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
November 2, 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. Davis and Tannenbaum were unable to attend this meeting.

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 29, 1985, in Research Triangle Park, North Carolina. For information, contact Dr. Larry G. Hart, (919) 541-3971; FTS 629-3971.

CONTENTS

Chlorinated Trisodium phosphate. Dr. Davis, a principal reviewer, was unable to attend the meeting. She had submitted written comments in advance and these were read by Dr. Hook, Panel Chairperson. The conclusions for the technical report on the toxicology and carcinogenesis studies of chlorinated trisodium phosphate were that:

> Under the conditions of these studies, there was no evidence of carcinogenicity for either male or female B6C3F$_1$ mice given chlorinated trisodium phosphate by gavage in water for 103 weeks at doses of 500 or 1,000 mg. The studies in F344/N rats were considered to be inadequate studies of carcinogenicity because the experiments were terminated at 35 weeks.

Dr. Davis stated that the study results did not fully justify the conclusions. In her opinion, survival was not sufficient to reach conclusions for either the rat or mouse studies. She recommended doing the experiments again using the results of the current study to estimate more appropriate dosage regimens.

As a second principal reviewer, Dr. Van Ryzin agreed with the conclusions. He thought the two-year studies in mice were adequate based on the survival and weight curves, although he thought new experiments could be designed due to the inadequacy of the two-year studies in rats. He noted that 91.75 percent of the test material is trisodium phosphate, for which little toxicity data exists. This should be more clearly pointed out to the reader.

As a third principal reviewer, Dr. Beliczky stated that the study was less than adequate to draw reasonable conclusions on the carcinogenicity. He questioned the inclusion complex used, and the problems of the water caustic gavage, such as differential solubility and excessive dosage volumes, along with the inadequate studies in rats which pointed to the need for additional studies to determine the carcinogenicity of chlorinated trisodium phosphate.

Dr. Hook commented that the issue was whether there was adequate survival in the mice. Dr. J. Haseman, NIEHS, said that survival in all groups of mice was above 50 percent at 18 months. Dr. Kociba said some laboratories conduct mouse studies for only 18 months. Dr. J. Huff, NTP, noted that only the female mice were at issue since 24 month survival of all male groups was above 60 percent. Dr. Turnbull observed that poor survival was generally more of an issue with a negative study, as was the case here. Dr. Hook proposed that there seemed to be a consensus for considering the mouse study adequate but with some type of qualifier wording to indicate percent survival in both sexes at 18 months.

Dr. Van Ryzin moved that the technical report on the toxicology and carcinogenesis studies of chlorinated trisodium phosphate be accepted with parenthetical inclusion of 18 and 24 months percentage survival for the mouse study in the conclusions. Dr. Kociba seconded the motion and the report was approved by nine affirmative votes. There was one negative vote (Dr. Beliczky).

Dr. Beliczky stated that he primarily based his negative vote on what appeared to be inadequate quality which qualified sound scientific judgment. He said the implementation of the study led to deficiencies which put the entire study under questionable light, regardless of the negative results reported in mice.

3-Chloro-2-Methylpropene. Dr. Slaga, a principal reviewer for the technical report on the toxicology and carcinogenesis studies of 3-chloro-2-methylpropene, agreed with the conclusions that:

> Under the conditions of these 2-year gavage studies, there was clear evidence of carcinogenicity for 3-chloro-2-methylpropene as shown by the increased incidences of squamous cell neoplasms in the forestomach of male and female F344/N rats and male and female B6C3F$_1$ mice.

As a second principal reviewer, Dr. Jones basically agreed with the conclusion but felt that neoplasms might be more accurately stated as "increased incidences of squamous cell papillomas and carcinomas, combined, in the forestomach...". He was concerned as to what effects the contaminant, dimethylvinyl chloride (up to 5 percent of the 3-chloro-2-methylpropene), may have had on the stomach lesions since preliminary findings from the NTP indicate it is a carcinogen for the forestomach. Dr. Jones wondered whether there might be a correlation between the poor survival of high dose male rats and the negative tumor trends, especially for thyroid C-cell adenomas and carcinomas.

As a third principal reviewer, Dr. Friess did not agree with the composite conclusion for both sexes of both species. Based on lack of dose response for squamous cell papillomas in rats and no significant increases in carcinomas alone in rats and female mice, he thought the category should be some evidence of carcinogenicity. He agreed with clear evidence of carcinogenicity for male mice. Dr. Kociba concurred with the exception of male rats. Dr. Friess questioned whether the estimated maximum tolerated doses (MTDs) had been achieved. Dr. Swenberg said the issue of whether an MTD was reached becomes an important point only with a negative study. Dr. Hook said there should be an explanation in the report as to how doses were set. Dr. Friess asked for further discussion in the text on two issues: 1) the potential contributions of dimethylvinyl chloride (DMVC) to the carcinogenic process in the forestomach, and 2) the finding of renal tubular cell adenomas and carcinomas, albeit at low incidences, in male rats, and whether this may be an effect related to low molecular weight hydrocarbons and chlorinated hydrocarbons in male rats.

