Board of Scientific Counselors
National Toxicology Program

Summary Minutes
from

Peer Review of Draft Technical Reports of Long-Term
Toxicology and Carcinogenesis Studies Studies
by the Technical Reports Review Subcommittee
and Panel of Experts

on

April 25, 1990

Research Triangle Park, North Carolina

The review meeting began at 9:00 a.m. on April 25, 1990 in the Conference Center, Building 101, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina. Members of the Subcommittee are: Drs. Robert Scala (Chairperson), Jay Goodman, Daniel Longnecker, and Ellen Silbergeld. Members of the Panel of Experts are: Drs. John Ashby, Gary Carlson, Harold Davis, Robert Garman, Lois Gold, David Hayden, Curtis Klaassen, Barbara McKnight and Lauren Zeise. Drs. Klaassen and Scala were unable to attend this meeting. Dr. Michael Gallo, former Board chair and member of the Subcommittee, served as Chairperson for this meeting. These minutes have been reviewed and approved by all members of the Subcommittee and Panel present. They were written by Dr. Larry G. Hart, Executive Secretary.

When available, a limited number of final NTP Technical Reports for the studies may be obtained free of charge from the NTP Public Information Office, MD B2-04, P. O. Box 12233, Research Triangle Park, NC 27709. Telephone: (919)541-3991; FTS: 629-3991. Subsequently, they may be purchased from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, Virginia 22161, (703)487-4650.

The next NTP technical reports peer review meeting will be held November 19-20, 1990, in Research Triangle Park, North Carolina. For information, contact Dr. Hart, (919) 541-3971; FTS 629-3971.

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SUMMARY MINUTES
PEER REVIEW PANEL MEETING

April 25, 1990

3,3'-Dimethylbenzidine Dihydrochloride. Dr. D.L. Morgan, NIEHS, NTP Study Scientist, introduced the toxicology and carcinogenesis studies of 3,3'-dimethylbenzidine by discussing uses of the chemical, describing its biotransformation, reporting on the experimental design for the studies, and reviewing the nonneoplastic and neoplastic lesions in male and female rats. The proposed conclusions were that:

> Under the conditions of these 15-month drinking water studies, there was clear evidence of carcinogenic activity of 3,3'-dimethylbenzidine dihydrochloride for male F344/N rats, as indicated by benign and malignant neoplasms of the skin, Zymbal's gland, preputial gland, liver, oral cavity, small and large intestine, lung, and mesothelium. Increased incidences of neoplasms of the brain may have been related to chemical administration. There was clear evidence of carcinogenic activity for female F344/N rats,as indicated by benign and malignant neoplasms of the skin, Zymbal's gland, clitoral gland, liver, oral cavity, small and large intestine, mammary gland, and lung. Increased incidences of neoplasms of the brain may have been related to chemical administration.

Dr. Morgan explained that the studies were intended to last 24 months but were terminated after 15 months because of rapidly declining survival of exposed animals, due primarily to neoplasia.

Dr. McKnight, a principal reviewer, agreed with the conclusions.

Dr. Zeise, the second principal reviewer, agreed with the conclusions with the exceptions that (1) indication shoud be made in the conclusions that the marginally increased incidences of benign pheochromocytomas of the adrenal gland medulla in male rats may have been treatment related, and (2) indication should be made in the conclusions that the marginally increased incidences of mononuclear cell leukemias in female rats may have been treatment related. Dr. Morgan said reasons for not including pheochromocytomas were that they are commonly occurring tumors in male rats and there was not an increased incidence of hyperplasias. With regard to leukemia, he noted that the study was terminated at 15 months and most leukemias develop after this time. Thus, the rats were not at risk long enough to determine if leukemia was treatment related. Dr. Zeise indicated that liver neoplasia in the rat should be reported according to the current classification system, whereby the diagnosis of "neoplastic nodule" is given as either "hepato cellular adenoma" or "hyperplasia." Dr. Morgan responded that "neoplastic nodule" was the accepted terminology when the slides for these liver lesions were read. However, for clarification there will be an explanation in the text that "neoplastic nodule" refers to the same lesion currently termed "hypatocellular adenoma." Dr. Zeise thought discussion should be added under study rationale on whether or not data obtained from studies under the benzidine dye initiative will be used in evaluating or predicting carcinogenicity of untested benzidine-derived dyes.

