

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
July 27, 1984
Research Triangle Park, North Carolina

The review meeting began at 9 a.m. in the Conference Center, Building 101, 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 of Experts are: Drs. Louis Beliczky, Devra Davis, Seymour Friess, Thomas Jones, Richard Kociba, David Kotelchuck, Tom Slaga, Steven Tannenbaum, Bruce Turnbull, and John Van Ryzin. Drs. Hook, Slaga and Swenberg were unable to attend this meeting. Dr. Harper served as Acting Chairperson.

When available, final NTP Technical Reports for the approved 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 November 2, 1984, in Research Triangle Park, North Carolina. For information contact Dr. Larry G. Hart, (919) 541-3971; FTS 629-3971.

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Benzene. The draft technical report on the toxicology and carcinogenesis studies of benzene was initially evaluated by the Peer Review Panel on October 28, 1983. The interpretative conclusions were accepted by the Panel at that time; however, approval of the technical report was deferred to allow for complete analyses of the hematology data and inclusion of reportable findings into the report, and to allow for editorial tightening and incorporation of a number of suggested changes. In the current review, Dr. Friess, a principal reviewer, again agreed with the conclusions that:

Under the conditions of these studies, there was clear evidence of carcinogenicity of benzene for male F344/N rats, for female F344/N rats, for male B6C3F₁ mice, and for female B6C3F₁ mice. For male rats, benzene caused increased incidences of Zymbal gland carcinomas, squamous cell papillomas and squamous cell carcinomas of the oral cavity, and squamous cell papillomas and squamous cell carcinomas of the skin. For female rats, benzene caused increased incidences of Zymbal gland carcinomas and squamous cell papillomas and squamous cell carcinomas of the oral cavity. For male mice, benzene caused increased incidences of Zymbal gland squamous cell carcinomas, malignant lymphomas, alveolar/bronchiolar carcinomas and alveolar/bronchiolar adenomas or carcinomas (combined), Harderian gland adenomas, and squamous cell carcinomas of the preputial gland. For female mice, benzene caused increased incidences of malignant lymphomas, ovarian granulosa cell tumors, ovarian benign mixed tumors, carcinomas and carcinosarcomas of the mammary gland, alveolar/bronchiolar adenomas, alveolar/bronchiolar carcinomas, and Zymbal gland squamous cell carcinomas.

He noted the conclusions relating to the hematologic findings, especially the dose related lymphocytopenia and associated leucocytopenia, and suggested they be added to the conclusions on carcinogenicity. Dr. J. Huff, NTP Chemical Manager, said this would be done.

As a second principal reviewer, Dr. Davis said some comment should be made on the use of corn oil as the vehicle in view of the possible co-carcinogenicity of corn oil. Dr. McConnell pointed out that the NTP was planning a study to investigate the mechanism for these apparent effects (pancreatic lesions) associated with corn oil gavage. Dr. Huff said a manuscript was in preparation regarding the incidence of neoplasms in untreated and corn oil gavage controls; where relevant, this reference would be cited in appropriate technical reports. Dr. Davis said more mention should be given to the extensive epidemiological studies on benzene. As a third principal reviewer, Dr. Van Ryzin said the technical report was complete.

There was some discussion about the relevance of the gavage route versus other routes by which human exposure is more likely to occur, especially inhalation and dermal. Dr. Beliczky asked that information be included on skin absorption as an important route of entry. He referred to a NIOSH study measuring skin absorption in hairless mice. Dr. Tannenbaum stated that the route of administration can have a major influence on the tumorigenicity of a chemical. Dr. Huff noted that Dr. C. Maltoni had demonstrated positive effects for benzene by both the inhalation and olive oil gavage exposure routes. Dr. Beliczky said that human risk assessments have been performed for benzene and these should be referenced. Dr. Huff responded that additional references would be included on epidemiological studies and situations of risk assessment.

