National Toxicology Program
Board of Scientific Counselors' Meeting
September 23 and 24, 1982

SUMMARY MINUTES

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Summary Minutes

The National Toxicology Program (NTP) Board of Scientific Counselors met on September 23 and 24, 1982, in the Auditorium, 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 March 10, 11 and 12, 1982, Board of Scientific Counselors' meeting were approved. Dr. N. Nelson, Board Chairman, said a number of issues were raised by the Technical Reports Review Subcommittee and Panel of Experts at the peer review meeting of the previous day, September 22, which were recurring problems in some of the bioassays and which could be addressed as an agenda item by the Board. Included were the issues of maximum tolerated dose, dose selection for chronic studies, and the appropriateness of corn oil gavage. Dr. Nelson suggested that the Subcommittee and Panel set aside time at their next meeting to examine these and related issues and report to the Board with conclusions, recommendations, etc. He said the Subcommittee would need to have background material to consider prior to the meeting.

Action Item: NTP should schedule time at the next bioassay reports peer review meeting for a discussion of problems with some bioassays, e.g., dose selection. The peer review members should receive background material on issues to be discussed prior to the meeting.

I. Overview of the National Toxicology Program: (Attachment 3) Dr. J. A. Moore, NTP Deputy Director, described the history and organizational structure of the NTP, and commented on the transfer of the NCI Carcinogenesis Bioassay Program to the NIEHS component of the NTP in FY 1981. He pointed out the proportions of NTP resources obligated to chemical testing, methods development, and validation for the four major program areas: carcinogenesis, toxicologic characterization, mutagenesis, and fertility and reproduction, and said NTP's aim was to gradually increase the proportion allocated to methods development and validation. A "fair" balance exists between testing and methods development and validation in the fertility and reproduction area. He noted the large methods development effort in cellular and genetic toxicology.

Dr. Moore discussed the three major types of studies which form the basis for setting priorities and establishing the experimental design for the two-year study: baseline toxicological characterization, a genetic toxicology battery which includes four major categories of tests, and basic chemical disposition.

He discussed the 45 chronic bioassays initiated in FY 1982 and said the experimental designs for many of these new starts demonstrated how NTP

now tailored the design to the chemical (Attachment 4). Twenty six of the starts included some type of interim sacrifice, while 18 included one or three-dose designs contrasted with the standard two-dose design. Dr. Whittemore asked whether an unbalanced design was used as proposed by Drs. Hoel and Portier, NIEHS, at the Board meeting on March 10, 1982. Dr. Moore said not specifically, but the doses used would fall within the dose range chosen for that design.

II. Discussion of Exocrine Pancreas Lesions in Male Fischer Rats: (Attachment 5: Investigation of Exocrine Pancreas Lesions) In view of the possible association between corn oil gavage and proliferative lesions of the exocrine pancreas in male F344 rats, NTP has been reevaluating slides of the pancreas from several recent studies and has refined diagnostic criteria for proliferative lesions of the exocrine pancreas. Dr. Maronpot, NIEHS, said this was initiated because of inconsistent or missed diagnoses of pancreatic acinar-cell hyperplasias and adenomas in certain recent studies. Corn oil (vehicle) controls were compared with untreated controls where available. He said there appeared to be no correlation between the volume or brand of corn oil administered and the development of lesions. Dr. Maronpot presented tentative conclusions (Attachment 5 updates these earlier incomplete observations). He said a causal relationship between corn oil administration and proliferative lesions of the exocrine pancreas had not been demonstrated. Among future plans were in-house experiments using the Longenecker short-term pancreas tumor model (with azaserine) to help clarify a possible role of corn oil in development of proliferative lesions of the exocrine pancreas.

Dr. Diamond asked whether NTP was examining slides from treated rats in the reevaluation studies. Dr. Moore said if the pancreas had been identified as a target organ the treated animals would be looked at also, e.g., the benzyl acetate study. There were several questions concerning analysis of the corn oil used. The NTP routinely analyzes for peroxides. Dr. Swenberg questioned whether there had been enough experience with the diagnostic criteria to be able to say whether there was progression from adenomas to carcinomas. Dr. McConnell, NIEHS, said the work statement indicates where a sample should be taken from the pancreas, and this along with the criteria would be amplified further and discussed in a fall meeting of NTP pathologists with contractor pathologists. Dr. Moore said that NCTR and the NTP have been examining microencapsulation as a means to administer volatile or unstable chemicals, as a possible alternative to gavage.