Dr. Davis, the third principal reviewer, agreed with the conclusions.

Dr. William Allaben, National Center for Toxicologic Research (NCTR), reported on the 2-year studies of 3,3'-dimethylbenzidine dihydrochloride administered to BALB/c mice at dose levels ranging from 5 to 140 ppm in drinking water. The only lesions of consequence in these studies were fatal alveolar cell tumors of the lung seen in a dose-related manner in male mice.

Dr. McKnight moved that the Technical Report on 3,3'-dimethylbenzidine dihydrochloride be accepted with the conclusions as written for male and female rats, clear evidence of carcinogenic activity. Dr. Davis seconded the motion, which was accepted unanimously with ten votes. Dr. Zeise then moved that mononuclear cell leukemia be added to the conclusion for female rats as "may have been related to chemical administration." Dr. McKnight seconded the motion, which was accepted by nine yes votes to one no vote (Gold).

Sodium Azide. Dr. K.M. Abdo, NIEHS, NTP Study Scientist, introduced the toxicology and carcinogenesis studies of sodium azide by discussing the uses, describing the experimental design for 14-day, 90-day and 2-year studies, reporting on survival and body weight effects in male and female rats, and commenting on the only compound-related lesions, those being non-neoplastic lesions in the brain. The conclusions were that:

> Under the conditions of these 2-year studies, there was no evidence of carcinogenic activity of sodium azide for male or female F344/N rats administered 5 or 10 mg/kg sodium azide in distilled water by gavage for up to 2 years.
>
> Sodium azide induced necrosis in the cerebrum and the thalamus in both male and female rats.

Dr. Ashby, a principal reviewer, agreed with the conclusions. However, he questioned why only rats were studied, and thought the use of only one species along with the poor survival in high dose groups made this a less useful reference non-carcinogen than most. Dr. Abdo said a program decision was made to do the 2-year studies in rats only after 14-day and 90-day studies in mice showed minimal tissue pathology. He said this would be noted in the Report. Dr. Ashby said the likelihood that the low dose was a maximum tolerated dose (MTD) compensated for the poor survival at the high dose.

Dr. Davis, the second principal reviewer, agreed with the conclusions. His major concern was that assessment of carcinogenic activity was made difficult by the fact that the MTD was exceeded in the high dose groups and there rarely were lesions in the low dose groups. He commented on the observation that some affected animals had acute brain lesions while others had chronic lesions, and that if there were animals with both types of lesions, this should be more clearly stated. Dr. M. Jokinen, NIEHS, agreed. Dr. Carlson interjected that in his experience with chemicals that produce similar types of brain lesions there were no animals with combinations of acute and chronic lesions. Usually, those animals with acute lesions died from the lesions.

Dr. Carlson, the third principal reviewer, agreed with the conclusions. He thought the doses chosen appeared to have been appropriate and concluded that the study was adequate based on at least 60% survival for 90 weeks in the high dose groups and the fact that the low dose was probably close to the MTD. Dr. Carlson asked for more detailed explanation of the comment that decreased incidences of some neoplasms "reflected to some extent, but could not be solely attributed to, the reduced survival of the high-dose group."

Dr. Silbergeld also had submitted a written review which Dr. L.Hart, NIEHS, read in her absence. Dr. Silbergeld did not agree with the conclusions. Rather she thought the correct interpretation was that of an inadequate study of carcinogenic activity based primarily on a very high rate of mortality in all animal groups and a high incidence of tumors, particularly leukemias, in controls. Dr. Abdo responded that in his judgement there were sufficient numbers of surviving animals in dose groups at 90 weeks to detect a carcinogenic effect, had there been one. Further, he commented that there has been a general trend for reduced survival in our control animals over the past several years so the survival in the sodium azide study was within the range of survival for

control animals in contemporary oral feed or water gavage studies. Dr. J. Haseman, NIEHS, noted that historically in NTP studies of rats, over time there has been an elevation in leukemia rates as well as a decrease in survival in controls.