Dr. Friess moved that the technical report on the toxicology and carcinogenesis studies of benzene be accepted with revisions as suggested. Dr. Beliczky seconded the motion and the report was approved by nine affirmative votes. There was one abstention (Dr. Kociba).

2-Chloroethanol. Dr. Beliczky, a principal reviewer for the technical report on the toxicology and carcinogenesis studies of 2-chloroethanol, agreed with the conclusions that:

Under the conditions of these dermal studies, there was no evidence of carcinogenicity of 2-chloroethanol for male and female F344/N rats or Swiss CD-1 mice.

He commented that inhalation or gavage routes would have been preferred; inhalation would be the expected route of exposure in the industrial setting. Dermal application would be more meaningful if the degree of absorption could be verified. Dr. Beliczky added that screening of human urine may have application.

As a second principal reviewer, Dr. Kociba agreed with the conclusions. He commented on the apparent dose-related incidence of acute inflammation and ulceration of the skin in male mice and said this may have a possible relationship to treatment of the high dose group. He also asked that the data for pancreatic acinar atrophy in male rats be evaluated to determine whether there was any treatment-related degenerative change in the pancreatic acini during the two-year study.

As a third principal reviewer, Dr. Kotelchuck did not fully agree with the carcinogenicity conclusion for female rats. He believed that there was equivocal evidence of carcinogenicity of 2-chloroethanol for pituitary adenomas in female rats because: (1) there were significant differences between high dose and vehicle control groups in the life-table and Fisher Exact tests; (2) two of the three trend tests showed a statistically significant increase in pituitary adenomas; (3) in an earlier study by Mason and coworkers there was an increased incidence of pituitary adenomas among female F344 rats exposed to 2-chloroethanol; and (4) it is biologically plausible for there to be a gender different effect of this chemical on an endocrine gland (there was not an increased incidence in male rats). Dr. Kotelchuck proposed modifying the conclusions to reflect the marginal increase in pituitary adenomas in female rats.

Dr. Haseman noted that the appropriateness of the life-table test for pituitary adenomas, (instead of the incidental tumor test which was not statistically significant) depends on whether the eight tumors in the high dose group occurring prior to the end of the study were related to the cause of death. Dr. McConnell said for the most part pituitary tumors are not thought of as being lethal. Dr. Kociba commented that there is a continuum of lesions in the pituitary from hyperplasias through adenomas to carcinomas. Dr. Boorman agreed and said that factors used to downgrade the importance of the adenomas in this study included the facts that there were no changes in hyperplasias and actually a decrease in pituitary carcinomas from control to dosed groups. Dr. Huff added that the findings in the study by Mason and coworkers were of borderline significance, and different dose groups had to be combined.

Dr. Harper asked for a vote on using the conclusion of equivocal evidence of carcinogenicity for describing the marginal increase of pituitary adenomas in female rats. There was one affirmative vote (Dr. Kotelchuck). Dr. Harper then asked for a vote on using the original conclusion in the report. There were four affirmative votes and one negative vote (Dr. Kotelchuck).

Dr. Kociba moved that the technical report on the toxicology and carcinogenesis studies of 2-chloroethanol be accepted with the conclusions as written in the report. Dr. Friess seconded the motion and the report was approved unanimously by the Peer Review Panel.

Chrysotile Asbestos. Dr. Jones, a principal reviewer for the technical report on the toxicology and carcinogenesis studies of chrysotile asbestos, agreed with the conclusions that:

Under the conditions of these studies, short range (SR) and intermediate range (IR) chrysotile asbestos did not induce any overt toxicity and did not affect survival when ingested at a level of 1% in the diet by male and female F344/N rats. There was no evidence of carcinogenicity in male or female rats exposed to SR chrysotile or in female rats exposed to IR chrysotile asbestos. There was some evidence of carcinogenicity in male rats exposed to IR chrysotile asbestos as indicated by an increased incidence of adenomatous polyps in the large intestine. The cocarcinogenic studies of 1,2-dimethylhydrazine dihydrochloride and IR chrysotile asbestos did not indicate that IR chrysotile asbestos had either a tumor-enhancing or protective effect.