III. Status Report on Proposed Modifications of Pathology Requirements for Chronic Bioassays: (Attachment 6) Dr. McConnell said that in response to suggestions by the Board and consultants at the March meeting, NTP deleted gall bladder from the proposed baseline list of 12 organs or tissues and added the following: heart, stomach, ovary/uterus, testes/epididymis, prostate/seminal vesicles, and submandibular lymph nodes. Subsequent to appearance in the NTP Technical Bulletin, there had been considerable response from government agencies, academia and industry. He said the International Life Sciences Institute, which includes several of the industrial respondents, was presenting the protocol to the Pharmaceutical Manufacturers Association for their consideration. The responses were mostly positive;

however, several contained criticisms which Dr. McConnell addressed (Attachment 6, page 3). In particular were suggestions for additional tissues which should be included in the baseline list and tissues which should be deleted (Attachment 6, page 4).

Discussion - Dr. Whittemore asked how the interim kill would be affected if the maximum tolerated dose were exceeded. Dr. McConnell replied that the experiment would be compromised only if there was high early mortality in the low-dose animals also. Dr. J. M. Holland, Oak Ridge National Laboratory, opined there was too much emphasis on detecting tumor lesions and not enough on detecting toxic lesions; Dr. McConnell replied that the likelihood of detecting toxic lesions was greater with addition of the 15-month sacrifice, and further, any animals dying prior to 21 months would receive a complete histopathologic examination. He then presented three alternatives to the protocol and discussed why they were less desirable than the NTP proposal chosen (Attachment 6, page 5). Dr. Moore emphasized that the rationale for the modified protocol derived from indepth analysis of more than 200 carcinogenesis bioassays done by the NCI and NTP. Dr. M. Wind, Consumer Product Safety Commission (CPSC), said her agency was concerned initially that the new protocol might miss a positive response but after discussions with Dr. McConnell they were supportive. Dr. C. S. Lin, Food and Drug Administration (FDA), said his agency's concerns were (1) too narrow a data base was used and (2) the Environmental Protection Agency (EPA), FDA and OECD (Organization for Economic Cooperation and Development) guidelines on required pathology were in agreement and would be different than the NTP proposal. Dr. Moore said the NTP guidelines would be different since they were based on different data sets.

Specific Comments and Recommendations by Peer Reviewers:

Dr. Swenberg - CIIT uses a much larger pathology protocol but was considering adopting the modified NTP protocol. Using three doses would be especially beneficial if the high-dose exceeded the MTD and would provide an extra data point for hazard assessment.

Dr. Nelson - This approach would probably not miss anything but stressed that more interaction sould be sought with international agencies, such as OECD. Further, he said that NTP needed to better brief the 'bench' scientists in the regulatory agencies. Dr. Moore said this would be done. Dr. McConnell said the proposed protocols would be submitted for publication in a peer reviewed journal after the agency briefing. There ensued considerable discussion among the Board and NTP staff about the need to have further communication by NTP with the regulatory agencies to inform and discuss agency concerns about the protocol. Dr. Nelson concluded the discussion by saying there was a consensus among the Board members that such a meeting was necessary.

Action Item: NTP should schedule a meeting in the near future with appropriate scientists at the regulatory agencies to describe and discuss the NTP proposed modified pathology protocol.

IV. Historical Control Tumor Data Base: (Attachment 7) Dr. J. Haseman, NIEHS, presented a brief background description of how detailed tumor and non-tumor pathology data have been generated from the NCI/NTP bioassays and entered into the computerized Carcinogenesis Bioassay Data System (CBDS). He said a large array of historical control data has been accumulated and is being used in a limited way by NTP to make comparisons with current bioassays. NTP is now trying to determine how this data base can be utilized more effectively. He stressed that concurrent or matched controls will always be the primary control group for evaluating effects of chemicals. Dr. Haseman discussed the problems encountered when attempting to utilize an NCI/NTP historical control data base (Attachment 7, page 1) and gave examples of how the NCI and the NTP had used these data (Attachment 7, pages 2 to 5). He showed how NTP displays historical control data in the technical reports (Attachment 7, page 6) and pointed out potential sources of variability in control tumor incidence rates (Attachment 7, page 7). He also presented an example illustrating variability between studies conducted at the same laboratory (Attachment 7, page 8).