There was considerable discussion about the gavage deaths in the high dose groups and whether they were due to accidents or at least in part whether they may have been secondary to the brain toxicity. Dr. Gold wondered about the adequacy of the study for detecting an effect when there was such poor survival compounded by the gavage deaths in high dose groups. Dr. McKnight said there should be a parallel survival analysis included which does not censor the gavage deaths but rather counts them as true deaths. Dr. Haseman said a pure survival curve would be added. Dr. Eustis opined that the survival in high dose groups at 90 weeks along with no hint of carcinogenic activity in low dose groups supported the adequacy of the studies.

Dr. Ashby moved that the Technical Report on sodium azide be accepted with the revisions discussed and the conclusions as written for male and female rats, no evidence of carcinogenic activity. Dr. Carlson seconded the motion, which was accepted by nine yes votes to one no vote (Gold).

Tris(2-Chloroethyl)Phosphate. Dr. H.B. Matthews, NIEHS, NTP Study Scientist, introduced the toxicology and carcinogenesis studies of tris(2-chloroethyl)phosphate (TRCP) by reviewing the uses, experimental design, results, and proposed conclusions. Dr. Matthews reported on step sectioning of the kidneys in mice which revealed in males an additional mouse with hyperplasia among controls, an adenoma in the low dose group, and two additional hyperplasias and two adenomas in the high dose group. The conclusions as written in the draft Technical Report are:

> Under the conditions of these 2-year gavage studies, there was clear evidence of carcinogenic activity for male and female F344/N rats receiving TRCP as shown by increased incidence of renal tubular adenomas. Thyroid follicular cell neoplasms and mononuclear-cell leukemia in male and female rats may have been chemically related. There was no evidence of carcinogenic activity for male B6C3F1 mice receiving 175 or 350 mg/kg TRCP. There was equivocal evidence of carcinogenic activity for female B6C3F1 mice as shown by increased incidence of Harderian gland adenomas.
>
> Renal tubular cell hyperplasia in male and female rats and gliosis, hemorrhage, pigmentation (hemosiderin accumulation), and mineralization in the brains of female rats were associated with the administration of TRCP. Karyomegaly of renal tubular epithelial cells in male and female mice was also chemically related.

Because of the additional kidney tumors found in dosed male mice, Dr. Matthews said that consideration should be given to changing the level to equivocal evidence.

Dr. Garman, a principal reviewer, was in general agreement with the conclusions. However, he was not convinced that the increased incidence of Harderian gland lesions in female mice was related to chemical treatment. And, with the additional information from the step sections of the kidneys in mice, he thought the level of evidence for male mice might be reconsidered.

Dr. Gold, the second principal reviewer, agreed with the conclusions in male rats and male and female mice. She thought that the evaluation in male rats should be based on combined renal tubular carcinomas and adenomas, rather than on the adenomas alone. In female rats, she thought the low incidence of only benign kidney tumors was supportive of only some evidence of carcinogenic activity. Dr. Gold questioned whether the incidence of a rarely observed tumor, granular cell tumors of the brain, in male and female rats might support equivocal evidence. Dr. S. Eustis, NIEHS, commented that these tumors are of meningeal origin in the rat and the meninges are rarely a site of carcinogenic activity even with a potent carcinogen, and thus, these tumors were not considered chemically related. Dr. Silbergeld was unconvinced that there wasn't a relationship particularly since the site and mode of neurotoxic action apparently had not been characterized for this chemical. Dr. Matthews stated that there had been neurotoxicity studies done including some brain chemistry as well as evaluation of delayed behavioral effects after a single dose, and said this information could be included in the report.

