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MANUFACTURING CHEMISTS ASSOCIATION

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ALBERT C. CLARK
VICE PRESIDENT
TECHNICAL DIRECTOR

VC Res
February 3, 1978

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R. N. WHEELER, JR.

Mr. A. E. Montagna
Operations Manager, Environmental
Protection and Occupational
Health
Union Carbide Corporation
Chemicals and Plastics
270 Park Avenue
New York, New York 10017

Research
Subject: Vinyl Chloride Chronic Vapor Inhalation Study -
Industrial BIO-TEST Laboratories

Dear Mr. Montagna:

As a result of a series of events, all operations of Industrial BIO-TEST Laboratories, Inc. (IBT) have been reorganized and consolidated at its Decatur, Illinois laboratories. These contributed to a lengthy delay in the preparation of a final report covering the chronic vapor inhalation study. Thus, the Vinyl Chloride Technical Panel unanimously recommended during its January 12, 1978 meeting that an in-depth audit be conducted at IBT, Decatur, during the week of February 20, 1978.

The Technical Panel has formed an Audit Task Group comprised of:

Dr. Z. G. Bell, Chairman
Dr. T. Benya
Dr. G. K. Hatfield
Dr. R. K. Hinderer

Dr. C. D. Kary
Dr. T. R. Torkelson
Dr. W. M. Busey

Mr. J. T. Seawell

PPG Industries, Inc.
Ethyl Corporation
Diamond Shamrock Corporation
The BFGoodrich Company,
Chemical Division
Shell Oil Company
The Dow Chemical Company
Consulting Pathologist,
Experimental Pathology
Laboratories, Inc.
MCA Staff

The Panel was unanimous in its approval of funds not to exceed \$5,000 for expenses incident to this audit, e.g., the f e

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for a consulting pathologist, his travel expenses, appropriate meeting facilities for the Task Group, and possible rental of the necessary microscopic equipment.

In view of timing, Dr. William M. Busey has been engaged to assist during the audit. Dr. Busey is a Board Certified Consulting Pathologist, and fully qualified to complete in-depth investigations of all histopathological phases of this inhalation study.

Any comments or suggestions regarding the conduct of this critical audit will be welcome.

Sincerely,



cc: Vinyl Chloride Technical Panel



INC A
Record of
Meeting

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—Manufacturing Chemists Association

Record of Meetings

TASK GROUP FOR AUDIT OF VINYL CHLORIDE CHRONIC INHALATION STUDY

Industrial BIO-TEST Laboratories, Inc.
Sheraton Inn

Decatur, Illinois
Decatur, Illinois

February 19-24, 1978

Dr. Bell presided and convened the meetings with the following in attendance at the respective meetings described below:

Industrial BIO-TEST Laboratories Meeting

MEMBERS PRESENT

Z. G. Bell, Chairman
T. J. Benya
G. K. Hatfield
R. K. Hinderer

C. D. Kary
T. R. Torkelson
J. T. Seawell

PPG Industries, Inc.
Ethyl Corporation
Diamond Shamrock Corporation
The BFGoodrich Company,
Chemical Division
Shell Oil Company
The Dow Chemical Company
MCA Staff

GUESTS PRESENT

W. M. Busey
P. Churukian
J. W. Goode
W. J. Koretke
D. C. Lindberg
J. H. Mennear
R. Rhudy
R. J. Roman -
D. J. Sullivan
I. Te Vault
M. Vlaovic

Experimental Pathology Laboratories,
Inc.
Industrial BIO-TEST Laboratories, Inc.
Industrial BIO-TEST Laboratories, Inc.
Industrial BIO-TEST Laboratories, Inc.
Industrial BIO-TEST Laboratories, Inc.
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Meetings of the Task Group for Audit of Vinyl Chloride (VC)
Chronic Inhalation Study at the Sheraton Inn

Dr. Zeb G. Bell, Chairman, and Mr. J. T. Seawell, Project Manager, began work on the development of basic and contingent audit design plans on Sunday, February 19, 1978. Dr. Bell, Dr. C. D. Kary, and Mr. Seawell conducted a general assessment review of all material available for the audit in the administrative offices and laboratories of Industrial BIO-TEST Laboratories, Inc. (IBT), Decatur, during the morning of February 20, 1978.

Dr. Bell opened the initial meeting of the entire Task Group at 1:35 p.m., February 20, 1978 at the Sheraton Inn with only Members Present (see Members Present roster listed above). Additional meetings of the Audit Task Group were held as follows:

February 20, 1978	7:10 p.m. - 10:30 p.m.
February 21, 1978	6:20 p.m. - 9:30 p.m.
February 22, 1978	9:45 p.m. - 12:15 a.m.

All other meetings were held at IBT with IBT management, project supervisors, specialists in necropsy and histopathology, and laboratory technicians present (see Guests Present listed above).

1.0 Background Information

Audit plans were designed with due recognition of and consideration given to the following factors which dictated conditions under which the audit was conducted:

- 1) Initial exposures of test animals began on September 10, 1973.
- 2) The test protocol involved three different animal species, i.e.:

Mice: CDI Swiss Charles River
Rats: COBS Charles River
Hamsters: COBS Golden Syrian

- 3) There were three different exposure levels for the mice and hamsters and four exposure groups of rats. The exposure levels were as follows:

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

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- 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

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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

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- . Random checks 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:

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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

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