid for possible toxic effects	3,4,8	-Potential for widespread exposure -Pos. in mouse lymphoma study -Structurally related to the carcinogen 2-nitropropane
11) β -Pinene 127-91-3	NCI	4.9×10^7 (1979) $10^3 \times 10^5$ (imports) (1977)	7,672 workers potentially exposed (NOHS)	--	--	Skin painting tumor promotion assay (Low)	3	-Structurally related to certain tumor promoters -Potential for exposure
12) 1,2,4,5- Tetrachloro- benzene 95-94-3	NCI	$10^7 - 6.2 \times 10^8$ 4×10^4 (imports) (1977)		-Neg. in Salm., as were 1,2,3,4- tetrachlorobenzene and 1,2,3,5-tetra- chlorobenzene -Chlorobenzene, three dichloro benzenes and three trichlorobenzenes also neg. in Salm. -1,2-Dichlorobenzene gavage bioassay complete -1,4-Dichlorobenzene in histopathology phase of gavage assay	-Designated by ITC in 1978 for consider- ation for mut- agenicity, carcinogeni- city, tera- togenicity, other toxic effects, epi- demiology and environmental effects testing as part of chloro- benzenes category -EPA proposed test rule in 1980 -Subject to TSCA Sections 8(a) and 8(d) reporting rules -Found in dumps	-In vivo cytogenetics -Acute neurotoxicity -Carcinogenicity in- cluding sperm morphol- ogy and vaginal cytol- ogy assays in prechronic portion of study -Short-term in vivo reproductive toxicity assay (High)	3,4,8	-Found in waste dumps -Potential for exposure -Structure activity consideration

Chemical CAS No.	Nominating Source	Production (lbs)	Worker Exposure	NTP Status	Other	Testing Recommendation (Priority)	Chemical Selection Principles	Remarks
13) Thiophene 110-02-1	NCI	10 ⁴ -10 ⁵ (Imports) (1977)	62,273 workers potentially exposed (NOHS)	-Neg. in Salm. -Structurally related furan neg. in Salm., in chronic phase of gavage bioassay	-Neg. in Salm., -pos. in mouse lymphoma with and without activation (NCI)	Carcinogenicity (Moderate)	3,4	-Interest in structure -Develop toxicological profile

7/30/84

Table II

Summary Data on Chemicals Reviewed by the NTP Chemical Evaluation Committee on November 2, 1983

Chemical CAS No.	Nominating Source	Production (lbs)	Worker Exposure	NTP Status	Other	Testing Recommendation (Priority)	Chemical Selection Principles	Remarks
1) Arsine 7784-42-1	United Auto Workers Union	10^3 - 1.3×10^4 (1977)	-587 workers ex- posed (est'd) -900,000 workers exposed to arsenic TLV: 0.05 ppm or 0.2 mg/m ³	--	--	Comparative study of chemical disposition of arsine and arsenic trioxide (Low)	3	-Concern as an arsenic compound -Low level exposure to workers
2) Black newsprint inks --	NIOSH	22.5×10^7 - letterpress 1.0×10^8 - offset (1981)	165,000 workers exposed (est'd) PEL: 5 mg/m ³ oil mist	--	--	-Skin painting carcino- genicity of two types of ink and of their petroleum pitch and petroleum oil vehicle components (High) -Chemical analyses of inks and their components to be performed prior to initiation of carcino- genicity studies (High)	4,5,8	-Generate animal data for comparison with epidemiological studies -Continuing worker exposure
3) Cinquasia red 1047-16-1	ITC/EPA	1.2×10^6 (1980)	74,444 workers exposed (est'd)	--	--	Inhalational chemical disposition study (Moderate)	4	-Ascertain if chemical can be absorbed prior to considering it for other toxicological testing -Potential for worker exposure