Dr. Haseman discussed certain problems to be resolved before an NCI/NTP data base can be used optimally. First, pathology nomenclature differences must be resolved, i.e., there should be a uniform terminology to identify a particular lesion. Second, is the issue of defining the historical control tumor data base. He said NTP has resolved this particular problem and will restrict the data base to more recent studies, specifically those whose draft technical reports were peer reviewed from February 1980 (Technical Report #193) to the present. CBDS has been enhanced to extend the usefulness of the historical control data. Third, once the data base has been defined, major sources of variability can be identified. Preliminary results from a study investigating this issue indicate that the laboratory appears to be the most important source of variation with pathologists within laboratories a lesser source; animal supplier seems the least important. Dr. Haseman gave illustrations of the variability within and between laboratories (Attachment 7, pages 10 and 11), and stated that in the future historical control data for comparisons with concurrent controls will most likely be restricted to the laboratory which carried out the bioassay. Cross-laboratory data would be used primarily in evaluating rare tumors. The fourth problem was that of developing appropriate statistical methods for use with the historical data base. Dr. Haseman said that the Biometry and Risk Assessment Program, NIEHS, is comparing several procedures that have recently been proposed to utilize historical control data in a formal testing framework and recommendations will be made soon as to which is best.

Discussion: Dr. Harper asked whether comparisons would be restricted to data from animals receiving the same vehicle, e.g., corn oil. Dr. Haseman said it would. Dr. Whittemore asked whether analyses which adjust for survival, e.g., life table analysis, could be used with historical control data. Dr. Haseman said that none of the procedures currently being evaluated that incorporate historical control

data adjust for intercurrent mortality and further research is needed in this area. Dr. Whittemore stated, and Dr. Haseman agreed, that we must develop statistical methodology that takes survival differences as well as extrabinomial variability among historical control groups into account if we are to use historical control data optimally.

V. Proposal For Combining Organ Site Tumors for Interpretation of Pathology Results: (Attachment 8: Guidelines for Combining Benign and Malignant Neoplasms as An Aid in Determining Evidence of Carcinogenicity) Dr. McConnell said the issue of the appropriateness of combining or not combining tumors had stimulated discussion at every bioassay peer review meeting. The working paper (Attachment 8) sent to the Board was an attempt to resolve the issue. Three important questions reappear routinely concerning interpretation of tumor data (Attachment 8, page 1). Certain factors need to be considered in determining the appropriateness of combining tumors, and he gave reasons for combining some benign and malignant tumors (Attachment 8, pages 2 to 4) and for why certain benign and malignant tumors should be clearly differentiated (Attachment 8, pages 4 to 5). Dr. McConnell emphasized he was presenting guidelines. Each situation should be examined separately. He then discussed guidelines for specific tumor types in different organs and tissues of F344 rats and B6C3F$_1$ mice (Attachment 8, pages 7 to 11). If tumors were combined, these always would be displayed separately as well in the technical report. Dr. Nelson stated that terminologic issues or disagreements should be separated from the biologic bases in considering the validity of combining tumors. Dr. McConnell said these guidelines will be most useful when the evidence for interpretation of carcinogenicity is not clearcut.

He presented some guidelines for evaluating the degree of evidence of carcinogenicity (Attachment 8, pages 12 and 13). He gave illustrations using hypothetical biological examples of how combining or not combining can affect the interpretation. In response to a question by Dr. Whittemore, Dr. McConnell said that with these guidelines NTP was not trying to assess or rank degrees of strength of evidence for carcinogenicity. Dr. Swenberg said that where evidence is specific to one type of tumor and combining does not add to the significance of the finding there was little value in displaying combined data in the report. Further, where a significant effect can be obtained only by combining benign and malignant tumors, one needs to look even harder at the biological basis. Dr. McConnell concluded by emphasizing again that tumor types would always be displayed separately and combined, where appropriate, in the technical report, and the guidelines were just guidelines, so that each situation would be assessed separately as to whether it was appropriate to combine tumors.

