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

#### SUMMARY MINUTES

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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:

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 interagency 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 o-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-dibromoantraquinone, CI Vat Blue 1) and reactive (ethyl acrylate, toluene 2,6-diisocyate, 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 in depth 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 extrapulmonary 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 n
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 lipoxygenase 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 immuno-toxic 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. Rail 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 concep: 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 ini-
tiated 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 Univers ty
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 sub-
ject from the Appropriations Committee, House of Representat i

(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. Rail 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.


The meeting was adjourned.
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:

<table>
<thead>
<tr>
<th>Time</th>
<th>Agenda Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:30 a.m. - 10:00 a.m.</td>
<td>Review of Biochemical Toxicology Program</td>
</tr>
<tr>
<td>10:15 a.m. - 12:15 p.m.</td>
<td>Review of Immunotoxicology Program</td>
</tr>
<tr>
<td>1:00 p.m. - 1:15 p.m.</td>
<td>Report of the Director, NTP</td>
</tr>
<tr>
<td>1:15 p.m. - 3:00 p.m.</td>
<td>Final Report to the Board of the Ad Hoc Panel On Chemical Carcinogenesis Testing and Evaluation</td>
</tr>
</tbody>
</table>

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
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 Schweitz, 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
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 Carcinogenesis 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 Disposition, Biochemical Toxicology, and Immunological Toxicology Board and Consultants
NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS

Dr. Norman Breslow
Professor, Department of Biostatistics, SC-32
University of Washington
Seattle, WA  98195

Dr. Jeanne Manson
Associate Director of Developmental Toxicology
Preclinical Research and Development
Smith Kline & French Laboratories, L60
P. O. Box 7929
Philadelphia, PA  19101

Dr. Leila Diamond
Professor
Wistar Institute
36th Street and Spruce
Philadelphia, PA  19104

Dr. Mortimer L. Mendelsohn
Associate Director
Biomedical and Environmental Research
Lawrence Livermore Laboratory
University of California
Livermore, CA  94550

Dr. Curtis Harper
Associate Professor
Department of Pharmacology
School of Medicine
University of North Carolina
Chapel Hill, NC  27514

Dr. Henry Pitot
Director, McArdle Laboratory
Professor of Oncology and Pathology
University of Wisconsin
Madison, WI  53706

Dr. Jerry B. Hook
Vice President
Preclinical Research and Development
Smith Kline & French Laboratories, L60
P. O. Box 7929
Philadelphia, PA  19101

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

Dr. Eric Johnson
Division of Biochemistry
BCR-7
Scripps Clinic and Research Foundation
10666 N. Torrey Pines Road
La Jolla, California 92037

Dr. Thomas A. Gasiewicz
Dept. of Radiation Biology and Biophysics
University of Rochester Medical Center
Rochester, New York 14642

Chemical Disposition

Dr. David J. Jollow
Dept. of Pharmacology
Medical University of South Carolina
Charleston, South Carolina 29425

Dr. John J. Lech
Dept. of Pharmacology and Toxicology
Medical College of Wisconsin
P.O. Box 26509
8701 Watertown Plank Road
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

[Diagram of seating arrangement]

Stage
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, B-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-a,a,a-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.

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:

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

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, 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. Swenben