Dr. P. Chan, NTP Chemical Manager, commented that the 3-chloro-2-methylpropene (containing about 5% DMVC), was the material commercially available and the formulation to which people are exposed. Dr. B. Schwetz, NTP, reported that completed NTP two-year gavage studies with DMVC in rats and mice showed a spectrum of neoplastic responses not seen in this study, including those of the nasal passages, oral cavity, and esophagus. Dr. Kociba and Dr. Swenberg asked that either the presence of the DMVC be given in the title of the report or "Technical Grade" be inserted. Dr. Hook added that the composition should be given more prominence in the abstract.

Considerable discussion centered around 1) whether there was some evidence of carcinogenicity or clear evidence of carcinogenicity in rats and female mice, and 2) whether the species and sexes should be separated in the conclusion. Dr. Huff explained that the clear evidence of carcinogenicity category allowed for a substantial increase in benign neoplasms, and further, the target organ in each of these four experiments was the same. Hence, the single category seemed appropriate. Dr. Friess could agree to the conclusions as stated. Dr. Swenberg and Dr. Slaga concluded that since there were only small differences between benign and malignant neoplasms of the forestomach and the lesions were the same in all groups, the single categorization for all made sense. Further, Dr. Swenberg said that with essentially a 50 percent incidence he could support clear evidence of carcinogenicity in all cases.

Dr. Jones moved that the technical report on the toxicology and carcinogenesis studies of 3-chloro-2-methylpropene be accepted with the conclusion as stated, with some additional discussion on certain mentioned items and on adding DMVC to the title. Dr. Beliczky seconded the motion and the report was approved by nine affirmative votes. There was one negative vote (Dr. Kociba).

Dimethyl Morpholinophosphoramidate. Dr. Kociba, a principal reviewer for the technical report on the toxicology and carcinogenesis studies of dimethyl morpholinophosphoramidate (DMMPA) agreed in principle with the conclusion that:

> Under the conditions of these studies, there was some evidence of carcinogenicity for male and female F344/N rats given dimethyl morpholinophosphoramidate by gavage, as indicated by increased incidences of mononuclear cell leukemia. There was no evidence of carcinogenicity for male and female B6C3F$_1$ mice given dimethyl morpholinophosphoramidate by gavage.

However, he questioned the interpretation of the Fischer rat leukemias in female rats as supporting some evidence of carcinogenicity. Based on the historical control incidence range (16 to 42 percent) which bracketed the rates for all female treatment groups, he leaned toward a designation of equivocal evidence of carcinogenicity. Dr. P. Chan, NTP Chemical Manager, explained that the conclusion of some evidence of carcinogenicity in rats was supported by comparison to concurrent controls and this was the first study completed by the NTP where there were significant increases in the incidences of mononuclear cell leukemia in both male and female rats. On two other issues, Dr. Kociba said that cholinesterase monitoring might have helped to define the toxicity which caused a restarting of the studies in male mice, and given the projected use for DMMPA, dermal application may have been a more appropriate route of exposure.

As a second principal reviewer, Dr. Van Ryzin agreed with the conclusions. He said the survival data suggest the estimated maximum tolerated dose (MTD) was exceeded for high-dose male and female rats and for female mice but the life table test adequately adjusted for this and the results were not compromised. Dr. Van Ryzin thought more supporting information was needed before the liver could be considered the site of DMMPA detoxification and that liver enlargement was related to microsomal enzyme induction; likewise, he felt that the speculation about the genetic toxicity being the basis for the carcinogenicity of DMMPA should be deleted. Dr. Beliczky considered that the speculation was reasonable based on increased liver weight. As a third principal reviewer, Dr. Harper stated he would have interpreted the rat leukemia data to be clear evidence of carcinogenicity for both sexes by giving more weight to concurrent control data. He also would support a conclusion of equivocal evidence of carcinogenicity in male mice based on the positive trend for hepatocellular carcinomas. Dr. Chan explained that pairwise comparisons did not show statistical increases for hepatocellular carcinomas, and for the leukemias, he said some evidence of carcinogenicity was chosen rather than clear evidence of carcinogenicity because the incidences were increased only at the high dose and this is a relatively common neoplasm in Fischer rats. Dr. Swenberg commented that the grading of the lesions into stages as reported tended to support a high dose effect and the appropriateness of some evidence of carcinogenicity.

