75-15-0

NATIONAL TOXICOLOGY PROGRAM

BOARD OF SCIENTIFIC COUNSELORS

May 11, 1993

Summary Minutes

National Toxicology Program
Board of Scientific Counselors
May 11, 1993
Summary Minutes

Contents

SUMMARY MINUTES
NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS MEETING

May 11, 1993

The National Toxicology Program (NTP) Board of Scientific Counselors (the Board) met on May 11, 1993, at the National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina. (Attachment 1: **Federal Register** Meeting Announcement; Attachment 2: Agenda and Roster of Members.) Members of the Board are Drs. Daniel Longnecker (Chairman), Paul Bailey, Arnold Brown, Elaine Faustman, Barbara Hansen, Claude Hughes, Curtis Klaassen, Lawrence Loeb, Fumio Matsumura, Kenneth Reuhl, Ellen Silbergeld, and Peter Working. All members were present except Dr. Working.

I. Report of the Director: Dr. Kenneth Olden, Director, NTP and NIEHS, again thanked the Board for their efforts in conducting the Advisory Review to aid the NTP in better carrying out their mission by providing advice on three issues. He noted that there had been considerable comment by the public on the Board's recommendations and on other aspects of the Program in public meetings and in writing. Dr. Olden said there was support expressed for more testing and for doing more mechanistic studies. He said there was a larger number of respondents who said we needed to do both, and there were others who would like to help us find the resources necessary. He said he has talked to persons in labor, industry and other sectors as well as to his predecessor as Director, Dr. David Rall, and they all expressed support for getting more resources.

Dr. Olden commented on the new format and monthly publication schedule for **Environmental Health Perspectives (EHP)** noting that the first volume was released on Earth Day, and will provide a source of information for individuals interested in the environment. He asked for input from the Board as well as submission of their letters and articles. There will be a report on the Advisory Review recommendations in an upcoming issue.

During the meeting, Dr. Olden presented certificates and acknowledged the contributions of retiring members of the Board, Dr. Longnecker and Dr. Silbergeld. In addition to serving as Chair, Dr. Longnecker had served on the Technical Reports Review Subcommittee as had Dr. Silbergeld.

II. National Toxicology Partnership: Dr. Olden reported on a meeting held March 11 on the NIH campus in Bethesda, Maryland, where he continued to seek broad-based input into planning and priority setting for the Program as he met with more than 60 representatives of government (Federal, state and county), industry, labor, academia, environmental organizations, local citizens groups, and Congressional staff. The discussion focused on three topics: how to determine research and testing priorities; how better to communicate research and testing results to the public; and what kinds of partnerships are possible and can be developed among the participants. He said we hoped to have subcommittees to work on fleshing out the three issues and making recommendations to bring back to the larger group. We will be seeking advice from groups like the Board and toxicology groups. In view of the national deficit, large budgetary increases are unlikely so the Program needs help in setting priorities and making tough choices. With only a slight increase in the testing line in the budget, we will not be able to increase test starts above current levels. Discussion: In response to questions from the Board, Dr. Olden said he thought a compelling case could be made for more resources to enable increasing the numbers of tests and he hoped the constituencies developed at the partnerships

meeting would give us more advocates. He said the experimental designs would reflect increased emphasis on endpoints of disease other than cancer. Dr. Richard Griesemer, NIEHS and NTP Deputy Director, noted that the testing line (R&D) covered many other types of tests than just carcinogenesis studies and was also applied to methods development and validation and related activities. Dr. Bernard Schwetz, NIEHS, elaborated by reporting that in addition to 8 to 10 two year study starts, there are double that number of chemicals in prechronic studies, about 50 or more per year in genotoxicity assays, 10-15 each in teratology and reproductive toxicity evaluations, 10-12 assayed for immunotoxic effects, and 15-20 in chemical disposition studies. In response to a question from Dr. Hughes about interagency coordination, Dr. Olden commented that through meetings of the NTP Executive Committee and other means such as an annual interagency 'summit' meeting, we managed to have effective communications with the other relevant agencies.

III. Update on Activities of the Technical Reports Review Subcommittee: Dr. Gary Boorman, ETP, NIEHS, said the Subcommittee would be reviewing the draft Technical Report of the extensive studies on ozone at their meeting November 16-17, 1993. Most of the first day will be devoted to presenting findings from extensive mechanistic studies performed either inhouse or by investigators around the country under the direction of the Health Effects Institute (HEI) examining effects of ozone on pulmonary function, structure and morphometry, and evaluating biochemical markers. Animal use was optimized by adding additional animals to the 20, 24 and 30-month studies. The draft NTP Technical Report, which also includes studies of co-carcinogenicity, will be peer reviewed following these presentations. The Board was given a printout detailing the conclusions for the draft Reports peer reviewed at the Subcommittee meeting of December 1, 1992, and giving information on the Reports to be reviewed on June 22, 1993. Discussion: Dr. Bailey inquired about the current review process for the draft Reports of short-term toxicity studies. Dr. Schwetz responded that for the most part these reports would be reviewed by mail enabling use of *ad hoc* reviewers with special expertise for a particular toxic endpoint or chemical class. Results would be summarized for the full Subcommittee and, on occasion, a Report still would be brought to a meeting for review.

IV. Advisory Review Report and Program Response—Update: Dr. Schwetz summarized the events subsequent to the Board review in April 1992, publication of their report in the **Federal Register** in July 1992, and receipt by the Program of responses to the report and its recommendations. He noted the presentation of the draft NTP staff response to the report and public comments to the Board on October 27 followed by publication of the response in the **Federal Register** in December. The majority of public comments focused on three issues: (1) selection of the MTD; (2) better use of mechanistic data; and (3) a proposed need to incorporate more mechanistic data into the Annual Report on Carcinogens. Dr. Schwetz reported that he and Dr. Longnecker had discussed the report and response with the NIEHS Advisory Council in January, and on January 28, the NTP Executive Committee had discussed and accepted the staff response. Dr. J. Donald Millar, Director, NIOSH, and retiring Chair of the Executive Committee, was unable to come to the Board meeting as planned so Dr. Schwetz shared some of Dr. Millar's thoughts with the Board. He said that Dr. Millar: (1) wanted to note that the Committee recognized and appreciated the extensive review performed by the Board; (2) commented that the reviewers did not seem to be cognizant that the NTP was an interagency program, i.e., the roles of NIOSH and NCTR were not fully recognized; and (3) emphasized that the Executive Committee in particular agreed with recommendations in the report that there needed to be incorporation of more mechanistic studies into experimental design to aid in risk assessment, there should be more evaluation of alternative test systems, emphasis should be increased on looking at toxic endpoints other than cancer, and finally, nominations should be sought from a wider spectrum of society.

V. Summary of Studies Planned, Ongoing, or Completed—By Endpoint: Dr. Errol Zeiger, NIEHS, said that beginning with the current meeting, the Board would receive a status report at each meeting of chemicals on study, studies completed since the last meeting, and studies planned. This listing will be separated by toxic endpoint, although this first time, carcinogenicity studies were not separated from short-term toxicity studies. Discussion: Dr. Silbergeld noted the listing of "Organ Systems Toxicity" under Completed Studies and asked that "Reproductive Assessment" be defined. Dr. Zeiger said that future listings would break out the former under more specific endpoints. Dr. Schwetz replied that "Reproductive Assessment" referred primarily to continuous breeding studies. Dr. Klaassen commented that publication of these lists in **EHP** at least annually would be helpful in furthering communication with the public. Dr. Schwetz said abstracts of completed studies would be published periodically in **EHP**. Dr. Loeb stated that what was important was the societal or regulatory action that derived from the completed studies.