Dr. Jones agreed with the decision to discount the biological significance of the increased incidences of keratoacanthomas in males and neoplasms of the clitoral gland in females, and asked that more discussion be given to the reasons for doing so. He noted that prior to the meeting, he had examined the slides of large intestinal sections from male rats exposed to the IR form and agreed that the adenomatous polyps were clearly neoplastic.

As a second principal reviewer, Dr. Turnbull also agreed with the conclusions. He suggested that in view of the one dose design more details might be given as to the basis for the one percent dose chosen and its relation to the maximum tolerated dose, if any. Dr. R. Shapiro, NIEHS, said the one percent level was significantly greater than estimated human exposure and also represented an appropriate dose based on earlier feeding studies in rats. Dr. Turnbull asked for clarification of the use and temporal relationship of the various control groups used. Dr. E. McConnell, NTP Chemical Manager, explained that the concurrent controls for this study and the pooled control groups for the three previous NTP dose feed studies in rats with the other asbestos fiber types came from the same animal source, were conducted at the same laboratory, and were on test at the same or overlapping times. Dr. J. Haseman, NIEHS, said the concurrent controls were used in the primary statistical analysis. Where a possible carcinogenic effect was observed, the additional control groups were employed to help evaluate further the biological significance of the effect. This would be clarified in the technical report.

As a third principal reviewer, Dr. Davis questioned the use of the pooled control data to support the biological importance and statistical significance of the intestinal tumors and, on the other hand, to discount the importance of the keratoacanthomas in male rats and clitoral gland neoplasms in female rats. Dr. McConnell stated that increased incidences of skin neoplasms have not been observed in asbestos inhalation studies by the NTP or others where the whole animal is exposed. Dr. Friess said the reason for discounting needed to be highlighted. She expressed concern with regard to worker safety as to whether the standard paper feed bags were impermeable to the pelleted asbestos, and if the pelleting process may have altered the fiber size of the asbestos. Dr. Beliczky wondered whether there may have been incidental inhalation exposure of the test animals. Dr. McConnell replied that a pelletized dosage form was used to minimize the amount of inhalation exposure and to minimize exposure of laboratory personnel. Dr. Shapiro noted that fiber size distribution was examined before and after pelleting for all the fiber types and there were little or no differences found.

Dr. Kotelchuck observed that the apparent kidney tumor enhancing effect of IR asbestos in dimethylhydrazine treated female rats should be noted in the conclusions. Dr. McConnell agreed. Dr. A. Berlin, Commission of the European Communities, asked if there had been any attempt to measure asbestos at the tumor sites. Dr. McConnell replied that since this was a lifetime exposure the presence of fibers throughout the intestine would be expected, and, further, translocation artifacts would likely confound such an analysis.

Dr. Jones moved that the technical report on the toxicology and carcinogenesis studies of chrysotile asbestos be accepted with the modifications as discussed. Dr. Turnbull seconded the motion and the report was approved unanimously by the Peer Review Panel.

Telone II® (1,3-Dichloropropene). Dr. Turnbull, a principal reviewer for the technical report on the toxicology and carcinogenesis studies of Telone II®, agreed with the conclusions that:

Under the conditions of these gavage studies, there was clear evidence of carcinogenicity for male F344/N rats, as indicated by a Telone II® - related increased incidences of squamous cell papillomas and carcinomas of the forestomach, as well as an increased incidence of neoplastic nodules of the liver. In female F344/N rats, there was some evidence of carcinogenicity because Telone II® caused an increased incidence of squamous cell papillomas of the forestomach. Even though the experiment in male B6C3F1 mice was considered an inadequate study of carcinogenicity because of reduced survival in the vehicle control group, Telone II® was probably associated with the increased incidences of transitional cell carcinomas of the urinary bladder, squamous cell papillomas of the forestomach, and alveolar/bronchiolar adenomas and carcinomas of the lung. There was clear evidence of carcinogenicity for female B6C3F1 mice since Telone II® caused increased incidences of transitional cell carcinomas of the urinary bladder; Telone II® also increased the incidences of alveolar/bronchiolar adenomas of the lung and of squamous cell papillomas or carcinomas of the forestomach in the female mice. Telone II® - related nonneoplastic lesions included basal cell or epithelial cell hyperplasia in the forestomach of male and female rats and male and female mice and epithelial hyperplasia of the urinary bladder in male and female mice.