Dr. McKnight, the third principal reviewer, agreed with the overall conclusions for rats and mice. However, for mice, she thought that based on survival rates

and weight gain in the 2-year studies, it was not clear that the maximum tolerated dose was achieved. Dr. Matthews said that the significantly increased incidences of renal tubular karyomegaly at low and high doses in both sexes indicated that adequate doses had been used. For female rats, Dr. McKnight noted that the significant positive trend for thyroid follicular cell neoplasms and the significantly greater incidence in high dose vs. control supported including them under clear evidence. Dr. Eustis responded that the small numbers of tumors and the absence of increases in preneoplastic lesions (hyperplasias) spoke against raising the level of evidence. For male rats, Dr. McKnight argued that mononuclear cell leukemias should be included under clear evidence based on a significant positive trend test and positive pairwise comparisons for both high and low dose groups with controls. Dr. McKnight thought too much emphasis was put on the highly variable historical control range as contrasted to the concurrent control values for leukemias in discounting their significance in the TRCP studies. Dr. J. Haseman, NIEHS, agreed that the primary emphasis should be on concurrent controls, but felt that it was also important to consider that the leukemia rate in high dose male rats for leukemia was essentially identical to the average control response for the three previous studies in the same laboratory.

Dr. Garman moved that the conclusions be accepted as written for male and female rats, clear evidence of carcinogenic activity. Dr. Longnecker seconded the motion, which was accepted by seven yes votes (Carlson, Davis, Hayden, Longnecker, McKnight, Silbergeld, Zeise) to four no votes (Ashby, Garman, Gold, Goodman). Dr. Garman moved that the conclusions be changed for male mice from no evidence of carcinogenic activity to equivocal evidence of carcinogenic activity based on the additional renal tubular neoplasms revealed in the resectioning experiments. Dr. Ashby seconded the motion, which was accepted unanimously with eleven votes. Dr. Garman moved that the conclusions be accepted as written for female mice, equivocal evidence of carcinogenic activity. Dr. Ashby seconded the motion, which was accepted unanimously with eleven votes.

dl-Amphetamine Sulfate -- Reevaluation. The NTP toxicology and carcinogenesis studies of dl-amphetamine sulfate in F344/N rats and B6C3F1 mice (draft Technical Report No. 387) were peer reviewed by the Subcommittee on November 20, 1989. During the November review, there was a suggestion that animals might have become tolerant to the amphetamine-induced body weight effects and might have tolerated higher doses without increasing the body weight-reducing effects of the drug. Accordingly, the Subcommittee moved to defer the Report to examine any new information available on tolerance to body weight effects.

Dr. J. Dunnick, NIEHS, NTP Study Scientist, began by reporting that the staff had gone back and thoroughly reviewed the literature on the pharmacologic effects of the drug and found no data that rats and mice in the NTP 2-year studies could have tolerated higher doses of dl-amphetamine without increasing the weight decrements. She noted that in these studies, dosed animals continued to show weight effects throughout the course of the study and the weight effect became more marked with increasing age of the animals. Based on these studies and the findings of other investigators, the staff thought that the dose selection for the 2-year studies on dl-amphetamine was appropriate. Dr. Dunnick added that the revised Technical Report responded to previous comments of the Subcommittee by including further discussion on tolerance, the body weight effects observed, pathology procedures, and recording of clinical signs. The conclusions were as follows:

> Under the conditions of these 2-year feed studies, there was no evidence of carcinogenic activity of dl-amphetamine sulfate for male or female F344/N rats or male or female B6C3F1 mice fed diets containing 20 or 100 ppm. The administration of dl-amphetamine sulfate was associated with decreased body weight. There were decreased incidences of total neoplasms in dosed rats and mice, of adrenal pheochromocytomas in male rats, of mammary gland fibroadenomas and uterine polyps in female rats, of pituitary gland adenomas in male and female rats and female mice, and of Harderian gland adenomas, liver neoplasms, and lung neoplasms in male and female mice.

Dr. Carlson, a principal reviewer, agreed with the conclusions. He commented that effects seen at the high dose such as excessive hyperactivity and reduction in body weight should be labeled "toxicologic effects" and not "pharmacologic effects" even though these endpoints may reflect an extension of the latter.