VI. Toxicology Review Team Activities:

1) **Introduction - Role of Review Teams** — Dr. Schwetz explained that toxicology review teams would be formed for chemicals that were to undergo long-term or other extensive kinds of studies, for toxicology issues, or for studies of mechanisms, e.g., peroxisome proliferation. A team would be composed of expert scientists from the NTP agencies, from other agencies, especially an agency that had nominated a chemical, other intramural scientists, and experts from outside the government as appropriate. The team will review protocols, monitor the progress of a study, review findings and advise on whether other studies are warranted. He said the Board would be asked for their input both prior to beginning a study and later on. Dr. Schwetz said the studies to be discussed included two Clean Air Act chemicals, carbon disulfide and dibutyl phthalate, and a FDA-priority chemical, chloral hydrate, for which studies were to be done at NCTR under an interagency agreement with NIEHS.

2) **Carbon Disulfide** — Dr. Robert Sills, NIEHS, said that carbon disulfide was considered a hazardous chemical under the Clean Air Act amendments and was being studied by the NTP because of high emissions, high production, potential for human exposure, and lack of mechanistic data. The chemical is used as a solvent and chemical intermediate and has been shown to be neurotoxic in both animals and humans. The toxicity to the peripheral nervous system is manifested as a distal neurofilamentous axonopathy, and cardiovascular toxicity is marked by focal hemorrhages and systemic arteriosclerosis. Among expert consultants used were Dr. Doyle Graham, Duke University, and members of the Chemical Manufacturers Association Carbon Disulfide Team and the EPA Carbon Disulfide Team. Among issues discussed with the consultants were the pathways of biotransformation, the role of metabolites especially in neurotoxicity, and the differences in strain sensitivities between the Wistar and Sprague Dawley rats used in developmental studies. Dr. Sills reported that research needs included the conduct of inhalation studies to examine the mechanism of the distal axonopathy, and to provide dose-response curves for biomarkers of exposure, neurobehavior, and neuroelectrophysiologic measurements. Developmental toxicity studies are needed to evaluate reported rat strain differences in sensitivity while attempting to replicate previous studies by others. An additional need is to characterize the toxicology of the CS_2 metabolite and Clean Air Act chemical, carbonyl sulfide. Dr. Sills described the planned studies on carbon disulfide and carbonyl sulfide designed to meet these research needs. Discussion: Dr. Silbergeld expressed concern about the lack of consultation with labor or environmental groups in view of occupational exposure and wondered whether this was likely to be too large an investment of resources in an already well-studied chemical. She asked whether the data obtained will aid in

understanding mechanisms for other neurotoxicants. Dr. Schwetz responded that although carbon disulfide had been extensively studied, there was minimal mechanistic information and, further, there was almost no data on the toxicity of carbonyl sulfide. He said we would expand the spectrum of consultants. Dr. Reuhl suggested there might be a conflict or overlap with grantees who also are studying the effects/mechanisms of carbon disulfide toxicity. Dr. Olden acknowledged this concern and stated that we very carefully scrutinize our portfolio of grants to minimize these conflicts. Dr. Derek Dunn, NIOSH, noted his agency's interest in the ototoxic effects of carbon disulfide and said they would be willing to consult.

3) **Dibutyl Phthalate —** Dr. Daniel Marsman, NIEHS, discussed issues with dibutyl phthalate (DBP) that had arisen within the toxicology review team and from consultations with outside experts. DBP had been nominated to the NTP as part of a larger phthalate class study under Superfund, and more recently, by EPA under the Clean Air Act, although human exposure was more likely from groundwater and food contamination. Carcinogenicity studies already have been completed by the NTP on five other phthalate-related compounds. A common effect of most of the phthalates in rodents is peroxisome proliferation in the liver. For the peroxisome proliferators that have been studied, potency of induction of peroxisomal enzymes in the liver of male rats did not correlate well with carcinogenic potential. This imperfect correlation may have some significance for risk assessment in that a presumed lower risk to humans from peroxisomal proliferators is based on an insensitivity of humans to peroxisomal induction. Dr. Marsman said that after consultations by the team with outside experts, the research issues identified included: the role of oxidative stress and cell proliferation in the mechanism of toxicity, species differences in sensitivity, testicular toxicity and carcinogenicity, tumor promotion, receptor-mediated toxicity, and route-to-route extrapolation. He addressed the research needs with DBP that NTP intends to pursue in the near term: 1) assessment of peroxisome proliferation and cell replication as predictors of carcinogenicity; 2) investigation of genetic determinants and biomarkers of liver cancer; and 3) studies of testicular toxicity and carcinogenicity. Dr. Marsman listed the 13-week study objectives that include: tissue dosimetry; dose-response for peroxisome proliferation, cell replication, and testicular toxicity; and comparison of the toxicity of DBP with other non-phthalate peroxisome proliferators in three species (mouse, rat and hamster). Discussion: Dr. Loeb inquired about costs for such a complex study and how it could be lowered. Dr. Marsman said that since most of the effects were seen in both species and the male was more sensitive, consideration was being given to using only males. Dr. Klaassen stated that this was a very important study that could provide answers relevant to many compounds as to their potential hazard for humans.

4) **Chloral Hydrate (FDA/NIEHS Interagency Agreement)** — Dr. William Allaben, Associate Director for Scientific Coordination, NCTR, and FDA NTP Liaison, said an Interagency Agreement (IAG) between FDA/NCTR and NIEHS/NIH had been signed on December 16, 1992, with the purpose being to conduct at NCTR and other FDA or NTP laboratories comprehensive toxicological assessments on FDA priority chemicals or agents nominated to the NTP. He noted that the FDA and other agencies on the NTP Executive Committee can nominate one chemical each year that will receive priority consideration for more rapid entrance into the toxicological evaluation process, and listed the FDA priority chemicals. Dr. Allaben commented that historically, the long-term studies performed on FDA chemicals had been long in being completed and incorporated few mechanistic considerations, often creating a regulatory problem for the Agency. The agency needed: 1) flexible protocol design, and 2) specific mechanistic studies to support the understanding and interpretation of bioassay results, all performed in a timely manner. The primary goal of the IAG is to develop a comprehensive scientific data base which can be used to: 1) reduce the uncertainty in risk assessment/risk benefit analysis; 2) enable a better estimate of true risk; and 3) lead to high quality, science-

based , risk management decisions. Included may be both applied and mechanistic studies, evaluation of non-cancer endpoints, and use of alternative assays. Toxicology protocol design, selection, and progress review will be performed by a Toxicology Study Selection and Review Committee composed of core FDA/NTP members, and *ad hoc* members who may change depending on the chemical studied. Dr. Allaben said the first chemical to be studied under the IAG was the FDA FY 1992 priority chemical, chloral hydrate. Chloral hydrate is a drug used for over 100 years that was "grandfathered" into the pharmacopoeia without clinical trials. Its primary use today is as a sedative/hypnotic for children undergoing medical tests and for elderly patients. Recent studies indicate the drug is a possible male mouse tumorigen; chloral hydrate and its principal metabolites, trichloroacetic acid and trichloroethanol, have been reported to be genotoxic in some assay systems. Dr. Allaben concluded by describing the comprehensive research plan. Discussion: Dr. Silbergeld commented that the IAG seemed to be a model for interagency collaboration that reflected in part a dissatisfaction by FDA with the NTP testing process. Dr. Olden agreed that it was a model that might be used by other agencies.