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>
<thead>
<tr>
<th>Chemical CAS No.</th>
<th>Nominating Source</th>
<th>Production (lbs)</th>
<th>Worker Exposure</th>
<th>NTP Status</th>
<th>Other Principles</th>
<th>Selection Principles</th>
<th>Testing Recommendation</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Antimony potassium tartrate 28300-74-5</td>
<td>NCI</td>
<td>1.05 x 10^6</td>
<td>3,554 workers</td>
<td>--</td>
<td>--</td>
<td>Subchronic study, with emphasis on identifying target organs such as liver, bladder, and heart (Moderate)</td>
<td>6</td>
<td>--Past usage in U.S., present usage in other countries --Investigate in animal model possible relationship between use of drug and higher rate of bladder cancer in Egypt</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.1 x 10^5</td>
<td>potentially exposed (NOHS)</td>
<td></td>
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<tr>
<td>2) 2-(2-Butoxyethoxy)ethyl thiocyanate 112-56-1</td>
<td>NCI</td>
<td>2 x 10^6</td>
<td>88,167 workers</td>
<td>Sel. for Salm. assay</td>
<td>--</td>
<td>Chemical disposition study</td>
<td>3</td>
<td>Potential for exposure from pesticidal use --Reproductive effects testing recommended because of structural relationship to celluloses --Evaluate for carcinogenicity testing following receipt of all data</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1983)</td>
<td>potentially exposed (NOHS)</td>
<td></td>
<td></td>
<td>--Subchronic study including morphological and vaginal cytology assays --Short-term in vivo reproductive toxicity assay (Moderate)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3) Methylene bis (thiocyanate) 6317-18-6</td>
<td>NCI</td>
<td>&gt;10^4</td>
<td>1,807 workers</td>
<td>Sel. for Salm. assay</td>
<td>--</td>
<td>Chemical disposition study</td>
<td>3</td>
<td>Interest in structure --Potential for exposure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1978)</td>
<td>potentially exposed (NOHS)</td>
<td></td>
<td></td>
<td>Subchronic study (Moderate)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemical CAS No.</td>
<td>Nominating Source</td>
<td>Production (lbs)</td>
<td>Worker Exposure</td>
<td>NTP Status</td>
<td>Other Testing Recommendation (Priority)</td>
<td>Chemical Selection Principles Remarks</td>
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<tr>
<td>4) p-Chloro-a,a,a-trifluoro-toluene 98-56-5</td>
<td>NCI</td>
<td>$10^7$-$5\times10^7$</td>
<td>20 workers exposed (NOHS)</td>
<td>Neg. in Salm., as were 4-chloro-3-nitro-a,a,a-trifluoro-toluene and 4-chloro-3,5-dinitro-a,a,a-trifluorotoluene</td>
<td>Defer until next CEC meeting</td>
<td>- Designated by ITC in 1981 for consideration for chronic effects, chemical fate and biocentrination testing - EPA accepted negotiated testing agreement with industry to include mutagenicity and subchronic studies - Found in dumps</td>
<td></td>
<td></td>
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<tr>
<td>5) Chromic acid 13530-68-2</td>
<td>United Auto Workers Union</td>
<td>$2\times10^7$-$10^8$</td>
<td>85,749</td>
<td>--</td>
<td>--</td>
<td>Comparative chemical disposition study of chromic acid and sodium dichromate (High)</td>
<td>3,4,8 - Industrial exposure - Because of increased incidence of pulmonary cancer in rats in study of sodium dichromate administered by intracheal installation, useful to compare chemical disposition of two chemicals</td>
<td></td>
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<tr>
<td>Chemical CAS No.</td>
<td>Nominating Source</td>
<td>Production (lbs)</td>
<td>Worker Exposure</td>
<td>NTP Status</td>
<td>Other</td>
<td>Testing Recommendation (Priority)</td>
<td>Chemical Selection Principles</td>
<td>Remarks</td>
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<tr>
<td>6) 2,3-Dichloro-propylene 78-88-6</td>
<td>NCI</td>
<td>&gt;5x10^3 (1975-78)</td>
<td>--</td>
<td>-Sel. for Salm. assay, on test in Drosophila</td>
<td>-Data on structurally related compound: 1,3-dichloro-propene in histopathology phase of gavage bioassay, also pos. in Salm. and selected for Drosophila testing</td>
<td>-Salm. assay</td>
<td>3,4</td>
<td>-Pos. in Salm. assay</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Mouse lymphoma assay</td>
<td>Structure activity considerations</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>-In vitro cytogenetics</td>
<td>-Examined further toxicologic potential of chlorinated alkenes</td>
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<td></td>
<td></td>
<td>-Subchronic study, possibly for longer than 90 days, to identify target organ toxicities</td>
<td>Subchronic and carcinogenicity studies should be performed by inhalational or skin painting routes</td>