In further discussion concerning the rationale for some evidence of carcinogenicity or for clear evidence of carcinogenicity for the rat leukemias, Dr. Friess suggested that since the leukemias are malignant in all stages this should support clear evidence of carcinogenicity. Dr. G. Boorman, NTP, said that because this lesion was common in the Fischer rat and was variable among different control groups, some evidence of carcinogenicity was appropriate. Dr. Haseman added that lack of agreement between the incidental tumor test (higher P values) and the life table test tended to support some evidence of carcinogenicity even though the life table test was probably the more appropriate

test for this generally life-threathening lesion. Finally, Dr. McConnell commented that we should resist trying to make the levels of evidence as currently used by the NTP too definitive, thus leaving sufficient room for interpretation of the wide variations of experimental outcomes.

Dr. Van Ryzin moved that the technical report on the toxicology and carcinogenesis studies of dimethyl morpholinophosphoramidate be accepted. Dr. Swenberg seconded the motion and the report was approved by nine affirmative votes. There was one negative vote (Dr. Beliczky).

Isophorone. The conclusions for the technical report on the toxicology and carcinogenesis studies of isophorone were that:

> Under the conditions of these studies, there was some evidence of carcinogenicity of isophorone in male F344/N rats as shown by the occurrence of renal tubular cell adenomas and adenocarcinomas in animals given 250 or 500 mg/kg per day; carcinomas of the preputial gland were also observed at increased incidence in male rats given 500 mk/kg. For male B6C3F$_1$ mice, there was equivocal evidence of carcinogenicity as shown by an increased incidence of hepatocellular adenomas and carcinomas and of mesenchymal tumors in the integumentary system in animals given 500 mg/kg per day, and by an increase in malignant lymphomas in animals given 250 mg/kg per day. There was no evidence of carcinogenicity of isophorone in female F344/N rats or female B6C3F$_1$ mice.

Dr. Swenberg, a principal reviewer, did not agree with the conclusions for male rats because the increased incidence of kidney tumors was not dose related and was a typical response in animals exposed to chemicals that cause nephrotoxicity and thereby likely represents a secondary response. He suggested a conclusion of equivocal evidence of carcinogenicity. More discussion of the observed nephrotoxicity would be useful. Regarding the preputial gland tumors, Dr. Swenberg said the variation in historical incidence made these lesions also equivocal evidence of carcinogenicity. Dr. Kociba also supported equivocal evidence of carcinogenicity for male rats. Dr. J. Bucher, NTP Chemical Manager, responded that the designation of some evidence of carcinogenicity for male rats was based on incidences of the uncommon neoplasms of the kidney not on a perceived mechanism. Further, the incidence of nephropathy was high in control animals but no neoplasms were observed. Dr. Swenberg agreed to some evidence of carcinogenicity but asked for inclusion in the discussion of a historical evaluation of renal tumors seen in studies that also showed nephrotoxicity.

As a second principal reviewer, Dr. Slaga agreed with the conclusion in male rats but felt the significant increase in mesenchymal tumors in the integumentary system called for a finding of some evidence of carcinogenicity rather than equivocal evidence of carcinogenicity in male mice. He noted that human exposure to isophorone is most likely either by the inhalation or dermal route and so, studies by one or both of those routes would have been desirable. As a third principal reviewer, Dr. Kotelchuck agreed with the conclusions. He commented on the number of apparent gavage errors which resulted in accidental killing of almost 10 per cent of the test animals. Dr. Friess asked if there were guidelines for how much gavage error is permitted. Dr. E. McConnell, NTP, said that gavage error must be placed in context of total accidental deaths and that two percent or less is acceptable while ten percent or more is unacceptable. The NTP requires practical evidence of gavage proficiency prior to contract award.

Further discussion by the Panel members suggested an agreement with the NTP selection of some evidence of carcinogenicity for male rats and equivocal evidence of carcinogenicity for the various tumors cited as increased in male mice.

Dr. Swenberg moved that the technical report on the toxicology and carcinogenesis studies of isophorone be accepted with the conclusions as stated and revisions discussed. Dr. Beliczky seconded the motion and the report was approved unanimously by the Peer Review Panel.

Post Data Audit Update on the Toxicology and Carcinogenesis Studies of Benzyl Acetate

Dr. J. E. Huff, NTP, introduced this topic by saying that the NTP would report routinely to the Panel on chemicals for which the technical report had been previously approved by the Panel and for which the data audit was completed later and there were some interesting findings from the audit or from other studies on the chemical. With respect to benzyl acetate there were two key types of findings, one related to NTP in-house metabolism studies, and the second concerned the key findings made and resolved during the audit. The technical report for benzyl acetate (TR #250) was approved by the Panel on June 29, 1983, which was prior to the decision that all studies would receive data audits before coming to the Panel for review. Dr. Huff reported that the new findings will be incorporated into a draft copy of the final technical report and would be sent to Panel members plus former members involved in peer review of the report prior to having the technical report printed.

