



MANUFACTURING CHEMISTS ASSOCIATION

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April 17, 1974

To: TECHNICAL TASK GROUP ON VINYL CHLORIDE RESEARCH

Subject: Report on Conference with Industrial BIO-
TEST Laboratories, April 15, 1974

Gentlemen:

As a result of the telephoned information received by MCA from Industrial BIO-TEST personnel last week, a conference at the Northbrook, Illinois offices of IBT was set up at which an oral status report on the chronic inhalation studies with vinyl chloride was presented to MCA, industry and federal agency representatives.

Those in attendance, and their affiliations, are shown below:

Z. G. Bell, Jr.	PPG Industries, Inc.
A. S. Cummin	Borden, Inc.
E. J. Fairchild	NIOSH
J. W. Goode	Industrial BIO-TEST Laboratories
D. E. Gordon	Industrial BIO-TEST Laboratories
W. D. Harris	UNIROYAL, Inc.
M. N. Johnson, M.D.	The B. F. Goodrich Company
Plynt Kennedy	Continental Oil Company
M. L. Keplinger	Industrial BIO-TEST Laboratories
R. J. Kociba	The Dow Chemical Company
H. L. Kusnetz	Shell Oil Company
D. V. Lassiter	OSHA
W. E. Rinehart	Ethyl Corporation
W. M. Smith	Air Products & Chemicals, Inc.
J. F. Stara	U. S. Environmental Protection Agency
T. R. Torkelson	The Dow Chemical Company
R. N. Wheeler	Union Carbide Corporation
B. M. G. Zwicker	B. F. Goodrich Chemical Company
R. F. Blewitt	MCA
A. C. Clark	MCA
E. D. Johnson	MCA

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Dr. Goode first presented the mortality data and gross observations, and then Dr. Gordon described the pathology observed in the mice. The data, as presented, are shown in the attached tables. There are apparent discrepancies between the total mortality data and the detailed listing of recent deaths. These will be resolved. No test-related pathology has yet been noted in any animals other than mice.

Dr. Fairchild, of NIOSH, reported that Dr. David Rall, of HEW, had appointed a committee to coordinate departmental toxicology and related programs, and that under this committee there has been named a subcommittee to develop a "white paper" on guidelines for research to determine "socially acceptable" levels of risk. A report from this subcommittee, which will cover both philosophical and statistical considerations, is expected in the next few weeks.

Dr. Stara expressed the view that the vinyl chloride problem presented industry with a unique opportunity to seek to demonstrate a "no effect level" of a human carcinogen with a sensitive animal model of well-documented validity.

Dr. Lassiter expressed a guarded judgment that the mouse data reported by IBT would not lead OSHA to modify the emergency temporary standard, but that it might well cause OSHA to accelerate the rule-making process for the development of a permanent standard.

Dr. Lassiter also reported briefly on the retrospective morbidity and mortality studies being conducted by NIOSH/CDC at nine or ten locations (six companies) around the country. No epidemiological data were presented.

In an afternoon session of the Research Coordinators, it was agreed that the exposure of the mice in the present project should be terminated at nine months, but that exposures of both rats and hamsters should proceed for the initially-planned twelve months.

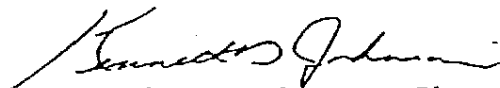
It was further moved, seconded and carried that the chairman appoint a group to begin investigating the cost and availability of facilities of new experiments to be conducted at lower levels of exposure, with larger groups of animals. He was asked specifically to seek to encourage the National Center for Toxicological Research, at Pine

Bluff, Arkansas, to offer to undertake such a program. Details of the test protocol are to be left open until after the Rall committee makes its report available.

The Research Coordinators asked MCA to call a meeting of the Technical Task Group on Vinyl Chloride Research as soon as the report of Tabershaw-Cooper Associates on their epidemiological study reaches them.

A copy of the MCA news release reporting the Industrial BIO-TEST mouse data has been sent to you in this morning's mail.

Sincerely,



Kenneth D. Johnson, Ph.D.
Secretary
Technical Task Group on
Vinyl Chloride Research

KDJ:mb

Tables Attached

cc : Mr. A. W. Barnes
D. P. Duffield, M.D.
Dr. Tiziano Garlanda
Vinyl Chloride Management Contacts

TABLE 1

Mouse Mortality Data

DATE	GROUP							
	<u>Controls</u>		<u>TI</u>		<u>TII</u>		<u>TIII</u>	
	<u>F</u>	<u>M</u>	<u>F</u>	<u>M</u>	<u>F</u>	<u>M</u>	<u>F</u>	<u>M</u>
February 10, 1974	2	8	6	26	2	4	7	8
April 12, 1974	5	11	9	31	13	7	13	18

Industrial BIO-TEST Laboratories, Inc.

