

National Toxicology Program
Board of Scientific Counselors' Meeting
March 14 and 15, 1983

SUMMARY MINUTES

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Summary Minutes

The National Toxicology Program (NTP) Board of Scientific Counselors met on March 14 and 15, 1983, 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 Board Members).

The minutes of the September 23 and 24, 1982, Board of Scientific Counselors' meeting were approved unanimously.

- I. Status Report on NIEHS/NTP Investigation of Exocrine Pancreatic Lesions in F344 Rats: (Attachment 3). Dr. G. A. Boorman, Chemical Pathology Branch, said a thorough reevaluation of these lesions was important because exocrine pancreatic cancer is common in humans and seems to be increasing in incidence, and that the lesions cause confusion in interpretation of bioassays because of the higher incidence in male F344 vehicle controls than in untreated controls in some gavage studies. He described the background of the study and the perceived need to establish criteria for diagnosis of proliferative exocrine pancreatic lesions which was effected by a special Pathology Working Group in 1982. Dr. Boorman described the morphology of the lesions and pointed out the four to five fold higher incidence in corn oil controls over untreated controls (Table 1) while cautioning that there appeared to be a marked variability in incidence even in studies conducted at the same laboratory (Table 2). Differences could not be attributed to batch of corn oil or peroxide levels. In looking at incidences of other tumors in mice and rats of both sexes, especially liver and lung, there were no differences between vehicle and untreated controls. On the other hand, in studies in male rats there was a significantly lower incidence of mononuclear cell leukemia in vehicle controls. Dr. Boorman said these findings would be published, and, further, NTP would convene a meeting in May, to include experts in pancreatic cancer, that would serve to validate diagnostic criteria for proliferative lesions, evaluate animal models, and make recommendations as to needed research. In conclusion, Dr. Boorman opined the NTP bioassays using corn oil gavage were valid. However, he noted that corn oil gavage would be used only if the preferred exposure route was oral and drinking water, water gavage or dietary administration could not be used due to stability or solubility problems.

Discussion: Dr. Nelson asked about the contribution of fat to the diet. Dr. Boorman said the corn oil provided 14% of the calories. Dr. Hurley wondered whether the oil might affect absorption of micronutrients. Dr. Boorman replied that rats ate at night while the gavage was usually given in the morning so this shouldn't be a problem. In response to a query by Dr. Hook, he agreed there may be hormonal effects. Dr. Manson

asked whether residues of trichloroethylene used to extract impurities from corn oil might be suspect with regard to pancreatic lesions. Dr. Boorman doubted this and replied that trichloroethylene given chronically in high doses to rats did not result in exocrine pancreatic lesions. In response to a question by Dr. Amann, Dr. Moore said genetic drift could be implicated in the variability between studies, and indicated NTP would evaluate this possibility. Dr. Boorman pointed out that in pancreata from F344 male rats allowed to live out their lifespan there was an incidence of proliferative lesions comparable to that in vehicle controls sacrificed at two years. Dr. Swenberg noted that more information was important on this issue in view of the fact that over the next two years roughly one-third of the bioassays to be evaluated by the Peer Review Panel will have involved corn oil gavage. Dr. Boorman agreed and said NTP would come back to the Board concerning proposed work which would undoubtedly include promotional studies and investigations on the sex differences.

II. NIEHS/NTP Cellular and Genetic Toxicology Program - Concept Review: Development of Human Cell Assay Systems for Genetic Toxicity:

(Attachment 4) Dr. R. Langenbach, NIEHS, proposed further development of human cell systems for use in determining potential genetic toxicity of chemicals. Human cell systems would be compared with established rodent cell test systems with regard to capabilities for metabolic activation of chemicals, and measurement of multiple genetic endpoints. He said the basic approach will be a cell-mediated activation system using co-cultivation of activating cells and target cells. Primary epithelial cells will be used for metabolic activation and, initially, normal human fibroblasts will serve as target cells. Endpoints measured will include gene mutations, sister chromatid exchanges, chromosome aberrations, and, possibly inhibition of DNA synthesis. As principal reviewer, Dr. Diamond asked what was considered to be the best approach from a screening point of view. Dr. Langenbach said to look at the listed endpoints using human liver cells for metabolic activation and fibroblasts as target cells. He stated NTP would try to define the spectrum of variability while minimizing variability due to tissue preparation. In response to other questions, Dr. Langenbach said the study would be done in two or possibly three laboratories, with three to four genetic endpoints per laboratory, and the test system would be validated with up to 12 chemicals yearly including standard mutagens, known human carcinogens, and NTP chemicals with good carcinogenicity data in more than one species. Dr. Diamond moved that as a logical extension of rodent cells, human cells should be studied but the variability of human cells must be looked at closely. The concept should be rewritten to make determination of variability an early step in the project. After some discussion, Dr. Nelson said the priorities and sequences in the project need to be spelled out in a more focused way. Dr. Langenbach agreed, and the motion for approval of the concept proposal was approved unanimously by the Board.

REVIEW OF NTP REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY PROGRAMS

A. Overview: (Attachment 5) Dr. C. Kimmel, NCTR, NTP Program Leader, gave the background and organizational makeup (NCTR, NIEHS and NIOSH)

of these programs, and discussed the Coordinating Group which develops program approaches, coordinates activities to provide thorough chemical evaluation and to avoid redundancy, and collaborates with other investigators in each agency to develop protocols for specific projects. The members of the Coordinating Group are Dr. Kimmel, Mr. B. Hardin, NIOSH, and Dr. J. Lamb, NIEHS. She discussed proposed and in place approaches to screening chemicals for reproductive and developmental toxicology. If little or no toxicologic information is available, there are three entry level protocols. These are (1) sperm morphology/vaginal cytology assays, (2) mating trial studies, and (3) the short-term in vivo reproductive toxicity assay ("Chernoff test"). The first protocol has been incorporated into the prechronic (90 day) toxicologic characterization study while the second, which involves exposure of animals prior to mating followed by examination of litters for effects, also can be included in the prechronic study when indicated. The Chernoff test has been used by NIOSH to examine structure/activity relationships for the glycol ethers. The results from the entry level protocols then can be used to set priorities for further testing which could include (1) a conventional teratology study, (2) fertility assessment by continuous breeding, (3) postnatal functional evaluation (this can be included as an extension of conventional teratology), as well as special designs. Newer procedures being developed and/or validated which were to be discussed in more detail included (1) in vitro teratology assays, (2) the collaborative teratology study, (3) male and female reproductive toxicity methods, and (4) human fertility assessment. Dr. Kimmel concluded that an important objective of the various programs was to develop basic research information that would provide bases for test development and interpretation of test results.