Dr. Turnbull opined that the design and conduct of the study were less than fully adequate, especially the lack of appropriate randomization, and the delay of more than a month in carrying out a scheduled 15-month kill. However, the drawbacks were well documented and did not compromise the findings. As a second principal reviewer, Dr. Jones agreed with the findings of the study; however, he questioned the appropriateness of including in the conclusions probable association of Telone II® with a number of tumors in male mice since this study was considered inadequate for male mice due to markedly reduced survival in the vehicle controls.

As a third principal reviewer, Dr. Kotelchuck basically agreed with the conclusions. He said the failure to randomize initial weights of the mice was a serious and avoidable error but he did not think it affected the carcinogenicity results. He shared Dr. Jones' concern about association of the chemical with increased incidences of tumors in an inadequate study. However, since there were dose trends for some tumors Dr. Kotelchuck thought a statement could be made, with deletion of the reference to the lung tumors as their incidences rate fell within the range, albeit the upper limit, of historical control rates. He proposed that the following conclusion for male mice: "The experiment on male B6C3F1 mice was an inadequate study of carcinogenicity because of reduced survival in the vehicle control group. However, there was some indication in the male mice of Telone II® - related increases of squamous cell papillomas of the forestomach and transitional cell carcinomas of the urinary bladder." Drs. Jones and Beliczky thought only the first sentence should be included while Dr. Tannenbaum said both sentences are appropriate because the carcinogenicity findings were consistent with those found in female mice and rats of both sexes. Dr. Haseman argued for retaining mention of the lung tumors based on their being at the upper limit of the historical control range, approximately double the mean historical control rate, and noted that a similar increase was seen in female mice. Drs. Friess and Van Ryzin supported these rationales.

Dr. Harper asked for a vote on the conclusion statement that: "The experiment on male B6C3F₁ mice was an inadequate study of carcinogenicity because of reduced survival in the vehicle control group." There were two affirmative votes (Drs. Jones and Kociba). Dr. Harper then requested a vote on the conclusion which would include this sentence followed by: "However, there was some indication in the male mice of Telone II[®] - related increases of squamous cell papillomas of the forestomach, transitional cell carcinomas of the urinary bladder, and alveolar/bronchiolar adenomas and carcinomas of the lung." The complete two sentence conclusion was approved with seven affirmative votes.

Dr. Kociba asked that either an appendix be added to include the hematology and clinical chemistry data or an availability statement be added. [A comment will be added that these data are available upon request.] The Panel discussed the possible carcinogenic effects of the 1.0% epichlorhydrin included as a stabilizer with the technical grade 1,3-dichloropropene. Dr. B. Schwetz, NTP, added that the 1,3-dichloropropene free of epichlorhydrin would not be stable enough to do a study. Dr. Tannenbaum noted that epichlorhydrin is an alkylating agent and a carcinogen in animals. Dr. Kotelchuck opined that epichlorhydrin contributed to the stomach tumors, yet he felt it was important to test the chemical formulation that humans are exposed to. Dr. Huff speculated that if Telone II[®] were not a complete carcinogen without epichlorhydrin, the formulation certainly has a cocarcinogenic effect since neoplasms were increased at sites different from where epichlorhydrin produces tumors.

Dr. Turnbull moved that the technical report on the toxicology and carcinogenesis studies of Telone II[®] be accepted with the revised conclusion for male mice and with other modifications discussed. Dr. Kotelchuck seconded the motion and the report was approved by eight affirmative votes. There was one abstention because of company affiliation (Dr. Kociba).