Chemical CAS No.	Nominating Source	Production (lbs)	Worker Exposure	NTP Status	Other	Testing Recommendation (Priority)	Chemical Selection Principles	Remarks
4) C.I. Acid Yellow 151 12715-61-6	NCI	7.2x105 (1983)	--	--	Neg. in Salm. with and without activation; on test in mouse lymphoma assay (NCI)	No testing	-	-Low exposure -Chemical structure of low interest, particularly when compared to other azo dye nominations
5) C.I. Basic Red 18 14097-03-1	NCI	9.0x103 (1983)	1684 workers exposed (est'd)	--	Pos. in Salm. with and without activation; on test in mouse lymphoma assay (NCI)	Derma. chemical disposition study (Moderate)	3	-Pos. in Salm. assay -Interest in chemical structure
6) C.I. Direct Red 80 2610-10-8	NCI	2.8x105 (1983)	109 workers exposed (est'd)	--	Neg. in Salm. with and without activation; on test in mouse lymphoma assay (NCI)	No testing	-	-Low exposure -Little interest in chemical structure
7) C.I. Direct Yellow 4 3051-11-4	NCI	3.3x105 (1983)	187 workers exposed (est'd)	--	Neg. in Salm. with and without activation; on test in mouse lymphoma assay (NCI)	-Chemical disposition study -Carcinogenicity study if absorption demonstrated (Moderate)	3	Structure activity considerations
8) C.I. Disperse Brown 1 23355-64-8	NCI	1.2x104 (1983)	1092 workers exposed (est'd)	--	Pos. in Salm. with and without activation; on test in mouse lymphoma assay (NCI)	No testing	-	Not as interesting a candidate for testing as C.I. Basic Red 18, which has been recommended for testing

Chemical CAS No.	Nominating Source	Production (lbs)	Worker Exposure	NTP Status	Other	Testing Recommendation (Priority)	Chemical Selection Principles	Remarks
9) D&C Yellow No. 11 8003-22-3	FDA	1.05x10 ⁵ * (1983)		--	--	-Salmonella assay -Dermal chemical disposition study -Oral carcinogenicity study (Moderate-Low)	3,6	-Regulatory interest as contaminant in D&C Yellow 10, which is under review by FDA for permanent listing as color additive -Interest in quinoline structure
10) Lumino1 521-31-3	NIOSH	0 in public TSCA Inventory (1977)		--	--	-Salmonella assay -Dermal chemical disposition study (Low)	3	-Lack of toxicity data -Exposure to small segment of population -Structure activity considerations
11) Malathion 121-75-5	Dr. A. Whittemore Stanford Univ.	1.6x10 ⁷ (1981)	106,700 workers expose (est.g) TLV: 10 mg/m ³	-Neg. for carcinogenicity in feeding studies in rats and mice -Neg. in Salm. -Pos. for chromosomal aberrations and	--	Defer pending receipt of reproductive studies from EPA	-	-Major agricultural commodity chemical -Under review by EPA for registration standard -Significant toxicological studies,

*Production reported by U.S. member companies of Dyes Environmental and Toxicological Organization, Inc. (DETO)/U.S. Operating Committee (USOC) of the Ecological and Toxicological Association of the Dyestuffs Manufacturing Industry (ETAD).

Chemical CAS No.	Nominating Source	Production (lbs)	Worker Exposure	NTP Status	Other	Recommendation (Priority)	Selection Principles	Remarks
12) Picloram 1918-02-1	Dept. of Health, State of West Virginia; Ms. E. Clark, Research Associates, Ltd., Exton, PA		2036 workers exposed (est'd) TLV: 10 mg/m ³	-Equivocal evidence of carcinogenicity in female rats in feeding study in rats and mice -Neg. in <u>Salm.</u> -Neg. in <u>Drosophila</u> for sex-linked re- cessive lethal mutations -Pos. for chromo- somal aberrations and sister chroma- tid exchanges in CHO cells	--	Defer pending receipt of data from EPA	-	-Major agricultural commodity chemical -Registration stan- dard to be published in early 1984 -Industry long-term feeding study under- way in rats; other toxicology studies also undertaken
13) Stannous fluoride 7783-47-3	Mr. P. Mock W'nepeg, Canada	Listed in public TSCA inventory (1977)	1433 workers exposed (est'd) TLV: 2 mg/m ³	Data on related compounds: <u>Stannous chloride:</u> -Neg. for carcino- genicity in feeding study in rats and mice -Neg. in <u>Salmonella</u> <u>Sodium fluoride:</u> -Chronic phase of drinking water study in rats and mice -Neg. in <u>Salmonella</u> -Sel. for mouse lymphoma	--	No testing	-	-Stannous chloride negative in NTP carcinogenicity testing; sodium fluoride presently under test for carcinogenicity by NTP

7/30/84

With this notice, the NTP solicits public comment on the 13 chemicals listed herein.

For Further Information and Submission of Comments, Contact

Dr. Dorothy Center, Assistant to the Director, National Toxicology Program, Room 2B55, Building 31, National Institutes of Health, Bethesda, Maryland 20205. (301) 498-3511.

Supplementary Information

As part of the chemical selection process of the National Toxicology Program, nominated chemicals which have been reviewed by the NTP Chemical Evaluation Committee (CEC) are published with request for comment in the *Federal Register* and *NTP Technical Bulletin*. This encourages outside individuals and groups to participate in the NTP evaluation process thereby helping the NTP to make better informed decisions as to whether to select, reject or defer chemicals for testing.

