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

June 29, 1983
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. Jerry Hook (Chairperson), Curtis Harper and James Swenberg. Members of the Panel are: Drs. Louis Beliczky, Devra Davis, Robert Elashoff, Seymour Friess, Michael Holland, Robert Scala, Tom Slaga, John Van Ryzin, Stan Vesselinovitch, and Mary Vore. Drs. Vesselinovitch and Vore were unable to attend the meeting.

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

The next NTP bioassay peer review meeting will be held October 28, 1983, in Research Triangle Park. For information contact Dr. Larry G. Hart (919) 541-3971; FTS 629-3971.

Contents

Benzyl Acetate. Dr. Hook, Chairperson, reviewed the two previous actions by the Peer Review Panel on the drafts of the technical report on the carcinogenesis studies of benzyl acetate. The initial report was reviewed and approved by the Panel during their meeting in June 1982, and, after modifications, was again reviewed and approved (by mail and telephone) in January/February 1983. Background: Subsequently, NTP staff met with representatives of the Flavor and Extract Manufacturers Association (FEMA) and Fragrance Materials Association (FMA) on February 24, 1983, in Bethesda, Maryland. The purpose of the meeting was to discuss the NTP benzyl acetate draft report and other issues pertaining to all NTP draft reports. Present for NTP were Drs. D. Rall, J. Moore, J. Huff and D. Canter, while present for FEMA/FMA were Dr. R. L. Hall, Mr. E. Grisanti, Mr. D. Thompson, and Dr. L. Golberg. The NTP offered FEMA/FMA the opportunity to present written documentation of their concerns about the conclusions of the benzyl acetate report, to meet with NTP scientific staff, and to come before the Peer Review Panel in June 1983. On May 1, FEMA/FMA submitted to the NTP an 80-page document responding to the technical report. NTP scientific staff (Drs. K. Abdo, G. Boorman, J. Haseman, J. Huff, E. McConnell and J. Moore) met with scientists representing FEMA/FMA (Drs. B. Bernard, L. Golberg and P. Newberne) on May 2 to discuss the document, and on May 6, copies of the document along with copies of the revised technical report were mailed by NTP to the Peer Review Panel. On June 3, the NTP sent to Panel members a 15 point response to the FEMA/FMA document; copies of letters to NTP from former Panel members Drs. N. Breslow and F. Mirer, who expressed general support for the conclusions in the current draft report, although Dr. Mirer believed the conclusion for the male rat pancreas data to be understated; a letter from FEMA to the Panel; and a letter to NTP from Dr. R. E. Landers, CPC International. Additional material received from FEMA/FMA was sent to Panel members, delivered to their hotel the night before the June 29 meeting, and handed out at the meeting.

At the meeting on June 29, 1983, Dr. B. Bernard, FEMA, and two consultants representing FEMA/FMA, Mr. N. Mantel and Dr. C. Weil, made presentations to the Panel to support their view that the benzyl acetate study was an inadequate study of carcinogenicity because of major qualitative or quantitative limitations, and thus, could not be interpreted as valid for showing either the presence or absence of a carcinogenic effect. Their position was that: (1) in male F344/N rats, the confounding variable of corn oil gavage leaves causation of pancreatic acinar cell adenomas unclear; (2) in female $B6C3F_1$ mice, intercurrent infection and other study factors resulted in excessive non-random deaths, greater than 50% in both control and low-dose groups, thus excluding analysis of the possible association of benzyl acetate with increased incidence of liver adenomas; and (3) in male $B6C3F_1$ mice, the incidence of liver adenomas in the corn oil controls was unusually low when compared with historical corn oil or untreated controls or concurrent untreated controls such that incidence of liver adenomas in benzyl acetate dose groups fell within the range of historical control values. Dr. Bernard recommended that changes be made in the conclusion of the report to reflect what they had presented.