Dr. Whittemore said the various programs appeared to have needs for complex statistical analyses and wondered how the needs were met. Dr. Kimmel replied that the programs at each agency had an active statistical group providing support, and in at least one case, the conventional teratology contract, a member of the project advisory group is a statistician. Dr. Swenberg asked how often sperm morphology/vaginal cytology is included in prechronic testing. Dr. Moore said NTP aimed to include the assessment in the testing of 25-28 chemicals per year.

B. Teratology

- (1) Conventional Teratology Testing: (Attachment 6) Dr. C. Kimmel said the basic design for most of the teratology studies did not differ from that used by other laboratories. She pointed out the results for all the conventional teratology assays, including inhalation exposure, done by NTP during FY 1980 - 1983 (Attachment 6). Dr. Kimmel discussed the basis for selection of a chemical to be tested. Some were chosen because of interest by individual investigators. However, most of those tested were chosen either because of special agency need, e.g., ethylene oxide because of a request by the Bureau of Medical Devices, FDA, or because they had passed through the regular NTP chemical selection process. Dr. Kimmel said that chemicals of most concern are those where there is fetotoxicity or malformations at doses

which do not produce maternal toxicity. She noted that the capacity of the contract for conventional teratology testing was five to six chemicals per year in each of two species.

Discussion - Dr. Hurley inquired as to how maternal toxicity was determined. Dr. Kimmel responded that maternal death, reduction in weight or changes in organ weight where a target organ was known, were determinants. In response to questions from Drs. Manson and Whittemore, she said there was no inhalation exposure capability in the current contract, and the choice of species to test was based on previous experience, information from the literature, or if there had been a carcinogenesis bioassay of the chemical, at least one species could be the same as used for the bioassay. Dr. Manson inquired as to how doses were chosen that would not be maternally toxic, and Dr. Kimmel said a dose-finding study was always used. The high dose chosen was about at LD₁₀ and the low dose was, hopefully, non-toxic to the mother. Dr. Mendelsohn wanted to know if the results were correlated with results from other types of studies. Drs. Kimmel and Moore said that with the possible exception of the Chernoff Test, there was not enough data with the newer assays for cross comparisons but within a few years there should be. Dr. Rall said that NTP needed to review the results with the Board in a few years when there was more of a data base. There was discussion between Dr. Swenberg and Dr. Kimmel concerning the Good Laboratory Practice (GLP) and quality assurance procedures required for the contract. All studies on the contract are GLP and the NTP quality assurance officer performs inspections. Dr. B. Johnson, NIOSH, said there is total adherence to GLPs written into inhalation teratology contracts, and monitoring by a NIOSH quality assurance audit group. Dr. Swenberg stated that quality assurance should be comparable to that in the carcinogenesis testing program.

- (2) Short-Term In Vivo Reproductive Toxicity Assay: (Attachment 7) Mr. B. Hardin, NIOSH, said the in vivo test, developed by Dr. N. Chernoff and coworkers at the EPA, had been approved for concept by the NTP Board in 1981. He said the test was being used primarily for priority - setting or for structure-activity relationship (SAR) studies. With regard to SAR, 15 glycols and glycol ethers were being evaluated. He cautioned against overinterpreting the results obtained; the test should not be used to label a chemical as a teratogen nor give a chemical a 'clean bill of health' but rather to identify chemicals of concern. Mr. Hardin described the experimental design and toxic endpoints measured with the test. He noted that the dose used was approximately a LD₁₀. He discussed results of the Chernoff test on a series of glycol ethers and other compounds in four contract laboratories (Attachment 8). A positive control, sodium selenite, and a negative control, ethylene thiourea, were tested in each laboratory, and assays were run 'blind'. When a scatter plot was made of percent maternal mortality (x axis) vs. percent viable litters (y axis), all of the methyl ethers were on the bottom (Attachment 9). Some of these derivatives have been shown by others to be teratogenic. Mr. Hardin discussed the factors considered in determining priorities for other testing or retesting at a lower or higher dose with degree of maternal mortality as the index (Attachments 10 and 11).

Discussion - There were questions from reviewers about the statistical analyses used and how the effects of other environmental factors on resorption of litters were measured.

- (3) In Vitro Teratology Test Development: (Attachment 12) Dr. G. Kimmel said in vitro teratology tests would aid in overall test evaluation and results would be used to set priorities for conventional in vivo teratology testing. A concept proposed in this area was approved by the Board in 1981. There are three major aspects which have been or are being addressed. The first aspect was the organization of a workshop to address issues specific to the development and application of in vitro test systems. This workshop was held in August 1981. Four specific questions served as foci for the workshop. These interrelated questions and the discussion relative to them are described (Attachment 13). Two recommendations from the workshop recently were addressed. The first was development of a list of agents that can be used for test validation. For the most part, only agents with an adequate literature data base were included, and a final list of 47 agents has been established which contains roughly equal numbers of known positive and negative teratogens. The second recommendation was to establish a repository for chemicals chosen, in order that a uniform source would be available for investigators evaluating particular in vitro assays.

The second aspect of the concept proposal was to initiate test validation. Dr. Kimmel briefly described the status of these efforts. At NIEHS, contract proposals have been approved for concept and are being advertised for assessing two cell culture systems, the tumor cell attachment inhibition assay and the human palatal mesenchyme cell growth inhibition assay, for their combined accuracy in predicting teratogenicity (Attachment 14). At NCTR, the rat whole embryo culture system will be developed and appropriate endpoints defined which will indicate teratogenic potential. At NIOSH, a system involving exposure of Drosophila larva is being developed. The third aspect was to establish a literature review system that could monitor the literature for studies on in vitro test development and validation. Dr. Kimmel spoke to future directions (1983-1985) as being concerned with: (1) publication and updating of the list of selected chemicals for validation studies and establishment of the repository to make supplies of these chemicals widely available, and (2) continued progress of the development and validation of in vitro tests described, as well as support of two to four contract laboratories at an annual cost of \$300,000 to \$500,000 in validation of other selected in vitro assays. In conclusion, he said that the workshop had indicated considerable work had been done with in vitro systems but relatively little effort had been given to validation and application of the systems studied. Further, NTP must define how the in vitro tests fit into an overall screening system.