1810 FRONTAGE ROAD

NORTHBROOK ILLINOIS 60062

TABLE II

Summary of Tumors in Vinyl Chloride Exposed Mice

IBT Number 603-03222-MCA

<u>Group, Animal No., Sex</u>	<u>Histopathologic Findings</u>			<u>Date of Death</u>
	<u>Lung</u>	<u>Liver</u>	<u>Skin</u>	
T-I				
1023 Male	AA (s)*	HS (s)**	***	
1110 Female	AA (s), Metastatic Skin Tumor		EC (para-aural)	3-20-74
1119 Female		HS (s)		3-24-74
1200 Female	Metastatic Skin Tumor		EC & MC+ (Femoral region)	3-30-74
T-II				
1347 Female	Metastatic Skin Tumor		EC (Abdomen)	3-5-74
1309 Female		HS (s)		3-18-74
1329 Male	AA (s)	HS		3-25-74
1362 Female		HS (s)		4-2-74
1359 Female	AA (s)	HS (s)		4-5-74
1299 Female	AA (s)		EC & MC (Inguinal Region)	4-9-74
T-III				
1538 Female	AA (s)	HS (s)		3-6-74
1532 Female	AA (s)		LSΦ	3-7-74
1562 Female	AA (s)	HS (s)		3-8-74
1598 Female	AA (s)	HS (s)		
1405 Male	AA (s)	HS (s)		2-25-74
1494 Male	AA (s)	HS (s)		3-22-74
1574 Female	AA (s)	HS (s)		3-22-74
1531 Female		HS (s)	EC & MC (Femoral region)	3-23-74
1588 Female		HS (s)		3-25-74
1593 Female	AA (s)	HS (s)		3-30-74
1505 Female	AA (s)	HS (s)		4-3-74
1565 Female	AA (s)	HS (s)		4-3-74
1409 Male	AA (s)	HS (s)		4-5-74
1543 Female	AA (s)	HS (s)		4-5-74
1544 Female	AA (s)	HS		4-5-74
1546 Female	AA (s)	HS (s)	MC (Axillary region)	4-5-74
1535 Female	AA (s)	HS (s)		4-7-74
1432 Male	AA (s)			4-8-74
1477 Female	AA (s) Metastatic Skin Tumor?	HS (s)	EC (Para-Aural) MC (Abdomen) EC (Pelvic region)	

TABLE III

*Industrial BIO-TEST Laboratories, Inc.*1810 FRONTAGE ROAD
NORTHBROOK, ILLINOIS 60062Summary of Mortality & Tumor Data Among Vinyl Chloride Mice
IBT Number 663-03222 (MCA)

Group	No. Mortalities with Neoplasms	Location of Tumors		
		Lung	Liver	Skin Metastasis → L
I-I	4 (1 Male, 3 Females)	2(50%)	2(50%)	2(50%) 2
I-II	6 (1 Male, 5 Females)	3(50%)	4(66.7%)	2(33%) 1
I-III	19 (4 Males, 15 Females)	17(89.5%)	17(89.5 %)	3(15.8%)

Key to Symbols

- * Alveologenic Adenoma of Lung (AA)
- ** Hemangiosarcoma of Liver (HS)
- *** Epidermoid Carcinoma of Skin (EC)
- * Mammary Carcinoma of Skin (MC)
- ① Lymphosarcoma of Thymus
- (s) Multiple tumors of indicated type

Controls

Group TE I - 50 ppm
Group TE II - 200 ppm
Group TE III - 2500 ppm
Group TE IV* - 2500 ppm

*Rats only, special cage
conditions for this test
group.

- 4) There were 2,500 test animals.
- 5) Inhalation exposures were initiated and terminated as follows:

<u>Species</u>	<u>Initiated</u>	<u>Terminated</u>
Mice	September 10, 1973	June 10, 1974
Rats*	September 10, 1973	September 10, 1974
Hamsters	September 10, 1973	September 10, 1974