Dimethyl Hydrogen Phosphite. Dr. Kociba, a principal reviewer for the technical report on the toxicology and carcinogenesis studies of dimethyl hydrogen phosphite, agreed with the conclusions that:

Under the conditions of these gavage studies, there was clear evidence of carcinogenicity in male F344/N rats receiving dimethyl hydrogen phosphite, as shown by increased incidences of alveolar/bronchiolar adenomas, alveolar/bronchiolar carcinomas, squamous cell carcinomas of the lung, and squamous cell papillomas or carcinomas of the forestomach. There was equivocal evidence of carcinogenicity in female F344/N rats receiving dimethyl hydrogen phosphite, as shown by marginally increased incidences of alveolar/bronchiolar carcinomas of the lung and of neoplasms of the forestomach. There was no evidence of carcinogenicity for male or female B6C3F₁ mice receiving dimethyl hydrogen phosphite.

Dr. Kociba asked for a more extensive discussion of the possible pathogenesis of the rat lung lesions (including a high incidence of interstitial pneumonia). He said the experimental design could have been improved by inclusion of appropriate parameters of toxicity, such as serum enzymes, organ weights, hematology, and urinalyses.

As a second principal reviewer, Dr. Davis agreed with the conclusions; however, since this was a report on the toxicity as well as the carcinogenicity of the chemical, she suggested that there should be a statement in the conclusions about the compound-related testicular atrophy in male mice in the 13-week study and focal calcification of the testis in male mice in the two-year study. She agreed with Dr. Kociba in calling for expanded discussion on the lung lesions in rats as well as the dose-related lung lesions in male and female mice in the 13-week studies. Several factors were mentioned, especially infectious agents, the gavage route, and the possibility of corn oil aspiration.

As a third principal reviewer, Dr. Tannenbaum agreed with the conclusions and concurred with the comments of the other reviewers. He wondered if the high incidence of pneumonia, especially if infectious, might not have compromised the conclusions. Dr. G. Boorman, NTP, explained that the pneumonia was chemically-induced and not infectious in origin. The lesions in dosed animals were not inflammatory but were characterized as hyperplasias of the alveolar epithelium around the smaller bronchioles and the terminal bronchioles. He said this would be expanded and clarified in the report. Dr. J. Dunnick, NTP Chemical Manager, added that the data from this and other gavage studies did not support any discernible relationship between the corn oil gavage and the lung lesions.

Dr. Van Ryzin questioned the conclusion pertaining to neoplasms of the forestomach in support of equivocal evidence of carcinogenicity in female rats. Dr. Haseman replied that even though there were only two neoplasms at the high dose this incidence was similar to that seen at the low dose in males. The low dose in males was the same on a mg/kg basis as the high dose in females.

Dr. Davis moved that the technical report on the toxicology and carcinogenesis studies of dimethyl hydrogen phosphite be accepted with the minor changes discussed. Dr. Kociba seconded the motion and the report was approved unanimously by the Peer Review Panel.

HC Blue No. 2. Dr. Tannenbaum, a principal reviewer for the technical report on the toxicology and carcinogenesis studies of HC Blue No. 2, agreed with the conclusion that:

Under the conditions of these studies, there was no evidence of carcinogenicity in male or female F344/N rats and in male and female B6C3F₁ mice receiving HC Blue No. 2 in the diet for two years.

He noted that two lots of test chemical were used, one having 98 percent purity and one with 75 percent purity, and said more detail was needed about which lots were used for which studies. Dr. J. Mennear, NTP Chemical Manager, replied that the 98 percent pure lot was used for one 14-day study, the two-year studies and the mutagenicity experiments and this would be emphasized in the report. As a followup to the earlier review of HC Blue No. 1 (NTP TR#271; peer reviewed by the Panel in March 1984), Dr. Mennear reported that following Dr. Tannenbaum's suggestion nitrosamine contents had been measured for both dyes; based on dietary concentrations of these dyes, animals in the HC Blue No. 2 study received nearly twice as much nitrosamine in the feed as those in the HC Blue No. 1 study, which was positive for carcinogenicity. Detailed results will be in the final technical reports for both dyes.

