Board of Scientific Counselors
National Toxicology Program

Summary Minutes
from
Peer Reviews of Draft Technical Reports of Long-Term
Carcinogenesis Bioassays by the Technical Reports
Review Subcommittee and Panel of Experts

on

June 16, 1982
Research Triangle Park, North Carolina

The review meeting began at 9 a.m. in the Conference Center, Building 101, South Campus, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina. Members of the Subcommittee are: Drs. Margaret Hitchcock (Chairperson), Curtis Harper and Alice Whittemore. Members of the Panel are: Drs. Norman Breslow, Robert Elashoff, Joseph Highland, Michael Holland, Frank Mirer, Robert Scala, Bernard Schwetz, James Swenberg, Stan Vesselinovitch, and Mary Vore. Drs. Vesselinovitch and Whittemore were unable to attend the meeting.

Final NTP Technical Reports for these bioassays will be available for sale in three to four months from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703)487-4650.

The next NTP bioassay peer review meeting will be held September 22, 1982 in Research Triangle Park. For information, contact Dr. Larry G. Hart (919) 541-3971; FTS 629-3971.

Diallyl Phthalate. Dr. Breslow was a principal reviewer for the report on the bioassay of diallyl phthalate. A revised conclusion was presented to the review panel and read as follows: "Under the conditions of this bioassay, the development of chronic inflammation, hyperplasia, and squamous cell papillomas of the forestomach in both male and female $B6C3F_1/N$ mice was considered to be related to the administration of diallyl phthalate. An increase (significant by trend tests, but not by pairwise comparisons) in the incidence of male mice with lymphomas was observed, but this increase was considered only to be equivocally related to diallyl phthalate administration. The results of this bioassay, therefore, do not indicate that diallyl phthalate is carcinogenic in $B6C3F_1/N$ mice although a MTD may not have been achieved. A carcinogenicity study by the National Toxicology Program of diallyl phthalate in male and female Fischer 344/N rats, employing daily gavage doses of 0 (vehicle control), 50, or 100 mg/kg body weight, is in progress." The major change from the conclusion printed in the draft report was removal of a speculative parenthetical statement: '(although circumstantial evidence suggests that diallyl phthalate can be metabolized in rodents to the mutagens acrolein and glycidol and to the dermal carcinogen glycidaldehyde).' Dr. Breslow's comments on the conclusions were that interpretation of this assay is complicated because (1) results are currently available on only a single test species, (2) the MTD may not have been achieved, and (3) benign neoplasms were produced at an unusual anatomic site and appear related to compound administration. On the basis of the benign neoplasms, the conclusions should state that: 'Since benign neoplasms of the forestomach were produced at dosages which were apparently well tolerated otherwise, this bioassay provides indirect evidence for the carcinogenicity of diallyl phthalate in $B6C3F_1N$ mice.' He said the discussion would be enhanced by including information on compounds besides allyl isothiocyanate which produce neoplasms of the mouse forestomach, and by further consideration of the extent to which papillomas could or should be considered as precursors to frank carcinomas.

As a second principal reviewer, Dr. Mirer said the conclusion of absence of proof of carcinogenicity depends on the weight given to the observation of squamous cell papillomas of the forestomach in male and female mice. The historical incidence of inflammation in control mice not subjected to gavage would assist in interpretation of the findings. However, to him, statistical criteria for biological significance had been met and it was the responsibility of the report writer to conclude whether an increase in these papillomas was evidence of carcinogenicity, based on the pathologist's evaluation of the nature of this tumor. With regard to the equivocal nature of hematopoietic tumors (lymphomas) in male mice, Dr. Mirer noted that among a series of phthalic acid esters and related compounds, there were statistically significant increases in hematopoietic tumors only for dimethylterephthalate. Finally, he concluded it would have been helpful to have the bioassay results in rats to help in interpreting the significance of the borderline findings in mice.