Two of the Panel members who served as principal reviewers of the benzyl acetate report in June 1982 responded: Dr. R. M. Elashoff (biostatistician) and Dr. J. M. Holland (pathologist). Dr. Elashoff said that to his knowledge there are no data available showing a synergism between corn oil and benzyl

acetate in producing tumors. He stated that the apparent genetic inhomogeneity for the $B6C3F_1$ mice is likely to lead to an increase in the false negative direction, not in the false positive rate. Dr. Elashoff had a number of comments on issues of experimental design and statistical analyses. He emphasized that the concurrent vehicle control group was always the most appropriate control group for any study, not the untreated controls (which were sacrificed at weeks 53 to 55, too early to provide meaningful data on tumor incidence) or historic controls. Further, if one considered the incidence of combined adenomas and carcinomas in male mice in this study and in historical controls receiving corn oil by gavage there was considerable variability among groups. He said the high variability in the presence of inhomogeneity made it difficult to label any of the control groups as aberrant, and strongly favored the use of concurrent controls rather than historical controls for comparison with treated groups. With regard to female mice, although there was decreased survival, the statistical tests which adjust for decreased survival, life table and incidental tumor analyses, show significance. For both male and female mice with respect to liver adenomas alone or adenomas and carcinomas combined, there were dose-response trends and vehicle control vs. high dose effects. He felt that the consistency of the effect in both male and female mice supported the biological significance of the increased liver tumor incidence, and he stated that he approved of the conclusions in the current draft technical report.

Dr. Holland said he did not believe there were any substantive errors in the data that would influence interpretation. He thought the issue of the low liver tumor frequencies in the concurrent male mice vehicle controls was indeed worthy of discussion and that this important topic had been addressed adequately by Dr. Elashoff. He suggested the use of confidence intervals with historical controls might allow the reader a better awareness for any degree of variability. He said the technical report needed to better reflect the differences in interpretation raised by the FEMA/FMA positions, and the responses by the NTP to those interpretations. He concluded that the current draft report should be accepted in its present form.

Dr. Swenberg proposed using the new NTP categories for describing the degrees of evidence which had been sent to the Panel prior to the meeting (see Attachment). Based on the low incidences in male mouse vehicle controls and the general controversy of variability in male $B6C3F_1$ mouse liver tumors, he proposed that the evidence was equivocal for carcinogenicity in mice. Dr. Van Ryzin suggested the historic controls should be used in analyzing the mouse data. Dr. Davis asked that increases in non-neoplastic effects in mice be discussed. Dr. Friess said the Panel needed to reach some consensus on a number of the issues raised including survival and health status in mice and the occurrence and interpretations of liver lesions; appropriateness of historical vs. concurrent vehicle controls; and statistical issues. Dr. Davis disagreed that concensus was required, and, further, was unlikely given the uncertainties discussed. Dr. Scala noted three issues he considered most important: survival in mice, corn oil gavage as an influencing factor, and the complex of statistical considerations.

Dr. Hook asked for a motion to (1) accept the draft technical report as written, (2) modify the conclusions using the new categories, or (3) send the report back to NTP for further revisions. Dr. Swenberg moved that the conclusion be modified to reflect the new categories; he suggested that the evidence was equivocal for both the rat pancreatic tumors and the mouse liver lesions. Dr. Beliczky seconded the motion. Before asking for a Panel vote, Dr. Hook

said the revised report should include discussion reflecting the divergence of opinions, an indication of the extent of the record reviewed and submissions by FEMA/FMA, and a definition of the new categories describing weight of evidence in the Note to Reader section of this and all future technical reports.

Dr. Bernard was given an opportunity to address the Panel and he reiterated several of the points made earlier by the FEMA/FMA consultants. He said one could not ignore the statistical differences seen in male mice between concurrent vehicle and historical vehicle controls that along with the incidence of liver adenomas in the concurrent untreated controls did not support the low rates in the concurrent vehicle control values. Thus, he said the evidence supported an equivocal finding. Dr. Friess interpreted the studies in mice as showing a marginal increase in neoplasms. "Marginal" needed to be emphasized to reflect the uncertainties in the data and the differing opinions on the conclusions. Dr. Huff, NTP, said that when liver adenomas and carcinomas in male mice are combined, the evidence for carcinogenicity is strengthened. The rate for combined tumors in vehicle controls is not different from historic rates for combined tumors in male mice. Dr. Swenberg noted that there was no difference in rates of hepatocellular carcinomas in high dose male mice compared to historical control mice at the same laboratory. After further discussion, Dr. Hook requested a vote: the motion for "equivocal evidence of carcinogenicity" was voted on by the Panel and rejected by 4 Yes/6 No votes.