As a second principal reviewer, Dr. Beliczky questioned several of the conclusions drawn, especially in comparing the toxicities of HC Blue No. 1 and 2, contending they were subjective or ambivalent and lacking scientific documentation. He also questioned statements to the effect that the presence of nitrosamines did not influence the findings. Dr. Huff suggested that because the dietary concentrations of HC Blue No. 2 were about three times greater than those for HC Blue No. 1 some might consider that the former chemical was at least three times less toxic; this extrapolation could be misleading and he said the sentence would be modified. Dr. Beliczky asked that an explanation be added as to why a second 14-day study was conducted, and that an expanded discussion be included on the significance of: mixed mesenchymal kidney tumors in female rats; C-cell carcinomas in male rats; and lymphomas in mice. Dr. Boorman said the kidney tumors were uncommon but the incidence in the treated animals was not significant so highlighting the effect in the abstract seemed appropriate emphasis. In response to a question about use of the dye, Dr. Mennear said its only use was in hair dyes.

As a third principal reviewer, Dr. Turnbull agreed with the conclusions. He asked for inclusion of information as to why the dermal route was not chosen for the study since that would be the likely route of human exposure.

There was some discussion about the dose-related increases in the incidence of hyperostosis in male and female rats, and the Panel agreed that this should be mentioned in the conclusion. Further discussion centered on whether the various nitrosamines present as impurities should be identified and whether significant in vivo nitrosation was likely.

Dr. Tannenbaum moved that the technical report on the toxicology and carcinogenesis studies of HC Blue No. 2 be accepted with the modifications discussed. Dr. Turnbull seconded the motion, and the technical report was approved by seven affirmative votes. There were two negative votes (Dr. Beliczky and Dr. Jones).

Overview of Results of the National Toxicology Program (NTP) Review of the Pathology From the Rat Portions of the National Cancer Institute (NCI) Long-Term Carcinogenesis Studies on Malathion and Malaoxon

Dr. E. McConnell, NTP, gave the background and reasons for the NTP decision to review the pathology from two carcinogenesis studies on malathion and one on its metabolite, malaoxon. The findings were originally published in 1978 and 1979 as technical reports (TRs) by the NCI (malathion, TR #024 and TR #192; malaoxon, TR #135). The purpose of this overview was to give the Board and the public the results of this re-examination prior to publication. Dr. McConnell indicated that this review was done with the full agreement of the NCI, and he kept them informed about the status.

Renewed public concerns about the potential toxic effects of malathion received attention over the past few years as a result of the ground and aerial spraying of the insecticide in California during 1980 to 1982, and more recently, in Miami, Florida in response to Mediterranean fruit fly infestations, and in Los Angeles in response to Mexican fruit fly infestations. Given the degree of public exposure and concern, the NTP, and the NCI believed it prudent to re-evaluate the pathology from those studies from the perspective of current NTP standards for pathology quality assurance and pathology peer review. The issue raised and resolved were histopathologic diagnoses; no data audits were done.

Dr. McConnell discussed the design and the findings of the NCI in the two malathion and one malaoxon studies (Attachment). He described the studies reviewed and the design of the re-examination of the pathology (Attachment). The review was done under one of the NTP pathology support contracts, Clement Associates, with Dr. Richard Bates, a pathologist with extensive experience in rodent pathology, and with expertise in the comparative pathology of endocrine lesions, doing the review. He commented on the composition and special expertise of the Pathology Working Group (PWG) which reviewed the slides, and noted the close agreement on the diagnoses between the PWG and Dr. Bates.