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<td></td>
<td></td>
<td>-Carcinogenicity to be performed in tandem with other commercially important chlorinated alkene (High)</td>
<td>-Suggest NTP staff select other alkene for study</td>
<td></td>
</tr>
<tr>
<td>7) Formic acid 64-18-6</td>
<td>NCI</td>
<td>6.9x10^7</td>
<td>532,799 workers potentially exposed</td>
<td>Formaldehyde pos./ weakly pos. in Salm.; pos. for chromosomal aberrations and pos./ weakly pos. for sister chromatid exchanges in CHO cells; on test in Drosophila Formaldehyde neg. in Salm.</td>
<td>--</td>
<td>-Inhalational carcinogenicity study</td>
<td>3,8</td>
<td>-High production</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.2x10^4 (Imports)</td>
<td></td>
<td></td>
<td></td>
<td>-Reproductive effects study (Med.-High)</td>
<td>-Widespread exposure</td>
<td></td>
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<td></td>
<td></td>
<td>(1979)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Structural relationship to formaldehyde, a rodent carcinogen</td>
<td></td>
</tr>
<tr>
<td>Chemical CAS No.</td>
<td>Nominating Source</td>
<td>Production (lbs)</td>
<td>Worker Exposure</td>
<td>NTP Status</td>
<td>Other</td>
<td>Testing Recommendation (Priority)</td>
<td>Chemical Selection Principles</td>
<td>Remarks</td>
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<tr>
<td>8) Linolelaidic acid 506-21-8</td>
<td>NCI</td>
<td>--</td>
<td>--</td>
<td>Structurally related compound, linoleic acid neg. in Salm.</td>
<td>--</td>
<td>No testing</td>
<td>--</td>
<td>Refer to NCI for possible entry into program investigating relationship between nutrition and cancer</td>
</tr>
<tr>
<td>9) Methyl isobutyl ketone 108-10-1</td>
<td>NCI</td>
<td>1.9x10^8</td>
<td>1,433,013</td>
<td>--</td>
<td>Designated by JC for consideration for mutagenicity, reproductive and developmental toxicology for evaluation of reproductive effects testing by industry</td>
<td>--</td>
<td>Ascertain progress of industry sponsored testing of chemical for genotoxicity subchronic effects and teratology</td>
<td></td>
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<td></td>
<td></td>
<td>2.4x10^6</td>
<td>workers</td>
<td></td>
<td></td>
<td>-Refer to NTP testing agreement to be coordinated by CMA</td>
<td></td>
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</tr>
<tr>
<td>Chemical CAS No.</td>
<td>Nominating Source</td>
<td>Production (lbs)</td>
<td>Worker Exposure</td>
<td>NTP Status</td>
<td>Other</td>
<td>Testing Recommendation (Priority)</td>
<td>Chemical Selection Principles</td>
<td>Remarks</td>
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</tr>
<tr>
<td>10) Nitromethane 75-52-5</td>
<td>NCI</td>
<td>TSCA inventory data: Amount claimed as confidential, but &gt;5x10³ (1977)</td>
<td>838,491 workers potentially exposed (NOHS)</td>
<td>Neg. in Salm., as were structurally related compounds nitroethane, 1-nitropropane, 1-nitrobutane; tetrinitromethane, 2-nitropropane pos. in Salm. Tetrinitromethane in chronic phase of inhal. bioassay</td>
<td>Deferred indefinitely by ITC in 1978</td>
<td>Carcinogenicity with examination of thyroid for -Def. in Salm., possible toxic pos. in mouse effects lymphoma without activation (NCI)</td>
<td>3,4,8</td>
<td>-Potential for widespread exposure -Pos. in mouse lymphoma study -Structurally related to the carcinogen 2-nitropropane</td>
</tr>
<tr>
<td>11) β-Pinene 127-91-3</td>
<td>NCI</td>
<td>4.9x10⁷ (1979)</td>
<td>7,672 workers potentially exposed (NOHS)</td>
<td>--</td>
<td>--</td>
<td>Skin painting tumor promotion assay</td>
<td>3,4,8</td>
<td>-Structurally related to certain tumor promoters -Potential for exposure</td>
</tr>
<tr>
<td>12) 1,2,4,5-Tetrachlorobenzene 95-94-3</td>
<td>NCI</td>
<td>10⁷-6.2x10⁸ 4x10⁴ (imports) (1977)</td>
<td>1,077 workers potentially exposed (NOHS)</td>
<td>Neg. in Salm., as were 1,2,3,4-tetrachlorobenzene and 1,2,3,5-tetrachlorobenzene -Chlorobenzene, three dichlorobenzenes and three trichlorobenzenes also neg. in Salm. -1,2-Dichlorobenzene gavage bioassay complete -1,4-Dichlorobenzene in histopathology phase of gavage assay</td>
<td>Designated by ITC in 1978 for consideration for mutagenicity, carcinogenicity, teratogenicity, other toxic effects, epidemiology and environmental effects testing as part of chlorobenzenes category</td>
<td>In vivo cytogenetics (Low)</td>
<td>3,4,8</td>
<td>-Found in waste dumps -Potential for exposure -Structure activity consideration</td>
</tr>
<tr>
<td>Chemical CAS No.</td>
<td>Nominating Source</td>
<td>Production (lbs)</td>
<td>Worker Exposure</td>
<td>WTP Status</td>
<td>Other</td>
<td>Testing Recommendation (Priority)</td>
<td>Chemical Selection Principles</td>
<td>Remarks</td>
