Board of Scientific Counselors
National Toxicology Program

Summary Minutes
from

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

August 19, 1986
Research Triangle Park, North Carolina

The review meeting began at 8:30 a.m. in the Conference Center, Building 101, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina. Members of the Subcommittee were: Drs. Robert Scala (Chairperson), Michael Gallo and Frederica Perera. Members of the Panel of Experts were: Drs. Charles Capen, Vernon Chinchilli, John Crowley, Kim Hooper, Donald Hughes, Franklin Mirer, James Popp, Ian Purchase, and Andrew Sivak. Dr. Hughes was unable to attend this meeting. These minutes have been reviewed and approved by all members of the Subcommittee and Panel. They were written by Dr. Larry G. Hart, Executive Secretary.

When available, final NTP Technical Reports for the studies 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 March 4, 1987, in Research Triangle Park, North Carolina. For information, contact Dr. Hart, (919) 541-3971; FTS 629-3971.

CONTENTS

Bromodichloromethane. Dr. J. K. Dunnick, NIEHS, NTP Chemical Manager, introduced the toxicology and carcinogenesis studies of bromodichloromethane by reviewing the experimental design, results, and proposed conclusions:

> Under the conditions of these 2-year gavage studies, there was clear evidence of carcinogenic activity of bromodichloromethane for male and female F344/N rats as shown by increased incidences of tubular cell adenomas and adenocarcinomas in the kidney and adenomatous polyps and adenocarcinomas in the large intestine. There was clear evidence of carcinogenic activity of bromodichloromethane for male and female B6C3F$_1$ mice as shown by increased incidences of tubular cell adenomas and adenocarcinomas in the kidney of male mice, and increased incidences of hepatocellular adenomas and carcinomas in female mice.

Dr. Capen, a principal reviewer, agreed with the conclusions as written. He questioned the rationale for giving female mice three fold higher doses than male mice. Dr. Dunnick reported that the dose levels used derived from marked differences in mortality in prechronic studies.

As a second principal reviewer, Dr. Chinchilli agreed with the conclusions. He said the experimental design appeared adequate but asked that more information on the randomization scheme be included in the report.

As a third principal reviewer, Dr. Perera also agreed with the conclusions. She said that the rationale for using corn oil gavage should be expanded since in studies by other investigators drinking water and microencapsulation were the exposure routes. Dr. Dunnick replied that the NCI/NTP studies with other trihalomethanes, chloroform and chlorodibromomethane, were by corn oil gavage so the same route was chosen to allow more direct comparison of the results.

Other discussion centered on whether formal statistical analyses should be carried out for nonneoplastic lesions, and whether results on these lesions should be included in the abstract of the report when deemed to be statistically and biologically significant. In particular, there was discussion as to whether the renal lesions in rats were similar to those observed primarily in male rats exposed to other hydrocarbons. Dr. Popp stated it would be worthwhile to compare these lesions in the current studies with renal lesions induced by other halogenated hydrocarbons. Dr. Scala suggested that the findings with the trihalomethanes be summarized.

Dr. Capen moved that the Technical Report on bromodichloromethane be accepted with the conclusions as written for male and female rats and mice, clear evidence of carcinogenic activity. Dr. Perera seconded the motion and it was approved unanimously with ten affirmative votes.

Dimethyl Methylphosphonate. Dr. J. K. Dunnick, NIEHS, NTP Chemical Manager, introduced the toxicology and carcinogenesis studies of dimethyl methylphosphonate by reviewing the experimental design, results, and proposed conclusions:

> Under the conditions of these 2-year gavage studies, there was some evidence of carcinogenic activity of dimethyl methylphosphonate for male F344/N rats as shown by increased incidences of tubular cell hyperplasia, tubular cell adenocarcinomas, hyperplasia of the transitional cell epithelium, and transitional cell papillomas of the kidney; there was an increased incidence of mononuclear cell leukemia in male rats at 1,000 mg/kg; and renal toxicity and decreased survival were seen in dosed male rats. There was no evidence of carcinogenic activity of dimethyl methylphosphonate for female F344/N rats given doses of 500 or 1,000 mg/kg. The study in male B6C3F$_1$ mice was considered to be an inadequate study of carcinogenic activity because of decreased survival in both dosed groups. There was no evidence of carcinogenic activity for female B6C3F$_1$ mice receiving dimethyl methylphosphonate at 1,000 mg/kg; decreased survival of female mice at 2,000 mg/kg made this group inadequate for determination of carcinogenic activity.