Dr. Silbergeld, the second principal reviewer, agreed with the conclusions. However, she remained concerned that the high dose used was not far from the therapeutic range (the range of doses taken by humans for certain prescribed conditions) and that the chemical is also a street drug of abuse. She suggested that the NTP needs to evaluate imaginative protocols for studying chronic toxicologic/carcinogenic effects of therapeutic agents in the presence of intended pharmacologic actions such as weight loss in the case of amphetamine. Dr. Silbergeld noted that the observations of reduced incidences of hormone dependent adrenergic tumors were consistent with the demonstration that dopamine inhibits release of prolactin, and amphetamine facilitates dopaminergic neurotransmission.

Dr. Carlson moved that the draft Technical Report on dl-amphetamine be accepted with the conclusions as written for male and female rats and mice, no evidence

of carcinogenic activity, and with the decreased incidences of several neoplasms that were listed. Dr. Silbergeld seconded the motion, which was accepted unanimously with eleven votes.

Ethylene Thiourea -- Reevaluation. The NTP toxicology and carcinogenesis studies of ethylene thiourea (ETU) in F344/N rats and B6C3F1 mice (draft Technical Report No. 388) were peer reviewed by the Subcommittee on November 20, 1989. The study designs included conventional two-year exposure of adult animals, perinatal exposure only, and perinatal plus adult exposure. The studies were intended to compare and evaluate the potential value of perinatal exposures in assessing chemical carcinogenicity. After much discussion, the consensus of the Subcommittee was that there was not an overwhelming effect of perinatal exposure to ETU on increased incidences of neoplastic lesions. However, better data presentation would help highlight for the reader what effects there were of treatment. At that time, Dr. Gold suggested that the results should be reorganized and reported in terms of three questions addressed by the experimental design: (1) were there effects of perinatal exposure?; (2) were there carcinogenic effects in a typical two-year bioassay?; and (3) did perinatal exposure enhance or potentiate carcinogenic effects seen in a subsequent two-year bioassay? The Subcommittee recommended unanimously that the Technical Report be deferred for further consideration so that the questions raised could be addressed in a revision of the report. An extensively revised draft was sent to members of the Subcommittee in February 1990 for further review, and although there was a consensus that the report was considerably improved, several members thought discussion and final resolution of the report should take place in public session.

Dr. S. Eustis, NIEHS, began by addressing the three questions raised. The conclusions of the staff were that: (1) perinatal exposure alone had no effect on incidence of neoplasms; (2) in groups of rats receiving the highest combined perinatal exposure of 90 ppm and adult exposure of 250 ppm, there was a slight enhancement of the toxicity and thyroid proliferative effects as compared to adult only exposure at 250 ppm, while, in mice, perinatal exposure at 330 ppm slightly enhanced the thyroid proliferative effects seen with adult only exposure at 330 ppm; and (3) in rats and mice receiving adult only exposure, there was clear evidence of carcinogenic activity for males and females with the conclusions being as follows:

> Under conditions of these 2-year studies, there was clear evidence of carcinogenic activity of ethylene thiourea for male and female F344/N rats, as shown by increased incidences of thyroid follicular cell neoplasms. Marginal increases in Zymbal's gland neoplasms and mononuclear leukemia in males and females and renal tubular cell neoplasms in males may have been chemically related. There was clear evidence of carcinogenic activity for male and female B6C3F1 mice as shown by increased incidences of thyroid follicular cell neoplasms, hepatocellular neoplasms, and adenomas of the pars distalis of the pituitary gland.