Discussion: Dr. Hitchcock inquired as to intramural staff efforts in the in vitro area. At NCTR, there are three persons working part time on whole

embryo culture while at NIOSH there is one person working part time on the Drosophila system. The NIEHS/NTP has no intramural staff effort as their two in vitro systems will be evaluated on contract. Dr. Manson asked for discussion on why the four in vitro systems described were chosen over others available. Dr. Kimmel said the whole embryo culture and Drosophila systems were being studied prior to the workshop. Dr. Lamb said the two test systems NIEHS was pursuing drew on experience of NIEHS investigators and had the advantage that the developers of the two systems were willing to serve as expert advisors. Dr. Manson observed that whole embryo culture was the most widely used at least in terms of numbers of laboratories studying the system. As regards support of extramural studies, Dr. Kimmel noted that a project advisory group will be established to determine which systems may be most appropriately included in the validation process, and that the proceedings of the workshop will aid in that determination.

- (4) Collaborative Behavioral Teratology Study: (Attachment 15)
 Dr. J. Adams, NCTR, gave background information which supports the need for development of sensitive and reliable tests for neurobehavioral dysfunction resulting from prenatal and perinatal insults. The NTP study, jointly sponsored by FDA and NIOSH, grew out of the awareness of the need for validation of such tests. Test methods were selected by an advisory panel, and the study was designed to evaluate intra- and inter-laboratory reliability and sensitivity of the tests with D-amphetamine sulfate and methylmercuric chloride chosen as positive control agents. The study is being conducted by the NCTR, Childrens' Hospital in Cincinnati, the VA Hospital in St. Louis, Syracuse University, the University of Missouri-Columbia, and Science Applications, Inc. Dr. Adams described questions addressed in design of the protocol and experimental design considerations. She presented data which (1) compared controls from the amphetamine study with controls from the methylmercury study which illustrated overall similarity of test responses in two studies from the same laboratory (NCTR), (2) examined alterations in test response in animals treated with amphetamine and methylmercury, and (3) showed that 'test experience' gained in testing during preweaning affected test results measured in the postweaning period. From the data obtained at NCTR, Dr. Adams concluded that auditory startle and pharmacologic challenge were the most useful tests so far.

Discussion: Dr. Hurley inquired as to how effects of the chemicals on the mother might affect responses in the offspring. Dr. Adams replied that the focus was on assessing reliability of the tests and potential maternal contributions had not been looked for. There was discussion around the issue of whether higher doses of amphetamine should have been used since minimal behavioral effects were seen. Dr. Adams commented that from a screening standpoint it was important to determine if behavioral test could detect chemical insults in the absence of gross physical signs of toxicity. Therefore, low doses of amphetamine were purposely chosen. Dr. Kimmel stressed the importance of longitudinal evaluation since the data may indicate that the critical times when behavioral effects can be seen with methylmercury may be quite different from times for amphetamine. Dr. Adams stated that animal age at testing may be critical with respect to sensitivity of test systems. The NCTR studies were begun six months prior to studies in

the other laboratories so that adjustments could be made in their protocols based on experience from the NCTR studies. Dr. Hook inquired as to the extent of interaction with related programs in other laboratories. Dr. C. Kimmel replied that they had considerable interaction both in design of the studies and subsequently with scientists from the NIEHS intramural program (Dr. H. Tilson) and from the EPA.

C. FERTILITY AND REPRODUCTIVE TOXICITY (Attachment 16)

Dr. J. Lamb, NIEHS, stated that the fertility and reproductive group has two goals: (1) develop and evaluate new testing systems in reproductive toxicology, and (2) provide hazard data as it becomes available on potential reproductive toxicants. He noted the close integration and application of intramural research and method development and validation and testing done on contracts. Data from testing and method development efforts are used to select chemicals for in-house research studies which in turn provide information to aid the contract studies. The primary contracted efforts are (1) fertility assessment by continuous breeding and (2) sperm morphology and vaginal cytology evaluation. In-house research efforts are concerned with indepth studies on tetrachlorodibenzofurans (TCDF), dibromochloropropane (DBCP), phthalate esters, glycol ethers, dimethylmethyl phosphonate, and Kepone (chlordecone).

(1) Fertility Assessment Using Continuous Breeding (FACB):

(Attachments 16 and 17) Dr. Lamb said FACB is a comprehensive screening system where both sexes are exposed to the test chemical and treated and control animals are cohabited continuously as breeding pairs. The FACB can yield data comparable to the more expensive and longer-term multigeneration assay. He said FACB was in the first year of a multiyear contract so only preliminary data were available. There are two laboratories, Research Triangle Institute and Environmental Health Research and Testing, each testing eight chemicals to evaluate the protocol. Most of the chemicals have known positive or negative reproductive toxicity and four chemicals are tested by each laboratory to assess interlaboratory reproducibility. Dr. Lamb described the protocol which includes a dose-finding study, 100 day breeding trial, determination of which sex is affected or offspring assessment, and, in some cases, hormone analyses. He then discussed in detail preliminary results of FACB studies with diethylhexyl phthalate (DEHP). Significant dose-related decreases in fertility were observed in mice of both sexes. Preliminary findings with the FACB indicates the system derives comprehensive data on chemical toxicity to fertility, offspring survival and target organs. Test development will continue over the next two years.

(2) Evaluation of Sperm Morphology and Vaginal Cytology in Prechronic Toxicity Testing: (Attachments 16 and 17) Dr. Lamb said the reproductive toxicity screen now is included in the protocol for all 13-week subchronic testing, and he listed chemicals selected for testing in FY 1982. The testing is done at each

individual testing laboratory; however, all the slides are read at one centralized laboratory. Dr. Lamb then described the protocol and findings for animals exposed to dimethylmethyl phosphonate. This study also included a mating trial. There was a significant decrease in male fertility at doses showing no clinical signs of toxicity, and decrease in pregnancy and litter size. He concluded by saying the protocol was a relatively inexpensive component of the subchronic study but was still being evaluated to determine whether it is significantly more sensitive than simple organ weight and histopathological endpoints.

Discussion: In response to a question by Dr. Manson, Dr. Lamb said with vaginal cytology they were trying to pick up responses such as estrogenic or anti-estrogenic effects which lead to persistent estrous or diestrous. He said they also need to look at ovarian functional effects. Dr. Swenberg praised the study and suggested NTP examine recovery after cessation of exposure.