Dr. Crowley, a principal reviewer, agreed with the conclusions for male and female rats and male mice. He proposed that the conclusion for female mice be changed to inadequate study of carcinogenic activity based on there being reasonable survival only in the low dose group. Dr. Popp said that since there was one valid dose group, he thought the study was adequate.

As a second principal reviewer, Dr. Purchase commented that the substantial reduction in body weight and survival in high dose male rats indicated the dose was excessive and made the findings difficult to interpret. Regarding mononuclear cell leukemias in male rats, he said it would be appropriate if the stage one or two leukemias were statistically analyzed by the incidental tumor test (non-lethal) while stage three leukemias (lethal) were analyzed by the life table test. Dr. J. Haseman, NIEHS, said analyses were done but because most of the tumors were stage three leukemias, this analysis gave results similar to that obtained for the life table test. Further, he noted that the kidney lesions rather than leukemias were the primary basis for the conclusion of some evidence of carcinogenic activity in male rats.

As a third principal reviewer, Dr. Gallo agreed with the conclusions as written. He thought that there should be expanded discussion of the hypothesis regarding chemical-induced renal lesions in male rats and increased renal tubular levels of alpha-2-microglobulin.

Dr. Mirer opined that a statement could be added in the conclusions for female mice that a higher dose could have been used. He noted the large number of accidental deaths in the high dose group.

Dr. Crowley moved that the Technical Report on dimethyl methylphosphonate be accepted with the conclusion as written for male rats, some evidence of

carcinogenic activity. Dr. Hooper seconded the motion and it was approved unanimously with eight affirmative votes. In separate votes, Dr. Crowley then moved for acceptance of the conclusion as written for female rats, no evidence of carcinogenic activity, and of the conclusion as written for male mice, inadequate study of carcinogenic activity. Dr. Hooper seconded both and they were approved unanimously with eight affirmative votes. Dr. Crowley moved that the conclusion for female mice, no evidence of carcinogenic acitivity, be changed to inadequate study of carcinogenic activity. Dr. Chinchilli seconded the motion and it was defeated by 6 No(N) to 2 Yes(Y) votes (Dr. Chinchilli and Dr. Crowley). Dr. Mirer moved that the conclusion as written be amended to state that higher doses might have been tolerated. Dr. Hooper seconded that motion and it was defeated by 7N to 1Y (Dr. Mirer). Dr. Purchase moved that the conclusion for female mice be accepted as written. Dr. Popp seconded the motion, and it was approved by 5Y to 3N votes (Dr. Chinchilli, Dr. Crowley and Dr. Mirer). Dr. Perera and Dr. Sivak were absent for the discussion and motions.

1,2-Epoxybutane. Dr. J. K. Dunnick, NIEHS, NTP Chemical Manager, introduced the toxicology and carcinogenesis studies of 1,2-epoxybutane by reviewing the experimental design, results, and proposed conclusions:

> Under the conditions of these 2-year inhalation studies, there was clear evidence of carcinogenic activity of 1,2-epoxybutane for male F344/N rats as shown by an increased incidence of papillary adenomas of the nasal cavity and alveolar/bronchiolar adenomas or carcinomas (combined). There was some evidence of carcinogenic activity for female F344/N rats as shown by the presence of papillary adenomas of the nasal cavity in two rats in the 400-ppm group. There was no evidence of carcinogenic activity for male or female B6C3F$_1$ mice exposed at 50 or 100 ppm. 1,2-Epoxybutane exposure was associated with nonneoplastic lesions of the nasal cavity in rats and mice.

Dr. Dunnick pointed out that the conclusion for female rats printed in the draft report, equivocal evidence of carcinogenic activity, had been changed during final staff review based on the rarity of the papillary adenomas of the nasal cavity, and supported by increases in the same lesions in male rats and in previous NTP studies of propylene oxide.