- 6) The last interim report on this research project issued on September 23, 1975. No additional data or reports subsequent to this date were available to the Task Group.
- 7) On Monday morning, February 20, 1978 it was learned that final shipments of VC test documents, organ and tissue evidence from IBT, Northbrook to IBT, Decatur were completed on Friday, February 17, 1978. There were available to the Audit Task Group, only gross inventories of the shipment components.
- 8) No summaries or detailed inventories were available on the:
 - a. Status of necropsy sheets or reports
 - b. Status of histopathology readings
 - c. Wet tissues inventoried or catalogued

d. Tissue blocks inventoried by designated animal numbers

e. Histologic slides available and inventoried by animal numbers

2.0 Audit Designs and Contingency Plan Developed by Task Group Chairman and Project Manager

2.1 Introductory Comments

It is to be emphasized that the intrinsic magnitude of test data and research evidence from 2,500 test animals (in the form of wet tissues, tissue blocks, and histopathologic slides) dictated that audit plans be comprehensive and well designed prior to the initiation of work by any of the audit teams. This being accomplished, then the teams could proceed rapidly and effectively within their respective audit parameters, complete their work within the limited time frame allowed, and have a limited time in which to summarize their findings.

Since no data pertinent to items 7) and 8) (see above) were available prior to the audit design work conducted on February 19, 1978, the Chairman and the Project Manager developed two basic plans by which the in-depth audit could be conducted. The third audit design developed on February 19, 1978 was a contingency plan which was based on an estimate of conditions prior to and immediately following shipment on February 17, 1978 of documents and research evidence from IBT, Northbrook to IBT, Decatur.

2.2 Audit Plan I

This plan was designed to incorporate criteria established by the Food and Drug Administration in their proposed Good Laboratory Practices (GLP) document. Among the more important GLP criteria which guided the audit designs were the following:

- . Was the research being conducted in strict conformity with the protocol and were all pertinent echelons of the research facility briefed on protocol specifications?

- . Analysis of the test agent and exposure chamber concentrations and investigations of possibilities of stratified flow in the test chambers.
- . Test animals - test facilities' procedures for quarantined, randomization, identification, and environment. Possible deviations from these procedures -

Execution of Study:

- . Frequency of observations of animals for possible abnormalities.
- . Clinical laboratory test conducted.
- . Recording of clinical observations in bound laboratory notebooks with appropriate signatures and initials of investigators.
- . Nature of test conducted on animals found dead.

Necropsies (Gross Pathology):

- . Were necropsies performed on all animals?
- . Examination of animals found dead and subject to postmortem autolysis.
- . Supervision of examination by Board Certified Pathologist.
- . Organs described and weighed.
- . Descriptive data on all lesions observed.
- . What wet tissues and tissue blocks were preserved and were these clearly identified or labeled and recorded?
- . Where are wet tissues and histopathologic slides stored and under what storage conditions?

Histopathology:

- . Who examined what tissues and when were they examined in relation to completion of gross pathology?
- . Records of all tumors or other unusual findings noted on gross examination.
- . Were these findings studied microscopically?

Data, Records, and Reports:

- . The overall laboratory plan for the collection of data.
- . Were all animals involved in the study accurately accounted for?
- . If any errors were observed, what could be their potential impact on the scientific integrity of the study?

Audit Teams and Parameters to be Covered by Each Team

Plan I provided for in-depth analyses of case histories of selected animals within given exposure groups. The audit teams were structured as follows:

Team 1 - Pathology

Audit Parameters

- . Tissue preparation
- . Slide - preparation
- . Slides - storage and retrievability
- . Uncut material or wet tissues - examination of storage of preserved and prepared tissue

- . Pathology - examination of prepared slides
- . Number of tissues being prepared
- . Organs selected for histopathologic study

Team 2 - General Laboratory Audit

Audit Parameters

- . Body weights
- . Organ weights
- . Analytical chemical data
- . Clinical chemical data
- . Hematological data - blood parameters
- . Clinical observations
- . Air flow in exposure chambers
- . Records of concentrations of test chemical in exposure chambers
- . Cross checks of necropsy sheets with behavioral sheets

Team 3 - Audit and Review of Mortality Data and Reported Lesions

Audit Parameters

All recorded and/or reported mortality data.

2.3 Audit Plan II

Team 1 - Good Laboratory Practices

Audit Parameters

Animal Data

Data on Shipment

Source

Shipping date and date of receipt at
test facility

Number shipped - by sex

How many shipped per case

Batch numbers

- . Historic background data - sires, dams
- . Ages at mating
- . Numbers in each litter
- . Individual or gross weights at time of shipment

Animal Preparatory and Test Data

- . Identification of individual animals -
procedure used and tie-in with
identification of tissues (both wet
tissues and tissue blocks)

- . Randomization - procedure used

- . Quarantine - conditions

- . Replacements

Source

Documentation

Previous Environment

- . Initial exposure(s)

- . Individual weights) _ _ weight change data
Organ weight) _ _ relevant to both