VII. Selected Research Projects:

1) **Electromagnetic Fields (EMF)** — Dr. Gary Boorman, NIEHS, said electric and magnetic fields (EMF) are very complex phenomena to which nearly all humans are exposed through power lines and most electric equipment used in homes, workplaces and elsewhere. Because the frequencies of most fields (~ 60 Hz) are much lower than the earth's static magnetic or electric fields, there was little reason to assume these fields could be hazardous to health. This changed with the report in 1979 suggesting that increased cancer rates in children might be associated with the proximity of homes to electric power distribution lines and wiring configuration. This report was replicated in a better controlled study by different researchers in 1988. However, most of the epidemiological studies reported to date are not definitive. The National Energy Policy Act of 1992 will coordinate and focus the Federal effort to address health concerns of exposure to EMF. The NIEHS has been designated the lead agency for the health related research. Dr. Boorman discussed some of the proposed mechanisms including effects on ion fluxes, especially calcium. The most reproducible effect of EMF in humans appears to be suppression of the nocturnal rise in melatonin. The first NIEHS studies will include evaluations for possible effects of magnetic fields on pineal and blood melatonin levels. Further, melatonin has been suggested to inhibit the growth of cancer cells, so initiation/promotion studies have been planned. The NTP studies will also evaluate 60 Hz magnetic fields for possible adverse effects on reproduction and development since some epidemiological studies have suggested such effects in humans. Finally, long-term toxicity and carcinogenicity studies in rats and mice are planned since there are no long-term studies. The facilities were completed and studies were expected to begin in July. Dr. Boorman stressed that this was a national program and reported that Dr. Olden had asked the CDC, NCI and FDA to collaborate. Additionally, there was an Interagency Testing Needs Committee as well as a Congressionally established advisory committee to provide advice and oversight. The latter group would include labor union and public interest representatives. Discussion: Dr. Loeb suggested that since cancer seemed to be the endpoint of most concern that a series of well-controlled *in vitro* studies on mutation rates, adducts, etc. should be considered. Dr. Boorman responded that many such studies had been performed with conflicting results. He said there was a strong sentiment for a concerted effort to provide more definitive answers. Dr. Olden stressed that the funding for doing these studies was not sought by the NIEHS. He said that we as scientists need to do a better job of educating the Congress and the public about the relative importance of various environmentally-related public health concerns so that we gain their support for study of scientific problems that should have high priority. Mr. Daniel Vandermeer,

NIEHS, argued that without carefully conducted studies to provide some answers about the effects of EMFs, there likely would be a much larger cost imposed on the public by virtue of all power lines having to be buried.

2) **Methylene Chloride** — Dr. Robert Maronpot, NIEHS, said that he spoke for a number of scientists at NIEHS who had been involved in research with methylene chloride over the last several years. The chemical was chosen for intensive study as a model chlorinated hydrocarbon that produced neoplasms, at least in mice, in two important organs, liver and lung, and demonstrated a high production volume and human exposure. The focus of the research was on the molecular biology of the lung or liver neoplasms, on the progressive development of neoplasms, and stop-exposure studies that have resulted in five papers in press in **Carcinogenesis** and one in **EHP** with others in preparation. A two-year inhalation study was performed in female B6C3F$_1$ mice at 2000 ppm with the tumor findings essentially replicating the earlier bioassay (TR 306). Target tissues were frozen for oncogene/suppressor gene analysis and fixed for histopathology. Dr. Maronpot described cell proliferation studies in the liver which demonstrated an effect on hepatocyte labeling indices at 13 weeks (decreased) but not at later time points while labeling indices in foci of cellular alteration were not different between control and methylene chloride exposed mice. Stop exposure studies indicated that liver tumor response continued to increase with exposure up to 24 months while a maximum lung tumor response was achieved with 12 months exposure. Patterns of activation of H-*ras* in the liver and K-*ras* in the lung were similar in treated and control animals while genetic alterations in the p53 tumor suppressor gene in lung tumors were similar to those observed in human adenocarcinomas. Dr. Maronpot concluded that guided by these findings, additional studies are being considered to further characterize the tumor response in mice exposed to methylene chloride.

3) **Hepatocarcinogenicity of Oxazepam in Mice** — Dr. John Bucher, NIEHS, reported that oxazepam was one of a number of widely prescribed benzodiazepine drugs that are used as sedatives and anti-anxiety agents. Because adequate long-term studies in mice had not been reported previously, the NTP performed two-year studies. Because there was an indication in the literature that oxazepam may have caused liver neoplasia in Swiss-Webster mice, dosed feed studies were conducted with both Swiss-Webster and B6C3F$_1$ mice. Dr. Bucher described the design for 14-week and 2-year studies noting that in the 2-year studies in B6C3F$_1$ mice, a third and much lower dose of 125 ppm was included in an attempt to produce a blood level of oxazepam that would be in the therapeutic range for humans. The studies in Swiss-Webster mice were terminated after 57 weeks due to high mortality believed due mainly to enhanced amyloid accumulation in the heart and other organs leading to pulmonary edema and heart failure. The other major effect in both strains was a marked increase in liver neoplasia, particularly carcinomas and a rare variant, hepatoblastomas. The conclusions for carcinogenicity in both strains was that there was **clear evidence of carcinogenic activity** based on increased incidences of hepatocellular adenomas and carcinomas, and in B6C3F$_1$ mice, hepatoblastomas as well.

Dr. Bucher discussed supplementary studies performed at NIEHS in view of the marked enhancement of liver neoplasia. Metabolism studies performed by Drs. Robert Griffin and Tom Burka showed similar pathways in both strains, primarily glucuronidation of the parent and oxidation of the phenyl ring. Dr. Jinhua Yuan and coworkers evaluated the toxicokinetics and found that half-lives for distribution and terminal elimination were similar in both strains, and the apparent bioavailability from feed was about 40%. Replicative DNA synthesis was measured in livers of mice in a 90-day feed study by Drs. Michael Cunningham, Robert

Maronpot and John Bucher, and significant increases in bromodeoxyuridine labeling even at 125 ppm were seen at 15 days but not thereafter. Clinical pathology studies by Drs. Morrow Thompson, Maronpot and Cunningham on male mice showed moderate increases in enzymes related to liver damage with liver cell hypertrophy mainly in the centrilobular region but little or no evidence of hepatocyte necrosis or inflammation. In a study by Ms. T.R. Devereux and coworkers to evaluate the frequency of activated H-*ras* oncogenes, 58% of liver neoplasms from control $B6C3F_1$ mice had activated H-*ras* while essentially none of the tumors from animals in the two high dose groups and an intermediate number of tumors from the low dose mice had an activated gene. Dr. Bucher concluded that based on the metabolism studies, the mouse was a fairly good surrogate for humans. Many aspects of the neoplasms and other responses of mice to oxazepam resemble those reported with phenobarbital including interactions with receptors on GABAergic neurons. However, phenobarbital has not been associated with liver cancer in humans. Discussion: Dr. Klaassen suggested that in this and other studies where there is a strong liver tumor response, careful evaluation should be done of alterations in P450 and glucuronyl transferase isoforms. Dr. Bucher said this was being done for oxazepam inhouse at earlier time points and by Dr. Julian Leakey at NCTR.