VI. Concept Reviews: Dr. Moore reiterated the NIH policy that requires where work under contract is proposed, the proposed work has to be reviewed for concept. Dr. Nelson said the Board needs to evaluate whether the idea is good and the general approach adequate; another group of expert reviewers assesses the technical merits of the proposal. Specific Board members are assigned in advance by the Chairman as a principal reviewer for each concept.

One reproductive and developmental toxicology proposal was reviewed for concept by the Board:

1) Validation of Two In Vitro Teratogenesis Prescreening Systems: (Attachment 9) Standard in vivo teratology assays are expensive and time consuming such that a limited number of chemicals can be assessed yearly. An in vitro prescreening system will improve the criteria for selecting chemicals to be tested in vivo, decrease the need for such testing, and provide some teratogenesis information on a larger number of chemicals. The proposal, presented by Dr. J. Lamb, NIEHS, is to validate two recently developed in vitro systems. The first system evaluates the ability of chemicals to inhibit ascites mouse ovarian tumor cell attachment to concanavalin A-coated disks (Braun, A.G., et al., Proc. Natl. Acad. Sci. USA, 79: 2056-2060, 1982). The second system uses human embryonic palatal mesenchyme (fibroblastic) cells (Pratt, R.M., et al., Teratogen. Carcinogen. Mutagen., 1982, in press). The systems complement each other and about 50 chemicals will be selected for simultaneous validation at two laboratories. As principal reviewer, Dr. Hook said the concept fits well into the NTP program methods development. Dr. R. Pratt, NIEHS, said his system was good at distinguishing false negatives, and further could clearly differentiate teratogenic effects from general cytotoxic effects. Dr. Hook moved that the proposal be approved for concept, and the motion was approved unanimously by the Board.

Seven cellular and genetic toxicology proposals were reviewed for concept. Two of the proposals are ongoing contract efforts which are due to be recompeted and awarded at the end of FY 1983. The concept proposals are:

1) In Vitro Cytogenetics Testing: (Attachment 10A) This project was initiated under two contracts in September 1979, with a third contract added two years later to standardize a testing protocol and to test chemicals for their ability to induce chromosome aberrations (CAs) and sister chromatid exchanges (SCEs) in cultured Chinese hamster ovary (CHO) cells. By the time the contracts will be completed in September 1983, about 190 chemical samples will have been tested. The proposal, presented by Dr. E. Zeiger, NIEHS, is to award competitively two contracts for the testing of 400 chemicals in CHO cells. These would be four-year contracts beginning in October 1983. The information will enhance the data base and aid in making decisions for carcinogenicity and other types of testing. As principal reviewer, Dr. Horning said there was a need to enhance the responsiveness of the system for picking up weak responders. She said the system needed to be tested with more chemicals to establish its optimal usefulness. Dr. Horning moved for approval of the concept proposal, and the motion was approved unanimously by the Board.

2) Drosophila Mutagenesis Testing: (Attachment 10B) This project was initiated under three contracts in September 1979 to test chemicals for mutagenicity in Drosophila melanogaster. Chemicals are tested for sex-linked recessive lethal effects, and chemicals

positive in this test are then tested for their ability to induce a heritable effect, reciprocal translocations. The proposal, presented by Dr. E. Zeiger, is to award two contracts for the testing of up to 140 chemicals. These would be four-year contracts beginning in October 1983. Continuation will enable NTP to broaden the range of chemical classes tested and enhance the data base for attempted correlation with carcinogenicity findings. As principal reviewer, Dr. Horning said the test system gives additional information on genetic effects not obtained with other systems. She moved for approval of the concept proposal, and the motion was approved unanimously by the Board.