Relevant comments and data submitted in response to this request are reviewed and summarized by NTP technical staff and then forwarded to the NTP Board of Scientific Counselors for its evaluation of the nominated chemicals and to the NTP Executive Committee for its decision-making about testing. The NTP chemical selection process is summarized in the *Federal Register*, April 14, 1991 (46 FR 21818), and also in the NTP FY 1993 Annual Plan, pages 213-215.

On May 31, 1993, the CEC evaluated 13 chemicals nominated to the NTP for toxicological testing. The table below lists each chemical, its Chemical Abstracts Service (CAS) registry number, and the types of testing recommended by the CEC.

Chemical	CAS No.	Committee Recommendation
1. Arsenic	20000-74-6	Subchronic study, with emphasis on identifying target organs
2. 2,2'-biphenyl	112-58-1	Subchronic study (also on embryonic/foetal mortality)
3. Methylene diisocyanate	6917-18-6	Subchronic exposure study Chemical disposition study Subchronic study Deter unit test CEC meeting (See below)
4. p-Chloro-aniline	98-58-6	Subchronic study Deter unit test CEC meeting (See below)
5. Chronic fluoride	13530-68-2	Comparative chemical disposition study of chronic acid and sodium fluoride

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Advisory Board Subcommittee on Activities and Agenda; Meeting

Pursuant to Pub. L. 92-463, notice is hereby given of the meeting of the National Cancer Advisory Board

Subcommittee on Activities and Agenda, National Cancer Institute, August 11, 1993, East Conference Room, Fred Hutchinson Cancer Research Center, 1124 Columbia Street, Seattle, Washington 98104. The entire meeting will be open to the public from 2:00 p.m. to adjournment, to review administrative details and plan the agenda and activities for the National Cancer Advisory Board and its meeting for October 1993. Attendance by the public will be limited to space available.

Mrs. Winifred Lumsden, the Committee Management Officer, National Cancer Institute, Building 31, Room 10A06, National Institutes of Health, Bethesda, Maryland 20205 (301) 498-5708) will provide summaries of the meeting and rosters of committee members, upon request.

Mrs. Barbara S. Bynum, Executive Secretary, Subcommittee on Activities and Agenda, National Cancer Institute, Board, National Cancer Institute, National Institutes of Health, Building 31, Room 10A03, Bethesda, Maryland 20205, (301) 498-5147, will furnish substantive program information.

Dated: July 18, 1993.

Betty J. Kaveridge,
Committee Management Officer, NIH

(PR Doc. 93-3008 Filed 7-23-93; 8:45 am)

BILLING CODE 4798-01-0

Dated: July 20, 1993.

Francis C. Henney,
Secretary.

(PR Doc. 93-3008 Filed 7-23-93; 8:45 am)

BILLING CODE 4798-01-0

Dated: July 20, 1993.

Francis C. Henney,
Secretary.

(PR Doc. 93-3008 Filed 7-23-93; 8:45 am)

BILLING CODE 4798-01-0

Dated: July 20, 1993.

Francis C. Henney,
Secretary.

(PR Doc. 93-3008 Filed 7-23-93; 8:45 am)

BILLING CODE 4798-01-0

On July 12, 1993, Orbe Freight Service, 5499 N.W. 72nd Avenue, Miami, FL 33166 requested the Commission to revoke its Independent Ocean Freight Forwarder License No. 2502-R.

Therefore, by virtue of authority vested in me by the Federal Maritime Commission as set forth in Manual of Order, Commission Order No. 1 (Revised), § 10.01(e) dated November 12, 1981.

It is ordered, that Independent Ocean Freight Forwarder License No. 2502-R issued to Orbe Freight Service, be revoked effective July 12, 1993, without prejudice to reapplication for a license in the future.

It is further ordered, that a copy of this Order be published in the Federal Register and served upon Orbe Freight Service.

Robert M. Skell,
Deputy Director, Bureau of Certification & Licensing

(PR Doc. 93-3008 Filed 7-23-93; 8:45 am)

BILLING CODE 4798-01-0

Dated: July 20, 1993.

Francis C. Henney,
Secretary.

(PR Doc. 93-3008 Filed 7-23-93; 8:45 am)

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Francis C. Henney,
Secretary.