VIII. Progress on Procedures for Chemical/Issue Nomination and Selection: Dr. Errol Zeiger, NIEHS, reported that in response to the Board's Advisory Review report and comments from others, the NTP has been evaluating the nomination and selection process and what changes should be made. He said we are seeking ways to broaden the spectrum of people and groups from whom we solicit nominations. Dr. Zeiger reviewed with the Board a draft flow chart beginning with review by a nomination prescreen committee at NIEHS. Input will then be solicited from members of the Interagency Committee for Chemical Evaluation and Coordination (ICCEC, and proposed to replace the Chemical Evaluation Committee or CEC). After further review, the ICCEC will formally meet to review nominations and will be asked to help set priorities by agent and toxicology endpoint. As a new step, the EPA Interagency Testing Committee (ITC) will interact with the ICCEC and provide access to their data base. Accepted chemicals will be reviewed by the NTP Steering Committee, who will develop final testing lists and priorities for review by the NTP Director. Following this an important step will be incorporation of the testing lists in the NTP Annual Plan which will be brought to the Board for review followed by review and approval by the NTP Executive Committee. Dr. Zeiger said the process does not reflect large changes from past practice but, hopefully, will be more coordinated on an annual basis so better priority setting can be done within limited resources. He stressed that the Executive Committee still must approve the new procedure. Discussion: Dr. Brown asked whether the new scheme would take longer and be more costly than the present one. Dr. Zeiger replied that reaching broader sources of nominations will likely cost more and take more time. Dr. Olden urged that the Program attempt to find ways to shorten the process. Dr. Silbergeld expressed concern that in the new process there was still a lack of opportunity for public involvement and input, particularly after the nomination step. Dr. Olden agreed and said that we need to incorporate ways for the broader segments of the public to comment during the review steps in the process. Dr. Zeiger noted that we intend to more actively try to keep nominators informed as to the status of their nominations.

IX. Proposed Scheme for Prioritizing Chemicals for Carcinogenesis Testing (Attachment 3): Dr. Schwetz said he hoped to stimulate discussion by presenting this scheme. He said we have much better knowledge today of the toxicological properties of carcinogenic chemicals and because of the time and resources required for a two-year study, we should use this knowledge to set better priorities for two-year studies. He said that chemicals which come into the Program do not go directly into a two-year study without preliminary information being developed, including genetic toxicology, chemical disposition and characterization of physical/chemical

properties. This is followed by short-term studies to develop information on endpoints such as reproductive and developmental toxicity, neurotoxicity, etc. with emphasis being given to developing more comprehensive short-term screens that will give us more guidance than the typical 14- and 90-day studies. Besides data on target organs, dose response and toxicokinetics obtained from current subchronic studies, we would also be accumulating data evaluating the potential for non-mutagenic mechanisms of carcinogenesis, e.g., peroxisome proliferation or induction of alpha-2-mu-globulin. All of this information would then be used to determine the priority for conducting carcinogenesis studies, as shown on the right side of the decision scheme.

Dr. Schwetz then reviewed the decision scheme (Attachment 3, p. 2). If the available data showed strong evidence of genotoxicity, especially in the presence of indicators of nonmutagenic or secondary mechanisms of carcinogenesis as well (category 4 chemicals), the agent would be considered a presumed carcinogen in animals. On the basis of the available toxicity data, he said we can also specify the dose range for carcinogenesis studies and thus the dose range for the presumed carcinogenic response. With this amount of knowledge and the high probability of the outcome, we would consider such an agent to have low priority for carcinogenesis testing. Agents in category 3 would be characterized by similarly strong evidence of genotoxicity and no evidence of a secondary mechanism. Agents here would have a higher priority for testing, but still not a really high priority because they would be considered a probable carcinogen at or below the MTD. For agents in category 2, there would be either equivocal or no evidence of genotoxicity or secondary mechanisms. The lower certainty that these would or would not be carcinogenic suggests a higher priority for testing than agents in categories 3 or 4. Agents in category 1 would be the highest priority for testing because there is evidence of secondary mechanisms of carcinogenicity. Unanticipated carcinogens are likely to come from categories 1 or 2. Thus, we feel that agents in categories 1 or 2 are a higher priority for testing than those in 3 or 4. Other studies of a more mechanistic nature would be conducted together with or following the toxicity testing to facilitate interpretation of the study results (Attachment 3, p. 3). The final decision by the NTP to test a chemical for carcinogenic potential, or not to test, would be based on several factors, including human exposure, special needs of regulatory agencies, as well as the toxicology data evaluation using the decision scheme. If the decision was made by the NTP that a carcinogenesis study would not be done on a chemical in categories 3 or 4, a report would be written that summarizes the available data and the basis for not conducting a two-year study. This report would undergo peer review in the same manner as for NTP Technical Reports of carcinogenesis studies. Discussion: Dr. Faustman opined that agents that fit the first part of category 2 should be given a higher priority for testing than those in the second part because of likely greater uncertainty as to probability of being either positive or negative for carcinogenesis. She inquired as to how problems with regulatory wording or requirements would affect these decisions. Dr. Schwetz replied that we would go to the regulatory agency with the profile of results particularly for a category 4 and ask them to explore other ways to test the agent, e.g., could they require the manufacturer to do the tests. Dr. Klaassen thought the scheme to be stimulating but questioned the relevance to humans of finding nonmutagenic carcinogens in animals. Dr. Schwetz said this challenged us to examine the meaning of secondary mechanisms in animals to man. Dr. Hansen cautioned that we not overlook the extent of human exposure to an agent in our decision process. Dr. Allaben stated that for some chemicals the regulatory agencies could not regulate in the absence of testing data.

X. Proposal for NTP Support Through Grant Mechanisms: Dr. Schwetz noted that the Board had already approved a concept (October 27, 1992) that the Program be involved in developmental toxicity testing and methods development, including the use of alternative species. He said that typically such studies are conducted through various means including

intramural research, contracts or interagency agreements. Pursuant to the Board's recommendations that the Program give greater emphasis to mechanistic research, there has been a realization that little is known about the mechanisms of developmental toxicity of chemicals. Thus, we need to develop more mechanistically-based models that will give us better predictive capabilities for developmental toxicity and other endpoints as well. Dr. Schwetz said that a series of NIEHS-sponsored workshops was held in the fall of 1992 to help determine whether there may be models in developmental biology that can be exploited for use in developmental toxicology. If so, awarding of grants in a targeted area could stimulate basic research in developmental biology that will result in better models for prediction of developmental toxicity.

