STANDARD OPERATING PROCEDURE		
SOP NO.: GLP-DA-08		Page No.: 1 of 7
Title: **AUDITING PATHOLOGY DATA**		
Revision: 1	Replaces: Original	Effective: 06/07/99

1. PURPOSE

To provide guidance and standard procedure for conducting pathology data and specimen audits of acute, subchronic, and chronic toxicology and carcinogenicity studies submitted to the Environmental Protection Agency (EPA) under compliance of the GLP Standards (40 CFR Part 160 [FIFRA] and 40 CFR Part 792 [TSCA]).

2. SCOPE

This standard operating procedure (SOP) will be used when conducting pathology data and specimen audits to ensure that applicable study records are fully reflected in the final report submitted to the EPA. The scope of this SOP entails verification of the data integrity and reconstruction of the study. Adherence to this SOP will also ensure proper documentation and presentation of the audit observations.

3. OUTLINE OF PROCEDURES

- Pre-Audit Preparation
- Conduct of the Data Audit
- Facility Walk-Through

4. REFERENCES

4.1 EPA OPPTS Test Guidelines Series 870: Health Effects Test Guidelines, U.S. Environmental Protection Agency, Office of Prevention, Pesticides and Toxic Substances (OPPTS), Washington, D.C.

4.2 Standard Evaluation Procedures, Hazard Evaluation Division, OPP, Washington, DC

5. AUDIT PROCEDURES

5.1 PRE-AUDIT PREPARATION

The protocol and the final report submitted to EPA will be reviewed. The accuracy of the calculations for the incidence of neoplastic and non-neoplastic lesions will be checked and any deviations from the study protocol will be noted. The final report is supposed to be a true reflection of the original study records. This fact needs to be verified during the audit. A checklist (Attachment 1) may be prepared showing the data and specimens to be reviewed during the audit based upon the type, nature, duration, and complexity of the study. A number of animals, parameters, and data points will be selected for longitudinal evaluation and/or verification of the raw data. Any questions arising from the review of the final report will be pursued during the audit. A mechanism will be set up to keep track of the materials to be collected for supporting the audit observations.

5.2 CONDUCT OF THE DATA AUDIT

5.2.1 General Procedure

The documentation and records pertaining to the study will be reviewed.

The laboratory procedures will be reviewed to assess adherence to the GLP standards as necessary. Any audit observations will be discussed with the Lead Inspector before discussing with the facility staff member(s) responsible for the particular items under scrutiny. The facility staff will be provided adequate time to respond, and the name and title of the specific individual responding as well as the response given for each question raised will be recorded.

To support the audit observations, all necessary evidence will be collected, documented, and collated according to the guidelines in SOP No. GLP-S-02.

5.2.2 Data and Records Audit

The auditor will check the study records for their completeness, accuracy, and consistency in the raw and calculated experimental data, as well as labeling, preservation and storage of specimens. Adherence to the study performance requirements specified in the protocol and compliance with the applicable SOPs and GLPs will be checked. Watch for consistency in recording. Look for altered data, omitted data, or manufactured data. Collect all evidences to support your observations in the audit report. For

pathological evaluation of toxicology and carcinogenicity studies, it is essential to record and keep track of the sequence of events in order to derive a meaningful conclusion, for example:

- The correlation of the necropsy observations with the clinical observations as well as the microscopic diagnoses is essential for assessment of the data trail and accountability of the tissues, especially the target organs,

- Wet tissue evaluation during the audit will be conducted under an exhaust hood to prevent formalin inhalation In addition, the auditor will wear the proper safety attire,

- Particular attention will be paid to the identifiers, untrimmed potential lesions, preservation of the tissues, and the presence of residual tissues. The untrimmed potential lesions will be described and recorded consistently as audit observations. If it is necessary to examine the hidden part of the lesion, the study pathologist or other appropriate pathology employee will be requested to open it,

- Similarly, block and slide matching discrepancies will be recorded. It will be a standing policy that the auditor will never have more than one container of wet tissues open at any given time to avoid any possible mix-up of tissues. The auditor will describe the untrimmed potential lesion(s), if any, but will not cut or open the tissues,

- The slides will be grossly examined for inventory, cleanliness, labeling, properly sectioning of the tissues, artifacts, preservation, and matching with the properly labeled and preserved tissue blocks,

- Histologically, the slides will be examined for quality of the staining; presence of lesions observed during postmortem; adequacy of the tissue components and their thickness; presence of extraneous material, debris, or air bubbles; and verification of the study pathologist's diagnoses and terminology used for the lesions.