Dr. Popp, a principal reviewer, agreed with the conclusions for male rats and male and female mice while questioning the new conclusion for female rats. He asked whether the conclusion in male rats was based on benign, malignant, or a combination of benign and malignant lung tumors. Dr. Dunnick replied that it was based on both carcinomas and combined adenomas or carcinomas. Dr. Popp commented that there should be mention in the text of the significance of the respiratory viruses identified by serology. Dr. Dunnick said there were no lesions to indicate an active infection.

As a second principal reviewer, Dr. Perera agreed with the conclusions as presented, endorsing the chemical-relatedness of the papillary adenomas of the nasal cavity in high dose female rats. Since two-year studies with 1,3-butadiene and ethylene oxide were conducted in the same animal room, she asked for inclusion of a statement that there was no contamination of room air by these chemicals. This was agreed.

As a third principal reviewer, Dr. Sivak agreed with the conclusions for male rats and male and female mice but thought the observation of two nasal cavity adenomas in high-dose female rats not enough to justify some evidence. Dr. S. Eustis, NIEHS, elaborated on the staff decision for the stronger level. Besides the rarity of the tumors and their occurrence in male rats, the occurrence of adenomatous hyperplasias, believed by some to be preneoplastic lesions, provided additional evidence.

Further discussion focused on the strength of the evidence for male rats. Dr. Purchase contended that the zero incidence of lung tumors in controls was low contrasted with the six tumors (6/249) observed in chamber controls from previous studies at the same laboratory. Considered along with the difficulty of distinguishing among pulmonary hyperplasias, adenomas, and carcinomas, he

believed some evidence of carcinogenic activity was more appropriate. Dr. Paul Cammer, representing the Halogenated Solvents Industry Alliance, made a brief presentation supporting a lower level of evidence. Dr. Eustis responded that the progressive nature of the pulmonary tumor process along with the consistency of diagnoses introduced through the NTP pathology quality assurance process eliminates inconsistent diagnoses. Dr. J. Huff, NIEHS, added that program pathologists have no difficulty in differentiating hyperplasias, benign tumors, and malignant tumors. Dr. J. Haseman, NIEHS, said that the increased incidence of lung neoplasms in high dose male rats (5/49) would likely have been even more significant compared to the historical control rate at the contract laboratory (6/249) than that obtained in the actual comparison with concurrent controls (0/50). Dr. Hooper expressed concern about the identity of the reported one percent impurity in the test chemical. Dr. Dunnick said more recent analyses indicated a purity of 99.9 percent or greater.

Dr. Popp moved that the Technical Report on 1,2-epoxybutane be accepted with the conclusions as originally written, clear evidence of carcinogenic activity for male rats, equivocal evidence of carcinogenic activity for female rats, and no evidence of carcinogenic activity for male and female mice. Dr. Sivak seconded the motion. Dr. Perera offered an amendment to the motion that the staff's modification to some evidence of carcinogenic activity be accepted. Dr. Hooper seconded the amendment and it was defeated by 6N to 3Y votes (Dr. Hooper, Dr. Mirer and Dr. Perera) with 1 Abstention (A) (Dr. Purchase). The original motion was then approved by 7Y to 2N votes (Dr. Hooper, Dr. Perera) with 1A (Dr. Purchase).

Ethylene Oxide. Dr. T. R. Lewis, NIOSH, NTP Chemical Manager, introduced the toxicology and carcinogenesis studies of ethylene oxide in mice by reviewing the experimental design, results, and proposed conclusions:

> Under the conditions of these 2-year inhalation studies, there was clear evidence of carcinogenic activity of ethylene oxide for B6C3F$_1$ mice as indicated by dose-related increased incidences in males of malignant, and in females of benign and malignant neoplasms of the lung and benign neoplasms of the harderian gland in both male and female B6C3F$_1$ mice following exposure to ethylene oxide vapors at 50 and 100 ppm. In female mice, ethylene oxide caused additional malignant neoplasms of the uterus, mammary gland, and hematopoietic system (lymphoma).