(PR Doc. 93-3008 Filed 7-23-93; 8:45 am)

BILLING CODE 4798-01-0

Public Health Service

National Toxicology Program; Chemicals (13) Nominated for Toxicological Testing; Request for Comments

Summary

On May 31, 1993, the Chemical Evaluation Committee (CEC) of the National Toxicology Program (NTP) met to review 13 chemicals nominated for toxicological testing and to recommend the types of testing to be performed.

Chemical	CAS No.	Committee recommendation
6. 2,2-Dichloropropane.	75-68-6	—Salmonella assay —Mouse lymphoma assay —In vitro cytogenetics —Subchronic study, possibly for longer than 90 days, to identify target organ toxicities. —Carcinogenicity to be performed in tandem with another commercially important chlorinated alkene.
7. Formic acid	64-18-6	—Preliminary carcinogenicity study—Reproductive effects study.
8. Linoleic acid.	808-21-8	No testing.
9. Methyl isobutyl ketone.	108-10-1	Defer until next CEC meeting.
10. Nitromethane.	75-62-6	Carcinogenicity with examination of thyroid for possible toxic effects.
11. β -Pinene	147-81-3	Skin painting tumor promotion assay.
12. 1,2,4,5-Tetrachlorobenzene.	85-64-3	—In vivo cytogenetics —Acute neurotoxicity —Carcinogenicity including sperm morphology and vaginal cytology assays in subchronic portion of study —Short-term in vivo reproductive toxicity assay.
13. Thiophene	110-02-1	Carcinogenicity.

The chemicals p-chloro-a,a,a-trifluorotoluene and methyl isobutyl ketone had previously been designated as priority chemicals by the Interagency Testing Committee (ITC) to the Administrator, Environmental Protection Agency (EPA), for consideration for industry-required testing. p-Chloro-a,a,a-trifluorotoluene was deferred to ascertain the extent of testing undertaken by industry following its designation by the ITC. Methyl isobutyl ketone was deferred to determine the progress of industry-sponsored testing of the chemical for genotoxicity, subchronic effects and teratology undertaken following negotiations between EPA and the affected industries. Both chemicals will be re-evaluated at the next CEC meeting.

The chemicals nitromethane, 1,2,4,5-tetrachlorobenzene and thiophene were previously selected by the NTP for genotoxicity testing in the *Salmonella* assay. All three chemicals were negative in four strains of *Salmonella* both with and without activation. None of the other ten chemicals were previously selected for any type of toxicological testing by the NTP.

Interested parties are requested to submit pertinent information. The following types of data are of particular relevance:

(1) Completed, ongoing and/or planned toxicological testing in the private sector including detailed experimental protocols and, in the case of completed studies, resultant data.

(2) Modes of production, present production levels, and occupational exposure potential.

(3) Uses and resulting exposure levels, where known.

(4) Results of toxicological studies for structurally related compounds.

Please submit all information in writing by August 24, 1983. Any submissions received after the above date will be accepted and utilized where possible.

Dated: July 12, 1983.

David P. Rall,

Director, National Toxicology Program.

(FR Doc. 83-19884 Filed 7-22-83; 8:45 am)

BILLING CODE 4140-01-46

National Toxicology Program; Availability of Carcinogenesis Studies of Allyl Isovalerate

The HHS' National Toxicology Program today announces the availability of carcinogenesis studies of allyl isovalerate, a synthetic fragrance and flavoring ingredient which may be found in soap, detergents, creams, perfumes, non-alcoholic beverages, ice cream, candy, baked goods, gelatins, and puddings.

Allyl isovalerate was administered in corn oil by gavage to F344/N rats and B6C3F₁ mice at doses of 0, 81, and 62 mg/kg body weight. Under the conditions of these studies, allyl isovalerate was carcinogenic for F344/N rats and B6C3F₁ mice, causing increased incidences of hematopoietic system neoplasms (mononuclear-cell leukemia in male rats and lymphoma in female mice).

Carcinogenesis Studies of Allyl Isovalerate in F344/N Rats and B6C3F₁ Mice (Gavage Studies) (T.R. 253) are available without charge by writing to: NTP Public Information Office, M.D. B2-04, P.O. Box 12233, Research Triangle Park, NC 27709. Telephone: (919) 541-3391. FTS: 629-3391.

Dated: July 15, 1983.

David P. Rall,

Director.

(FR Doc. 83-19883 Filed 7-22-83; 8:45 am)

BILLING CODE 4140-01-46

Privacy Act of 1974; Establishment of System of Records

AGENCY: Public Health Service, Department of Health and Human Services.

ACTION: Notification of establishment of a new Privacy Act system of records: 09-25-0153, "Biomedical Research: Records of Subjects in Biomedical and

Behavioral Studies of Child Health and Human Development, HHS/NIH/NICHD."