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<tr>
<td>104-105</td>
<td>NCI (Imports)</td>
<td>62,273</td>
<td>-Neg. in Salm.</td>
<td>-Neg. in Salm., Carcinogenicity (Moderate)</td>
<td>3.4</td>
<td>-Interest in structure, -Develop toxicological profile</td>
<td>(1977)</td>
<td></td>
</tr>
<tr>
<td>Chemical CAS No.</td>
<td>Nominating Source</td>
<td>Production (lbs)</td>
<td>Worker Exposure</td>
<td>NTP Status</td>
<td>Other</td>
<td>Testing Recommendation</td>
<td>Chemical Selection Principles</td>
<td>Remarks</td>
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</tr>
<tr>
<td>1) Arsine 7784-42-1</td>
<td>United Auto Workers Union</td>
<td>10^3-1.3x10^4 (1977)</td>
<td>-587 workers exposed (est'd)</td>
<td>--</td>
<td>--</td>
<td>Comparative study of chemical disposition of arsine and arsenic trioxide</td>
<td>3</td>
<td>-Concern as an arsenic compound -Low level exposure to workers</td>
</tr>
<tr>
<td>2) Black newsprint inks NIOSH</td>
<td></td>
<td>22.5x10^7 - letterpress 1.0x10^6 - offset (1981)</td>
<td>165,000 workers exposed (est'd) PEL: 5 mg/m^3 oil mist</td>
<td>--</td>
<td>--</td>
<td>Skin painting carcinogenicity 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 carcinogenicity studies (High)</td>
<td>4,5,8</td>
<td>-Generate animal data for comparison with epidemiological studies -Continuing worker exposure</td>
</tr>
<tr>
<td>3) Cinquasia red 1047-16-1</td>
<td>ITC/EPA</td>
<td>1.2x10^6 (1980)</td>
<td>74,444 workers exposed (est'd)</td>
<td>--</td>
<td>--</td>
<td>Inhalational chemical disposition study (Moderate)</td>
<td>4</td>
<td>-Ascertain if chemical can be absorbed prior to considering it for other toxicological testing -Potential for worker exposure</td>
</tr>
<tr>
<td>Chemical CAS No.</td>
<td>Nominating Source</td>
<td>Production (lbs)</td>
<td>Worker Exposure</td>
<td>NTP Status</td>
<td>Other</td>
<td>Testing Recommendation (Priority)</td>
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</tr>
<tr>
<td>4) C.I. Acid Yellow 151 12715-61-6</td>
<td>NCI</td>
<td>7.2x10^5 (1983)</td>
<td>--</td>
<td>--</td>
<td>Neg. in Salm. with and without activation; on test in mouse lymphoma assay (NCI)</td>
<td>No testing</td>
<td>-Low exposure -Chemical structure of low interest, particularly when compared to other azo dye nominations</td>
<td></td>
</tr>
<tr>
<td>5) C.I. Basic Red 18 14097-03-1</td>
<td>NCI</td>
<td>9.0x10^3 (1983)</td>
<td>1684 workers exposed (est'd)</td>
<td>--</td>
<td>Pos. in Salm. with and without disposition study activation; on test in mouse lymphoma assay (NCI)</td>
<td>3</td>
<td>-Pos. in Salm. assay -Interest in chemical structure</td>
<td></td>
</tr>
<tr>
<td>6) C.I. Direct Red 80 2610-10-8</td>
<td>NCI</td>
<td>2.8x10^5 (1983)</td>
<td>109 workers exposed (est'd)</td>
<td>--</td>
<td>Neg. in Salm. with and without activation; on test in mouse lymphoma assay (NCI)</td>
<td>No testing</td>
<td>-Low exposure -Little interest in chemical structure</td>
<td></td>
</tr>
<tr>
<td>7) C.I. Direct Yellow 4 3051-11-4</td>
<td>NCI</td>
<td>3.3x10^5 (1983)</td>
<td>187 workers exposed (est'd)</td>
<td>--</td>
<td>Neg. in Salm. with and without study activation; on Carcinogenicity study test in mouse if absorption demonstrated lymphoma assay stratified (NCI)</td>
<td>3</td>
<td>Structure activity considerations</td>
<td></td>
</tr>
<tr>
<td>8) C.I. Disperse Brown 1 23355-64-8</td>
<td>NCI</td>
<td>1.2x10^4 (1983)</td>
<td>1092 workers exposed (est'd)</td>
<td>--</td>
<td>Pos. in Salm. with and without activation; on test in mouse lymphoma assay (NCI)</td>
<td>No testing</td>
<td>Not as interesting a candidate for testing as C.I. Basic Red 18, which has been recommended for testing</td>
<td></td>
</tr>
<tr>
<td>Chemical Source</td>
<td>CAS No.</td>
<td>Nominating Source</td>
<td>Production Exposure</td>
<td>Worker Exposure</td>
<td>NTP Status</td>
<td>Other</td>
<td></td>
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</tr>
<tr>
<td>D&amp;C Yellow No. 11</td>
<td>8003-22-3</td>
<td>FDA</td>
<td>1.05x10^5a</td>
<td>--</td>
<td>--</td>
<td>-Salmonella assay, -Dermal chemical disposition study, -Oral carcinogenicity study (Moderate-Low)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luminol 521-31-3</td>
<td></td>
<td>NIOSH</td>
<td>0 in public TSCA inventory (1977)</td>
<td>--</td>
<td>--</td>
<td>-Salmonella assay, -Dermal chemical disposition study (Low)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malathion 121-75-5</td>
<td></td>
<td>Dr. A. Whittemore Stanford Univ.</td>
<td>1.6x10^7 106,700 workers exposed (est'd) TLV: 10 mg/m^3</td>
<td>--</td>
<td>--</td>
<td>Defer pending receipt of reproductive studies from EPA</td>
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</tr>
</tbody>
</table>