Public comment was taken from representatives of member companies comprising the EBDC/ETU Task Force. Dr. Peter Chan, Rohm and Haas Company, presented information which he opined supported conclusions that the NTP studies did not provide evidence for carcinogenicity of ETU in Zymbal's gland, for mononuclear cell leukemias, or for renal tubular cell tumors in rats. As well, the NTP studies do not show a potentiation of tumorigenesis by perinatal exposure, and finally, the weight of evidence indicates that ETU is not mutagenic or genotoxic. Dr. Ray Brown, Research Pathology Services, Inc., representing the Task Force, discussed the data and statistics used by the NTP. He noted that

the life table test, which was the only test to yield statistical significance for Zymbal's gland tumors and mononuclear cell leukemia, was not the appropriate test to use in that these neoplasms are often not lethal. Further, he opined that there was insufficient evidence to support increases in renal tubular cell tumors in male rats as being chemically related. Dr. Greg Sykes, E.I. du Pont de Nemours and Company, reiterated some of the points made by the previous speakers while making additional ones leading to the conclusion that there was insufficient evidence to indicate that increases in the three types of neoplasms may have been chemically related. Dr. Harvey Scribner, Rohm and Haas Company, spoke to the socio-economic importance of the EBDC fungicides and stressed the need for the NTP conclusions to be as accurate as possible. He stated that the term "may have been chemically related" as applied to the three tumor types was unsupported by the data and should be removed from the report.

Dr. Gold, a principal reviewer, said the report was much improved. She stated that as written, the conclusions on thyroid tumors relate only to the 2-year studies alone while the levels of equivocal evidence in rats associated with Zymbal's gland neoplasms and mononuclear cell leukemia don't belong here as they relate only to perinatal plus adult exposure. Dr. Gold said there needed to be more clarifying discussion of the possible enhancing effects of perinatal exposure to ETU on the incidence of thyroid neoplasms in high dose adult rats and female mice. She suggested that information should be added about exposure of pups between four and eight weeks of age, as contrasted to the adult-only exposure with feeding of chemical beginning at eight weeks.

Dr. Hayden, the second principal reviewer, agreed with the conclusions that the principal neoplastic effects of ETU were on the thyroid in adult rats and mice, and supported the conclusions that there were enhancing effects of perinatal exposure to ETU on the incidence of thyroid neoplasms in high dose male and female rats. With regard to Zymbal's gland tumors, mononuclear cell leukemia, and kidney neoplasms, he felt there was insufficient evidence to discern an effect of chemical. Dr. Hayden thought a summary page of the 2-year studies results should be added to the Abstract.

Dr. Zeise agreed with the speakers for the EBDC/ETU Task Force that it was important to make accurate interpretations of the other tumors. She thought the Abstract should include a description of the observations of leukemia and Zymbal gland neoplasms of both sexes, and renal tubular cell neoplasms in male rats. She asked whether resectioning could be done with the Zymbal's gland and renal tumors noting a precedent for this with renal tumors in other NTP studies where there were marginal increases observed. Dr. S. Eustis, NIEHS, responded regarding Zymbal's glands that there was usually not enough tissue to resection, and that past experience indicated the likelihood of finding additional tumors was very small. With regard to the kidney, the sectioning technique used in this study left only the margins of the kidneys which would not be very good samples for step sectioning. Dr. Zeise commented that in the Abstract, the enhancing effect of perinatal exposure should not be referred to as "only slight" because it was observed to double the incidence of thyroid tumors in female rats, increase it by 70% in male rats, and more than double the incidence in F_1 female mice.

Dr. Zeise commented that the lack of effect on tumor incidence for perinatal exposure only may indicate that an MTD was not achieved. Dr. R. Chhabra, NIEHS,

Study Scientist, pointed out the high mortality at the top dose (250 ppm) in the study used to determine the maximum perinatal dose.

Dr. Gold moved that the conclusions be accepted as written with respect to thyroid follicular cell neoplasms in male and female rats, clear evidence of carcinogenic activity, and for thyroid follicular cell neoplasms, hepatocellular neoplasms, and adenomas of the pituitary gland in male and female mice, clear evidence of carcinogenic activity. Dr. Hayden seconded the motion, which was accepted with nine yes votes and one abstention (Ashby). Dr. Ashby's abstention on this and subsequent motions was for reasons of company affiliation.