Dr. Mirer, a principal reviewer, agreed with the conclusions as written. He felt that higher doses could have been used since there were no declines in weight gain, increases in mortality, or increases in nontumor pathology; thus there may have been a reduction in sensitivity for detecting tumor induction potential at other organ sites. Dr. Lewis said ethylene oxide has a moderately steep dose response curve so increasing the top dose might have resulted in inadequate survival. Dr. Mirer said a more complete tabular comparison of the results of the NTP studies with the other two epoxy compounds, 1,2-epoxybutane and propylene oxide, would be helpful.

As a second principal reviewer, Dr. Capen agreed with the conclusions as written.

As a third principal reviewer, Dr. Hooper also agreed with the conclusions. He asked that more exposure information and dose levels from various studies be cited, including a number of genetic toxicology studies. This would allow the reader to compare exposure levels with those in the current study as well as with allowable workplace exposure concentrations. Dr. Lewis replied that such detailed information could be included although so much has been reported previously perhaps inclusion of references to pertinent review articles would be appropriate.

In other discussion, Dr. Purchase commented on the metabolic conversion of ethylene to ethylene oxide in mammals and the fact that ethylene oxide can be detected in exhaled air in untreated mammals. Dr. Scala said that since lesions were observed in several organs in the prechronic study, a simple statement should be made that these lesions were not seen in the chronic study.

Dr. Mirer moved that the Technical Report on ethylene oxide be accepted with the conclusions as written for male and female mice, clear evidence of carcinogenic activity. Dr. Capen seconded the motion and it was approved by 10Y votes with 1A (Dr. Purchase).

Methyl Carbamate. Dr. P. Chan, NIEHS, NTP Chemical Manager, introduced the toxicology and carcinogenesis studies of methyl carbamate by reviewing the experimental design, results, and proposed conclusions:

> Under the conditions of these 6-, 12-, and 18-month and 2-year gavage studies, there was clear evidence of carcinogenic activity for male and female F344/N rats given methyl carbamate as indicated by increased incidences of neoplastic nodules and carcinomas of the liver. There was no evidence of carcinogenic activity for male and female B6C3F$_1$ mice given methyl carbamate at doses of 500 or 1,000 mg/kg. Methyl carbamate also induced retinal atrophy, cataracts, and inflammation of the harderian gland in male and female rats, and adenomatous hyperplasia and histiocytosis of the lung in male and female mice.

Dr. Purchase, a principal reviewer, began a discussion on the significance of the neoplastic lesions in the livers of rats. He opined that the high incidence of necrosis and other extensive tissue damage in the liver of animals from the 12 and 18 month studies diluted and confounded the significance of the neoplastic effects. This, along with the small numbers of carcinomas in treated male and female rats on the two-year studies made the designation of clear evidence of carcinogenic activity less certain. Dr. Purchase also noted some statistically significant decreases in incidences of tumors compared to controls which might be mentioned in the conclusions. Dr. Chan emphasized that the conclusions in rats were based on the composite findings from animals in the six, 12 and 18 months experiments as well as from the two-year studies. Dr. Huff noted that the exposures for the 24-month experiments were one-half the doses used in the shorter term studies.

As a second principal reviewer, Dr. Gallo agreed with the conclusions as written. He thought the more appropriate route of exposure would have been by inhalation or dermally. He suggested that the studies were good examples of dose-time responses compared to tissue burden which indicated that tissue concentration and metabolism often play a major role in comparative toxicity between species.

Dr. Scala read the review from Dr. Hughes, the third principal reviewer, who was absent due to illness. Dr. Hughes did not agree with the conclusions in rats. He said the data from the two-year studies alone were insufficient to support a conclusion of clear evidence of carcinogenic activity while exposure of rats for six, 12 or 18 months at higher doses than used in the 24 month studies resulted in a cumulative toxic response as well as a progressive carcinogenic response in rat liver. Dr. Chan disagreed that the dose level (400 mg/kg) for the six, 12, or 18 month studies was too high at least as reflected by reductions in body weight gain and survival compared with controls. Dr. S. Eustis, NIEHS, responded to the reviewer's comments that toxic effects of the chemical diminished the significance of the carcinogenic effects in that same organ. Dr. Eustis said that one should not generalize but rather must consider the specific type of histologic changes. With methyl carbamate, he said the toxicity in the liver consisted of foci of cellular alteration and atypical proliferative changes which experimentalists usually find with other potent liver carcinogens.