As third principal reviewer, Dr. Holland had several comments regarding conjectures about mode of metabolism, site of metabolism and major metabolites of diallyl phthalate. He said that since there was no pathological

evidence given for hepatocellular necrosis in prechronic studies, some of the conjecture relating to certain metabolites causing this lesion should be deleted. Thus, he agreed with the conclusions except for the parenthetical comment on metabolism, which had already been deleted. He questioned the absence of pathologic findings in mice that died during the 13 week prechronic study. His concern was that too low a dose might have been chosen for the chronic study as a result of a gavage error in mice killed at 400/mg/kg. Dr. Swenberg commented that the dose related increase in forestomach lesions may have been a better indicator than decreased body weight gain that an MTD was achieved in this study.

Dr. W. Kluwe, NTP chemical manager, responded to the reviewer's critiques. He said there were significant differences observed for the forestomach lesions in dosed mice only when compared with historical controls, and, then only marginally. Thus, the effects were compound related but not frank evidence of a carcinogenic response. In response to Dr. Holland, he said there was a consensus among the pathologists that there were no signicant lesions in the prechronic study. Dr. Kluwe conceded that speculative comments about metabolism should be removed from the abstract as the only information available is from rat studies.

In further discussion, Dr. Highland argued that the evidence presented for forestomach lesions along with the likely if hypothetical metabolism of diallyl phthalate leads to a conclusion that suggests a carcinogenic effect. Dr. Breslow said he had problems with saying there was a dose-related increase in papillomas while on the otherhand this increase had nothing to do with carcinogenicity. Dr. Kluwe agreed, and said it might be more clear to say simply that development of inflammation and hyperplasia of the forestomach was clearly compound related, while the papillomas may have been compound related but less clearly so. He said this distinction would be made by revising the first sentence of the conclusion. Dr. Breslow withdrew his earlier statement attributing the production of papillomas of the forestomach as indirect evidence for carcinogenicity. His final impression was that the papillomas could well have been produced by a local toxic reaction and, in any event, were only equivocally related to compound administration.

Dr. Breslow then moved that the report on the bioassay of diallyl phthalate be accepted with the revisions indicated. Dr. Holland seconded the motion and the report was approved by nine affirmative votes with one abstention (Dr. Highland).

4,4'-Methylenedianiline Dihydrochloride (MDA). Dr. Scala, as a principal reviewer for the report of the bioassay of 4,4'-methylenedianiline dihydrochloride, said the conclusions were supported by the data and statistical analyses as presented. The conclusions were: "Under the conditions of this bioassay, 4,4'-methylenedianiline dihydrochloride was carcinogenic for F344/N rats and B6C3F1/N mice of each sex, causing significantly increased incidences of thyroid follicular-cell carcinomas in male rats, follicular-cell adenomas in female rats and mice of each sex, neoplastic nodules in the liver of male rats, hepatocellular carcinomas in mice of each sex, malignant lymphomas in female mice, and adrenal pheochromocytomas in male mice. In addition, several rare tumors observed in this study (bile duct adenoma in male rats and ovarian granulosa-cell tumors and urinary bladder transitional-cell papillomas in female rats) may also have been related to administration of 4,4'-methylenedianiline dihydrochloride." Dr. Lamb, NTP chemical manager, stated that increased incidences of C-cell adenomas of the thyroid in female rats were inadvertently left out of the summary paragraph of the abstract although noted elsewhere in the abstract. Dr. Scala said the doses used (150 and 300 ppm MDA) may have been too high; 100 and 200 ppm would have been more appropriate. He had several comments relating to the possible inpact of water deprivation, room temperature and relative humidity excursions on the results obtained. He specifically called for a more balanced discussion of mechanisms to include the possibility of hepatocarcinogenic activity being secondary to reported hepatotoxicity and being via a non-genetic mechanism, but noted that in all other areas the report did present a balanced viewpoint.