Dr. K. M. Abdo, NTP Chemical Manager, described the new information, the first of which concerned a study of the metabolism and disposition in adult male F344 rats and $B6C3F_1$ mice of ring labeled 14^C-benzyl acetate (BA) by the NIEHS/NTP Chemical Disposition section. Rats were given single oral doses of BA of 5, 50 or 500 mg/kg or repeated doses of BA of 500 mg/kg/day, five days per week for 14 days, and mice received 10, 100 or 1000 mg/kg or repeated doses of BA of 1000 mg/kg, five days per week for 14 days. The high dose in each case was the high dose used in the two-year studies. Results from both groups indicated rapid and nearly complete absorption from the gastro-intestinal tract, rapid excretion primarily in the urine, and no detectable tissue retention of BA-derived radioactivity. There was no diminution of clearance upon repeated dosing (Attachment 1, tables 1 and 2). Analyses of urine by high performance liquid chromatography (HPLC) show that hippuric acid accounted for over 90% of the urinary radioactivity with mercapturic acid and benzyl alcohol being other metabolites while no benzyl acetate was detected (Attachment 1, tables 3 and 4 and figure 1). There was no alteration in the pattern of chemical disposition after repeated dosing. Thus, there was no evidence to indicate any saturation of the mechanisms of absorption, metabolism, and excretion of benzyl acetate in either rats or mice over the dose range studied.

Secondly, Dr. Abdo reported on the NTP short-term genetic toxicology findings. BA was not mutagenic in several strains of Salmonella Typhimurium with or without metabolic activation and did not induce sister chromatid exchanges or chromosome aberrations in Chinese hamster ovary cells; BA was mutagenic in cultured mouse lymphoma cells in the presence but not in the absence of rat liver S9 extracts.

Thirdly, Dr. Abdo reported on the findings from the data audit of the two-year studies of BA in rats and mice. He said the audit supported the findings previously reported and, further, confirmed the forestomach as a target organ for carcinogenicity in the mouse as noted in the amended conclusion (Attachment 1). The results indicate that squamous cell papillomas or carcinomas and hyperplasia of the forestomach of mice of either sex were associated with BA administration (Attachment 1). He emphasized that the information presented did not change the level of evidence for the carcinogenic effect of BA.

Discussion on the Status of the Toxicology and Carcinogenesis Studies Performed at Gulf South Research Institute (GSRI) (Attachment 2)

Dr. E. McConnell, NTP, provided the Panel with an update of the NTP activities regarding the auditing of studies performed at GSRI, and proposed future plans for reporting the findings. He noted that data audits were begun on GSRI studies and studies from other laboratories in late 1983. Dr. McConnell described the kinds of problems identified in audits of the GSRI studies (page 2 of Attachment), emphasizing that not all of the problems were observed in every study. The status of the 28 studies at GSRI are indicated (pages 3 to 6 of Attachment 2) and of these, eight have been restarted as new studies. He emphasized that studies from eight other laboratories have been audited and no flaws were found sufficient to invalidate any study (pages 7 and 8 of Attachment 2).

Dr. McConnell then discussed the proposed NTP strategy for disposition of the GSRI studies, and asked for comments and suggestions from the Panel. He said a new audit contractor will be assigned to work solely on the GSRI studies. Those studies that are judged to be adequate will be brought before the Panel with one possibility being to devote an entire meeting to GSRI studies. He said the Panel would be told that the study is worth reporting and the flaws would be highlighted. For studies identified as being severely flawed so they should not be reported, the Panel will be informed and there will be a notice to this effect in the Federal Register. In response to a question by Dr. Jones, Dr. McConnell said all the records and materials from the GSRI studies are now in the NTP Archives and are being inventoried for completeness.

TABLE 1

BENZYL ACETATE CLEARANCE[a] - RAT

Dose Route	Dose (mg/kg)	Average % Total Dose ± SD			
		Urine	Feces	CO2	Volatile
iv	5[b]	85.5 ± 4.81	1.81 ± 1.69	0.20 ± 0.5	2.54 ± .91
oral	5[c]	69.3 ± 6.7	1.35 ± 1.58		
oral	50[c]	94.5 ± 5.1	0.37 ± 0.25		
oral	500[c]	91.3 ± 6.5	0.98 ± 1.01		
oral	500 x 14[d]	91.0 ± 6.25	0.36 ± 0.57		

[a]% Total dose cleared in 24 hr by 3 rats at each dose ± SD.

[b]Intravenous injection into a tail vein.

[c]Oral gavage in 5ml corn oil/kg body wt.