*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.

-Lack of toxicity data -Exposure to small segment of population -Structure activity considerations.

-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).
<table>
<thead>
<tr>
<th>Chemical CAS No.</th>
<th>Nominating Source</th>
<th>Production (lbs)</th>
<th>Worker Exposure</th>
<th>NTP Status</th>
<th>Other</th>
<th>Recommendation (Priority)</th>
<th>Selection Principles</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>12) Picloram 1918-02-1</td>
<td>Dept. of Health, State of West Virginia; Ms. E. Clark, Research Associates, Ltd., Exton, PA</td>
<td>2036 workers exposed (est'd)</td>
<td>TLV: 10 mg/m³</td>
<td>--</td>
<td>Equivocal evidence of carcinogenicity in female rats in feeding study in rats and mice; -Neg. in Sal. -Neg. in Drosophila for sex-linked recessive lethal mutations; -Pos. for chromosomal aberrations and sister chromatid exchanges in CHO cells; Defer pending receipt of data from EPA</td>
<td>- Major agricultural commodity chemical - Registration standard to be published in early 1984 - Industry long-term feeding study underway in rats; other toxicology studies also undertaken</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13) Stannous fluoride 7783-47-3</td>
<td>Mr. P. Mock Winnipeg, Canada</td>
<td>Listed in public TSCA inventory (1977)</td>
<td>1433 workers exposed (est'd)</td>
<td>TLV: 2 mg/m³</td>
<td>Data on related compounds: Stannous chloride: -Neg. for carcinogenicity in feeding study in rats and mice -Neg. in Salmonella Sodium fluoride: Chronic phase of drinking water study in rats and mice -Neg. in Salmonella -Sel. for mouse lymphoma</td>
<td>No testing</td>
<td>- Stannous chloride negative in NTP carcinogenicity testing; sodium fluoride presently under test for carcinogenicity by NTP</td>
<td></td>
</tr>
</tbody>
</table>

7/30/84
### National Toxicology Program; Availability of Carcinogenesis Studies of Allyl Isosorbide

The HHS' National Toxicology Program today announces the availability of carcinogenesis studies of allyl isosorbide, 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 isosorbide was administered in corn oil by gavage to F344/N rats and B6C3F1 mice at doses of 0, 51, and 62 mg/kg body weight. Under the conditions of these studies, allyl isosorbide was carcinogenic for F344/N rats and B6C3F1 mice, causing increased incidences of hematopoietic system neoplasms (mononuclear-cell leukemias in male rats and lymphomas in female mice).