As a second principal reviewer, Dr. Vore agreed with the conclusions. She said that dose-related increases in a number of non-neoplastic lesions of the liver and kidneys should be included in the discussion section. She said kidney, like the liver, possesses enzymes which could convert MDA to proposed reactive intermediates which may in turn be responsible for the renal toxicity; she felt that mention of this would enhance the discussion. She thought the statement that MDA has a special affinity for the thyroid "by virtue of its binding to the hormone receptor" was highly speculative and should be deleted or modified. There was also considerable discussion concerning the inclusion of general scientific speculations in this and other reports, and it was agreed that some speculation was appropriate and should be encouraged as long as it was balanced.

As a third principal reviewer, Dr. Mirer agreed with the conclusions. He noted that the decrease in hematopoietic tumors in male rats is similar to observations in tests of other amine and dye compounds in the bioassay program, and said the association between the decrease in hematopoietic tumors and an increase in tumors at other sites should be explored.

There was discussion concerning inclusion of information on 'genetic drift' of the animals in some reports but not others. This resulted because the 'drift' or contamination was not a problem in some laboratories. For these, it was agreed that where there was a lack of contamination that fact should be stated in the report. Dr. Holland discussed the effects of water deprivation and water pH on the health and survival of animals, especially mice, and indicated he didn't see either as a problem with the MDA study.

Dr. Lamb responded point by point to the reviewer's critiques. He said that statements on possible non-genetic mechanisms requested by Dr. Scala would

be added to the discussion as well as information about the non-neoplastic lesions in the liver and kidneys as requested by Dr. Vore. In response to Dr. Mirer's observation, Dr. J. Haseman, NTP, said that in a review of 25 to 30 of the most recent bioassays, particularly feeding studies, there does seem to be a recurring association of increased liver tumor incidence with concurrent decreases in hematopoietic tumors. Dr. Holland cautioned trying to draw too general a biological significance from this analysis.

Dr. Scala moved that the report on the bioassay of 4,4'-methylenedianiline dihydrochloride be accepted with the modifications discussed. Dr. Mirer seconded the motion and the report was approved unanimously.

Trichloroethylene (Epichlorhydrin-free). Dr. Swenberg was a principal reviewer for the report on the bioassay of trichloroethylene (TCE). The conclusions stated that "under the conditions of this bioassay, trichloroethylene (epichlorhydrin-free) was carcinogenic for male F344/N rats, inducing an increase in renal tubular adenomas and adenocarcinomas. These findings may be confounded because both dose levels of TCE exceeded the maximum tolerated dose (MTD) for male rats. Trichloroethylene was not carcinogenic for female F344/N rats. Trichloroethylene was carcinogenic for male and female B6C3F1/N mice, causing increased incidences of hepatocellular carcinomas and of hepatocellular adenomas." Dr. Swenberg said the conclusion should be restricted to the renal adenocarcinomas in male rats since there was no evidence for progression of the renal adenomas. The adenomas occurred only in low dose animals and were not present at terminal sacrifice whereas the adenocarcinomas occurred only in the high dose group and were present only at terminal sacrifice. He noted the experimental design was faulty, particularly in that the MTD was exceeded in male and female rats in both dose groups and in male mice, and felt the relevance of the results could be seriously questioned especially since the rats did not die from renal tumors. He objected to the combining of different types of tumors or benign and malignant tumors in the text and certain tables. Among numerous other criticisms, Dr. Swenberg commented on lack of explanation for the large number of accidental deaths in high dose male rats, and very poor tissue accountability. He concluded that it was difficult to discern whether the study should be labeled inadequate or whether the report could be embellished with enough scientifically sound data to make it adequate. At present, he considered the report unacceptable.

As a second principal reviewer, Dr. Harper said it was not clear to him that the increased incidence of renal tubular adenomas and carcinomas in male rats was confounded because the MTD for TCE was exceeded. He noted that since only 3/748 (0.4%) of historical controls have had renal tubular adenomas, carcinomas or adenocarcinomas, and carcinoma of the renal pelvis has never been reported in F344/N rats, the findings in the bioassay should not be minimized by overstating the effects of exceeding the MTD. He commented that caution should be used in statements speculating on the non-genetic mechanism of carcinogenicity; a misunderstanding of the mechanism could lead to an underestimation of the risk associated with human exposure.