- (3) Experimental Models of Male Reproductive Toxicity: (Attachment 16) Dr. R. Chapin, NIEHS, said the objectives of this program were: (1) to classify types of, and understand mechanisms leading to, chemically-induced male sterility, and (2) to develop screening methods for reliably identifying reproductive toxicants. He reviewed the anatomy and physiology of the male accessory sex organs including stages of spermatogenesis. The experimental design uses serial sacrifices and high resolution light and electron microscopy to identify the target site(s) and the initial stages of a developing reproductive lesion. For example, does a chemical produce a lesion in a certain stage of spermatogenesis or does it affect the progression of spermatogenesis through all 14 stages. Dr. Chapin discussed lesions observed histopathologically in the testes and epididymides after exposure of animals to 2,5-hexanedione and methyl chloride, and effects of dimethylmethyl phosphonate on sperm function and morphology. After morphologic studies have identified cell types and/or compartments affected, biochemical studies are designed to analyze earlier or concomitant changes in cell physiology. He described studies with dimethylmethyl phosphonate and ethylene glycol. Morphologic and biochemical analyses will be complemented by serial mating studies and sperm tests, when appropriate, to further define effects of a chemical on fertility. Additionally, Dr. Chapin said the laboratory is focusing on developing and validating screening tests for male reproductive toxicity with current emphasis on Sertoli cell function. Normal Sertoli cell function is necessary for normal spermatogenesis. One of the proteins secreted by the cell is called Androgen Binding Protein (ABP). ABP secretion is known to decrease after treatment with a number of chemosterilants. This correlation is being exploited in developing a predictive test for testicular toxicity.
- (4) Methods for Male Fertility Assessment: (Attachment 18) Dr. S. Schrader, NIOSH, said the objective was to develop an andrology lab and examine semen from men who may have been exposed to

occupational hazards. He noted that traditional NIOSH field studies assessed sperm count and morphology which measures may be adequate for demonstrating sterility but not subtle decrements in male fertility. Recent reports indicate percent motility has the highest and only significant correlation with fertilizing capacity. Dr. Schrader described the procedures to be evaluated during the next year in rabbits challenged with a known male reproductive toxin. Analyses to be evaluated include: (1) methods for sperm counting both using a Makler chamber and a hemacytometer; (2) morphology using two types of measurement; (3) sperm viability using vital staining and newer methods such as hypo-osmotic swelling; (4) progressive motility using videographic analysis and time exposure darkfield photomicrographs; and (5) a mucus penetration assay using either bovine cervical mucus or a synthetic mucus. During the first year after these procedures have been developed, they will be tested further in rabbits exposed to other known reproductive toxins. He said the best procedures will be applied in NIOSH field studies of men exposed to possible toxicants. The second year a mobile andrology laboratory will be collecting and doing preliminary analyses on semen samples. The project will cost about \$70,000 per year and one and a half staff years.

Discussion: Dr. Amann inquired as to how the problem of variable abstinence would be dealt with. Dr. Schrader conceded it would be a problem and said they were going to evaluate the validity of data obtained by dividing the number of days of abstinence into the total volume of ejaculate.

- (5) Experimental Models of Female Reproductive Toxicity: (Attachment 19) Dr. Lamb stated the aim of this project was to try and separate neuroendocrine effects of chlordecone (Kepone) from direct reproductive effects in female rats using a silastic implant chemical delivery system to provide sustained release of the chemical. He described the human toxicity and biological activity of Kepone. The NTP studies compared estrogenic effects of Kepone with those of diethylstilbestrol (DES). At the highest tolerated dose of Kepone, increases in uterine wet weight, increases in uterine peroxidase (biochemical and histochemical assays), and effects on uterine morphology (scanning electron microscopy) were comparable to that observed in DES-treated animals. Dr. Lamb then described neuroendocrine responses. There was increased pituitary weight after exposure to DES, but not Kepone; decreases in luteinizing and follicle-stimulating hormones were greater with DES than with Kepone; and there was a slight increase in prolactin after Kepone, and a large increase with DES. In vitro studies with or without GnRH indicated that, without hypothalamic control, pituitaries from Kepone-treated rats respond very much like pituitaries from DES-treated animals. He concluded that Kepone serves as an excellent model compound for neuroendocrine effects, female reproductive toxicity and evaluation of in vitro systems such as pituitary culture for applicability to the testing program.
- (6) Postnatal Toxicity: (Attachments 20 and 21) Dr. B. Schwetz, NIEHS, said his area of research would complement others in

the program in reproductive and developmental toxicology. Efforts are proposed to improve our ability to characterize the toxicity of chemicals relative to that in adults, and to identify the role of lactation in the induction of neonatal toxicity. Early on, the aim will be to quantify doses in neonates by doing chemical disposition in neonates and mothers. He cited an example of such a study in the clinical literature with theophylline. Dr. Schwetz said the F344 rat would be used and described the experimental design and techniques to be established. He said chemicals chosen for study would be ones for which there is evidence that the neonate is "more sensitive" than the adult animal. Additional criteria are: (1) analytical methods are available, (2) the chemical is not highly metabolized, and (3) the chemical can be handled in NIEHS laboratories. The best candidates for study include acrylamide, benzo(a)pyrene, glycol ethers, and pentachlorophenol. In conclusion, they hoped to quantify toxicity data seen in other NTP reproduction studies, and relate excretion in milk to the toxicity seen.

Discussion: Dr. Manson said these were studies which needed to be done. She commented on the probable difficulty of getting enough milk for analysis on postnatal day two. Dr. Schwetz replied that with the high dose levels and analytical methods available there should be enough. Drs. Manson and Hurley suggested that the nutritional quality of the milk and the effects of milking itself should be investigated. Dr. Schwetz agreed.

- (7) Concluding Remarks: Dr. C. Kimmel summed up by pointing out the several areas in both developmental toxicology and reproductive toxicology in which investigations were proceeding. She said no one agency could have addressed all of these areas while the integrated ongoing efforts reflected close interagency coordination as exemplified by the Coordinating Group. She noted limitations in manpower and resources, and pointed out proportional distribution of efforts among function areas as follows:

	NTP Man Years (14 total)	Contract Effort (equivalent of 24 man years)*	Total Effort
Method Development & Improvement	68%	42%	49%
Safety Evaluation	20%	58%	46%
Mechanism Studies	12%		5%

* Contract dollars converted to one man year/\$60k

III. A Proposal to Develop Guidelines for the Detection and Evaluation of Chemical Carcinogens: (Attachment 22) Dr. Nelson introduced the topic and said that in simple terms the objective of this proposal would be to generate information on how best to test for chemical carcinogenesis. Dr. Moore said carcinogenesis testing was the most visible component of

the NTP. He commented on the large time commitment long-term testing involved, and noted the many changes made in test protocols by the NTP which were made also to enhance broader toxicologic characterization of chemicals. These changes include chemical disposition studies, addition of a third dose to two-year studies, an interim sacrifice for chronic toxicity evaluation, and establishment of a current historical control data base. He said that to the casual observer these changes may appear haphazard, although they are not. NTP asks the Board to endorse the concept that current and more thorough evaluation should be done by an ad hoc group of scientists in chemical carcinogenesis expert on the best approaches for testing chemicals for carcinogenic effects. This group should include all viewpoints. After review of the resulting report presented to the Board, NTP staff should respond to the Board as to how recommended practices may differ from current NTP practices, and what NTP proposes to do about the differences. Dr. Moore discussed the topic areas (Attachment 22) and said others may be added.