There then ensued discussion that the mouse data supported "some evidence of carcinogenicity". Dr. Elashoff supported this noting the significantly increased incidence in both male and female mice for both adenomas and combined adenomas and carcinomas as well as generally a dose-response effect when compared to vehicle controls. Dr. Slaga agreed.

Dr. Davis moved that the conclusion be accepted stating there is "some evidence of carcinogenicity", and with an addendum reflecting the discussion including discussion of the reproductive-related lesions. Dr. Beliczky seconded the motion. There was some discussion as to whether the untreated control group should be included since it was considered inappropriate to compare tumor incidences in one and two year studies. This should be stated in the technical report explaining that a program decision was made to terminate a number of untreated control groups. The fact that the untreated controls had liver tumors diagnosed at the one year sacrifice date served to further highlight the lower than usual rates in the concurrent vehicle control mice. The Panel agreed that the motion referred only to the findings in $B6C3F_1$ mice; the rat data were not at issue.

Dr. Hook asked that the conclusion to be voted on be read, and is as follows: "Under these conditions, benzyl acetate caused an increased incidence of acinar-cell adenomas of the exocrine pancreas in male F344/N rats; the gavage vehicle may have been a contributing factor. No evidence of carcinogenicity was found for female F344/N rats. For male and female $B6C3F_1$ mice there was some evidence of carcinogenicity in that benzyl acetate caused increased incidences of hepatocellular adenomas." Dr. Swenberg pointed out that the conclusion in male mice was based on a comparison with concurrent vehicle controls. Dr. Hook said all the concerns as discussed will be added to the report.

The technical report on benzyl acetate with the conclusions as read was approved by eight affirmative votes. There were two negative votes (Dr. Scala and Dr. Swenberg).

1,2-Dichloropropane (DCP). Dr. Beliczky was a principal reviewer for the technical report on the carcinogenesis studies of 1,2-dichloropropane. The report had been reviewed previously on February 28, 1983, but was deferred for revision. The conclusions of the revised report are: "Under the conditions of these studies there was some evidence of carcinogenicity for male and female B6C3F_1 mice, since 1,2-dichloropropane caused an increased incidence of hepatocellular adenomas. For female rats there was equivocal evidence of carcinogenicity in that 1,2-dichloropropane caused a marginally increased incidence of adenocarcinomas in the mammary gland, concurrent with decreased survival and body weight gain indicating that the 250 mg/kg dose was toxic. There was no evidence of carcinogenicity for male F344/N rats." Dr. Beliczky agreed with the conclusions; in the new categories of evidence he considered the connotation of "some evidence" to be negative and said the "some" should be eliminated. He said that in retrospect, the selection of a more representative high dose might have resulted in more definitive conclusions. He said there was no question that 1,2-dichloropropane is toxic to the liver, and the judgment as to whether or not DCP is a complete animal carcinogen depends on its action as a promoting agent.

As a second principal reviewer, Dr. Swenberg agreed with the conclusions with minor rewording of the next-to-last sentence. He noted the experimental design was appropriate except for excessive toxicity in the high dose rats. He said mention should be made in the technical report that the animals had titers to numerous pathogenic organisms even though the significance of the findings remains unknown. He submitted a computer search listing from the National Library of Medicine that contained references showing that stress can influence (both increase and decrease) the incidence of mammary tumors. Where appropriate these citations should be added to the technical report.

As a third principal reviewer, Dr. Friess stated he agreed with the conclusions within the framework of the new categories for strength of evidence recently defined by the NTP (see Attachment). He expressed concern about the low survival in high dose female rats although he could accept the data as adjusted for survival by the life table and incidental tumor tests.

In discussions from the floor, Dr. T. Torkelson, Dow Chemical USA, said the current draft was much improved over the February draft. Their major concern was that the mutagenesis data were overstated.

Dr. Davis said the dose related increases in hematopoiesis in female rats and mice should be mentioned in the text, and, in general, non-neoplastic effects should be included in the abstract. Dr. Friess asked whether NTP plans to focus more attention on chronic toxicity. Dr. Moore, NTP, said yes, but NTP had been limited until now by the uneven quality of the non-tumor data, and where acceptable to the Program these data will continue to be included.