3) The Genotoxic Evaluation of Potentially Hazardous Chemicals in the In Vivo - In Vitro UDS Rat Hepatocyte Assay: (Attachment 10C) This proposal recommends a study to develop further the in vivo - in vitro unscheduled DNA synthesis (UDS) rat hepatocyte system as an assay to identify hepatocarcinogenic and hepatotoxic chemical agents as part of NTP's short-term testing capabilities. The proposal, presented by Dr. J. Spalding, NIEHS, stressed that this assay has the advantage of combining the elements of metabolic capability and chemical disposition in the intact animal with the sensitivity of the DNA repair endpoint detected in cultured rat hepatocytes. The objective is to test about 40 chemicals per year for three years. As principal reviewer, Dr. Hitchcock's principal concern was with whether the project was a validation exercise which she thought it should be or actual testing. Dr. R. Tennant, NIEHS, said it was primarily a development-validation project. Ultimate use of the assay would be to detect genetic toxicity with chemicals negative in other systems. Also, the system would complement the in vivo rat liver model system being evaluated by NTP. Dr. Hitchcock moved for approval of the concept proposal, and the motion was approved unanimously by the Board.

4) Evaluation of In Vivo DNA Binding as an Approach to Gain Understanding of Mechanism(s) of Carcinogenesis and as an Adjunct to Genetic Toxicity Assays for Carcinogens: (Attachment 10D) The purpose of this proposal is to award a contract or interagency agreement to investigate the utility of in vivo DNA-binding for gaining insight into the biological mechanisms of carcinogenesis of selected NTP chemicals and for determining the usefulness of DNA-binding as an adjunct to the current short-term test battery used in the NTP. Dr. R. Langenbach, NIEHS, presented background and rationale for the proposal and a brief description of methodology. Drs. Harper and Hook questioned the sensitivity of the assay, especially for extrahepatic organs. As principal reviewer, Dr. Swenberg said the work scope was too large and as a screening project in a contract laboratory it was unlikely to be successful. He also agreed that sensitivity for detection of adducts would be poor. To get adequate sensitivity, chemicals would have to be custom synthesized with very high specific activity of radiolabels, and cost would be high. Dr. Tennant said NTP would table the proposal until enough supporting data could be developed which might satisfy the Board's concerns.

5) Increased Tumor Incidence in the Offspring of Mutagen- Treated Mice: (Attachment 10E) The primary purpose of the proposed project is to improve the ability to predict the impact of induced germ cell mutations on human health by investigating a mouse system in which cancer incidence is observed in the first generation following mutagen exposure. Dr. M. Shelby, NIEHS, presented the proposal and discussed the background and approaches to be used. He said a second major objective is to gain a better understanding of the genetics of cancer susceptibility, both spontaneous and induced. As principal reviewer, Dr. Swenberg said the concept for looking at germ cell damage was good but too focused on cancer, and endpoints for other genetically transmitted diseases needed to be considered. He questioned the use of the $B6C3F_1$ mouse. He said the expectations for the project's output such as prediction of effects on human health and gaining a better understanding of the genetics of cancer susceptibility were unrealistic. Dr. Swenberg moved for approval of the concept proposal, and the motion was approved unanimously by the Board.

6) Assay of Chemically-Induced Gene Transposition in Drosophila: (Attachment 10F) Dr. Tennant presented the background, objectives, and approaches for this project. The aim was to develop an assay system to measure chemically-induced gene mobility which would involve development of specific molecular probes for transposable elements. He said it is possible that some chemical mutagens may act exclusively by production of transpositions and therefore would not be identified under existing assays. A single interagency agreement or contract would be awarded for development of methodology to detect chemically-induced transpositions in Drosophila using specific marker loci. As principal reviewer, Dr. Diamond asked whether the preliminary work of Rasmuson et al. (Mutat. Res., 54: 33-38, 1978), reporting that chemical mutagens increased frequency of transposition, had been repeated. Dr. B. Judd, NIEHS, said it had not. He said the possible role of transposition in inducing mutations is very new yet materials are available for development of the probes. Dr. Diamond moved for approval of the concept proposal, and the motion was approved unanimously by the Board.