As a third principal reviewer, Dr. Elashoff said that based on the 13-week study, the doses chosen for the chronic study were reasonable but the results from the earlier NCI bioassay should have suggested the high dose was too high. He agreed with the conclusions for mice except that, in male mice, the time to death with hepatocellular adenomas was shorter in the high dose than for vehicle controls; yet, the incidence rate was not increased. With regard to male rats, the high dose induced lethal nontumorigenic toxicity with the evidence based upon the small P-value comparing survivorship curves between each dose group and vehicle controls. One result of this lethality in male rats would be to reduce the number of animals at risk for developing tumors leading to unadjusted incidence analysis of low power. Life table or incidental tumor analyses lead to the conclusions that TCE is carcinogenic and this becomes also a biological conclusion if the predominant nontumorigenic toxicity, cytomegaly, is not associated with the carcinogenic process. On the other hand, if there is an ambiguous relationship between toxicity and carcinogenicity no statement can be made as to carcinogenicity and the validity of the bioassay for male rats comes into question.

with one abstention (Dr. Schwetz). Dr. Swenberg moved that the report be deferred for rewriting. Dr. Harper seconded and the motion was approved by nine affirmative votes with one abstention (Dr. Schwetz).

Subsequent discussion dealt with what should be covered in a rewrite of the report. Dr. Highland said (1) the untreated controls should be included and discussed, (2) there should be a balanced discussion of MTD and how it's being exceeded could have led to either over- or underestimating effects, and (3) there should be an explanation for the missing tissues. Dr. Swenberg said the confounding factors must be clearly stated, while Dr. Holland asked that non-neoplastic chronic effects not be addressed as confounding factors, rather let the readers draw their own conclusions. Dr. Elashoff said the untreated control data should be included but not a statistical analysis of the data since vehicle controls were the relevant controls for comparison. Dr. Moore concluded that NTP could rewrite the report to be more balanced and to be agreeable to the divergent view points expressed by the panel members.

In discussion by other reviewers, Dr. Highland stressed the point that the high mortality from exceeding the MTD as well as from gavage error in high dose males could have lead to an underestimation of the carcinogenic effect. Dr. Breslow questioned whether the randomization process might have been faulty. He suggested that the abstract should call attention to the fact that five of the hepatocellular carcinomas in treated male mice vs. only one in controls were metastatic as support for the carcinogenic effect. Drs. Schwetz and Elashoff said the report should indicate whether or not the results from the earlier NCI study were considered in dose setting. Dr. Mirer stated that the findings in mice, e.g., a high percentage of males with hepatocellular carcinomas at sacrifice, should be emphasized. He cautioned against drawing a conclusion that the renal tumors in male rats were secondary to the toxic nephrosis, and, further, these toxic effects should be explored further for their significance to human industrial exposure. Several panel members called for more balance and perhaps less speculation in the discussion of genetic vs. epigenetic effects and mechanisms. There was also considerable discussion of the MTD, what it means and especially when it appears to have been severely exceeded. Does the toxicity and poor survival confound the carcinogenic effects observed?

Dr. J. Mennear, NTP chemical manager, responded to several of the comments. He said that only the 13-week study was used to select the doses for the chronic study and the tendency to overestimate the MTD was a common problem with halogenated hydrocarbons. In response to a suggestion from Dr. Highland, he said further discussion would be included on MTD and how its being exceeded could lead to either underestimating or overestimating effects. In response to Dr. Swenberg's request for inclusion of Serology data, Dr. Mennear said serologies were run and would be included in the report

In discussion from the floor, Mr. L. Schlossberg, Detrex Chemical Industries, read a letter and report from three scientists which contended that poor survival and renal tumors in male rats, where MTD was severely exceeded, may be due to a combination of epigenetic factors such as kidney damage and immune system depression. Other criticisms also focused on the confounding effects of toxicity in male rats in that the toxicity, renal nephrosis, was in the same organ as the tumors.