Further discussion focused on the interim sacrifice studies as they related to the level of evidence chosen for rats. Dr. Popp tended to agree that the tumor data from the two-year studies alone were insufficient to justify the conclusion; rather, the conclusion was drawn from the shorter term results. Dr. Hooper argued that the increases in cytologic alterations in livers of control rats from six to 12 to 18 months with no corresponding appearance of neoplasia indicated the alterations were aging lesions and unrelated to the neoplastic process. Dr. J. Huff, NIEHS, stated that it was highly unusual to observe neoplastic nodules of such a magnitude at six months or likewise carcinomas at 12 and 18 months. He acknowledged that groups exposed to 400 mg/kg should have been carried to 24 months.

Regarding species differences in chemical metabolism, Dr. B. Schwetz, NIEHS, reported on recent chemical disposition studies. Using a wide range of doses, the studies confirmed a longer half life in rats, about three days, than in mice, about four hours. He said these findings with appropriate discussion would be added to the report.

Dr. Jane Hixson, Mobay Corporation, stated that the toxicity to the liver in animals exposed to 400 mg/kg was so severe as to preclude use of the data, and assessment of carcinogenicity should be based strictly on the two year studies in rats. Dr. Huff noted that virtually all rats, control and exposed alike, showed evidence of cytologic alterations at 18 months. Dr. Ronald Lorentzen, FDA, observed that among the most significant findings were the anticarcinogenic effects on the pituitary gland in male rats and female mice and on the adrenal glands in male rats. Dr. Huff said these findings would be given more emphasis, yet, wondered how relevant this was compared to the carcinogenic effects observed in the liver of rats.

Dr. Purchase moved that the Technical Report on methyl carbamate be accepted with the conclusions as written for male and female mice, no evidence of carcinogenic activity. Dr. Gallo seconded the motion and it was approved unanimously with 10 affirmative votes. Dr. Purchase moved that the conclusions for male rats be changed to some evidence of carcinogenic activity. As there was no second, Dr. Purchase then moved to accept the conclusions as written, clear evidence of carcinogenic activity. Dr. Mirer seconded the motion and it was approved unanimously with 10 affirmative votes. Dr. Purchase moved that the conclusions for female rats be accepted as written, clear evidence of carcinogenic activity. Dr. Perera seconded the motion and it was approved unanimously with 10 affirmative votes.

Rotenone. Dr. K. M. Abdo, NIEHS, NTP Chemical Manager, introduced the toxicology and carcinogenesis studies of rotenone by reviewing the experimental design, results, and proposed conclusions:

> Under the conditions of these 2-year feed studies, there was equivocal evidence of carcinogenic activity of rotenone for male F344/N rats as indicated by the increased incidence of parathyroid gland adenomas (uncommon tumors) and for female F344/N rats as indicated by the increased incidence of subcutaneous tissue tumors. There was no evidence of carcinogenic activity for male or female B6C3F$_1$ mice fed diets containing 600 or 1,200 ppm rotenone for 2 years. The decreased incidence of liver neoplasms in male mice may have been related to the administration of rotenone.

Dr. Scala read the review from Dr. Hughes, a principal reviewer, who was absent due to illness. Dr. Hughes agreed with the conclusions as written for male and female mice. For male rats, he suggested that the increased incidence of parathyroid gland adenomas in high dose rats may have been due to sampling error, and the absence of increases in parathyroid gland hyperplasia also mitigated against rotenone influence. Dr. S. Eustis, NIEHS, said the tissue accountability of parathyroid glands from control, low dose, and high dose animals, respectively, was 41/50, 44/50, and 44/50 which shows an even sampling across all groups. Dr. J. Huff, NIEHS, mentioned that these numbers of sections were quite good given the smallness of the parathyroid glands. Dr. Purchase argued that unless step sectioning is used sampling error with such a tiny organ could still be a factor. Dr. Eustis thought the potential problem was being overemphasized, in that similar numbers of sections were evaluated for each group and that serial sectioning would not influence the overall proportions of neoplasia. For female rats, Dr. Hughes suggested that the lack of dose-response and atypical zero incidence of subcutaneous tumors in controls helped mitigate against a rotenone effect.