Developmental Biology Research - Review of Concept:

Molecular and Cellular Mechanisms of Abnormal Development — (Attachment 4) Dr. Jack Bishop, NIEHS, presented a concept proposal for expansion of NTP developmental toxicology research to include more studies of molecular and cellular mechanisms. He said a major aim of NTP research in developmental toxicology is to effect a reduction in infertility, genetic disease and malformations in the human population. One way to accomplish this is through the use of animal models to identify causal environmental factors. He reviewed the enormous societal and human costs of abnormal development, and noted that for as much as 68% of all human malformations , the causes are unknown. Dr. Bishop presented an overview of the series of six NIEHS workshops on "Molecular and Cellular Mechanisms of Early Mammalian Development" cosponsored with EPA. The overall goal of these workshops was to facilitate the integration of progress being made in the field of developmental biology into the field of developmental toxicology. Based on the recommendations emanating from each of the six workshops, the NTP is identifying promising new areas of molecular research at the interface between developmental biology and developmental toxicology where major initiatives are believed to be most warranted. It was proposed that the NTP support this research through a combination of intramural and extramural mechanisms. Discussion: As principal reviewer, Dr. Faustman addressed the four specific areas that a project concept should include: (1) scientific, technical or program significance - the project, if implemented, would provide more mechanistic information about abnormal development and the role of environmental factors; (2) availability of the technology and resources to achieve the goals - the workshops emphasized that the 'tools' are available and provided a good start toward getting scientists from different backgrounds to work together; (3) what are the practical scientific or clinical uses for the results - she noted three such areas where the mechanistic information provided via this project would be of use — risk assessment, improvement of testing protocols, and improving identification of early biomarkers of effect; and (4) adequacy of the methodology to be used - new technology is available but there there needs to be more application of this technology. She commended the approach of using investigator initiated research in concert with more directed research. In discussion by the Board, there was general agreement with Dr. Faustman's assessment. Dr. Hughes stated that although the technology was available and adequate, there needs to be more of an effort to apply the 'tools'. Dr. Brown moved that the concept be approved. Dr. Klaassen seconded the motion which was approved unanimously by the Board.

supplying all data necessary to meet FDA standards and to obtain an IND.

2. Provide the drug before January 1, 1994.

3. Provide funds to support a technician to carry out analyses needed for the clinical trial. These will include measurement of LMB–7 in patients' blood samples, measurements of antibodies to LMB–7, and related activities.

4. Provide funds to support a postdoctoral fellow and associated expenses to work on improvements to LMB–7.

5. Provide funds to support a research nurse and expenses associated with the exploratory clinical trials.

6. If efficacy is demonstrated in the human trials, the company would be responsible for the large scale production, packaging, marketing, and distribution of this recombinant immunotoxin.

Criteria for choosing the cooperating company will include the following:

1. Experience in producing recombinant proteins for human use and conducting clinical trials with recombinant proteins.

2. Experience and ability to produce, package, market and distribute pharmaceutical products in the United States and to provide the product at a reasonable price.

3. Willingness to cooperate with the NCI in the collection, evaluation, publication and maintenance of data from clinical trials of investigational agents.

4. Willingness to cost share in laboratory studies and clinical trials as outlined above.

5. An agreement to be bound by the DHHS rules involving human and animal subjects.

6. The aggressiveness of the development plan, including the appropriateness of milestones and deadlines for clinical development.

7. Provisions for equitable distribution of patent rights to any inventions. Generally the rights of ownership are retained by the organization which is the employer of the inventor, with: (1) An irrevocable, nonexclusive, royalty-free license to the Government (when a company employee is the sole inventor); or (2) an exclusive or nonexclusive license to the company on terms that are appropriate (when the Government employee is the sole inventor).

Dated: April 5, 1993.

Reid Adler,

Director, Office of Technology Transfer, National Institutes of Health.

[FR Doc. 93–8687 Filed 4–13–93; 8:45 am]

BILLING CODE 4140–01–M

Public Health Service

National Toxicology Program; Board of Scientific Counselors Meeting

Pursuant to Public Law 92–463, notice is hereby given of a meeting of the National Toxicology Program (NTP) Board of Scientific Counselors, U.S. Public Health Service, in the Conference Center, building 101, South Campus, National Institute of Environmental Health Sciences (NIEHS), 111 Alexander Drive, Research Triangle Park, North Carolina, on May 11, 1993.

The meeting will be open to the public from 9 a.m. to adjournment with attendance limited only by space available. The preliminary agenda topics with approximate times are as follows:

9 a.m.–11:45 a.m.—The NTP staff will provide the Board with reports of information about recent meetings, an update of status of the Advisory Review report and the Programs's response to the report, and summary of toxicity studies planned, ongoing or recently completed. The Board will be briefed on NTP Toxicology Review Teams and a recent Interagency Agreement between the NIEHS and the Food and Drug Administration.

12:45 p.m.–4 p.m.—The NTP staff will discuss with the Board selected ongoing or recently completed research projects on low frequency electromagnetic fields, methylene chloride, and oxazepam. The Board will be informed about progress on changes in procedures for the nomination and selection of chemicals and scientific issues or concepts. The Board's advice will be sought on a proposed scheme for prioritizing chemicals for carcinogenesis testing. Other scientific issues may be discussed as appropriate.

The Executive Secretary, Dr. Larry G. Hart, National Toxicology Program, P.O. Box 12233, Research Triangle park, North Carolina 27709, will have available a roster of Board members and other program information prior to the meeting and summary minutes subsequent to the meeting.

Kenneth Olden,

Director, National Toxicology Program.

[FR Doc. 93–8685 Filed 4–13–93; 8:45 am]

BILLING CODE 4160–17–M

Public Health Services

National Institutes of Health; Statement of Organization, Functions, and Delegations of Authority; Correction

AGENCY: National Institutes of Health.

ACTION: Notice correction.

The notice published in the February 16, 1993 **Federal Register** (58 FR 8605) announcing amendment of Part H, Chapter HN (National Institutes of Health) of the Statement of Organization, Functions, and Delegations of Authority for the Department of Health and Human Services (40 FR 22859, May 27, 1975, as amended most recently at 58 FR 6288, January 27, 1993) to reflect the reorganization of the National Center for Human Genome Research, incorrectly listed some of the alpha prefixes for the organizational codes as "HNA". NIH is publishing this notice to correct these alpha prefixes to read "HN".

Dated: March 31, 1993.

Bernadine Healy,

Director, NIH.

[FR Doc. 93–8688 Filed 4–13–93; 8:45 am]

BILLING CODE 4140–01–M

DEPARTMENT OF THE INTERIOR

Bureau of Mines

Information Collection Submitted to the Office of Management and Budget for Review Under the Paperwork Reduction Act

A request extending the collection of information listed below has been submitted to the Office of Management and Budget (OMB) for approval under the provisions of the Paperwork Reduction Act (44 U.S.C. chapter 35). Copies of the proposed collection of information and related forms and explanatory material may be obtained by contacting the Bureau's clearance officer at the phone number listed below. Comments and suggestions on the requirement should be made within 30 days directly to the Bureau clearance officer and to the Office of Management and Budget, Paperwork Reduction Project (1032–0004), Washington, DC 20503, telephone 202–395–7340.

Title: Consolidated Consumers' Report

OMB approval number: 1032–0084

Abstract: Respondents supply the Bureau of Mines with domestic production and consumption data on nonfuel mineral commodities. This information is published in Bureau of Mines publications including the Mineral Industry Surveys, Volumes I, II, and III of the Minerals Yearbook, and Mineral Commodity Summaries for use by private organizations and other Government agencies.

Bureau form number: 6–1109–MA

Frequency: Monthly and Annual

Description of respondents: Operations that consume ferrous metals.

