



MANUFACTURING CHEMISTS ASSOCIATION

1825 CONNECTICUT AVENUE, N.W. WASHINGTON, D. C. 20009 (202) 483-6126

January 30, 1978

TO: Task Group on Audit of Vinyl Chloride Chronic Inhalation Study

Dr. Z. G. Bell, Chairman	PPG Industries, Inc.
Dr. T. Benya	Ethyl Corporation
Dr. G. K. Hatfield	Diamond Shamrock Corporation
Dr. R. K. Hinderer	The BFGoodrich Company, Chemical Division
Dr. C. D. Kary	Shell Oil Company
Dr. T. R. Torkelson	The Dow Chemical Company
Dr. W. M. Busey	Consulting Pathologist, Experimental Pathology Laboratories, Inc.
Mr. J. T. Seawell	MCA Staff

Gentlemen:

The audit will begin on Monday, February 20, 1978 at a luncheon meeting at the Sheraton Inn, Decatur. Heretofore, most connecting flights have arrived at Decatur about 11 a.m. and this has enabled a luncheon meeting to begin shortly after 12 m.

Acknowledging from the onset the intrinsic magnitude of the requirements of this audit, e.g., three different animal species, four exposure groups, 600 animals per exposure level, and an initial exposure date of September 10, 1973, strategic planning will be necessary in order to conduct incisive analyses of critical research areas. Therefore, the noon meeting will be the initial stage of an overall planning session which could extend well into the afternoon. In-depth planning will be concerned with the structuring of audit procedures, analyses of the most critical areas to be covered during the first phase of the audit, assignment of missions to the individual audit teams, and analyses of and planning for critical data sampling designed to reflect the most effective spot checks possible of the various exposure levels and animal test groups. Should the initial planning meetings on the afternoon of February 20th be completed prior to the closing time of Industrial BIO-TEST Laboratories (IBT)

BFG09199

21081046

then the Task Group will proceed immediately to IBT for its initial work.

It is expected that each day of the in-depth audit will be followed by early and late evening meetings concerned with analyses of the findings on a given day, plans for the investigation of special areas, and modifications of the overall audit procedure should this prove necessary because of interim findings.

Enclosed for your review in advance of your audit work are all documents pertinent to the protocol, its modification, and organization of test groups.

Hotel space has been reserved for each of you at the Sheraton Inn, Decatur, Illinois (Telephone 217/877-7255) for Monday night (February 20, 1978) through Thursday night (February 23, 1978). Each member of the Task Group is responsible for arranging for guaranteed late arrival (if this be necessary) and for cancellation of his space should this prove necessary.

In the event that your travel arrangements will not permit you to arrive in time for the luncheon meeting, on Monday, then inquire at the Sheraton reservation desk concerning the number of the meeting room. Should the Task Group already have departed for work at IBT, then telephone Mrs. Donna Mundy of IBT at 875-3700 concerning the location of the Group's various audit operations at IBT.

Should you have any questions concerning the audit or arrangements pertinent to its conduct, please contact the Project Manager at the earliest possible time.

Sincerely,



J. T. Seawell
Project Manager
Vinyl Chloride Research

JTS:ec
Enclosures
cc: Vinyl Chloride Technical Panel

21081047

BFG09200

1

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.
Industrial BIO-TEST Laboratories, Inc.
Industrial BIO-TEST Laboratories, Inc.
Industrial BIO-TEST Laboratories, Inc.
Industrial BIO-TEST Laboratories, Inc.
Industrial BIO-TEST Laboratories, Inc.
Industrial BIO-TEST Laboratories, Inc.

BFG09201

21081048

- 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?

21081051

- . 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?

BFG09205

21081052

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

21081053

- . 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.

21081054

BFG09207

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

21081054B

. 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

21081055

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

21087056

BFG09211

- . 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

21081057

BFG09212

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

21081058

BFG09213

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:

21081059

BFG09214

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

21081060

BFG09215

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

21081062

BFG09217