As a second principal reviewer, Dr. Sivak agreed with the conclusions for mice but thought the conclusions in male and female rats should be lowered to no evidence of carcinogenic activity. He said the low incidence of microscopic tumors in the parathyroid gland in males and, in females, the need to pool subcutaneous tumors from different areas to attain statistical significance, along with the inverted dose-response and the longer time to tumor in the high dose groups than in controls supported these changes. Dr. Sivak requested that the rationale for dose selection in mice should be expanded, and more discussion should be given about the large species differences in biological response to the chemical. Dr. Abdo said the species differences in sensitivity represented large biological variation which couldn't be explained on the available data although metabolism studies might be useful and the discussion certainly would be expanded.

As a third principal reviewer, Dr. Chinchilli agreed with the conclusions as written for both rats and mice. Since the only tumors increased in rats occur rarely, he said it would be helpful if the NTP could provide statistical tests incorporating historical control data from the same laboratory to aid in

evaluating the significance of rare tumors. Dr. J. Haseman, NIEHS, responded that the NTP generally does not use historical control data in a formal testing framework because there is no consensus as to which statistical technique is best, and even more importantly, there are unresolved uncertainties regarding the comparability of tumor diagnoses and reported incidence rates across studies.

In other discussion, Dr. Huff pointed out with regard to the decreased incidence of liver neoplasms in male mice that this was the first time the Program has stated that a decreased incidence of a tumor was associated with chemical administration. Dr. Purchase noted that the Program, in evaluating significance of increased tumor incidence, considers a finding of increased incidence of the same tumor in the other sex or the other species to be supportive. Conversely he thought the significant negative trend for subcutaneous tumors in male mice should weaken the rationale for association with chemical treatment of these lesions in female rats. Dr. Huff responded that correlations from one sex of one species to the other sex of another species were somewhat more difficult.

Dr. Sivak moved that the Technical Report on rotenone be accepted with the conclusions as written for mice, no evidence of carcinogenic activity but with the conclusions for rats changed to no evidence of carcinogenic activity. Dr. Purchase seconded the motion. Dr. Mirer made an alternate motion to consider male and female rats separately. As Chair, Dr. Scala indicated that better progress could be made by separate motions. He moved that the conclusions for male mice be accepted. The motion was approved unanimously by 10 affirmative votes. Dr. Scala then moved that the conclusions for female mice be accepted. The motion was approved unanimously by 10 affirmative votes. He moved for approval of Dr. Mirer's procedural motion to consider male and female rats separately. Dr. Hooper seconded the motion and it was approved by nine affirmative votes to one negative vote (Dr. Popp). Dr. Sivak restated his motion of no evidence of carcinogenic activity for male rats based on possible sampling error and on a low control tumor incidence; the motion was defeated by 5N to 4Y votes (Dr. Capen, Dr. Crowley, Dr. Purchase and Dr. Sivak) with 1A (Dr. Mirer). Dr. Sivak restated the motion of no evidence of carcinogenic activity for female rats and it was approved with 6Y to 4N votes (Dr. Chinchilli, Dr. Hooper, Dr. Perera and Dr. Popp). To complete the evaluation on male rats, Dr. Hooper moved that the conclusion for male rats be accepted as written, equivocal evidence of carcinogenic activity. Dr. Gallo seconded the motion. Dr. Purchase offered an amendment to add the qualifier that there be a reexamination of the parathyroid glands to assess whether there was a sampling error. Dr. Eustis said trying to go back and get additional sections would be extremely difficult. Dr. Popp agreed and said step sections would yield an incomplete answer because part of the tissue was already gone due to previous sectioning. The amendment was defeated by 8N to 2Y votes (Dr. Purchase, Dr. Sivak). Dr. Hooper's motion to accept the conclusions as written in male rats was approved by 5Y to 4N votes (Dr. Capen, Dr. Crowley, Dr. Purchase and Dr. Sivak) with 2A (Dr. Gallo, Dr. Mirer). It should be noted that Dr. Scala, the Chairman, voted affirmatively to break a tie vote (4Y to 4N).