Dr. J. Lamb, NTP Chemical Manager, said the concerns about high mortality in female rats were reflected in the decision to describe the findings as equivocal evidence. He agreed that DCP was a hepatotoxin but did not believe the conclusions were dependent on whether or not one considers DCP to be a promoter. Dr. Moore said that since the liver was a target organ for neoplastic and non-neoplastic effects in mice the hepatotoxicity data would be included in the abstract.

There was considerable discussion as to what should be the minimum survival in animal groups for a study to be considered adequate. Dr. Hook noted there seemed to be a consensus on the Panel for development of guidelines in the area. Dr. Huff, NTP, said a draft working paper was in preparation. Dr. Swenberg said the new categories describing the strength of evidence for carcinogenicity should be displayed in the front of each technical report. (They will be given in the Note-to-Reader section of each technical report.)

Dr. Beliczky moved that the technical report on the carcinogenesis studies of 1,2-dichloropropane be accepted with modifications discussed and with inclusion of the definitions of the new categories. Dr. Swenberg seconded the motion and the technical report was approved unanimously by the Peer Review Panel.

Fluorescein Sodium (C.I. Acid Yellow 73). Dr. Davis, a principal reviewer for the technical report on the carcinogenesis studies of fluorescein sodium, agreed essentially with the conclusions: "Under the conditions of these studies, there was some evidence of carcinogenicity in male rats, since fluorescein sodium caused increased incidences of islet cell carcinomas and islet cell hyperplasia, adenomas, or carcinomas (combined) of the pancreas; survival of high-dose male rats was decreased. There was no evidence of carcinogenicity in female F344/N rats or in female B6C3F$_1$ mice; survival in high-dose female rats was decreased. The experiment in high-dose male B6C3F$_1$ mice was an inadequate study of carcinogenicity because of significant decreases in survival. The incidence of nephrosis was increased in male and female rats and mice; mineralization of the kidney tubules was increased in male rats and mice." Dr. Davis suggested adding information that renal mineralization was dose-related for male rats, with significant increases in high dose male mice; nephrosis was also dose-related for female and male mice, with significant increases in high-dose male and female rats. Further, two renal tubular cell adenocarcinomas in low dose male mice do provide some indication of carcinogenicity in male mice. The discussion of the nephrotoxicity should be quantified. Dr. Scala agreed with Dr. Davis that the discussion of the kidney effects should be strengthened. As with the other reports, Dr. Davis said information on behavioral effects should be included.

As a second principal reviewer, Dr. Scala said the composition of the tested chemical came from two lots that were considerably different. The Panel discussed the use of two different grades of fluorescein sodium for the chronic studies. Dr. J. Mennear, NTP Chemical Manager, said this occurred because the United States Pharmacopeia-grade materials were used more rapidly than anticipated and a sufficient amount of this grade was apparently not available; thus, the technical grade was substituted for the remainder of the study. Dr. Holland stated that there should be an explicit statement in the abstract that for the major part of the 104 week study technical grade fluorescein sodium was used. The purity should be clearly indicated and major contaminants given if known. Dr. B. Schwetz, NTP, and Dr. Harper wondered whether the use of two grades of fluorescein sodium affected the adequacy of the study. The Panel agreed that the study could be interpreted although the fact of two grades of material and their purities needed to be highlighted in the report. Dr. J. Huff, NTP, said the technical report title would reflect the use of two grades with percent purity of each.

Dr. Scala thought the discussion of pancreatic lesions could be misleading; the carcinoma effects were the important ones while the carcinoma/adenoma or carcinonoma/adenoma/hyperplasia combinations were positive because of the carcinoma response. Dr. Swenberg had reviewed the slides of the pancreatic lesions from control and high dose male rats with Dr. Boorman. Dr. Swenberg said there were fewer carcinomas than diagnosed in the original draft report and these were low grade. He said the low-grade nature of the lesions should be noted. (ED - The final report reflects the rediagnosis of the pancreatic lesions.) Dr. Boorman, NTP, and Dr. Huff indicated that these lesions represented progressions in the carcinogenesis process and were better combined.