AGENDA
BOARD OF SCIENTIFIC COUNSELORS
NATIONAL TOXICOLOGY PROGRAM

May 11, 1993

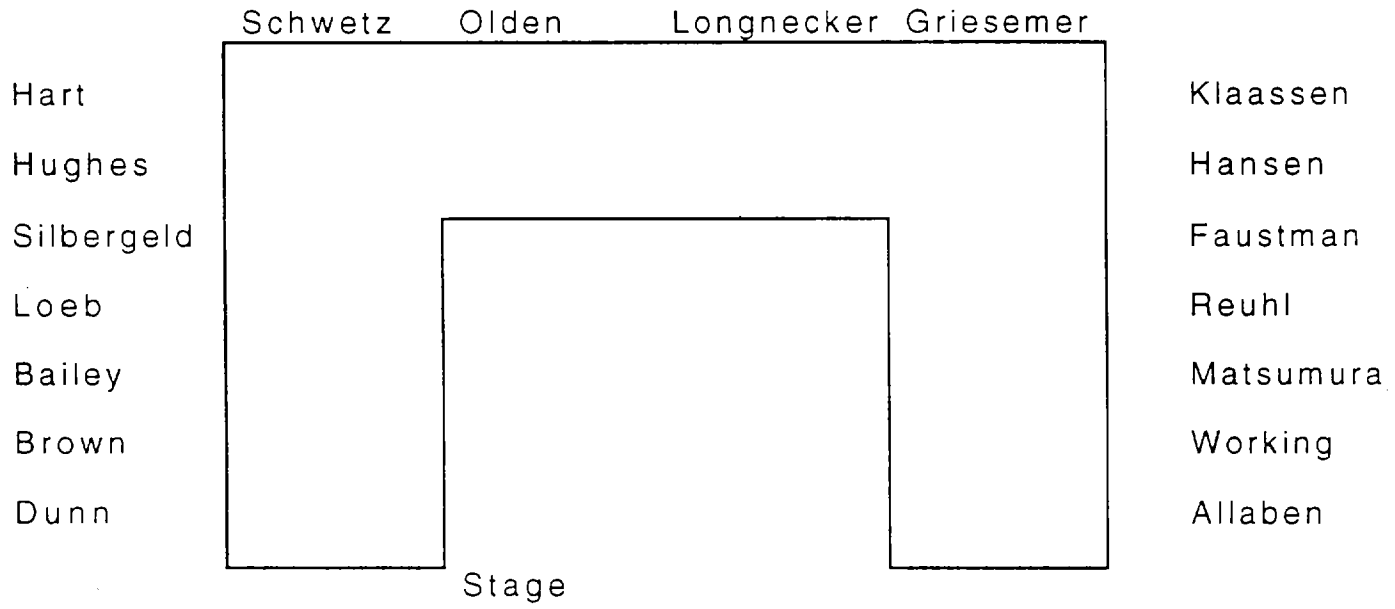
Conference Center, Building 101, South Campus
National Institute of Environmental Health Sciences (NIEHS)
Research Triangle Park, North Carolina

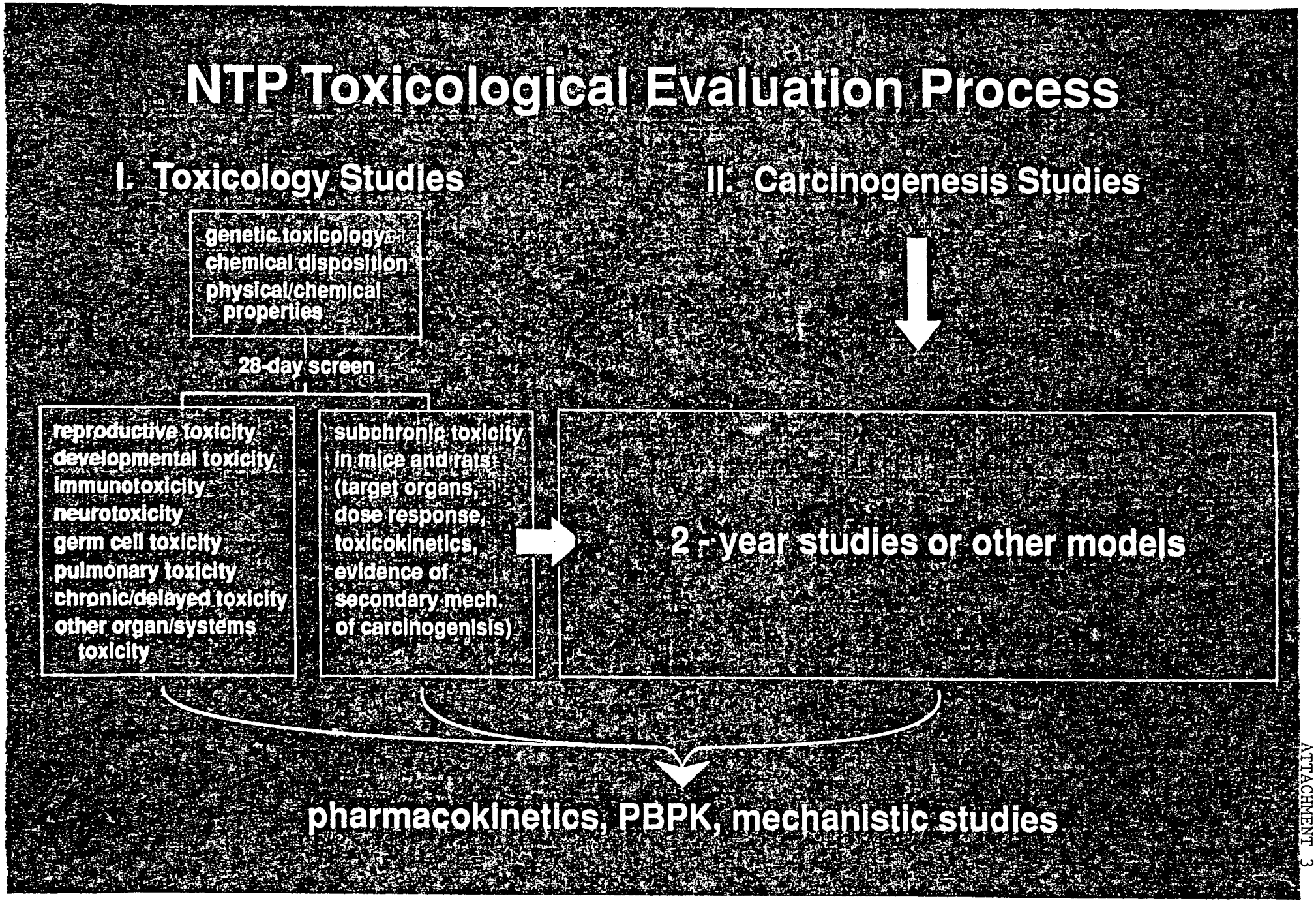
9:00 a.m.-9:15 a.m.	Report of the Director, NTP	Dr. K. Olden, NIEHS
9:15 a.m.-9:45 a.m.	Meeting Reports	
	I. National Toxicology Partnership-3/11/93	Dr. K. Olden, NIEHS Dr. R. Griesemer, NIEHS Dr. B. Schwetz, NIEHS
	II. Technical Reports Review Subcommittee-12/1-2/92	Dr. S. Eustis, NIEHS
9:45 a.m.-10:00 a.m.	Advisory Review Report and Program Response-Update	Dr. B. Schwetz, NIEHS
10:00 a.m.-10:15 a.m.	Summary of Studies Planned, Ongoing, or Completed-By Endpoint	Dr. E. Zeiger, NIEHS
10:15 a.m.-10:30 a.m.	BREAK	
10:30 a.m.-11:45 a.m.	Toxicology Review Team Activities	
	I. Introduction-Role of Review Teams	Dr. B. Schwetz, NIEHS
	II. Carbon Disulfide	Dr. R. Sills, NIEHS
	III. Dibutyl Phthalate	Dr. D. Marsman, NIEHS
	IV. FDA/NIEHS Interagency Agreement (Chloral Hydrate)	Dr. W. Allaben, NCTR
11:45 a.m.-12:45 p.m.	LUNCH	
12:45 p.m.-2:00 p.m.	Selected Research Projects	
	I. EMF	Dr. G. Boorman, NIEHS
	II. Methylene Chloride	Dr. R. Maronpot, NIEHS
	III. Hepatocarcinogenicity of Oxazepam in Mice	Dr. J. Bucher, NIEHS
2:00 p.m.-3:00 p.m.	Progress on Procedures for	
	I. Chemical/Issue Nomination and Selection	Dr. E. Zeiger, NIEHS
	II. Prioritizing Chemicals for Carcinogenesis Testing	Dr. B. Schwetz, NIEHS
3:00 p.m.-3:15 p.m.	BREAK	
3:15 p.m.-3:45 p.m.	Proposal for NTP Support through Grant Mechanisms	Dr. B. Schwetz, NIEHS
	Developmental Biology Research-Review of Concept--Molecular and Cellular Mechanisms of Abnormal Development	Dr. J. Bishop, NIEHS
4:00 p.m.	Adjourn	