Trichloroethylene. Dr. J. A. Mennear, NIEHS, NTP Chemical Manager, introduced the toxicology and carcinogenesis studies of trichloroethylene in four rat strains by reviewing the experimental design, results, and proposed conclusions:

> Under the conditions of these 2-year gavage studies of trichloroethylene in male and female ACI, August, Marshall, and Osborne-Mendel rats, trichloroethylene administration caused renal tubular cell cytomegaly and toxic nephropathy in both sexes of the four strains. However, these studies are considered to be inadequate for assessing either the presence or absence of carcinogenic activity because of chemically induced toxicity, reduced survival, and deficiencies in the conduct of the studies.

The draft report initially had been peer reviewed by the Panel on December 9, 1985 and deferred for further revision.

Dr. Hooper, a principal reviewer, stated this version was improved considerably over the previous draft especially in justifying dose selection, comparing renal toxicity in five rat strains (including F344), eliminating mention of gavage trauma as the major cause of decreased survival, and summarizing audit findings and deficiencies in the execution of the studies. Among many comments, Dr. Hooper suggested that significant carcinogenic effects should be included in the summary, even though the overall studies were judged to be inadequate for assessing carcinogenicity, and he cited specific increases in renal and testicular tumors. He asked for a clarifying discussion on what is meant by "accidental" deaths since some of the excessive mortality could be due to anesthetic or toxic properties of the chemical. Dr. Hooper suggested that a more balanced discussion be given to the carcinogenic effects of chlorinated aliphatics and should include findings from inhalation studies where the carcinogenic responses appeared to be broader in terms of site.

As a second principal reviewer, Dr. Popp basically agreed with the conclusion that these were inadequate studies; however, the report should more clearly and specifically state the basis for the studies' inadequacies. Dr. Popp indicated that statements in the text about significant increases in renal tumors could lead to a misunderstanding that this was a positive study. He thought these statements could be better qualified.

As a third principal reviewer, Dr. Crowley questioned whether the report yet comes to grips with how serious are the data problems. For example, the results of the data audit indicate that analyses by dose group and evaluations of dose response may be potentially misleading. He said if this was an inadequate study, the significant tumor findings should be downplayed or not presented at all. Dr. Crowley noted a possible exception, testicular tumors in Marshall rats, which did not involve a compromised organ and were statistically significant regardless of dose identification.

Most of the discussion was concerned with the weight that should be given to the renal and testicular tumors observed and whether statistical significances should be given within the context of an inadequate study. One viewpoint as

supported by Dr. Purchase, Dr. Crowley and Dr. Popp was that conclusions about carcinogenic activity from an inadequate study and assigning statistical significance to the tumor findings, especially in view of the low numbers and uncertainty of animal identification, are unwarranted. A second viewpoint as supported by Dr. Hooper, Dr. Mirer and Dr. Perera was that, while conclusions cannot be drawn from an inadequate study, more emphasis could be given to the tumor data if it is believed that there is a probable association between chemical administration and increased tumor incidence. Dr. J. Huff, NIEHS, stated that staff agreed these renal tumors were related to trichloroethylene administration and he reported that combining data from male and female animals for both control and treated groups shows only two renal tumors in controls versus 26 in treated animals. Dr. S. Eustis, NIEHS, noted that there was an overemphasis regarding the purported misidentification of animals. Dr. J. Selkirk, NIEHS, said the audit summary reinforced the idea that animals were indeed identifiable and could be separated easily into dosed and control animals.

Dr. Hooper moved that the Technical Report on trichloroethylene be accepted with the conclusions as written that this is an inadequate study of carcinogenic activity in the four strains of rats and with addition of a statement to the summary that there were increased incidences of renal tubular cell tumors observed in exposed rats and an increased incidence of interstitial cell tumors of the testes in exposed Marshall rats. Dr. Mirer seconded the motion and it was approved by 6Y to 3N votes (Dr. Capen, Dr. Crowley and Dr. Popp) with 1A (Dr. Purchase).