Dr. McConnell reported there were no chemically-related proliferative or neoplastic lesions of note in the first malathion study, while in the second malathion study the only lesions that came up for discussion were some adrenal medullary lesions (Attachment). The biological importance of these lesions was discounted because the increases were significant only in the life table analysis, and these rarely are lethal neoplasms. Additionally, hyperplasia usually is also increased when there is an increase in adrenal medullary neoplasms. In this case, hyperplasias were decreased in the high dose group.

In the malaoxon study, there were statistically significant increases in C-cell adenomas of the thyroid gland in male rats and for adenomas and carcinomas combined in males and females (Attachment). He said combining of lesions was appropriate since the benign and malignant lesions form a continuum, and, in fact, may be a continuum beginning with the hyperplasias. Dr. McConnell summarized the bases for or against assigning biological importance to these lesions (Attachment). Weighing these arguments and using the current NTP categories for strength of evidence, the conclusion was that there was equivocal evidence of carcinogenicity for malaoxon in male and female rats based on the C-cell lesions of the thyroid. He noted that the NCI did not use such descriptive categories. He said that the NTP findings substantiate the results as published by the NCI, and would be submitted for publication.

In discussion, Dr. Turnbull inquired as to the reasonableness of pooling the control group values from the second malathion study and the malaoxon study since the studies essentially were run concurrently. Dr. Haseman replied that the significance of the combined thyroid lesions in high dose males would remain pretty much the same if controls were pooled. However, since the incidence of combined lesions in female controls in the second malathion study was about double that of the female controls in the malaoxon study, the effect of pooling controls would be to weaken considerably the effects in high dose females.

CALIFORNIA MED-FLY PROBLEM

PHASE I: JUNE 1980 - DEC 1980 - STERILE FLY RELEASE

PHASE II: DEC 1980 - JUNE 1981 - STERILE FLY RELEASE,
FRUIT STRIPPING AND GROUND SPRAYING

PHASE III: JULY 1981 - SUMMER 1982 - AERIAL SPRAYING

BACKGROUND

REASON FOR PATHOLOGY RE-EXAMINATION:

- MED-FLY PROBLEM - CALIFORNIA (1981-1982)

CONTRACTOR - CLEMENT ASSOCIATES (MARCH 1982)

PATHOLOGIST - DR. RICHARD BATES

STUDIES REVIEWED:

- MALATHION I - OM RATS
- MALATHION II - F344 RATS
- MALAOXON - F344 RATS

ORGANS EXAMINED - 14/ANIMAL

METHOD - "BLIND" REVIEW

DATA RECORDING - CBDS

NTP PATHOLOGY WORKING GROUP REVIEW

MALATHION I - NCI/TR 24

SPECIES: OM RATS AND B6C3F1 MICE

DOSED FEED: RATS - 0, 4,700 AND 8,150 PPM FOR 80 WKS. OBSERVED
FOR 33 WKS

MICE - 0, 8,000 AND 16,000 PPM FOR 80 WKS. OBSERVED
FOR 14-15 WKS

SACRIFICE DATE: 1975

CLINICAL SIGNS: NONE

WEIGHT GAIN EFFECTS: MINIMAL

SURVIVAL EFFECTS: MINIMAL

CONCLUSION: NO CLEAR EVIDENCE OF CARCINOGENICITY

RATS - FEMALE, THYROID FOLLICULAR CELL NEOPLASMS

MICE - MALE, HEPATOCELLULAR NEOPLASMS

MALATHION II - NCI/TR 192

SPECIES: F344 RATS

DOSED FEED: 0, 2,000 AND 4,000 PPM FOR 103 WKS

SACRIFICE DATE: 1977

CLINICAL SIGNS: NONE

WEIGHT GAIN EFFECTS: NONE

SURVIVAL EFFECTS: DECREASED - HIGH DOSE MALES AFTER 18 mo.

CONCLUSION: NOT CARCINOGENIC.