Dr. Scala suggested there were two issues: acceptability of the assay and acceptability of the report. He opined that the assay was marginally acceptable but the report wasn't and needed to be rewritten to reflect the many comments and the question of balance. Dr. Swenberg proposed the panel defer acceptance until having a chance to review a revised report, and said the results have to be reported whether or not they are adequate or acceptable. He was disturbed by the fact that there were untreated controls which were not discussed. Dr. J. Huff, NTP, said existence of these controls had been discovered only recently but should have been brought to the attention of the panel at the outset, and would be described in the revised report. Dr. Moore commented that if the report was deferred for a rewrite, the NTP needed more guidance from the panel, some sort of consensus.

Dr. Highland moved that the bioassay of TCE be considered acceptable. Dr. Harper seconded the motion and it was approved by nine affirmative votes

Melamine. Dr. Highland, a principal reviewer for the report on the bioassay of melamine, agreed with the conclusion that: "Under the conditions of this bioassay, melamine was carcinogenic for male F344 rats, causing transitional-cell carcinomas in the urinary bladder. Melamine was not carcinogenic for female F344 rats or for B6C3F1 mice of either sex." Dr. R. Melnick, NTP chemical manager, reported that at the request of American Cyanamid Company there had been a meeting between representatives of the company and NTP to discuss the draft report. The NTP incorporated some of the information received into the introduction and into the discussion and these revised sections were given to the Panel. Further, slides used to make the diagnoses of the transitional cell carcinomas, as well as re-cuts, were re-reviewed by 13 pathologists from the Washington, D.C. and Research Triangle Park areas. The consensus opinion of these reviews was to confirm the original diagnosis in the high dose group. Finally, further experiments are planned, some by American Cyanamid and some by NTP, to examine the relationship between bladder stones and bladder tumors in male rats resulting from ingestion of melamine.

Dr. Highland expressed concern that the discussion was far too heavily biased toward the possible role of bladder stones in the etiology of the carcinomas, and stated the conclusion should be rewritten to reflect a more balanced presentation including discussion of a possible biochemical mechanism. He noted that stones were found in rats without tumors, and vice versa, and, also, mice had stones but no tumors. He also objected to inclusion of reference to an American Cyanamid study since the work is still in progress. He asked for an explanation as to why female rats were dosed at twice the levels of male rats.

As a second principal reviewer, Dr. Scala said that evidence for association of bladder stones with the bladder tumors was strong in this study, in the cited literature, and in other work, specifically the CIIT studies of terephthalic acid. Thus, he suggested insertion of a sentence in the conclusion to the effect that the transitional-cell carcinomas may have been secondary to the production of bladder stones. He expressed concern that a more integrated discussion of urinary tract pathology was not given.

As a third principal reviewer, Dr. Schwetz agreed with the stated conclusions of the bioassay. He agreed with Dr. Highland that remarks in the discussion on page 104 which cite significant association between bladder stones and tumors, and then concludes that "These findings suggest that bladder stones in male rats may contribute to the development of urinary bladder tumors" may be too strong. At most, the results would suggest a correlation between the two, but say nothing about cause and effect. He said the discussion ignores one important point that should be mentioned, that being whether the sex difference in sensitivity is related to a sex difference in metabolism or kinetics.

In further discussion, Dr. Swenberg suggested that the first sentence of the conclusion should read: "Under the conditions of this bioassay, melamine was carcinogenic for male F344 rats at doses resulting in bladder stones, causing transitional-cell carcinomas." There was considerable discussion concerning statistical associations vs. cause and effect. It was agreed that there should be a separate statement in the conclusion that bladder stones were seen in high-dose male rats.