SUMMARY: In accordance with the requirements of the Privacy Act, the Public Health Service (PHS) is publishing notice of a proposal to establish a new Privacy Act system of records 09-25-0153, "Biomedical Research: Records of Subjects in Biomedical and Behavioral Studies of Child Health and Human Development, HHS/NIH/NICHD." This system will be used to support research on maternal health, child health, and human development. We are also proposing routine uses for this new system.

PHS invites interested persons to submit comments on the proposed routine uses on or before August 24, 1983.

DATE: PHS has sent a Report of New System to the Congress and to the Office Management and Budget on June 1, 1983. The system of records will be effective 60 days from the date submitted to OMB unless PHS receives comments on the routine uses which would result in a contrary determination.

ADDRESS: Comments should be addressed to the National Institutes of Health (NIH) Privacy Act Coordinator at the address listed below. Comments received will be available for inspection during office hours in Room 3B03, Building 31, at that address.

FOR FURTHER INFORMATION CONTACT: Dr. Kenneth Thibodeau, NIH Privacy Act Coordinator, Building 31, Room 3B07, 9000 Rockville Pike, Bethesda, MD 20205, or call 301-496-4606. This is not a toll-free number.

SUPPLEMENTARY INFORMATION: NIH proposes to establish a new system of record: 09-25-0153, "Biomedical Research: Records of Subjects in Biomedical and Behavioral Studies of Child Health and Human Development, HHS/NIH/NICHD." This proposed umbrella system of records will comprise records generated in research projects supported by the National Institute of Child Health and Human Development (NICHD) in fulfilling its congressionally mandated responsibility for biomedical and behavioral research on maternal health, child health, and human development.

Such research will involve both scientists on the staff of NICHD and other scientists working under contracts awarded competitively by NICHD. NICHD may award research contracts to hospitals and clinics, to educational and research institutions, to Federal,

provide an agenda and roster of members. Summaries of the meeting may be obtained by contacting Carole A. Frank, Committee Management Office, NIADDK, National Institutes of Health, Room 9A46, Building 31, Bethesda, Maryland 20205, (301) 496-6917.

Dated: January 4, 1984.

Betty J. Beveridge,
NIH Committee Management Officer.

[FR Doc. 84-408 Filed 1-9-84; 8:45 am]
BILLING CODE 4140-01-M

Clinical Applications and Prevention Advisory Committee; Meeting

Pursuant to Pub. L. 92-463, notice is hereby given of the meeting of the Clinical Applications and Prevention Advisory Committee, Division of Heart and Vascular Diseases, National Heart, Lung, and Blood Institute, National Institutes of Health, March 21-22, 1984. The meeting will be held in Conference Room B119, Federal Building, 7550 Wisconsin Avenue, Bethesda, Maryland 20205.

This meeting will be open to the public on March 21 from 9:00 a.m. to recess and from 8:30 a.m. to adjournment on March 22 to discuss new initiatives, program policies and issues. Attendance by the public is limited to space available.

Ms. Terry Bellicha, Chief, Public Inquiry Reports Branch, National Heart, Lung, and Blood Institute, Building 31, Room 4A21, National Institutes of Health, Bethesda, Maryland 20205, phone (301) 496-4236, will provide a summary of the meeting and a roster of committee members upon request. Dr. William Friedewald, Executive Secretary of the Committee, Federal Building, Room 212 Bethesda, Maryland 20205, phone (301) 496-2533, will furnish substantive program information.

(Catalog of Federal Domestic Assistance Program No. 13.837, Heart and Vascular Diseases Research, National Institutes of Health.)

Dated: January 4, 1984.

Betty J. Beveridge,
NIH Committee Management Officer.

[FR Doc. 84-408 Filed 1-9-84; 8:45 am]
BILLING CODE 4140-01-M

Biomedical Research Support Subcommittee of the General Research Support Review Committee; meeting

Pursuant to Pub. L. 92-463, notice is hereby given of the meeting of the Biomedical Research Support Subcommittee of the General Research

Support Review Committee, Division of Research Resources, National Institutes of Health, February 24, 1984, Building 31C, Conference Room 8, Bethesda, Maryland 20205, from 9:30 a.m. to adjournment.

The meeting will be open to the public on February 24, from 9:30 a.m. to adjournment to discuss program policies and planning for the Biomedical Research Support Grant Program, the Biomedical Research Support Shared Instrumentation Grant Program and the Minority High School Student Research Apprentice Program. Attendance by the public will be limited to space available.