MALAOXON - NCI/TR 135

SPECIES: F344 RATS AND B6C3F1 MICE

DOSED FEED: RATS AND MICE - 0, 500 AND 1,000 PPM FOR 103 WKS

SACRIFICE DATE: 1977

CLINICAL SIGNS: NONE

WEIGHT GAIN EFFECTS: RATS - NONE

MICE - FEMALE, MINIMAL

SURVIVAL EFFECTS: INCREASED - FEMALE RATS, HIGH AND LOW DOSE

DECREASED - MALE MICE, HIGH DOSE

CONCLUSION: NOT CARCINOGENIC

RATS - FEMALE, C-CELL NEOPLASMS

TISSUES EXAMINED

LIVER	PARATHYROID
KIDNEY	PANCREAS
URINARY BLADDER	LUNG
BRAIN	SPLEEN
PITUITARY	GONADS
ADRENAL	STOMACH
THYROID	MAMMARY GLAND

NTP PATHOLOGY WORKING GROUP

DR. R. BATES (PATHOLOGIST RESPONSIBLE FOR STUDY)

DR. G. BOORMAN - NTP

DR. C. CAPON - OHIO STATE UNIVERSITY

DR. S. EUSTIS - NTP (PWG CHAIRMAN)

DR. C. HOLLANDER - INSTITUTE FOR EXPERIMENTAL GERONTOLOGY,
NETHERLANDS

DR. E. McCONNELL - NTP

DR. J. QUAST - DOW CHEMICAL

DR. J. SWENBERG - CIIT

DR. K. YOSHITOMI - NTP

MALATHION II: ADRENAL MEDULLA LESIONS

	<u>C</u>	<u>MALES</u> <u>L</u>	<u>H</u>
HYPERPLASIA	11/49	12/48	4/49
PHEOCHROMOCYTOMA	5	9	5
MALIGNANT PHEOCHROMOCYTOMA	0	1	1

MALAOXON: THYROID C-CELL LESIONS

ADENOMA	MALES			FEMALES		
	C	L	H	C	L	H
RATES	2/49	3/45	8/49	4/48	7/48	8/48
P-VALUES						
LIFE TABLE	.028	.496	.051	.214	.469	.259
INC. TUMOR	.019	.426	.031	.158	.313	.195
C-A/FISHER	.027	.459	.046	.146	.262	.178
CARCINOMA						
RATES	1/49	0/45	2/49	0/48	0/48	4/48
P-VALUES						
LIFE TABLE	.360	.508N	.497	.017	*	.091
INC. TUMOR	.480	.508N	.604	.014	*	.067
C-A/FISHER	.362	.526N	.500	.015	*	.059
COMBINED						
RATES	3/49	3/45	10/49	4/48	7/48	11/48
P-VALUES						
LIFE TABLE	.020	.654	.040	.059	.469	.091
INC. TUMOR	.019	.597	.033	.035	.313	.052
C-A/FISHER	.019	.620	.035	.033	.262	.045
HYPERPLASIA	8/49	11/49	8/49	24/48	24/48	25/48

C-CELL ARGUMENTS

PLUS

1. TREND - DOSE RESPONSE
2. BOTH SEXES
3. ABOVE HISTORICAL AVERAGE
4. CARCINOMAS

MINUS

1. HYPERPLASIA - NO EFFECT
2. SMALL NEOPLASMS
3. MICE - NO EFFECT
4. MALATHION II - NO EFFECT IN F344 RAT
5. NO EFFECT COMPARED TO MALATHION II CONTROLS
6. MALATHION I - NEGATIVE TRENDS

CONCLUSIONS - RAT

MALATHION I: MALE - NO EVIDENCE OF CARCINOGENICITY
FEMALE - NO EVIDENCE OF CARCINOGENICITY

MALATHION II: MALE - NO EVIDENCE OF CARCINOGENICITY
FEMALE - NO EVIDENCE OF CARCINOGENICITY

MALAOXON : MALE - EQUIVICAL EVIDENCE OF CARCINOGENICITY
FEMALE - EQUIVICAL EVIDENCE OF CARCINOGENICITY