Dr. Nelson viewed the proposed activity as a hallmark in the testing of chemicals for carcinogenesis. He said the last thorough evaluation was published by the NCI in 1976, and a further document was published by the National Cancer Advisory Board in 1978. He also mentioned the International Agency For Research on Cancer international conference in June 1980 (Supplement 2). He saw the review as following three primary areas: (1) Protocol design - including statistics, diet, dose selection, etc., (2) Pathological evaluation - quite current due to recent NTP efforts to improve, and (3) Evaluation - a difficult area to which NTP continues to devote considerable scientific effort.

Discussion. Dr. D. Hughes, Proctor and Gamble, representing the American Industrial Health Council (AIHC), said the AIHC believes the NTP programs should be state-of-the-art as the data are used by regulatory agencies. AIHC acknowledged improvements which the NTP has made in the carcinogenesis testing process. The AIHC welcomes the formation of an independent review committee and feels the outcome should be important for hazard evaluation leading to improvements in scientific risk assessment. Dr. Nelson said the effort literally will be watched around the world.

The Board charged the ad hoc Panel: "To review the basic biology and chemistry of chemical carcinogenesis and recommend to the Board methods that the NTP should use for the detection and evaluation of chemical carcinogens". The nominees for the ad hoc Panel have been contacted and have agreed to participate. (Attachment 23) Three NTP Board members on the Panel will serve as liaison between the Board and the Panel. Dr. Rall said all meetings would be open and announced in advance in the Federal Register. All are encouraged to input to the ad hoc Panel. He said there was no specific time limit for completion of a report but we would like a preliminary report by autumn and a final report by the spring of 1984. There would be ample time for public comment on the preliminary report.

IV. Peer Review and Priority Ranking of Chemicals Nominated for NTP Testing: (Attachment 24) There were 16 chemical nominations to be considered by the Board. All had been reviewed previously by the NTP Chemical Evaluation

Committee (CEC) on July 15, 1982, and announced along with types of testing recommended by the CEC in the Federal Register of October 12, 1982. Of the 14 chemicals nominated for testing by the NCI, 12 were thiazole compounds selected from a class study of this group of chemicals; the other two nominations were D-fructose and cromolyn sodium. Thiabendazole was nominated by an industrial representative as a representative benzimidazole compound. Butyl benzyl phthalate was nominated for reproductive effects testing by the Environmental Protection Agency. In response to a request by the Board at the September 24, 1983 meeting, references compiled by the NCTR Chemical Review staff and other materials submitted on the 16 chemicals were available at the meeting.

The Chairperson of the CEC, Dr. L. Fishbein, NCTR, and two members, Dr. D. Canter, NIEHS, and Dr. B. Johnson, NIOSH, were present to assist the Board. Each Board member had been asked to review two or three chemicals prior to the meeting. Following oral presentation of the members' review and of the CEC testing recommendations for each chemical and discussion, a motion was made and voted on by the Board members. The approved recommendations, priority for testing, and additional remarks are summarized (Attachment 25).

- V. Other Business: Dr. D. Rall reported that the House of Representatives Committee on Appropriations has asked the NIEHS to develop a Third Task Force for Research Planning in Environmental Health Sciences, six years having passed since the Second Task Force completed its report. He said this task force would be structured like the last one; however, it will be less global in approach, and more focused on specific environmental health problems anticipated through the end of the decade. Dr. Rall asked for input from the Board as to a potential chairperson for the Task Force. He said that a small planning committee had been formed composed of members drawn from various NIEHS advisory committees and the NTP Board. Dr. M. Horning is the representative on the Committee from the NTP Board.

Dr. Rall thanked the four retiring charter members of the Board, Dr. Nelson, Dr. Hitchcock, Dr. Horning, and Dr. Whittemore, for their service. Dr. Nelson, retiring Chairman, praised Dr. Hitchcock for her contributions as the first Chairperson of the Technical Reports Review Subcommittee. Beginning in June, 1980, the Subcommittee and associated ad hoc Panel of Experts have been responsible for providing peer review of draft reports of NTP long-term carcinogenesis and toxicology studies.

The meeting was adjourned.

National Center for Health Services Research; Assessment of Medical Technology Cardiac Pacemaker Monitors

The Public Health Service (PHS) through the Office of Health Technology Assessment (OHTA) announces that it is coordinating an assessment of what is known of the safety and clinical effectiveness of self-contained cardiac pacemaker monitors. Specifically, we are interested in: (1) Generically defining a self-contained pacemaker monitor that will permit us to: (a) distinguish between a telephone transmitting device and a self-contained monitor; and (b) permit the patient to acquire sufficient information to enable him or her to make an informed decision as to whether to seek medical intervention; (2) medical indications for the type or types of patient(s) who would benefit from a self-contained pacemaker; and (3) whether the use of a self-contained pacemaker monitor eliminates or reduces the need for transtelephonic monitoring of the patient's pacemaker. If research data for the third query are positive, then appropriate guidelines are needed for screening transtelephonic pacemaker monitoring. Also, frequency guidelines for transtelephonic pacemaker monitoring will need review in the light of the newest research data related to the effectiveness and accuracy of self-contained pacemaker monitors in detecting, e.g., state of the battery, electronic circuitry component failure, electrode displacement, generator-electrode junction failure, and exit block. For the purposes of this announcement, self-contained pacemaker monitors are a type of indirect pacemaker generator function analyzers that are used to identify early signs of possible cardiac pacemaker failure or malfunction.

The PHS assessment consists of a synthesis of information obtained from appropriate organizations in the private sector and from PHS agencies and others in the Federal Government. PHS assessments are based on the most current knowledge concerning the safety and clinical effectiveness of a technology. Based on this assessment, a PHS recommendation will be formulated to assist the Health Care Financing Administration (HCFA) in establishing Medicare coverage policy. Any person or group wishing to provide OHTA with information relevant to this assessment should do so in writing no later than May 30, 1983, or approximately 90 days from the date of publication of this notice.

The information being sought is a review and assessment of past, current, and planned research related to this technology, a bibliography of published, controlled clinical trials and other well-designed clinical studies since 1979, and other information related to the characterization of the patient population most likely to benefit, the clinical acceptability, and the effectiveness of this technology. Proprietary information is not being sought.

Written material should be submitted to: Office of Health Technology Assessment, Park Bldg., Room 3-10, Stop #2, 5600 Fishers Lane, Rockville, Maryland 20852.