As a third principal reviewer, Dr. Elashoff was concerned about the two lots of chemical and by the poor survival, especially in high-dose male mice and female rats. He considered the evidence for carcinogenicity in male rats more closely fit the equivocal category.

Dr. Scala moved that the technical report on the carcinogenesis studies of fluorescein sodium be accepted with the statement that the evidence for carcinogenicity was equivocal; and that the purity of the materials should be given in the abstract. Dr. Elashoff seconded the motion and the technical report was approved unanimously by the Peer Review Panel.

Gilsonite. Dr. Friess, a principal reviewer for the carcinogenesis technical report on gilsonite, agreed with the conclusion that: "Under the conditions of these studies, there was no evidence of carcinogenicity in F344/N rats or B6C3F$_1$ mice given gilsonite in the diet at 20,000 or 40,000 ppm for 103 weeks." In view of the poorly defined nature of this natural asphaltic substance, he inquired whether any information was available on components of the mixture, whether these were leachable in biological fluids, identifiable, and might be involved in the reversible liver changes in mice. Dr. J. Chu, NTP Chemical Manager, said no leachability studies had been done or were contemplated.

As a second principal reviewer, Dr. Van Ryzin agreed with the conclusion and said the report was well written. As a third principal reviewer, Dr. Holland also agreed with the conclusions. He said that given the very low incidence of renal neoplasms in historical controls (0.29%), in contrast with the dosed animals in the present study (2.17%), more mention of this should be made. The ensuing discussion indicated that these represent single tumor occurrences in the low and high dosed groups. Moreover, there was no evidence of non-neoplastic kidney toxicity.

Dr. Friess moved that the technical report on the carcinogenesis studies of gilsonite be accepted with the minor revisions indicated. Dr. Van Ryzin seconded the motion and the technical report was approved by nine affirmative votes with one abstention (Dr. Holland).

Monuron. Dr. Davis, a principal reviewer for the technical report on the carcinogenesis studies of monuron, agreed with the conclusion that: "Under the conditions of these studies, there was clear evidence of carcinogenicity for male F344/N rats in that monuron caused an increased incidence of tubular cell adenocarcinomas of the kidney, tubular cell adenomas of the kidney, and neoplastic nodules of the liver. Monuron induced cytomegaly of the renal tubular epithelial cells in both male and female F344/N rats. There was no evidence of carcinogenicity for female F344/N rats or for male and female $B6C3F_1$ mice." Dr. Davis requested that the observations on chromosomal damage in cultured Chinese hamster ovary cells and reproductive tract damage in female mice be included in the abstract. She commented that the reasons given for weight loss in mice were speculations. She asked for any available information on behavior to be included routinely in the technical reports, even if anecdotal or clinical.

As a second principal reviewer, Dr. Slaga agreed in principle with the conclusions but thought more emphasis should be given to the subcutaneous tumors in the low-dose group of male mice. He said that with the two doses used a dose-response may have been missed. As a third principal reviewer, Dr. Van Ryzin said the evidence for liver neoplastic lesions in male rats would be strengthened by citing "neoplastic nodules or carcinomas". He said the comparative statistical analyses were considerably more significant for the combined tumors. Dr. D. Goldman, NTP Chemical Manager, replied that the combined tumors would be shown in the conclusion. Dr. Van Ryzin also asked for an expanded discussion of the P values for the renal tumors.

Dr. Friess asked for an expanded discussion of the renal tubular cell adenocarcinomas suggesting this may be a lesion that could be unique to the male F344/N rat. Dr. E. McConnell, NTP, responded that the lesion might be unique to male rats but not just to Fischer strain. An NTP study has shown occurrence of these tumors in four other rat strains. Dr. Scala expressed concern over the fluctuations in animal room temperature, and the low relative humidity. He asked the NTP to investigate the impact of these variables on overall animal stress and health using available literature. Dr. Scala commented on the negative tumor incidences.

Dr. Davis moved that the technical report on the carcinogenesis studies of monuron be accepted with suggested revisions. Dr. Van Ryzin seconded the motion and the technical report was approved unanimously by the Peer Review Panel.