In discussion from the floor, Dr. C. Frith, pathologist-consultant for American Cyanamid, made a presentation which contended that there was a strong correlation between melamine stones and urinary bladder tumors in the NTP study, disputed the diagnoses of some of the transitional-cell carcinomas in the NTP bioassay based on his examination, and stated that in an ongoing melamine study sponsored by American Cyanamid there were no compound-related bladder tumors. Dr. L. Golberg, also a consultant for American Cyanamid, talked about the historical background of the relationship between bladder stones and bladder neoplasia. Dr. R. Mast, American Cyanamid, commented on specific portions of the NTP melamine report, and made suggestions for changes in the report.

Dr. Boorman, NTP, responded to Dr. Frith's disagreement with the diagnoses of some of the bladder tumors. He said the recent review of the bladder slides, including recuts for additional sections in some cases, confirmed the original diagnoses of transitional-cell carcinomas. The pathologists involved were from industry and private laboratories as well as NTP, and the studies were done in a blind fashion. He concluded that the diagnoses would be accepted by most rodent tumor pathologists. Dr. Swenberg said that he and other pathologists from CIIT had examined the slides, including the recuts, and agreed with Dr. Boorman's assessment. His opinion still remained that the tumors were related to bladder stone formation but were also related to melamine since the chemical is found in the stones.

Dr. Highland moved that the report on the bioassay of melamine be accepted with the inclusion of a separate sentence in the conclusion concerning the observation of bladder stones in male rats having transitional-cell carcinomas, as well as other modifications requested by the reviewers. These should include a revision of the discussion to provide more balance in consideration of mechanisms in that a mechanism is not yet known. Dr. Breslow seconded the motion and the report was approved unanimously.

Ascorbic Acid. Dr. Vore, a principal reviewer for the report on the bioassay of L-ascorbic acid, agreed with the conclusion that: "Under the conditions of this bioassay, L-ascorbic acid was not carcinogenic for F344/N rats or B6C3F1/N mice of either sex." She noted the high dose chosen, 50,000 ppm, is the highest concentration recommended for chronic feeding by the Program. She said no mention was made of the significant negative trend for pituitary adenomas in female rats. Also, the pairwise comparison for high dose vs. control was statistically significant. She opined that negative trends for both neoplastic and non-neoplastic lesions should be highlighted although not necessarily be included in the abstract. She raised the question as to what the implications of highlighting such information would be for a popular over-the-counter preparation as ascorbic acid.

As a second principal reviewer, Dr. Breslow agreed with the conclusion as stated. He criticized as misleading some of the phrasing used to describe the statistical significance of observed results. He observed that rather routine and uncritical use was being made of historical control data in order to interpret marginally significant differences in incidence rates between control and treated animals which appear in isolated species/sex/site combinations. Better understanding of factors responsible for inter-laboratory and within laboratory inter-experiment variation is desirable before one can confidently exclude all such results as being statistical aberrations. He noted the significant negative trends for a variety of non-neoplastic degenerative lesions were interesting and merited further investigation.

As a third principal reviewer, Dr. Swenberg agreed that the bioassay was well conducted and the report well written and documented. He noted several items that needed minor revision. He included an abstract for referencing of work reported by a Japanese researcher showing that L-ascorbate can promote bladder cancer in rats.

Dr. J. Douglas, NTP chemical manager, responded to Dr. Vore's comment about pituitary adenomas in female rats. He said they were not mentioned in the discussion because the negative trend was marginally significant, the life table test was not significant, and the control incidence was higher than historical control incidences.

Dr. J. Haseman, NTP, responded to Dr. Breslow's comments. He said there were three problems that have kept NTP from utilizing fully historical control data. First, was defining the NTP historical data base; second, was identifying and quantifying the factors responsible for extra binomial variation frequently seen in tumor incidence; and third, was selection of appropriate statistical methodology to utilize the historical control data. He said that the first of these problems has recently been resolved and progress is being made in resolving the other two issues. He expressed the hope that within the near future NTP would be able to make use of the historical data base in a formal testing framework.