For further information contact: Dr. Rita K. Chow, Health Science Analyst, at the above address or by telephone (301) 443-4990.

Dated: February 10, 1983.

Harold Margulies,

Director, Office of Health Technology Assessment, National Center for Health Services Research.

[FR Doc. 83-4619 Filed 2-23-83; 8:45 am]

BILLING CODE 4160-17-M

National Toxicology Program Board of Scientific Counselors; Meeting

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 March 14 and 15, 1983.

The meeting will be open to the public from 9:00 a.m. to 4:00 p.m., March 14. The preliminary agenda with *approximate* times are as follows:

9:00 a.m.—10:00 a.m. Status Report on NIH/NTP Investigation of Exocrine Pancreas Lesions in Male F344 Rats

10:00 a.m.—10:30 a.m. NIH/NTP Cellular and Genetic Toxicology Program—Concept Review: Evaluation of Human Cells *In Vitro* for Genetic Toxicity Assay

Review of NTP Reproductive and Developmental Toxicology Programs:
11:00 a.m.—12:00 p.m.—I. Overview of Programs

1:00 p.m.—4:00 p.m.—II. Teratology
a. Conventional Teratology Testing
b. Short-Term *In Vivo* Reproductive Toxicity Assay
c. *In Vitro* Teratology Test Development
d. Collaborative Behavioral Teratology Study

The meeting on March 15 will be open to the public from 8:30 a.m. to 12:30 p.m.,

and from 3:00 p.m. to adjournment. The preliminary agenda with *approximate* times are as follows:

8:30 a.m.—11:30 a.m.—III. Fertility and Reproductive Toxicity
a. Evaluation of Sperm Morphology and Vaginal Cytology in Prechronic Toxicity Testing
b. Fertility Assessment Using Continuous Breeding
c. Experimental Models of Female Reproductive Toxicity
d. Experimental Models of Male Reproductive Toxicity
e. Methods for Fertility Assessment
f. Postnatal Toxicity

11:30 a.m.—12:30 p.m.—IV. A Proposal To Develop Guidelines for the Detection and Hazard Evaluation of Chemical Carcinogens

3:00 p.m.—5:00 p.m.—Peer Review and Priority Ranking of Chemicals Nominated for NTP Testing. (Sixteen chemical nominations will be reviewed and are listed in the *Federal Register*, Volume 47, No. 197, pp. 44884-44885, October 12, 1982.)

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 March 14 from 4:00 p.m. to adjournment and on March 15 from 1:00 p.m. to 3:00 p.m. for further evaluation of NTP programs in reproductive and developmental toxicology, 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 closed meeting will be used also to discuss professional qualifications and select members for an ad hoc scientific panel which will report to the NTP Board with an evaluation and recommendations concerning the proposal to develop guidelines for the detection and hazard evaluation of chemical carcinogens. Disclosure of these discussions would constitute a clearly unwarranted invasion of personal privacy with regard to persons being considered for the panel.

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.

Dated: January 28, 1983.

David P. Rall,

Director, National Toxicology Program.

[FR Doc. 83-4734 Filed 2-23-83; 8:45 am]

BILLING CODE 4140-01-M

Office of the Secretary

Advisory Council on Social Security; Meeting

AGENCY: Office of the Secretary, HHS.

ACTION: Notice of meeting.

SUMMARY: Pursuant to Section 10(a)(2) of Pub. L. 92-463, the Federal Advisory Committee Act, notice is hereby given of a meeting of the Advisory Council on Social Security, as established by the Secretary of Health and Human Services in accordance with Section 706 of the Social Security Act, 42 U.S.C. 907.

DATE/ADDRESS: The meeting will be held on March 13 from 12 noon to 6:00 p.m. and on March 14 from 9:00 a.m. to 4:00 p.m. at the Columbia Club, 121 Monument Circle, Indianapolis, Indiana 46204.

FOR FURTHER INFORMATION CONTACT: Thomas R. Burke, Executive Director, Advisory Council on Social Security, 200 Independence Avenue, S.W., Washington, D.C. 20201; telephone (202) 755-8670/71.

SUPPLEMENTARY INFORMATION: The meeting is open to the public. Attendance will be limited to the space available. Interested parties may submit written presentations for consideration by Council until March 15, 1983.

Correspondence can be addressed to Advisory Council on Social Security, 200 Independence Avenue, S.W., Washington, D.C. 20201.

Sign language interpreting services will be provided if requested in advance.

The proposed meeting agenda includes further briefings and discussion on the Medicare program; and such other business as the Chairperson, the Executive Director, or the membership may put before the Council.

A previous meeting of the Advisory Council on Social Security was announced in 48 FR 4048-4049, January 28, 1983.

Records are kept of all Council proceedings and are available for public inspection at the Office of the Administrative Officer, Advisory Council on Social Security, Room 317-H,

HHH Building, 200 Independence Avenue, S.W., Washington, D.C. 20201.

Philip M. Jos,

Acting Executive Director.

[FR Doc. 83-4670 Filed 2-23-83; 8:45 am]

BILLING CODE 4120-03-M

Advisory Council on Social Security; Public Hearing

AGENCY: Office of the Secretary, HHS.

ACTION: Notice of public hearing.

SUMMARY: The Secretary of Health and Human Services announced on September 16, 1982 the establishment of the Advisory Council on Social Security. The Council is charged to place particular emphasis on a review of the Medicare program, and to prepare and submit reports on its findings and recommendations.

In an effort to obtain the views of interested organizations and individuals, within the constraints of available time, the Council decided to conduct public hearings in designated locations around the country. Notice is hereby given that a 1-day hearing will be held in New Brunswick, New Jersey on March 22, 1983. Similar 1-day hearings were previously announced in 47 FR 56723, December 20, 1982 for San Francisco, California on February 24; in 48 FR 1549, January 13, 1983 for the Chicago area on March 9, and in 48 FR 5312, February 4, 1983 for St. Petersburg, Florida on March 1. All hearings will run from 9:00 a.m. to 5:00 p.m.

ADDRESS: The New Brunswick hearing will be held in the Labor Education Center, Rutgers University, Ryder's Lane and Clifton Avenue, New Brunswick, New Jersey 08903

FOR FURTHER INFORMATION CONTACT: Thomas R. Burke, Executive Director, Advisory Council on Social Security, 200 Independence Avenue, S.W., Washington, D.C. 20201; telephone (202) 755-8670 or 755-8671.