[d]Repeat oral dose, 5 days/wk for 14 days.

TABLE 2

BENZYL ACETATE CLEARANCE[a] - MOUSE

Dose Route	Dose (mg/kg)	Average % Total Dose ± SD Urine	Feces
iv	10[b]	62.3 ± 3.0	0.43 ± 0.38
oral	10[c]	63.0 ± 4.7	0.52 ± 0.33
oral	100[c]	89.0 ± 11.8	0.58 ± 0.58
oral	1000[c]	95.4 ± 3.6	0.70 ± 0.20
oral	1000 x 14[d]	88.3 ± 6.3	0.26 ± 0.06

[a]% Total dose cleared in 24 hr by 3 mice at each dose ± SD.

[b]Intravenous injection into a tail vein.

[c]Oral gavage in 10 ml corn oil/kg body wt.

[d]Repeat oral dose, 5 days/wk for 14 days.

TABLE 3

BENZYL ACETATE METABOLITES IN RAT[a] URINE

Dose Route	Dose mg/kg	% Total Dose In urine	Benzyl Acetate	Hippuric Acid	Benzyl Alcohol	Mercapturic Acid	Other
iv	5	85.0	--	90.9 ± 4.3	4.1*	5.2 ± 2.5	7.2*
Oral	5	69.3	--	98.9 ± 1.9	--	3.2*	---
Oral	50	94.5	--	97.0 ± 0.2	--	2.9 ± 0.2	--
Oral	500	91.3	--	94.6 ± 1.0	--	2.5*	3.6*
Oral	500 x 14	91.0	--	96.2 ± 3.4	--	3.1*	2.2*

*Not found in all animals.

[a]Average values obtained with 3 rats at each dose

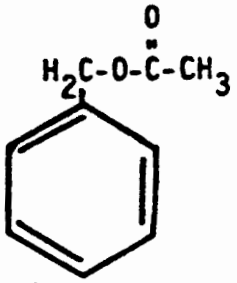
TABLE 4

BENZYL ACETATE METABOLITES IN MOUSE[a] URINE

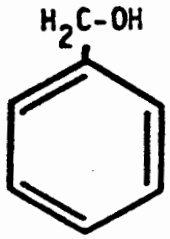
Dose Route	Dose mg/kg	% Total in Urine	Benzyl Acetate	Hippuric Acid	Benzyl Alcohol	Mercapturic Acid	Other
ivv	10	62.3	--	98.7 ± 0.2	--	--	1.6 ± 0.2
oral	10	63.0	--	93.9 ± 7.1	--	1.1*	5.6 ± 6.5
oral	100	89.0	--	99.3 ± 0.2	0.6*	0.7*	0.3*
oral	1000	95.4	--	97.9 ± 0.2	--	--	1.9*
oral	1000 x 14	88.3	--	97.6 ± 2.6	0.6*	--	3.2*

*Not found in all animals.

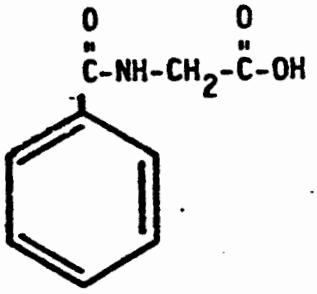
[a]Average values obtained with 3 mice at each dose.



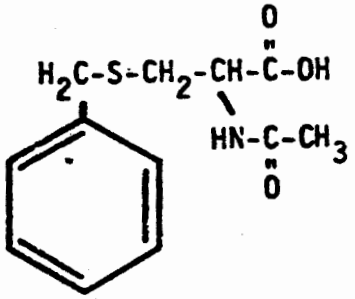
Benzyl Acetate



Benzyl Alcohol



Hippuric Acid



Benzyl Mercapturic Acid

FIGURE 1

AS AMENDED

UNDER THE CONDITIONS OF THESE STUDIES, 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 INCIDENCE OF HEPATOCELLULAR ADENOMAS AND SQUAMOUS CELL NEOPLASMS OF THE FORESTOMACH.