7) Development of an Assay System to Determine if Mammalian Transposable Gene Elements are Targets for Toxic Environmental Agents: (Attachment 10G) Dr. Tennant presented the background and scientific basis for this proposed project. A highly sensitive molecular detection method must be used in combination with highly specific molecular probes. The aim of the project would be to develop such probes to determine whether chemically-induced transposition is a "real" biological phenomenon in mammalian cells. As principal reviewer, Dr. Diamond said this was an elegant study which should be done. Dr. Hook questioned why it would not be more appropriate for a research grant. Dr. Rall said it was appropriate for both extramural and NTP because of potential [illegible] of the assay. Dr. Diamond moved for approval of the [illegible] approved unanimously by the

VII. Peer Review and Priority Ranking of Chemicals Nominated For NTP Testing: There were 31 chemical nominations to be considered by the Board. Fifteen had been reviewed previously by the NTP Chemical Evaluation Committee on December 9, 1981, and the other 16 on March 3, 1982. Comments recently received on four of the chemicals in response to Federal Register announcements were given to the principal reviewers for those chemicals. (Comments received earlier were incorporated into the draft Executive Summaries.) Dr. D. Canter, NIEHS, described the current NTP chemical nomination and selection process for the benefit of the new Board members. She reported that eighteen of the chemical nominations were selected by the NCI Chemical Selection Working Group as part of a chemical class study on biological intermediates and endogenous compounds.

Dr. Horning, Chairperson of the Board Subcommittee on Chemical Nomination and Selection, chaired the review. The Chairperson of the NTP Chemical Evaluation Committee (CEC), Dr. L. Fishbein, NCTR, one member, Dr. Canter, and the Executive Secretary, Mr. Schad, were present to assist the Board. Each Board member had been asked to review two (for new members) or five (for old members) chemicals prior to the meeting. Following oral presentation of the 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 and/or caveats are summarized (Attachment 11: Testing Recommendations for Chemicals Reviewed by the NTP Board of Scientific Counselors on September 24, 1982).

Dr. Horning made several comments on the draft Executive Summaries. She said: (1) there were some errors in chemical formulas, (2) references were missing, (3) a more uniform format would be desirable, and (4) a better evaluation of the quality and completeness of previous toxicologic studies was needed in the summaries. Dr. Nelson said NTP might supply to the Board or use as a model the NCI Clearinghouse summaries which were orderly, adequately detailed and more consistent or uniform. He also requested reprints of a few key references be sent to principal reviewers. Dr. Rall said that as a minimum we might try to have some of these references available for the Board at the beginning of the meeting.

Action Item: NTP should (1) make available to the Board selected copies of summaries on chemicals used by the NCI Clearinghouse on Environmental Carcinogens, and (2) make available copies of key references on nominated chemicals to principal reviewers prior to the next meeting.

VIII. Other Business: Dr. Moore gave the Board a brief update of the progress and status of the NTP benzidine congener initiative. The major activities were in chemical disposition and genetic toxicology. Quantitative pharmacokinetic studies are being done with benzidine and the dimethyl and dimethoxy congeners, while more cursory studies are being performed with some of the derivative dyes to confirm metabolism to the parent compound. A major focus in genetic toxicology is development of methodology to incorporate reductive metabolism into the Ames test. Additionally, the dimethyl and dimethoxy

congeners and a derivative of each will be examined in vivo in two-year studies, as may be Blue 218, a copper chelate. NTP pathologists are reexamining slides of liver from the 90-day studies with Blue 6, Black 38, and Brown 95.

Dr. Nelson proposed that NTP staff and two members of the Board, Drs. Swenberg and Diamond, convene a half day meeting to assess the scope of what is available in test systems for cocarcinogenesis and provide NTP with some guidance in this area.

The meeting was adjourned.