National Toxicology Program
Board of Scientific Counselors Meeting

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

May 11, 1993





ATTACHMENT 3

NTP Toxicological Evaluation Process

II. Carcinogenesis Studies

Evidence of: Genotoxicity		Nonmutagenic mech. of carcinogenesis	Carcinogenic potential	Priority for NTP carcinogenesis studies
+		+	presumed carcinogen at or below MTD	4 (low)
+		−	probable carcinogen at or below MTD	3
±	or	±	unknown	2
−		+	unknown	1 (high)
−		−	unknown	2

NTP Toxicological Evaluation Process

I. Toxicology Studies

genetic toxicology
chemical disposition
physical/chemical properties

28-day screen

reproductive toxicity
developmental toxicity
immunotoxicity
neurotoxicity
germ cell toxicity
pulmonary toxicity
chronic/delayed toxicity
other organ/systems toxicity

subchronic toxicity in mice and rats (target organs, dose response, toxicokinetics, evidence of secondary mech of carcinogenis(s)

II. Carcinogenesis Studies

Evidence of: Genotoxicity		Nonmutagenic mech of carcinogenesis	Carcinogenesis potential	Priority for NTP carcinogenesis studies
+		+	presumed carcinogen at or below MTD	4 (low)
+		−	probable carcinogen at or below MTD	3
±	or	±	unknown	2
−		+	unknown	1 (high)
−		−	unknown	2

pharmacokinetics, PBPK, mechanistic studies

BACKGROUND CONCEPT REVIEWS

NTP contracts, interagency agreements, and grants support a variety of activities -- toxicologic characterization, testing, methods development, and program resources (i.e., chemistry, occupational health and safety, animal production, pathology, quality assurance, archives, etc.).

Prior to issuance of a Request for Proposal (RFP) or a Request for Application (RFA), a project concept review is required. These project concepts in many instances may consist of more than one contract, interagency agreement, or grant. Concept reviews are needed for new projects, recompetitions with changes in statements of work, and projects ongoing for 5 years or more since the last concept review.

The project concept reviews are conducted by the NTP Board of Scientific Counselors and are open to the public so long as discussions are limited to review of the general project purposes, scopes, goals, and various optional approaches to pursue the overall program objectives. The meeting will be closed to the public, however, if the concept discussions turn to the development or selection of details of the projects or RFPs/RFAs, such as specific technical approaches, protocols, statements of work, data formats, or product specifications. Closing the session is intended to protect the free exchange of the advisory group members' opinions and to avoid premature release of details of proposed contract projects or RFPs/RFAs.

The Board members are asked to review the project concepts for overall value and scientific relevance as well as for fulfilling the program goal of protecting public health. Specific areas should include:

a. scientific, technical or program significance of the proposed activity;

b. availability of the technology and other resources necessary to achieve required goals;

c. extent to which there are identified, practical scientific or clinical uses for the anticipated results; and

d. where pertinent, adequacy of the methodology to be used in performing the activity.

NATIONAL TOXICOLOGY PROGRAM CONCEPT REVIEW

PROGRAM/PROJECT AREA: Molecular and Cellular Mechanisms of Abnormal Developm

PROJECT OFFICERS: Jack B. Bishop (919) 541-1876
Jerrold J. Heindel (919) 541-5130
E. Sidney Hunter (919) 541-2274

OBJECTIVE: To identify and support NTP research initiatives that integrate developmental biology and developmental toxicology, with the goal of defining the molecular and cellular processes associated with the etiology of abnormal development. Based on this knowledge, mechanistically based approaches for the identification of agent-induced developmental abnormalities will be sought to improve the prediction of potential hazard to humans from exposure to environmental agents.

BACKGROUND: One aim of NIEHS/NTP sponsored research is to achieve a greater understanding of the molecular and cellular causes of abnormal development. Despite several decades of intensive research and testing efforts, our understanding of the mechanisms of abnormal development is minimal. This is largely due to the complexities of normal development and our lack of knowledge about the various processes involved, or how these processes may be perturbed. Enhanced knowledge of mechanisms associated with normal and abnormal developmental is essential to improving our ability to use the results of animal studies to protect human health.

There have been many advances made in the field of developmental biology resulting from the application of new molecular technologies. To facilitate the integration of progress being made in the rapidly advancing field of developmental biology into the field of developmental toxicology, the NIEHS recently conducted a series of workshops on "*Molecular and Cellular Mechanisms of Mammalian Development.*" These workshops brought together, for the first time, a diverse group of scientists (molecular embryologists, developmental biologists, geneticists, developmental toxicologists, teratologists, genetic toxicologists, human embryologists and fetal pathologists) all having a common interest in understanding the causes of abnormal development.

The workshop topics, all based upon crucial determinative processes, were: 1) growth and differentiation factors; 2) genomic imprinting; 3) gamete-derived determinants; 4) pattern formation; 5) cell migration; and 6) cell lineage and cell fate. Workshop presentations and discussions highlighted prospects for research on the molecular and cellular basis of mammalian development and provided insight as to which are most promising for addressing environmental health related issues. Most importantly, these workshops have fostered an exchange of information between the fields of molecular developmental biology and developmental toxicology. Based upon the recommendations emanating from each of the six workshops, we are identifying promising research areas at the interface of developmental biology and toxicology where we feel major initiatives are most warranted. Research will be supported through a combination of intramural and extramural mechanisms.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health
National Institute of
Environmental Health Sciences
P. O. Box 12233
Research Triangle Park, NC 27709

Memorandum

Date May 12, 1993

From Dr. William Eastin, ETP

Subject Dibutyl Phthalate and Carbon Disulfide Study Plans Presented to BSC

To Study Files

On May 11, 1993 two chemical study plans were presented to the NTP Board of Scientific Counselors (BSC). Dr. Dan Marsman presented the NTP/NIEHS plan to study Dibutyl Phthalate (Cas No. 84-74-2) and Dr. Robert Sills presented Carbon Disulfide (Cas No. 75-15-0). The information presented to the BSC is attached.