Tumor Incidence In The Forestomach Of B6C3F$_1$ Mice

Given Benzyl Acetate In Corn Oil By Gavage For Up To 2 Years

	Tumor Incidence[a]					
	Males			Females		
Dose (mg/kg)	0	500	1000	0	500	1000
Squamous Cell Papilloma	3/49(+2)[b]	3/48(+2)	9/49(+5)	0/50(0)	0/50(0)	4/48(+3)
Life Table Tests	p=0.038	p=0.597	p=0.065	p=0.054	c	p=0.180
Incidental Tumor Tests	p=0.038	p=0.597	p=0.065	p=0.065	c	p=0.180
Squamous Cell Papilloma or Carcinoma	4/49(+2)	4/48(+2)	11/49(+5)	0/50(0)	0/50(0)	4/48(+3)
Life Table Tests	p=0.032	p=0.588	p=0.052	p=0.054	c	p=0.180
Incidental Tumor Tests	p=0.028	p=0.619	p=0.051	p=0.054	c	p=0.180

a Number of Tumor Bearing Animals / Number of Animals Examined

b Change From Earlier Report In The Number Of Tumor Bearing Animals

c No Statistical Analysis Was Done Because The Incidences In The Control and The 500 mg/kg Dose Group Was Zero

Incidence of Epethelial Hyperplasia of the Forestomach

In Male and Female B6C3F$_1$ Mice Given Benzyl Acetate

In Corn Oil By Gavage For Up to Two Years

	Epethelial Hyperplasia Incidence[a]					
	Males			Females		
Dose (mg/kg)	0	500	1000	0	500	1000
Epethelial Hyperplasia	1/49 (2%)	7/48 (15%)	22/49 (45%)	1/51 (2%)	6/50 (12%)	17/48 (35%)

a $\frac{\text{Number of Lesion Bearing Animals}}{\text{Number of Animals Examined}}$

GSRI PLANNING REPORT

Board of Scientific Counselors
National Toxicology Program

October 31 - November 1, 1984

INTRODUCTION

1. History of GSRI problem
2. Study Audits at GSRI
   a. Some studies are severely flawed.
   b. Audit findings are inconsistent.
   c. Types of audit findings (attached).
   d. Status of studies at GSRI (attached).
3. Only lab showing flaws which would invalidate studies.
   - List of labs audited (attached).
4. Concern about releasing results of GSRI studies.

PLAN

1. Audit remaining GSRI studies with single auditor.
2. Report studies when the quality of the data warrants.
3. Note in Federal Register on studies not considered adequate to bring to Peer Review.

PROBLEMS IDENTIFIED IN AUDITS OF GSRI STUDIES

1. Misidentification of animals
2. Mislabeling of slides
3. Lack of dosage records
4. Misdosage of animals
5. Poor histotechnique/slide quality
6. Animal care inconsistencies (temperature, humidity, ventilation)
7. Staffing problems
8. Laboratory procedures behind current technology
9. Necropsy - (gross lesions not identified)
10. Non-compliance with GLP's and/or SOP's
11. Improper chemical analyses/documentation
12. Inadequate inhouse QA
13. Incomplete data reporting

CODE	NAME
ABDK	DR. K. ABDO
BIRL	DR. L. BIRNBAUM
CHHR	DR R. CHHABRA
COLJ	DR. J. COLLINS
EASW	DR. W. EASTIN
FREJ	DR. J. FRENCH
GUPB	DR. B. GUPTA
HUFJ	DR. J. HUFF
IRWR	DR. R. IRWIN
MARR	DR. R. MARONPOT
MELR	DR. R. MELNICK
MENJ	DR. J. MENNEAR
WHIC	DR. C. WHITMIRE

CODE	USE
ADHS	USED AS OR IN THE MANUFACTURE OF ADHESIVES, GLUES AND TAPES
COSM	COSMETICS
DTRG	DETERGENTS AND CLEANSERS (HOUSEHOLD AND COMMERCIAL)
DYE	USED AS OR IN THE MANUFACTURE OF DYES, INKS AND PIGMENTS
FUNG	FUNGICIDE(S)
INTR	CHEMICAL INTERMEDIATE OR CATALYST
NATL	NATURALLY OCCURING SUBSTANCES
PEST	UNCLASSIFIED OR GENERAL PESTICIDES
PHAR	PHARMACEUTICALS
SOLV	VEHICLES AND SOLVENTS
TEXL	USED IN MANUFACTURE OF TEXTILES

CODE	ROUTE
FEED	ORALLY WITH FOOD
GAV	ORAL, GAVAGE
SP	SKIN PAINT
WATER	ORAL WITH WATER

CODE	SPECIES/STRAIN
MA	MICE: B6C3F1 (CHARLES RIVER - PORTAGE)
M1	MICE: B6C3F1 (FCRF)
M2	MICE: SWISS (CHARLES RIVER - WILMINGTON)
M3	MICE: B6C3F1 (HARLAN)
M4	MICE: B6C3F1 (CHARLES RIVER - WILMINGTON)
M6	MICE: B6C3F1 (CHARLES RIVER - KINGSTON)
M9	MICE: B6C3F1 (UNKNOWN)
RE	RATS: LONG-EVANS (CHARLES RIVER - WILMINGTON)
RF	RATS: WISTAR (CHARLES RIVER - WILMINGTON)
RG	RATS: FISCHER 344 (CHARLES RIVER - PORTAGE)
RK	RATS: FISCHER 344 (CHARLES RIVER - KINGSTON)
R1	RATS: FISCHER 344 (FCRF)
R2	RATS: FISCHER 344 (CHARLES RIVER - WILMINGTON)
R3	RATS: FISCHER 344 (HARLAN)
R4	RATS: SHERMAN (GSRI)
R9	RATS: FISCHER 344 (UNKNOWN)