TABLE 34

TESTING RECOMMENDATIONS FOR CHEMICALS REVIEWED BY
THE NTP BOARD OF SCIENTIFIC COUNSELORS ON SEPTEMBER 24, 1982

	CHEMICAL	CASE No.	RECOMMENDATION (Priority)	REMARKS
1)	2-Amino-6-nitro-benzothiazole	682-57-0	Salmonella assay Mouse lymphoma	Concur with CEC recommendation
2)	Benzonitrile	100-47-0	Skin painting tumor promotion assay 90-Day subchronic test (inhalation) (L)	Obtain additional information regarding production and exposure
3)	Benzo(f)quinoline	85-02-9	General toxicology Carcinogenicity (inhalation) Metabolism (L)	-Air pollutant -Mutagenic in Salmonella -Structure activity considerations -Low production
4)	Carminic acid*	1260-17-9	Battery of short-term mutagenicity tests (M)	Significant toxicology testing already performed
5)	Cholesterol	57-88-5	No testing	Concur with CEC recommendation for possible study through research grants mechanism
6)	Cholesterol 5δ, 6δ-epoxide	1250-95-9	No testing	Concur with CEC recommendation for possible study through research grants mechanism
7)	Colchicine	64-86-8	No additional testing	Refer to NCI for consideration of epidemiology study
8)	L-Cysteine	52-90-4	No testing	Concur with CEC recommendation for possible study through research grants mechanism

TABLE 34 (Continued)

	CHEMICAL	CASE No.	RECOMMENDATION (Priority)	REMARKS
9)	Cytidine	65-46-3	No testing	Concur with CEC recommendation for possible study through research grants mechanism
10)	2-Ethylhexanol*	104-76-7	Carcinogenicity (H)	-Important commercial chemical -Metabolite of hepatocarcinogens di(2-ethylhexyl) phthalate and di(2-ethylhexyl) adipate -CIIT will test in hepatocyte initiation -promotion assays
11)	Ferrous sulfate	7720-78-7	No testing	Concur with CEC recommendation for possible study through research grants mechanism
12)	Folic acid	59-30-3	No testing	Concur with CEC recommendation for possible study through research research grants mechanism
13)	Fumaric acid*	110-17-8	Salmonella assay	Concur with CEC recommendation
14)	Guanine	73-40-5	No testing	Concur with CEC recommendation for possible study through research grants mechanism
15)	L-Isoleucine	73-32-5	No testing	

TABLE 34 (Continued)

	CHEMICAL	CASE No.	RECOMMENDATION (Priority)	REMARKS
16)	Linoleic acid*	60-33-3	No testing	
17)	Linolenic acid*	463-40-1	No testing	
18)	L-Lysine	56-87-1	No testing	
19)	Methylene bis (o-chloroaniline	101-14-4	Teratogenicity and reproductive effects (M)	-Known animal carcinogen -Contamination incident in Michigan
20)	Mono(2-ethylhexyl) Phthalate	4376-20-9	No additional testing	-CIIT will test in a hepatocyte initiation-promotion assays -Not produced commercially
21)	m-Nitrobenzoyl chloride	121-90-4	Battery of short-term mutagenicity tests Metabolism General toxicology and subchronic testing (L)	-Present in dump sites
22)	p-Nitrobenzoyl chloride	122-04-3	Battery of short-term mutagenicity tests Metabolism General toxicology and subchronic testing (M)	-Present in dump sites
23)	Phenamiphos	22224-92-6	Defer	Consult with EPA concerning toxicology data submitted for pesticide registration
24)	Potassium iodide*	7681-11-0	No testing	Concer with CEC recommendation for possible study through research grants mechanism

TABLE 34 (Continued)

	CHEMICAL	CASE No.	RECOMMENDATION (Priority)	REMARKS
25)	1-Chloro-2-propanol	127-00-4	Battery of short-mutagenicity tests (H) Carcinogenicity (M)	-Important commercial chemical -Potential for wide-spread exposure
26)	2-Chloro-1-propanol	78-89-7	Battery of short-mutagenicity tests (H) Carcinogenicity (M)	-Important commercial chemical -Potential for wide-spread exposure
27)	Pyruvic acid	127-17-3	No testing	
28)	Riboflavin	83-88-5	No testing	Concur with CEC recommendation for possible study through research grants mechanism
29)	Thiamin hydro-chloride	57-03-8	No testing	Concur with CEC recommendation for possible study through research grants mechanism
30)	L-Tyrosine	60-18-4	No testing	Concur with CEC for possible study through research grants mechanism
31)	Vitamin E* (δ-tocopherol)	59-02-9	No further testing beyond selected toxicological end-points	Board to review protocols developed by NTP and FDA

*Information submitted to the NTP in response to the notice published in the Federal Register requesting public comment on the nominated chemicals.