<table>
<thead>
<tr>
<th>Chemical</th>
<th>CAS No.</th>
<th>Committee recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allyl isosorbide</td>
<td>76-02-1</td>
<td>Carcinogenecity.</td>
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</table>

**Carcinogenesis Studies of Allyl Isosorbide in F344/N Rats and B6C3F1 Mice (Gavage Studies)**

<table>
<thead>
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<tr>
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</table>

### 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, 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 20892, or call 301-480-6080. This is not a toll-free number.

### Supplementary Information

NIH proposes to establish a new system of records 09-25-0153, "Biomedical Research; Records of Subjects in Biomedical and Behavioral Studies of Child Health and Human Development, 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, State, local agencies, and other organizations.

**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, NIH/NICHD."
provide an agenda and roster of members. Summaries of the meeting may be obtained by contacting Carole A Frank, Committee Management Office, NAADDK, National Institutes of Health, Room 9A48, Building 31, Bethesda, Maryland 20205, (301) 496-0919.

Betty J. Beveridge.
NIH Committee Management Officer.
[FR Doc. 84-406 Filed 1-4-84: 8:30 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, 7500 Wisconsin Avenue, Bethesda, Maryland 20205.

This meeting will be open to the public on March 21 from 9:00 a.m. to 8:30 p.m. 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) 496-4236, will provide a summary of the meeting and a roster of committee members upon request. 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. 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.

[Catalog of Federal Domestic Assistance Program No. 13,337, Biomedical Research Support, National Institutes of Health]

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. Hurst, Acting Executive Secretary of the Committee, Westwood Building, Room 6A18, National Institutes of Health, Bethesda, Maryland 20205, phone (301) 496-7206, will furnish substantive program information.

[Catalog of Federal Domestic Assistance Program No. 13,838, Lung Diseases Research, National Institutes of Health]


Betty J. Beveridge.
Committee Management Officer.
[FR Doc. 84-406 Filed 1-4-84: 8:30 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.
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/microsome assay when tested in four strains of the bacteria 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/microsome assay in all four strains tested both with and without metabolic activation. Picloram did not induce sex-linked recessive lethal mutations when tested in Drosophila. It is currently 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 carcinogenicity when stannous chloride was tested in a feed study in male and female rats and mice. The chemical was also negative in the Salmonella/microsome 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/microsome 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 5, 1984.

David P. Rall,
M.D., Ph. D., Director, National Toxicology Program.
### Chemicals Reviewed by the NTP Board of Scientific Counselors on August 16, 1984