Mr. James Augustine, Information Officer, Division of Research Resources, Room 5B10, Building 31, National Institutes of Health, Bethesda, Maryland 20205, (301) 496-5545, will provide summaries of the meeting and rosters of the Committee members. Dr. Marjorie A. Tingle, Executive Secretary, Biomedical Research Support Subcommittee of the General Research Support Review Committee will furnish substantive program information and will receive any comments pertaining to this announcement.

(Catalogue of Federal Domestic Assistance Program No. 13.337, Biomedical Research Support, National Institutes of Health)

Dated: January 4, 1984.

Betty J. Beveridge,
Committee Management Officer, National Institutes of Health.

[FR Doc. 84-407 Filed 1-9-84; 8:45 am]
BILLING CODE 4140-01-M

Pulmonary Diseases Advisory Committee; Meeting

Pursuant to Pub. L. 92-463, notice is hereby given of the meeting of the Pulmonary Diseases Advisory Committee, National Heart, Lung, and Blood Institute, on February 16-17, 1984 at the National Institutes of Health, Building 31, Conference Room 7, 9000 Rockville Pike, Bethesda, Maryland 20205.

The entire meeting, from 8:30 a.m. on February 16 to adjournment on February 17, will be open to the public. The Committee will discuss the plans for fiscal year 1985. Attendance by the public will be limited to the space available.

Ms. Terry Bellicha, Chief, Public Inquiry Reports Branch, National Heart, Lung, and Blood Institute, Building 31, Room 4A-21, National Institutes of Health, Bethesda, Maryland 20205, phone (301) 496-4236, will provide summaries of the meeting and rosters of the Committee members.

Dr. Suzanne S. Hurd, Acting Executive Secretary of the Committee, Westwood Building, Room 6A16, National Institutes of Health, Bethesda, Maryland 20205, phone (301) 496-7208, will furnish substantive program information.

(Catalog of Federal Domestic Assistance Program No. 13.838, Lung Diseases Research, National Institutes of Health)

Dated: January 4, 1984.

Betty J. Beveridge,
Committee Management Officer.

[FR Doc. 84-408 Filed 1-9-84; 8:45 am]
BILLING CODE 4140-01-M

Public Health Service

National Toxicology Program; Chemicals (13) Nominated for Toxicological Testing; Request for Comments

SUMMARY: On November 8, 1983, the Chemical Evaluation Committee of the National Toxicology Program (NTP) met to review 12 chemicals and one group of substances nominated for toxicology testing and to recommend the types of testing to be performed. With this notice, the NTP solicits public comment on the 13 chemicals listed herein.

For Further Information and Submission on Comments, Contact: Dr. Dorothy Canter, Assistant to the Director, National Toxicology Program, Room 2B55, Building 31, National Institutes of Health, Bethesda, Maryland 20205, (301) 496-3511.

SUPPLEMENTARY INFORMATION: As part of the chemical selection process of the National Toxicology Program, nominated chemicals which have been reviewed by the NTP Chemical Evaluation Committee (CEC) are published with request for comment in the *Federal Register* and *NTP Technical Bulletin*. This encourages outside individuals and groups to participate in the NTP chemical evaluation process thereby helping the NTP to make better informed decisions as to whether to select, reject or defer chemicals for testing.

Relevant comments and data submitted in response to this request are reviewed and summarized by NTP technical staff and then forwarded to the NTP Board of Scientific Counselors for its evaluation of the nominated chemicals and to the NTP Executive Committee for its decision-making about testing. The NTP chemical selection process is summarized in the *Federal Register*, April 14, 1981 (46 FR 21818), and also in the NTP FY 1983 Annual Plan, pages 213-215.

On November 8, 1983, the CEC evaluated 12 chemicals and one group of substances nominated to the NTP for toxicological testing. The table below lists the chemicals and the group of

substances, the Chemical Abstracts Service (CAS) registry numbers, where applicable, and the types of testing recommended by the CEC.

Chemical	CAS No.	Committee recommendation
1. Arane	7784-42-1	Comparative study of chemical disposition of arane and arsenic trioxide.
2. Black newsprint inks		Skin painting carcinogenicity of two types of ink and of their petroleum pitch and petroleum oil vehicle components. Chemical analyses of inks and their components to be performed prior to initiation of carcinogenicity studies.
3. Cinquase red	1047-18-1	Inhalational chemical disposition study.
4. C.I. Acid Yellow 151	12715-81-6	No testing.
5. C.I. Basic Red 18	14097-03-1	Dermal chemical disposition study.
6. C.I. Direct Red 80	2610-10-8	No testing.
7. C.I. Direct Yellow 4	3051-11-4	Chemical disposition study. Carcinogenicity study if absorption demonstrated.
8. C.I. Disperse Brown 1	23355-84-4	No testing.
9. D&C Yellow No. 11	8003-22-3	Salmonella assay. Dermal chemical disposition study. Oral carcinogenicity study.
10. Luminal	521-31-8	Salmonella assay. Dermal chemical disposition study.
11. Malathion	121-75-5	Defer pending receipt of reproductive studies from EPA.
12. Picloram	1916-02-1	Defer pending receipt of data from EPA.
13. Stannous fluoride	7788-47-3	No testing.