CHEMICALS TESTED AT GULF SOUTH RESEARCH INSTITUTE

Sorted by Status

CHEMICAL NAME	USE CODE	CHEM MGR	ROUTE	SPEC	CHRONIC SACRF DATE	STATUS
* TETRAHYDROFURAN	SOLV INTR	CHHR	GAV	R1M1		PRECHRONIC TESTING COMPLETED
2-BUTANONE PEROXIDE	INTR	ABDK	SP	RGMA	05/12/83A	CHRONIC HISTOPATHOLOGY IN PROGRESS
* TERT-BUTYL ALCOHOL	INTR SOLV	MARR	WATER	RKMA	05/13/82A	CHRONIC HISTOPATHOLOGY IN PROGRESS
CASTOR OIL	PNT PHAR	COLJ	FEED	RKM6	03/26/82A	CHRONIC HISTOPATHOLOGY IN PROGRESS
* CHLORAMINE	INTR	WHIC	WATER	R9M9	12/15/83A	CHRONIC HISTOPATHOLOGY IN PROGRESS
COCONUT DIETHANOLAMIDE	INTR DYE	MELR	SP	RGM6	02/14/83A	CHRONIC HISTOPATHOLOGY IN PROGRESS
DIETHANOLAMINE	INTR NATL	MELR	GAV	RGM6	09/09/82A	CHRONIC HISTOPATHOLOGY IN PROGRESS
2-ETHOXYETHANOL (EGMEE)	SOLV DYE	MELR	GAV	RGMA	03/19/82A	CHRONIC HISTOPATHOLOGY IN PROGRESS
GLUTARALDEHYDE	ADHS INTR	HUFJ	SP	RGMA	11/15/82A	CHRONIC HISTOPATHOLOGY IN PROGRESS
LAURIC ACID DIETHANOLAMINE CONDENSATE	DTRG INTR	CHHR	SP	RGMA	04/01/83A	CHRONIC HISTOPATHOLOGY IN PROGRESS
* P-NITROPHENOL	INTR FUNG	IRWR	SP	M2	11/01/83A	CHRONIC HISTOPATHOLOGY IN PROGRESS
OLEIC ACID DIETHANOLAMINE	COSM NATL	CHHR	SP	RGMA	03/14/83A	CHRONIC HISTOPATHOLOGY IN PROGRESS
SODIUM XYLENESULFONATE	DTRG IND	IRWR	FEED	RKM6	08/09/82A	CHRONIC HISTOPATHOLOGY IN PROGRESS

* RESTART

CHEMICALS TESTED AT GULF SOUTH RESEARCH INSTITUTE

Sorted by Status

CHEMICAL NAME	USE CODE	CHEM MGR	ROUTE	SPEC	CHRONIC SACRF DATE	STATUS
* DMBA(DIMETHYLBENZANTHRACENE)/TPA(TETRADE	PEST PHAR	EASW	SP	RG	02/27/81A	TECHNICAL REPORT BEING DRAFTED
	PEST PHAR	EASW	SP	M6	02/16/81A	TECHNICAL REPORT BEING DRAFTED
1,2-EPOXYHEXADECANE	INTR	MELR	SP	RGMA	06/08/82A	TECHNICAL REPORT BEING DRAFTED
TETRACHLOROETHYLENE	SOLV PHAR	MENJ	GAV	RE	06/30/80A	TECHNICAL REPORT BEING DRAFTED
	SOLV PHAR	MENJ	GAV	RF	11/19/80A	TECHNICAL REPORT BEING DRAFTED
	SOLV PHAR	MENJ	GAV	R3	09/11/80A	TECHNICAL REPORT BEING DRAFTED
	SOLV PHAR	MENJ	GAV	R4	02/04/80A	TECHNICAL REPORT BEING DRAFTED
	SOLV PHAR	MENJ	GAV	MA	09/11/80A	TECHNICAL REPORT BEING DRAFTED
* TRICHLORFON	PEST	CHAP	GAV	RKM6	03/23/82A	TECHNICAL REPORT BEING DRAFTED
PYRIDINE	SOLV PHAR	FREJ	GAV	RGMA	11/03/81A	TECHNICAL REPORT BEING STAFF REVIEWED
SODIUM DODECYL SULFATE	COSM DTRG	IRWR	FEED	RGMA	06/26/81A	TECHNICAL REPORT BEING STAFF REVIEWED
* 1,1,1-TRICHLOROETHANE (METHYL CHLOROFORM	SOLV PEST	BIRL	GAV	R3M3	05/15/81A	TECHNICAL REPORT BEING STAFF REVIEWED