Dr. Gold moved that the first and second paragraphs of the conclusions refer only to the 2-year studies in adult animals, and that the second sentence, should be deleted i.e., "Marginal increases in Zymbal's gland neoplasms and mononuclear cell leukemia in males and females and renal tubular cell neoplasms in males may have been chemically related." She opined that the sentence to be deleted related to tumor increases based on combined perinatal and adult exposure. Dr. Longnecker seconded the motion with the understanding that something would be put back later regarding the combined exposure. There ensued a lengthy discussion as to whether the incidences of any of these tumors may have been associated with 2-year exposure of adults only. Especially, there was some support for possible association of chemical administration with renal tubular cell neoplasms in male rats. Dr. J. Haseman, NIEHS, commented that in his judgement a no evidence call was not indicated for renal tumors, since the incidence in the low dose group was above the historical range and the incidence in the high dose was at the historical limit; further, the high dose group had seven renal tubular hyperplasias. After additional discussion, Dr. Gold's motion was accepted by six yes votes (Davis, Gold, Garman, Goodman, Hayden, Longnecker) to three no votes (Carlson, McKnight, Zeise) with one abstention (Ashby).

The Subcommittee and NTP staff discussed whether there should be separate conclusionary statements for results of perinatal exposure alone and results of combined perinatal and adult exposure, or whether these results should be published in separate reports. Dr. Hayden moved that the perinatal exposure studies and combined exposure studies as experimental protocols be published as a separate technical report. Dr. Davis seconded the motion. After discussion speaking against separating out these studies, Dr. Hayden withdrew the motion. Dr. R. Griesemer, NIEHS, noted that the ETU study was the first of three to use the experimental protocols for perinatal and perinatal plus adult exposure, and the other two would be brought to the Subcommittee in the near future.

Dr. Longnecker moved that the following statement be included (as taken from the last sentence on p. 53): "Perinatal exposure alone had no effect on incidences of neoplasms after two years." Dr. Gold seconded the motion. Dr. Eustis cautioned against taking the perinatal exposure alone as a carcinogenicity study. Dr. Zeise offered an amendment that the lack of neoplastic effect may have been due to the low doses used. She noted that in the gestational study conducted to determine the dietary concentrations for perinatal exposure there was reported thyroid follicular cell adenomas in 4/10 male rats at the top dose (250 ppm). Yet, 90 ppm was chosen as the top dose for perinatal exposure in the 2-year study. Drs. Longnecker and Gold agreed to accept the amendment. The amended motion was accepted by nine yes votes with one abstention (Ashby).

Dr. Longnecker moved that "in male and female rats, combined perinatal and adult exposure compared with untreated control animals, was associated with a marginal increase in Zymbal's gland neoplasms and mononuclear cell leukemia that may have been chemically related." Dr. Zeise seconded the motion. Dr. Gold added for clarification that in the combined exposure groups, exposure in the diet to young animals began at four weeks of age. The motion was accepted by seven yes votes (Carlson, Davis, Hayden, Longnecker, McKnight, Silbergeld, Zeise) to three no votes (Garman, Gold, Goodman) with one abstention (Ashby).

Dr. Gold moved that the following be added to the conclusions: "in rats, compared with adult-only exposure at 250 ppm; perinatal exposure at 90 ppm marginally increased the incidence of thyroid neoplasms in adults exposed to 250 ppm; however increasing perinatal exposure from 0 to 30 to 90 ppm had no effect on the incidence of such neoplasms in adult animals exposed to 83 ppm." Dr. Garman seconded the motion, which was accepted by six yes votes (Davis, Garman, Gold, Hayden, McKnight, Zeise) to three no votes (Carlson, Goodman, Silbergeld) with two abstentions (Ashby, Longnecker).

Dr. Gold moved that "in female mice, increasing perinatal exposure from 0 to 330 ppm marginally increased the incidence of thyroid neoplasms in adult animals exposed to 330 ppm, but there were no enhancing effects of perinatal exposure on adult animals exposed to 1000 ppm." Dr. Davis seconded the motion, which was accepted by nine yes votes with two abstentions (Ashby, Silbergeld).