Exposure Chamber Data

- . Concentrations of test chemical
- . Computer printouts
- . Detailed records of down-times and reasons for, duration of
- . Checks for stratified flow in chamber(s)
- . Number of full exposure days
- . Criteria used to determine a full exposure day

Team 2 - Research Procedures up to and Including Necropsy

Audit Parameters

- . Laboratory Notebooks -
Type
System of recording entries
Tie-in with computer entries and printouts
- . Types of observations recorded
- . Mortality incidences
- . Mortality curves
- . Records of postmortem autolysis
- . Clinical observations
- . Mortality Curves Versus Calendar Incidences

Comparative summations of:

Animals found dead versus day of week
Animals sacrificed versus day of week
Records of all tissues saved

. Necropsy Sheets

What tissues were actually saved - check for individual animals or conduct random checks within given exposure groups

Tissues saved versus protocol requirements

Recorded tissue masses -

Time to first tumor observations

Behavioral reactions

Detailed examinations and analyses of histopathology sheets

Team 3 - Histopathology

Audit Parameters

- . Residual tissues
- . Wet tissue preparation
- . Wet tissue preservation
- . Preservative used for eyes
- . Cataloguing of missing tissues
- . Inventory of "good" tissues and check of source animal (animal number)

Complete this inventory as soon as possible to enable Board Certified Pathologist to conduct confirmatory observations or readings

- . Number of tissues prepared
- . Type of examinations of pathologic slides
- . Organs selected for histopathologic study

Possible Target Organs and Organs of Major Concern, e.g.,

Brain	Lungs
Heart	Mammary Gland
Kidneys	Spleen
Liver	Stomach

. Tissue Blocks

Preparation procedure
Preservation
Inventory records - by test animal number

2.4 Audit Plan III

This plan was designed on the basis of findings evolving from the general assessment and review of research documents and materials conducted on February 20, 1978.

The results of the general assessment survey conducted during the morning of February 20, 1978 showed clearly that Plan III would have to be used. Detailed audits based on the original necropsy/histopathology sheets for each control and test animal would have to be conducted and the tissues histopathologically read and/or retained for each test animal would have to be recorded on master audit sheets showing each of the possible 38 organs of each test animal from which tissues reportedly had either been taken, or for which histologic slides had been prepared, or from which wet tissues had been preserved.

The organization of this audit plan is as follows:

Team 1- Histopathology

Audit Team 1, Members

Dr. W. M. Busey
Dr. G. K. Hatfield
Drs. D. J. Sullivan and M. Vlaovic and members
of the IBT histopathology and necropsy staffs

Areas Audited and Work Performed by Audit Team 1

. Inventory of tissues examined microscopically

- . Random shecks of slide readings against recordings on histopathologic summary sheets
- . Verification of slide readings
- . Verification of selected tumor diagnosis
- . Tabulation of angiosarcomas
- . Summary prepared of all tumor diagnoses

Audit Team 2, Members

Dr. T. J. Benya
Dr. R. K. Hinderer
Dr. D. J. Sullivan, Mr. W. J. Koretke,
Ms. I. Te Vault and members of the IBT
staff

Areas Audited and Work Performed by Audit
Team 2, Test Animal - Mice

- . Review of all research entries under "Gross Pathological Observations"
- . Review of all recorded data under "Histological Observations"
- . Preparation of summaries of all gross pathological observations and histological observations recorded on a possible total of 38 organs
- . Verification cross checks of "Days on Test" as recorded on necropsy sheets versus computer printouts
- . Summaries prepared under 44 classifications of all tumor data recorded for 17 organs for all animals in Control and Test Groups T-I, T-II, and T-III

Audit Team 3, Members

Dr. Z. G. Bell
Dr. C. D. Kary
Dr. D. J. Sullivan, Dr. M. Vlaovic,
Mr. W. J. Koretke, Ms. I. Te Vault,
and members of IBT staff

Areas Audited and Work Performed by Audit
Team 3, Test Animals - Hamsters

The areas audited and investigations conducted by Audit Team 3 are covered by the descriptive work titles shown under this comparable section under Audit Team 2.

Audit Team 4, Members

Dr. T. R. Torkelson
Mr. J. T. Seawell
Dr. D. J. Sullivan, Dr. M. Vlaovic,
Mr. W. J. Koretke, Ms. I. Te Vault,
and members of IBT staff

Areas Audited and Work Performed by Audit
Team 4, Test Animals - Rats

The areas audited and the investigations performed by Audit Team 4 are covered by the descriptive work titles shown under this comparable section under Audit Team 2. However, Audit Team 4 reviewed all research entries under "Gross Pathological Observations" and "Histological Observations" for Controls, Test Group I, II, III, and IV. The fourth test group for this species of test animal was included in this exposure series to enable comparison with animals subjected to comparable test conditions in the laboratories of Dr. Cesare Maltoni.