Propylene. Dr. Swenberg, a principal reviewer for the technical report on the carcinogenesis studies of propylene, agreed with the conclusions that: "Under the conditions of these studies, there was no evidence of carcinogenicity in F344/N rats or $B6C3F_1$ mice exposed to propylene by inhalation at concentrations of 5,000 or 10,000 ppm for 103 weeks. In male and female rats propylene induced squamous metaplasia and epithelial hyperplasia of the respiratory epithelium in the nasal cavity." He described a number of corrections, many of them intended to elaborate on or clarify pathologic changes. He noted some variations in inhalation exposures during the first year.

As a second principal reviewer, Dr. Scala agreed with the conclusions. He said that more attention should be given to safety considerations owing to the explosive properties of propylene. More information on toxicity would enhance the discussion as contrasted with the lack of carcinogenicity. As a third principal reviewer, Dr. Beliczky also agreed with the conclusions and he wondered whether the increased incidence of focal inflammation of the kidneys in mice might not have been related to the experimental use of propylene oxide during the studies and/or biotransformation of propylene to the epoxide. Dr. Scala said there were ongoing studies using hemoglobin alkylation as a marker in humans exposed to propylene and propylene oxide. Dr. J. Quest, NTP Chemical Manager, said that the renal effects were increased in treated groups; yet the biological importance was unknown. Dr. Davis asked whether behavioral activities had been evaluated in view of the possible anesthetic effects at the high concentration. Dr. Quest replied that none were recorded, or specifically requested.

Dr. Swenberg moved that the technical report on the carcinogenesis studies of propylene be accepted with changes discussed. Dr. Scala seconded the motion and the technical report was approved unanimously by the Peer Review Panel.

Propylene Oxide. Dr. Holland, a principal reviewer for the technical report on the carcinogenesis studies of propylene oxide, agreed in essence with the conclusions that: "Under the conditions of these studies, there was some evidence of carcinogenicity for F344/N rats, as indicated by increased incidences of papillary adenomas of the nasal turbinates in male and female rats exposed to propylene oxide at the 400 ppm level. For male and female B6C3F$_1$ mice, there was clear evidence of carcinogenicity in that propylene oxide caused hemangiomas or hemangiosarcomas of the nasal turbinates at the 400 ppm concentration. In the respiratory epithelium of the nasal turbinates, propylene oxide also caused suppurative inflammation, hyperplasia, and squamous metaplasia in rats and inflammation in mice." He questioned whether propylene oxide "caused" hemangiomas and hemangiosarcomas in mice, and said, "associated with" the increased incidences would be preferred wording. Given the strong irritant properties of the chemical, tumor formation could be through indirect mechanisms. Dr. Friess supported the contention of Dr. Holland that the induction of nasal hemangiomas and hemangiosarcomas could be said to be associated with chemical exposure but not caused considering the evidence. He suggested also that the tumors may have arisen from an action secondary to irritation, an action expressed only above a threshold level. Dr. Swenberg stated that these types of vascular tumors are so rare that he agreed there was clear evidence of carcinogenicity as stated. Dr. G. Boorman, NTP Chemical Manager, noted that we do not know the mechanisms for most chemical carcinogens. Further, there is evidence by others that propylene oxide is a site-specific carcinogen. Dr. Holland recommended that P values for assessing significance of survival between control and treated groups should be summarized in the technical report. Dr. Haseman, NTP, indicated this would be done in the future.

As a second principal reviewer, Dr. Slaga agreed with the conclusions but requested more discussion as to why the increased incidence of adenomas and carcinomas of the thyroid in rats was not considered chemically related. Dr. Boorman said the thyroid C-cell lesions were discounted because the neoplasms were statistically significant only when combined, there was a negative trend for hyperplasias, and there is not evidence or rationale for C-cells being a target tissue.

As a third principal reviewer, Dr. Harper agreed with the conclusions, and agreed that the significance of differences in survival should be added routinely to the technical reports.

Dr. Davis noted that propylene oxide is an alkylating agent and is mutagenic, and requested that non-tumor data be given more prominent treatment. Dr. Scala emphasized the temperature fluctuations which occurred in the inhalation chambers and the variations in the concentrations of propylene oxide in the chamber which reflected both over and underexposure, and which could temper the conclusions attributing a carcinogenic effect to a particular dose concentration. Dr. Boorman replied that there were only three accidental overexposures, the longest of which was 38 minutes, and he did not think that would invalidate the study. Dr. Scala agreed.