Dr. Swenberg moved that the report on the bioassay of L-ascorbic acid be accepted with the revisions discussed. Dr. Schwetz seconded the motion and the report was approved unanimously.

Benzyl Acetate. Dr. Holland, a principal reviewer for the report on the bioassay of benzyl acetate, agreed with the conclusion that: "Under the conditions of this bioassay, benzyl acetate was carcinogenic to male F344/N rats, causing an increased incidence of animals with pancreatic acinar-cell adenomas. Benzyl acetate was not carcinogenic in female F344/N rats. Benzyl acetate should be considered carcinogenic in B6C3F1/N mice, since it caused increased incidences of liver tumors (primarily hepatocellular adenomas) in both males and females. In addition, increased incidences of squamous cell papillomas or carcinomas of the stomach in male mice (an uncommon neoplasm) may have been related to administration of benzyl acetate." Dr. Holland added that the evidence indicating the potential tumorigenicity of benzyl acetate was strengthened further by the increased incidence of preputial gland neoplasms (benign and malignant) in high dose male rats, a finding not mentioned in the abstract. He commented on the diagnostic ambiguity between testicular hyperplasia and neoplasia as being inconsistent with the numerical tabulation and discussion, and recommended that NTP pathologists develop criteria specifying what would be accepted as leydig cell neoplasia relative to hyperplasia.

As a second principal reviewer, Dr. Schwetz agreed with the overall conclusions but said the comment on papillomas and carcinomas of the stomach should be deleted from the abstract since the marginal incidence doesn't warrant such attention. Further, since benzyl acetate was given by gavage, there is reason to expect reaction at the site of deposition and it should be mentioned in the discussion. Importantly, very little change was observed in the stomach of either sex of either species. With regard to testicular tumors, if hyperplasia was included with tumors, he questioned whether there was an effect of benzyl acetate in the high-dose male rats.

As a third principal reviewer, Dr. Elashoff agreed with the conclusions in the report. He had several other questions or comments concerning errors in the report. Dr. K. Abdo, the NTP chemical manager, responding to Dr. Schwetz, said the stomach tumors were included in the abstract because the combined incidence of papillomas and carcinomas in high-dose male mice was much higher than observed in historical control animals.

Dr. L. Golberg, as an expert consultant for the Research Institute for Fragrance Materials, made a number of comments on the bioassay. He said the known metabolites of benzyl acetate were non-mutagenic and likely not carcinogenic per se; he speculated that the stomach tumors were due to a promotional effect or local formation of benzyl chloride; and he criticized some of the statistical procedures used. Dr. Breslow said the current statistical procedures resulted from an intensive evaluation by a group which included members of the Peer Review Panel.

Dr. Elashoff moved that the report on the bioassay of benzyl acetate be accepted subject to the minor modifications discussed. Dr. Highland seconded the motion and the report was approved unanimously.

Propyl Gallate. The draft technical report on the carcinogenesis bioassay of propyl gallate was peer reviewed by the NTP Peer Review Panel in December 1981. Final approval of the draft bioassay report was deferred. Subsequently, the principal reviewers, Drs. Mirer and Elashoff, drafted revised conclusions which, along with their original reviews, the summary minutes, and a copy of the meeting transcripts, were sent by NTP to all of the other members of the review panel present at the meeting. All of the panel members replied by telephone or letter that they agreed with the revised conclusions. Dr. Hitchcock announced the unanimity of agreement and read the revised conclusions which are: "Under the conditions of this bioassay, propyl gallate was not considered to be carcinogenic in F344 rats, although there was evidence of an increased number of male rats with preputial gland tumors, islet cell tumors of the pancreas, and pheochromocytomas of the adrenal glands. Propyl gallate was not considered carcinogenic for B6C3F1 mice of either sex, but an increased number of malignant lymphomas in male mice may have been related to the administration of the test compound."