The chemicals malathion and picloram were previously tested by the NTP in various toxicology test systems. Malathion was negative for carcinogenicity in feeding studies in male and female rats and mice. The chemical was also negative in the *Salmonella* microsomal assay when tested in four strains of the bacteria both with and without metabolic activation. Malathion was positive for both chromosomal aberrations and sister chromatid exchanges when tested in cultured Chinese hamster ovary cells.

In an NCI/NTP feeding study of picloram in male and female rats and mice, an increased incidence of neoplastic nodules of the liver in female rats was associated with treatment with picloram. No tumors were observed in male or female mice or male rats at incidences that could be significantly associated with treatment. On the basis of these results, it was judged that there is equivocal evidence of carcinogenicity for picloram. The chemical was negative in the *Salmonella* assay in all four strains tested both with and without metabolic activation. Picloram did not induce sexlinked recessive lethal mutations when tested in *Drosophila*. It currently is being tested in cultured Chinese hamster ovary cells for its ability to induce chromosomal aberrations and sister chromatid exchanges.

Although stannous fluoride has not previously been selected for testing by the NTP, two related compounds, namely stannous chloride and sodium fluoride, have been. There was no evidence of carcinogenesis when stannous chloride was tested in a feed study in male and female rats and mice.

The chemical was also negative in the *Salmonella* assay in all four strains tested with and without activation. Sodium fluoride is currently being administered in the water to rats and mice in a carcinogenesis study. It was negative in all four strains tested in the *Salmonella* assay but yielded positive results in the L5178Y mouse lymphoma assay.

None of the other chemicals evaluated for testing at the November 8, 1983 meeting have previously been selected by the NTP for any type of toxicological testing.

Interested parties are requested to submit pertinent information. The following types of data are of particular relevance:

(1) Completed, ongoing and/or planned toxicological testing in the private sector including detailed experimental protocols and, in the case of completed studies, resultant data.

(2) Modes of production, present production levels, and occupational exposure potential.

(3) Uses and resulting exposure levels, where known.

(4) Results of toxicological studies of structurally related compounds.

Please submit all information in writing by (thirty days after date of publication). Any submissions received after the above date will be accepted and utilized where possible.

Dated: January 3, 1984.

David P. Rall,
M.D., Ph. D., Director, National Toxicology Program.

[FR Doc 84-406 Filed 1-9-84, 8:45 am]
BILLING CODE 4160-01-M

DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT

Office of the Under Secretary

[Docket No. H-83-1328]

Advisory Committee on Contract Document Reform; Meeting

AGENCY: Department of Housing and Urban Development.

ACTION: Notice of meeting of the Advisory Committee on Contract Document Reform.

SUMMARY: The second meeting of the Committee on Contract Document Reform will be held on January 31, 1984 at 9:30 a.m. in the Under Secretary's Conference Room (10106) at the Department of Housing and Urban Development, 451 7th Street, SW., Washington, D.C. 20410.

The purpose of the meeting is to discuss the Committee members' written comments on the contract documents used in connection with the Department's insured housing programs.

This meeting is open to the public. Any interested persons may attend, appear before, or file statements with the Committee. Oral statements may be made at the meeting at the time and in the manner permitted by the committee.

FOR FURTHER INFORMATION CONTACT: Joseph R. Lupica, Special Assistant to the Secretary, Department of Housing and Urban Development, 451 7th Street, SW., Washington, D.C. 20410. Telephone: (202) 755-5719. [This is not a toll-free number.]

Dated: December 30, 1983.

Philip Abrams,

Under Secretary, Department of Housing and Urban Development.

[FR Doc. 84-473 Filed 1-9-84; 8:45 am]

BILLING CODE 4210-32-M

DEPARTMENT OF THE INTERIOR

Bureau of Indian Affairs

Big Sandy Rancheria, California; Distribution Plan

December 30, 1983.