Dr. Holland moved that the technical report on the carcinogenesis studies of propylene oxide be accepted with the revisions discussed. Dr. Harper seconded the motion and the technical report was approved unanimously by the Peer Review Panel.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
National Institutes of Health

Memorandum

Date May 20, 1983

From Assistant to Deputy Director, NTP
Through Deputy Director, NTP [redacted]

Subject Terminology for Evaluative Conclusions For Use in the Toxicology and Carcinogenesis Technical Reports

To Peer Review Panel Members

For several years the Technical Reports Review Staff, NIEHS, has attempted to develop and use language that would describe the interpretative conclusions about carcinogenicity results. These five categories have been adopted for use in the Technical Reports series to specifically emphasize consistency and the concept of actual evidence of carcinogenicity.

- Clear Evidence of Carcinogenicity is demonstrated by studies that are interpreted as showing a chemically-related increased incidence of malignant neoplasms, studies that exhibit a substantially increased incidence of benign neoplasms, or studies that exhibit an increased incidence of a combination of malignant and benign neoplasms where each increases with dose.

- Some Evidence of Carcinogenicity is demonstrated by studies that are interpreted as showing a chemically-related increased incidence of benign neoplasms, studies that exhibit marginal increases in neoplasms of several organs/tissues, or studies that exhibit a slight increase in uncommon malignant or benign neoplasms.

- Equivocal Evidence of Carcinogenicity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms.

- No Evidence of Carcinogenicity is demonstrated by studies that are interpreted as showing no chemically-related increases in malignant or benign neoplasms.

- Inadequate Study of Carcinogenicity demonstrates that because of major qualitative or quantitative limitations the studies cannot be interpreted as valid for showing either the presence or absence of a carcinogenic effect.

For each definitive study result (male rats, female rats, male mice, female mice) one of the above quintet will be selected to describe the findings. These categories refer to the strength of the experimental evidence and not to either potency or mechanism. These explanations would be given in the Note-to-the-Reader Section of each Technical Report.

In addition and since the "bottom line" conclusions are often used solitarily, a single sentence can be added to repeat the experimental conditions. As a current example, the interpretive conclusions dictated by the benzyl acetate carcinogenesis studies would read:

> Benzyl acetate was administered in corn oil by gavage to F344/N rats (0, 250, or 500 mg/Kg body weight) and to B6C3F$_1$ mice (0, 500, or 1000 mg/Kg b.w.) five times per week for 103 weeks. Under these conditions, benzyl acetate caused an increased incidence of acinar cell adenomas of the exocrine pancreas in male F344/N rats; the gavage vehicle may have been a contributing factor. No evidence of carcinogenicity was found for female F344/N rats. For male and female B6C3F$_1$ mice there was some evidence of carcinogenicity, in that benzyl acetate caused increased incidences of hepatocellular adenomas.

Contrast this version with the previous statement:

> Under the conditions of these studies, benzyl acetate should be considered carcinogenic for male and female B6C3F$_1$ mice, causing increased incidences of hepatocellular adenomas. Benzyl acetate also caused an increased incidence of acinar cell adenomas of the pancreas in male F344/N rats; the vehicle may have been a contributing factor. For female F344/N rats there was no evidence of carcinogenicity.

Additionally, we have adopted the following concepts (as patterned from the IARC Monographs) to give further clarification of these important issues. This will be added to the Note-to-the-Reader:

> The term chemical carcinogenesis generally means the induction by chemicals of neoplasms not usually observed, the earlier induction by chemicals of neoplasms that are commonly observed, or the induction by chemicals of more neoplasms than are usually found. Different mechanisms may be involved in these three situations. Etymologically, the term carcinogenesis means the induction of cancer, that is, of malignant neoplasms; however, the commonly accepted meaning is the induction of various types of neoplasms or of a combination of malignant and benign neoplasms. In the Technical Reports the words tumor and neoplasm are used interchangeably.

These five categories of evidence have been used to describe the conclusions reached in the Technical Reports scheduled for Peer Review on 29 June. We find them useful. We hope these terms will assist you in your review of this latest set of Reports.

[redacted]

J. E. Huff, Ph.D.