SUPPLEMENTARY INFORMATION: The hearings are open to the public. Attendance will be limited to the space available. Interested parties are invited to present testimony on Medicare issues; however, only those requesting in advance, preferably in writing, to appear will be permitted to present oral statements. Presenters should submit, 5 days in advance, 20 copies of their presentation, and should bring an additional 50 copies to the hearing to be made available to the public. Oral presentation should summarize the written statement, and will be limited to a maximum of 5 minutes. Other written material can be submitted for the record. Submit written requests to

present testimony to the Advisory Council on Social Security, ATTN: Public Hearing, 200 Independence Avenue, S.W., Washington, D.C. 20201, or telephone (202) 755-8670 or 755-8671. The designated Chairperson or the Executive Director reserves the right to determine order of presentation, but will make every effort, within available time, to hear all who wish to be heard.

Sign language interpreting services will be provided if requested in advance.

Records will be kept of all public hearings and will be available for public inspection at the Office of the Administrative Officer, Advisory Council on Social Security, Room 317-H, HHH Building, 200 Independence Avenue, S.W., Washington, D.C. 20201.

Philip M. Jos,

Acting Executive Director.

[FR Doc. 83-4671 Filed 2-23-83; 8:45 am]

BILLING CODE 4120-03-M

Social Security Administration

Conformity of Public Assistance Plan of the State of Minnesota With the Social Security Act; Change of Date and Location of Hearing

The date and location of the hearing to reconsider the disapproval of Minnesota's State Plan Submittal No. 82-24 noticed in 48 F.R. 3658, January 26, 1983, have been changed.

The hearing is rescheduled for 10 A.M. on March 10, 1983, in rooms 337-339A of the Hubert H. Humphrey Building, 200 Independence Avenue, S.W., Washington, D.C.

Dated: February 14, 1983.

Alexander G. Teitz,

Presiding Officer.

[FR Doc. 83-4669 Filed 2-23-83; 8:45 am]

BILLING CODE 4190-11-M

1983 Contribution and Benefit Base Under Pre-1977 Amendment Law

AGENCY: Social Security Administration, HHS.

ACTION: Notice of determination of the "Old-Law" Social Security contribution and benefit base.

SUMMARY: The Social Security Amendments of 1977 set the contribution and benefit base at \$22,900 for 1979, \$25,900 for 1980 and \$29,700 for 1981. After 1981, the base increases as average wage levels rise. The contribution and benefit base is the maximum annual amount of earnings that is subject to Social Security taxes and is creditable toward Social Security

AGENDA

Board of Scientific Counselors
National Toxicology Program
March 14-15, 1983

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

Monday, March 14, 1983

OPEN

- | | | |
|-------------------------|---|---------------------------------|
| 9:00 a.m. - 10:00 a.m. | STATUS REPORT ON NIH/NTP
INVESTIGATION OF EXOCRINE
PANCREATIC LESIONS IN F344
RATS | Dr. Gary Boorman,
NIEHS |
| 10:00 a.m. - 10:30 a.m. | NIH/NTP CELLULAR AND
GENETIC TOXICOLOGY
PROGRAM - CONCEPT REVIEW:
Evaluation of Human Cells
<u>In Vitro</u> for Genetic
Toxicity Assay | Dr. Robert Langenbach,
NIEHS |

REVIEW OF NTP REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY PROGRAMS:

- | | | |
|-------------------------|--|----------------------------|
| 11:00 a.m. - 12:00 p.m. | I. OVERVIEW OF PROGRAMS | Dr. Carole Kimmel,
NCTR |
| 1:00 p.m. - 4:00 p.m. | II. TERATOLOGY | |
| | a. Conventional Teratology
Testing | Dr. Kimmel |
| | b. Short-Term <u>In Vivo</u>
Reproductive Toxicity
Assay | Mr. Bryan Hardin,
NIOSH |
| | c. <u>In Vitro</u> Teratology
Test Development | Dr. Gary Kimmel,
NCTR |
| | d. Collaborative Behavioral
Teratology Study | Dr. Jane Adams,
NCTR |

CLOSED

- | | | |
|-----------------------|--|-----------------------|
| 4:00 p.m. - 5:00 p.m. | EVALUATION OF PROGRAMS
AND PERSONNEL IN REPRO-
DUCTIVE AND DEVELOPMENTAL
TOXICOLOGY | Board and Consultants |
|-----------------------|--|-----------------------|

Tuesday, March 15, 1983

OPEN

REVIEW OF NTP REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY PROGRAMS (Continued):

8:30 a.m. - 11:30 a.m.	III. FERTILITY AND REPRODUCTIVE TOXICITY	
	a. Evaluation of Sperm Morphology and Vaginal Cytology in Prechronic Toxicity Testing	Dr. James Lamb, NIEHS
	b. Fertility Assessment Using Continuous Breeding	Dr. Lamb
	c. Experimental Models of Female Reproductive Toxicity	Dr. Lamb
	d. Experimental Models of Reproductive Male Toxicity	Dr. Robert Chapin, NIEHS
	e. Methods for Fertility Assessment	Dr. Steven Schrader, NIOSH
	f. Postnatal Toxicity	Dr. Bernard Schwetz, NIEHS
11:30 a.m. - 12:30 p.m.	A PROPOSAL TO DEVELOP GUIDELINES FOR THE DETECTION AND HAZARD EVALUATION OF CHEMICAL CARCINOGENS	Dr. John Moore, NIEHS
		CLOSED
1:00 p.m. - 3:00 p.m.	EVALUATION OF PROGRAMS AND PERSONNEL IN REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY; EVALUATION AND SELECTION OF AN AD HOC PANEL TO DEVELOP GUIDELINES FOR DETECTION AND HAZARD EVALUATION OF CHEMICAL CARCINOGENS	Board and Consultants
		OPEN
3:00 p.m. - 5:00 p.m.	PEER REVIEW AND PRIORITY RANKING OF CHEMICALS NOMINATED FOR NTP TESTING	Board Dr. Dorothy Canter, NIEHS

March 1983

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS

Dr. Norton Nelson (Chairman) (1983)
Professor, Institute of Environmental
Medicine
550 First Avenue
New York, New York 10016
(212) 340-5281
(Toxicology, Environmental Carcinogenesis)

Dr. Jerry B. Hook (1986)
Professor and Director
Center for Environmental Toxicology
Michigan State University
East Lansing, Michigan 48824
(517) 353-6469
(Environmental Toxicology)

Dr. Leila Diamond (1985)
Professor
Wistar Institute
36th Street and Spruce
Philadelphia, Pennsylvania 19104
(215) 243-3931
(Chemical Carcinogenesis/Mutagenesis)