This notice is published pursuant to the order issued June 13, 1983, in *San Joaquin or Big Sandy Band of Indians, et al. v. Watt, et al.*, Civil No. C-80-3787-MHP, by the United States District Court for the Northern District of California. Plaintiffs and class members in that lawsuit retain their status as Indians under the laws of the United States. The Distribution Plan for the Big Sandy Rancheria which was approved

TESTING RECOMMENDATIONS FOR CHEMICALS REVIEWED BY THE
NTP BOARD OF SCIENTIFIC COUNSELORS
ON AUGUST 16, 1984

<u>Chemical (CAS No.)</u>	<u>Recommendation (Priority)</u>	<u>Remarks</u>
1. Antimony potassium tartate (28300-74-5)	Subchronic study (Low)	-Past usage in U.S. -Current usage in other countries. -Structural interest.
2. Arsine (7784-42-1)	Comparative study of chemical disposition of arsine and arsenic trioxide (Low)	Low occupational exposure
3. Black newsprint inks (No CAS Number)	Skin painting carcinogenicity studies on composite samples of each of the two types of ink, namely offset and letterpress inks. (High)	-Increased level of buccal and pharyngeal cancer among newsprint pressroom workers. -Determine appropriate solvent control.
4. 2-(2-Butoxyethoxy)-ethyl thiocyanate (112-56-1)	- <u>Salmonella</u> assay -Subchronic studies including sperm morphology and vaginal cytology evaluation -Short-term <u>in vivo</u> reproductive toxicity assay (Moderate)	-Potential for exposure -Structural interest -Evaluate for carcinogenicity testing upon completion of short-term studies
5. Chromic acid (13530-68-2)	Comparative chemical disposition study of chromic acid and sodium dichromate (Moderate)	-Occupational exposure -Increased incidence of pulmonary cancer in rats in sodium dichromate intratracheal instillation study
6. Cinquasia red (1047-16-1)	Inhalation chemical disposition studies (Moderate)	Potential for worker exposure.

<u>Chemical (CAS No.)</u>	<u>Recommendation (Priority)</u>	<u>Remarks</u>
7. C.I. Acid Yellow 151 (12715-61-6)	Deferred	((((((((((
8. C.I. Basic Red 18 (14097-03-1)	Deferred	(Further information (requested on rationale (for nomination of the (five dyes as representa- (tives of azo and nitro (dyes class.
9. C.I. Direct Red 80 (2610-10-8)	Deferred	((((((((((
10. C.I. Direct Yellow 4 (3051-11-4)	Deferred	((((((((((
11. C.I. Disperse Brown 1 (23355-64-8)	Deferred	((((((((((
12. 2,3-Dichloropropylene (78-88-6)	-Salmonella assay - <u>Mouse lymphoma, in vitro</u> cytogenetics assays. -Subchronic study -Carcinogenicity to be performed in tandem with another commercially important alkene (Moderate)	-Positive results in Salmonella assay -Structure activity considerations
13. Formic acid (64-18-6)	-Inhalational carcinogeni- city study -Reproductive effects study (Moderate)	-High production and widespread expo- sure. -Structural relation- ship to formaldehyde
14. Linolelaidic acid (506-21-8)	No testing	Refer to NCI for consideration of research on relation- ship between nutrition and cancer.

<u>Chemical (CAS No.)</u>	<u>Recommendation (Priority)</u>	<u>Remarks</u>
15. Luminol (521-31-3)	- <u>Salmonella</u> assay (Moderate)	-Lack of toxicity data -Structural interest -Low exposure
16. Methylene bis (thiocyanate) (6317-18-6)	- <u>Salmonella</u> assay -Chemical disposition study -Subchronic study (Moderate)	-Structural interest -Potential for human exposure
17. Nitromethane (75-52-5)	-Carcinogenicity (Moderate)	-Interest in nitro-alkanes
18. β -Pinene (127-91-3)	Two-stage promotion study. (Moderate)	-Structurally related compounds are tumor promoters. -Potential for human exposure.
19. Stannous fluoride (7783-47-3)	-Genotoxicity tests -Short-term in vivo reproductive toxicity assay. (Moderate)	-Human exposure due to use in dental products
20. 1,2,4,5-Tetrachloro- benzene (95-94-3)	-In vivo cytogenetics -Acute neurotoxicity -Carcinogenicity including sperm morphology and vaginal cytology assays in prechronic portion of study -Short term in vivo reproductive toxicity assay. (High)	-Potential for exposure -Possible substitute for PCBs -Potential for bio-accumulation -Environmental occurrence
21. Thiophene (110-02-1)	-Subchronic study (Moderate) -Carcinogenicity (Low)	-Structural interest -Develop toxicological profile.