Test Group 4 audited gross and histopathological data for 900 test animals, 38 organs per animal, or a total of 34,200 organ

data summaries. Teams 2 and 3 audited gross and histopathological data for 800 test animals, 38 organs per animal, or a total of 30,400 possible organ entries.

Audit Team 4, as did the other teams, gave special consideration to the following organ tissues of possible specific importance with respect to VC exposure:

Brain	Mammary Gland
Kidney	Spleen
Liver	Stomach
Lung	Zymbal Gland
Lymph Nodes	

3.0 Combined Meeting of the Members of the Task Group for the Audit of Vinyl Chloride Chronic Inhalation Study and the Executive Staff of IBT, Decatur, for the Purpose of Reviewing Findings and Presenting the Recommendations of the Audit Task Group

Dr. T. R. Torkelson presented a thoroughgoing history of the project to date to include work leading up to the acceptance of the protocol by the Technical Panel, a summary of conditions pertinent to the initial exposures, and a chronological recapitulation of dates on which research findings have been made available to the Research Coordinators, and ultimately the Technical Panel.

Dr. Z. G. Bell presented a review of the findings reported in the 23-month status report, and observations evolving from the studies made by the four audit teams of necropsy sheets and histopathologic findings reported to date.

The VC Audit Task Group recommended to the IBT Executive Staff that the following course of action be taken. It was emphasized that these recommendations are based on investigations and observations made at IBT, Decatur during the week of February 20, 1978.

The recommendations presented are as follows:

3.1 Phase I - An Inventory of All Wet Tissues, Tissues in
Blocks, and Histologic Slides

The Task Group was unanimous in its recommendation that IBT complete the following at the earliest possible time:

1. A complete inventory is to be made of:
 - A. All wet tissues in preservative in plastic containers are to be inventoried by opening each container and specifically identifying all tissues present.
 - B. All tissues in blocks with specific identification of each tissue therein.
 - C. All histologic slides with a complete identification and listing of each tissue for each animal.
 - D. A histopathology sheet is to be used for recording all entries evolving from inventories under A., B., C. above.
 - E. Summary sheets similar to those developed by the Audit Task Group, i.e., 50 animals per sheet/38 organs per animal, are to be used when preparing data summaries.
2. Arrange in order all animals as to the days on test at death by:
 - A. Species
 - B. Group
 - C. Exposure level
 - D. Sex
 - E. Animal numbers

All animals for which there are no wet tissues, tissue blocks or slides are to be excluded.

3. Data obtained in 1. and 2. (of section 3.1) above are to be sent to MCA for immediate distribution to the Vinyl Chloride Audit Task Group.
4. A meeting is to be arranged in the Chicago area within 4-6 weeks to be attended by the Chief Pathologist of IBT, any other IBT executive concerned with this study, and the members of the Vinyl Chloride Audit Task Group for the purpose of discussing the results of the inventory and reaching a decision concerning the next course of action.
5. If the inventory reveals that adequate data are available to enable the investigations of target organs and suspicious lesions recommended by the consulting pathologist, Dr. W. M. Busey, then IBT is to draft a report which will be forwarded to MCA.
6. The Audit Task Group will comment on the IBT draft report.

3.2 Phase 2 - Alternative Recommendations on IBT Action in the Event that Data Evolving from the Inventory are Insufficient for the Resolution of a Consensus on Effects

In the event that data evolving from the inventories cited above are not sufficient to resolve a consensus on effects, then tissues will be worked-up for specific target organs in low and high exposure levels. If this proves inadequate, then tissues for exposure groups T-I and T-II animals will be histologically examined and reported to the members of the Vinyl Chloride Audit Task Group.

Item 2 - At this stage, the IBT pathologist and members of the Audit Task Group will proceed according to Phase 1, Step 4 (of section 3.1) described above.

3.3 Procedure to Govern Reading of Histologic Slides

Only one pathologist should be assigned tissue examinations. By no means should different pathologists histologically examine animal tissues from the same species. Further, IBT should use a consistent code of findings when summarizing histopathologic data.

4.0 Concluding Comment by Dr. John H. Mennear, Technical Director, IBT, Decatur

Dr. Mennear stated that he fully recognized the importance of this study and concluded by saying that he wanted to get it completed as promptly as possible.



J. T. Seawell
Project Manager
Vinyl Chloride Research

JTS:ec
Record Subject to Approval
March 31, 1978