Dr. Marjorie G. Horning (1983)
Professor of Biochemistry
Institute for Lipid Research
Baylor College of Medicine
1200 Moursund
Room 826-E
Houston, Texas 77030
(713) 790-4721
(Analytical Pharmacology/Toxicology)

Dr. Curtis Harper (1985)
Associate Professor
Department of Pharmacology
School of Medicine
University of North Carolina
Chapel Hill, North Carolina 27514
(919) 966-4495
(Environmental Toxicology)

Dr. James A. Swenberg (1986)
Chief, Pathology Department
Chemical Industry Institute of Toxicology
6 Davis Drive
Research Triangle Park, NC 27709
(919) 541-2070
(Veterinary Pathology/Carcinogenesis)

Dr. Margaret Hitchcock (1983)
Associate Fellow
John B. Pierce Foundation Laboratory
New Haven, Connecticut 06519
(203) 562-9901
(Environmental Toxicology)

Dr. Alice S. Whittemore (1983)
Adjunct Professor
Department of Family, Community
and Preventive Medicine
School of Medicine
Stanford University
Stanford, California 94305
(415) 497-5460
(Biomathematics)

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS

MEETING OF MARCH 14 and 15, 1983

EXPERT CONSULTANTS FOR REVIEW OF
NTP REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY PROGRAMS

Dr. Rupert Amann
Animal Reproduction Laboratory
Colorado State University
Fort Collins, Colorado 80523

Dr. Lucille Hurley
Department of Nutrition
University of California at Davis
Davis, California 95616

Dr. Jeanne Manson
Department of Obstetrics and Gynecology
University of Cincinnati
Cincinnati, Ohio 45267

Board of Scientific Counselors

Review of 16 Chemicals

<u>Chemical</u>	<u>Recommendation</u>	<u>Remarks</u>
1) Thiazole	No additional testing	Low production, low exposure potential
2) 2-Thiazolamine	<u>Salmonella</u> assay In vitro cytogenetics	Examine genotoxic potential
3) 5-Phenyl-2,4-thiazole- diamine	No testing	Not produced or used in U.S.
4) 4-(6-Methyl-2-benzothia- zoly)benzenamine	<u>Salmonella</u> assay <u>Mouse lymphoma</u> assay In vitro cytogenetics	-Examine genotoxic potential -Consider additional toxicological test- ing following com- pletion of genotoxi- city testing
5) N,N-Diethyl-4-((5-nitro- 2-thiazoly)azo) benzenamine	No testing	Low production and usage
6) 3-Methyl-5-isothiazol- amine	<u>Salmonella</u> assay In vitro cytogenetics	Structure activity considerations
7) 6-Methoxy-2-benzothiazo- lamine	Carcinogenicity (Low)	-Evidence of mutagenicity -Potential for exposure
8) 5,6-Dichloro-2-benzothia- zolamine	<u>Salmonella</u> assay <u>Mouse lymphoma</u> assay	-Evaluate genotoxic potential -Consider additional toxicological testing following completion of genotoxicity testing
9) C.I. Basic Red 29	<u>Salmonella</u> assay (including special NTP protocol for azo compounds) in vitro cytogenetics Cell transformation studies Chemical analysis (Mod-Low)	Evaluate genotoxic potential

<u>Chemical</u>	<u>Recommendation</u>	<u>Remarks</u>
10) 2-Octyl-3-isothiazolone	<u>Salmonella</u> assay <u>Mouse Lymphoma</u> assay	Examine genotoxic potential
11) (4,4'-Bithiazole)-2,2'-diamine	No testing	Compound not commercially available
12) 2-Mercapto-4-methyl-5-thiazolyl methyl ketone	No testing	Low production and usage
13) Thiabendazole	No additional testing	Sufficient carcinogenicity testing already performed
14) Butyl benzyl phthalate	Reproductive effects (High) Carcinogenicity -- male and female rats (Moderate)	-Important plasticizer with high production and potential for exposure -CEC neurotoxicity test recommendation not supported
15) Cromolyn sodium	No testing	Substantial data available on animal toxicology and human health effects
16) D-Fructose	No testing	Low suspicion of toxicity

TESTING RECOMMENDATIONS FOR CHEMICALS REVIEWED BY
THE NTP BOARD OF SCIENTIFIC COUNSELORS ON MARCH 15, 1983

<u>Chemical</u>	<u>Recommendation</u>	<u>Remarks</u>
1) Thiazole	No additional testing	Low production, low exposure potential
2) 2-Thiazolamine	<u>Salmonella</u> assay <u>In vitro</u> cytogenetics	Examine genotoxic potential
3) 5-Phenyl-2,4-thiazole- diamine	No testing	Not produced or used in U.S.
4) 4-(6-Methyl-2-benzothia- zoly)benzenamine	<u>Salmonella</u> assay Mouse lymphoma assay <u>In vitro</u> cytogenetics	-Examine genotoxic potential -Consider additional toxicological test- ing following com- pletion of genotoxi- city testing
5) N,N-Diethyl-4-((5-nitro- 2-thiazoly)azo) benzenamine	No testing	Low production and usage
6) 3-Methyl-5-isothiazol- amine	<u>Salmonella</u> assay <u>In vitro</u> cytogenetics	Structure activity considerations
7) 6-Methoxy-2-benzothiazo- lamine	Carcinogenicity (Low)	-Evidence of mutagenicity -Potential for exposure
8) 5,6-Dichloro-2-benzothia- zolamine	<u>Salmonella</u> assay Mouse lymphoma assay	-Evaluate genotoxic potential -Consider additional toxicological testing following completion of genotoxicity testing
9) C.I.Basic Red 29	<u>Salmonella</u> assay (including special NTP protocol for azo com- pounds) <u>In vitro</u> cytogenetics Cell transformation studies Chemical analysis (Mod-Low)	Evaluate genotoxic potential

<u>Chemical</u>	<u>Recommendation</u>	<u>Remarks</u>
10) 2-Octyl-3-isothiazolone	<u>Salmonella</u> assay <u>Mouse Lymphoma</u> assay	Examine genotoxic potential
11) (4,4'-Bithiazole)-2,2'-diamine	No testing	Compound not commercially available
12) 2-Mercapto-4-methyl-5-thiazolyl methyl ketone	No testing	Low production and usage
13) Thiabendazole	No additional testing	Sufficient carcinogenicity testing already performed
14) Butyl benzyl phthalate	Reproductive effects (High) Carcinogenicity -- male and female rats (Moderate)	-Important plasticizer with high production and potential for exposure -CEC neurotoxicity test recommendation not supported
15) Cromolyn sodium	No testing	Substantial data available on animal toxicology and human health effects
16) D-Fructose	No testing	Low suspicion of toxicity