CARBON DISULFIDE

(CAS No. 75-15-0)

NTP Toxicology Studies

CARBON DISULFIDE (CS_2)

RATIONALE FOR STUDY

BACKGROUND

CONSULTATION

ISSUES

RESEARCH NEEDS

STUDY PLAN

RATIONALE FOR TESTING CS_2

NAMED ON LIST OF HAZARDOUS AIR POLLUTANTS UNDER CLEAN AIR ACT AMENDMENT

PRIORITIZED FOR FURTHER RESEARCH
-JOINT MEETINGS BETWEEN NIEHS AND EPA
-DATA NEEDS IDENTIFIED BY ATSDR

CARBON DISULFIDE
HIGH PRIORITY CAA CHEMICAL

HIGH EMISSIONS (50-60K TONS/YR)

HIGH PRODUCTION VOLUME

POTENTIAL FOR HUMAN EXPOSURE

LACK OF MECHANISTIC DATA

CARBON DISULFIDE
USES

VISCOSE RAYON FIBERS

CELLOPHANE & CELLULOSE SPONGES

CARBON TETRACHLORIDE

DISINFECTANTS

FUMIGANTS

RUBBER CHEMICALS

CLINICAL/EPIDEMIOLOGIC STUDIES

NEUROTOXICITY

REPRO/DEVELOPMENTAL TOXICITY

CORONARY HEART DISEASE

OCULAR TOXICITY

CARBON DISULFIDE CONSULTANTS

GOVERNMENTAL AGENCIES

ACADEMIA (DOYLE GRAHAM)

CMA CS_2 PANEL

EPA CS_2 TEAM

CARBON DISULFIDE
ISSUES

METABOLISM AND TOXICITY

BIOMARKER OF EXPOSURE

MECHANISM OF DISTAL AXONOPATHY

DEVELOPMENTAL TOXICITY

COMPARISON OF DEVELOPMENTAL TOXICITY STUDIES OF CS_2

	STUDY/AUTHOR		
PARAMETERS	**TABACOVA**	**SAILLENFAIT**	**PAI/CMA**
SPECIES	**RAT**	**RAT**	**RABBIT**
EXPOSURE CONC.	**64, 32 16 PPM**	**100, 200, 400 800 PPM**	**60, 100, 300, 600, 1200 PPM**
MATERNAL TOXICITY	**32 ↑ PPM**	**400 ↑ PPM**	**600 ↑ PPM**
DEVELOP. TOXICITY	**32 ↑ PPM**	**400 ↑ PPM**	**600 ↑ PPM**

CARBON DISULFIDE
RESEARCH NEEDS

MECHANISM - DISTAL AXONOPATHY

DOSE RESPONSE
-BIOMARKER OF EXPOSURE
-FUNCTIONAL OBSERVATIONAL BATTERY
-ELECTROPHYSIOLOGY

DEVELOPMENTAL STUDY
-REPEAT TABACOVA STUDY
-STRAIN SENSITIVITY

CARBONYL SULFIDE STUDY
14-DAY
13-WEEK

NIEHS STUDIES FOR CS_2 AND COS

SHORT AND LONG-TERM INHALATION

AIM OF NIEHS STUDIES

CHARACTERIZE TOXIC EFFECTS

MECHANISTIC STUDIES

CARBON DISULFIDE RESEARCH TEAM

DR. EASTIN (PHYSIOLOGIST)

DR. GOEHL (TOXICOKINETIST)

DR. HARRY (NEUROTOXICOLOGIST)

DR. HEINDEL (DEVELOPMENTAL TOXICOLOGIST)

DR. IRWIN (CHEMIST)

DR. MORGAN (INHALATION TOXICOLOGIST)

DR. SILLS (TEAM LEADER/PATHOLOGIST)

NIEHS STRATEGY CS_2/COS
SHORT AND LONG TERM STUDIES

PHASE I: TOXICOKINETIC STUDY (CS_2/COS)

PHASE II: NEUROTOXICITY STUDY (CS_2)
DEVELOPMENTAL STUDY (CS_2)
14-DAY/13-WEEK STUDY (COS)

PHASE III: DATA FROM I AND II USED IN IV

PHASE IV: CONDUCT CHRONIC CS_2 AND COS STUDIES

PHASE I
TOXICOKINETIC STUDY (CS_2/COS)

OBJECTIVES

DETERMINE PLASMA CONC. OF CS_2 AND COS AFTER CS_2 EXPOSURE

DETERMINE BASIC KINETIC PARAMETERS (COS)

PROVIDE AN ESTIMATE OF THE INTERNAL DOSE BASED ON AUC VERSUS TIME

DETERMINE DOSE PROPORTIONAL RANGE

CHARACTERIZE STRAIN SENSITIVITY DIFFERENCES

PHASE II

NEUROTOXICITY STUDY (CS_2)

DEVELOPMENTAL STUDY (CS_2)

14-DAY/13-WEEK STUDY (COS)

CARBON DISULFIDE
NEUROTOXICITY STUDY

NIEHS

EPA

DUKE UNIVERSITY

NEUROTOXICITY STUDY
EXPERIMENTAL DESIGN

MALE AND FEMALE F344 RATS

13-WEEK INHALATION STUDY

EXPOSURES
6 HRS/DAY, 5 DAYS/WEEK

4 TIME POINTS/3 EXPOSURE CONC.

NEUROTOXICITY STUDY OBJECTIVES

CHARACTERIZE PROGRESSION OF CS_2 NEUROTOXICITY

IDENTIFY BIOMARKER OF CS_2 EXPOSURE

EXAMINE MOLECULAR MECHANISM OF CS_2 NEUROTOXICITY

CHARACTERIZE MORPHOLOGY OF NEUROTOXIC LESIONS

CORRELATE NEUROBEHAVIORAL/ELECTROPHYSIOLOGY STUDIES WITH NEUROPATHOLOGY, MECHANISMS AND DOSE RESPONSES

DEVELOPMENTAL STUDY
OBJECTIVES

DEFINE THE SENSITIVITY FOR CS_2 TOXICITY

-MALFORMATIONS, FETAL DEATH AND FETAL WEIGHT

-POSTNATAL BEHAVIORAL TOXICITY

COMPARE TOXICITY OF CS_2 IN SPRAGUE DAWLEY AND WISTAR RATS.

CARBONYL SULFIDE (COS)
14-DAY/13-WEEK STUDIES

OBJECTIVES
CHARACTERIZE TOXICOLOGIC EFFECTS OF COS

END POINTS
TOXICOKINETICS
GROSS AND HISTOPATHOLOGY
HEMATOLOGY/CLINICAL CHEMISTRY
FOB, NEUROPHYSIOLOGY
REPRO./DEVELOPMENTAL TOXICOLOGY
GENETIC TOXICOLOGY