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Recommendation</th>
<th>Remarks</th>
</tr>
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</table>
| Antimony potassium tartate       | Subchronic study (Low)                                                        | - Past usage in U.S.  
- Current usage in other countries.  
- Structural interest. |
| (28300-74-5)                     |                                                                               |                                                                        |
| Arsine                           | Comparative study of chemical disposition of arsine and arsenic trioxide (Low) | Low occupational exposure                                              |
| (7784-42-1)                      |                                                                               |                                                                        |
| Black newsprint inks             | 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 pharangeal cancer among newsprint pressroom workers.  
- Determine appropriate solvent control. |
| (No CAS Number)                  |                                                                               |                                                                        |
| 2-(2-Butoxyethoxy)ethyl thiocyanate | Salmonella assay  
- Subchronic studies including sperm morphology and vaginal cytology evaluation  
- Short-term in vivo reproductive toxicity assay (Moderate) | Potential for exposure  
- Structural interest  
- Evaluate for carcinogenicity testing upon completion of short-term studies |
| (112-56-1)                       |                                                                               |                                                                        |
| Chromic acid                     | 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 |
<p>| (13530-68-2)                     |                                                                               |                                                                        |
| Cinquasia red                    | Inhalation chemical disposition studies (Moderate)                           | Potential for worker exposure.                                        |
| (1047-16-1)                      |                                                                               |                                                                        |</p>
<table>
<thead>
<tr>
<th>Chemical (CAS No.)</th>
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<tbody>
<tr>
<td>7. C.I. Acid Yellow 151 (12715-61-6)</td>
<td>Deferred</td>
<td>(Further information requested on rationale for nomination of the five dyes as representatives of azo and nitro dyes class.</td>
</tr>
<tr>
<td>8. C.I. Basic Red 18 (14097-03-1)</td>
<td>Deferred</td>
<td>(Further information requested on rationale for nomination of the five dyes as representatives of azo and nitro dyes class.</td>
</tr>
<tr>
<td>9. C.I. Direct Red 80 (2610-10-8)</td>
<td>Deferred</td>
<td>(Further information requested on rationale for nomination of the five dyes as representatives of azo and nitro dyes class.</td>
</tr>
<tr>
<td>10. C.I. Direct Yellow 4 (3051-11-4)</td>
<td>Deferred</td>
<td>(Further information requested on rationale for nomination of the five dyes as representatives of azo and nitro dyes class.</td>
</tr>
<tr>
<td>11. C.I. Disperse Brown 1 (23355-64-8)</td>
<td>Deferred</td>
<td>(Further information requested on rationale for nomination of the five dyes as representatives of azo and nitro dyes class.</td>
</tr>
<tr>
<td>12. 2,3-Dichloropropylene (78-88-6)</td>
<td>Salmonella assay</td>
<td>Positive results in Salmonella assay</td>
</tr>
<tr>
<td></td>
<td>Mouse Lymphoma, in vitro</td>
<td>Structure activity considerations</td>
</tr>
<tr>
<td></td>
<td>cytogenetics assays</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subchronic study</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carcinogenicity to be</td>
<td></td>
</tr>
<tr>
<td></td>
<td>performed in tandem with</td>
<td></td>
</tr>
<tr>
<td></td>
<td>another commercially</td>
<td></td>
</tr>
<tr>
<td></td>
<td>important alkene</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Moderate)</td>
<td></td>
</tr>
<tr>
<td>13. Formic acid (64-18-6)</td>
<td>Inhalational carcinogenicity study</td>
<td>High production and widespread exposure.</td>
</tr>
<tr>
<td></td>
<td>Reproductive effects study (Moderate)</td>
<td>Structural relationship to formaldehyde</td>
</tr>
<tr>
<td>14. Linolelaidic acid (506-21-8)</td>
<td>No testing</td>
<td>Refer to NCI for consideration of research on relationship between nutrition and cancer.</td>
</tr>
<tr>
<td>Chemical (CAS No.)</td>
<td>Recommendation (Priority)</td>
<td>Remarks</td>
</tr>
<tr>
<td>-----------------------------</td>
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</tr>
<tr>
<td>15. Luminol (521-31-3)</td>
<td>-Salmonella assay (Moderate)</td>
<td>-Lack of toxicity data</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Structural interest data</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Low exposure</td>
</tr>
<tr>
<td>16. Methylene bis thiocyanate (6317-18-6)</td>
<td>-Salmonella assay</td>
<td>-Structural interest</td>
</tr>
<tr>
<td></td>
<td>-Chemical disposition study</td>
<td>-Potential for human exposure</td>
</tr>
<tr>
<td></td>
<td>-Subchronic study (Moderate)</td>
<td></td>
</tr>
<tr>
<td>17. Nitromethane (75-52-5)</td>
<td>-Carcinogenicity (Moderate)</td>
<td>-Interest in nitroalkanes</td>
</tr>
<tr>
<td>18. β-Pinene (127-91-3)</td>
<td>Two-stage promotion study. (Moderate)</td>
<td>-Structurally related compounds are tumor promoters. -Potential for human exposure.</td>
</tr>
<tr>
<td>19. Stannous fluoride (7783-47-3)</td>
<td>-Genotoxicity tests</td>
<td>-Human exposure due to use in dental products</td>
</tr>
<tr>
<td></td>
<td>-Short-term in vivo reproductive toxicity assay. (Moderate)</td>
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<tr>
<td>20. 1,2,4,5-Tetrachlorobenzene (95-94-3)</td>
<td>-In vivo cytogenetics</td>
<td>-Potential for exposure</td>
</tr>
<tr>
<td></td>
<td>-Acute neurotoxicity</td>
<td>-Possible substitute for PCBs</td>
</tr>
<tr>
<td></td>
<td>-Carcinogenicity including sperm morphology and vaginal cytology assays in prechronic portion of study</td>
<td>-Potential for bioaccumulation</td>
</tr>
<tr>
<td></td>
<td>-Short term in vivo reproductive toxicity assay. (High)</td>
<td>-Environmental occurrence</td>
</tr>
<tr>
<td>21. Thiophene (110-02-1)</td>
<td>-Subchronic study (Moderate)</td>
<td>-Structural interest</td>
</tr>
<tr>
<td></td>
<td>-Carcinogenicity (Low)</td>
<td>-Develop toxicological profile.</td>
</tr>
</tbody>
</table>