* RESTART

CHEMICALS TESTED AT GULF SOUTH RESEARCH INSTITUTE

Sorted by Status

CHEMICAL NAME	USE CODE	CHEM MGR	ROUTE	SPEC	CHRONIC SACRF DATE	STATUS
C. I. ACID YELLOW 73 (FLUORESCEIN SODIUM)	DYE	MENJ	WATER	R3M3	05/05/81A	PEER REVIEWED AND FINAL TECHNICAL REPORT IN PREPARATION
ETHOXYLATED DODECYL ALCOHOL	TEXL COSM	GUPB	FEED	R3M3	04/23/81A	PEER REVIEWED AND FINAL TECHNICAL REPORT IN PREPARATION
GILSONITE	PNT NATL	HUFJ	FEED	RGMA	09/14/81A	PEER REVIEWED AND FINAL TECHNICAL REPORT IN PREPARATION
HAMAMELIS WATER (WITCH HAZEL)	COSM PHAR	HUFJ	SP	RGMA	01/29/82A	PEER REVIEWED AND FINAL TECHNICAL REPORT IN PREPARATION
SODIUM (2-ETHYLHEXYL)ALCOHOL SULFATE	PHAR	IRWR	FEED	R3M3	03/20/81A	PEER REVIEWED AND FINAL TECHNICAL REPORT IN PREPARATION
PENTACHLOROETHANE	SOLV INTR	MENJ	GAV	R2M4	12/00/79A	TECHNICAL REPORT PUBLISHED
*1,1,1,2-TETRACHLOROETHANE	INTR	BIRL	GAV	R2M4	11/11/79A	TECHNICAL REPORT PUBLISHED
VINYLIDENE CHLORIDE (1,1-DICHLOROETHYLEN	INTR	CHHR	GAV	R1M1	06/00/79A	TECHNICAL REPORT PUBLISHED

*RESTART

AUDITS PERFORMED AT THE ARCHIVES LISTED BY CONTRACT LABORATORY
October 1984

Battelle Columbus (5 Audits)

Benzene
1,2-Dichlorobenzene
C.I. Acid Orange 10
o-Phenylphenol
Chlorobenzene

Battelle Pacific Northwest (4 Audits)

1,3-Butadiene
Propylene Oxide
Propylene
Methylene Chloride (inhalation) -- started 10/29/84

Bioassay Systems Corporation (0 Audits)

EG&G Mason Research Institute (7 Audits + 3 Audits Scheduled)

Chlorodibromomethane
8-Hydroxyquinoline
Di(2-Ethylhexyl) Phthalate
Butyl Benzyl Phthalate
C.I. Basic Red 9
Chlorinated Trisodium Phosphate
Diglycidyl Resorcinol Ether
n-Butyl Chloride--scheduled 11/5/84
1,2-Dichloropropane--scheduled 11/5/84
Di(2-Ethylhexyl) Adipate--scheduled 11/26/84

Frederick Cancer Research Center (1 Audit + 1 Audit Scheduled)

Telone
Mirex--scheduled for 12/03/84

Gulf South Research Institute (7 Audits)

1,1,1-Trichloroethane
Methylene Chloride
Sodium Dodecyl Sulfate
Hamamelis Water (Witch Hazel)
Tetrachloroethylene
Pyridine
Ethylene Glycol Monoethyl Ether

Hazleton Laboratories America--Virginia (2 Audits)

Ethylene Dibromide
Asbestos Chrysotile (rats)

Hazleton Laboratories America--Wisconsin (0 Audits)

International Research and Development Company (0 Audits)

Litton Bionetics, Inc. (10 Audits)

Tris(2-Ethylhexyl) Phosphate
Diallyl Phthalate
Dimethyl Hydrogen Phosphite
2-Chloroethanol
Dimethyl Morpholinophosphoramidate
3-Chloro-2-Methylpropene
Melamine
Toluene Diisocyanate
Dimethylvinyl Chloride (DMVC)

Lovelace ITRI (0 Audits)

Papanicoloaou Cancer Research Institute (2 Audits)

Trichloroethylene
Isophorone

Physiological Research Laboratories (0 Audits)

SRI International (0 Audits)

Southern Research Institute (5 Audits + 2 Scheduled)

Benzyl Acetate
H.C. Blue 2
H.C. Red 3
Eugenol
C.I. Disperse Blue 1
Chlorowax 40--scheduled 11/26/84
Chlorowax 500C--scheduled 12/3/84