The following general items will be audited:

- Study protocol including modifications and amendments - The protocol will be checked to ensure that it contains all essential elements applicable to a particular study (e.g., Dosed feed, gavage, skin pain, necropsy and

histology techniques, etc.). Failure to have a protocol is citable under 40 CFR 160.120,

- Special attention should be paid to incident reports, correspondence, phone conversations, and work performed by subcontractors or consultants, if any,

- Equipment operation - Pertinent SOPs and the calibration and maintenance records for the equipment: weighing balance used for organ weights, euthanasia apparatus, microtome, tissue processing unit maintenance of water bath and tissue embedding station temperatures, etc., used to conduct the study will be reviewed,

- Data recording and analysis - The original raw data will be reviewed for test start and completion dates, legibility, entries in indelible ink, corrections, omissions, and completion of records including evaluation of recut or rewet cut tissues. Ten percent of any statistical and/or mathematical calculations, or more as time allows or if the error rate is high, will be verified. All items merit particular attention when preprinted work sheets are used by the technical staff,

- Standard operating procedures - All study specific SOPs (e.g., infusion of lungs, flash freezing in liquid nitrogen, serial sectioning, organ weights clinical pathology evaluations, etc.) will be evaluated for adequate content, review, and distribution as well as for their compliance during the conduct of the studies to be audited. It will be verified if SOPs exist for each function or parameter and are reviewed annually for modification. QA approvals initiation dates, and dates of revision, particularly for SOPs that were introduced during the conduct of the studies being audited, will be checked. In these cases, the applicable archived SOPs covering the entire duration of the studies will be requested and the records evaluated. Failure to maintain SOPs is citable under 40 CFR 160.81 and failure to follow laboratory SOPs without documentation in the raw data is citable under 40 CFR 160.81(a),

- Final report - The final report will be compared with the study records to validate the information presented (including calculations) and to confirm the study initiation and completion dates, study methods, results and conclusions, and any protocol deviations and/or amendments. It will be verified that any unusual circumstances or results along with their impact on the

study outcome have been adequately explained in the final report including the implementation of corrective measures, if any. The signed and dated QA statement, GLP compliance statement, and the study director's dated signature will be checked and their failure is citable under FIFRA codes §160.35, §160.12, and §160.185 respectively.

Generally the auditor should pay particular attention to the following:

a. The volume of tissue taken from each organ designated for histopathologic evaluation must be the same in all study groups (Increased volumes of tissues in certain animals groups may produce false positives/negatives),

b. Gaps in the data trail or missing a study record or document,

c. Erasure marks, white-out or crossed-out data masking the original entries with or without data,

d. Any change in the writing style or in the ink color of the data collected during the same day may suggest delayed entry or fraudulent data,

e. Any break in the numbering system of the pages or a sign of possible replacement of the original data pages,.

5.3 FACILITY WALK-THROUGH

At the time of necropsy, the necropsy technicians need to have the clinical observations available for each animal. Similarly, the histology staff and study pathologist need to have the necropsy observations available.

The facility inspection should include a review of the following items:

- Space, equipment, processing, evaluation, and storage of tissues. To ensure adequacy for proper conduct of the study, the applicable equipment will be inspected for availability of specimen jars, necropsy tools, preservatives and normal saline.

- The facilities will be observed for appropriate tissue collection, preservation, evaluation, labelling, accountability, storage, and disposal space. The applicable calibration, maintenance, and inspection records will be reviewed for equipnent such as tissue processors, hoods,

freezers, water baths, refrigerators, scales, microscopes, water purifiers (stills, de-ionizers), stainers, etc. It necropsies are scheduled during the audit period, it is advisable to observe the entire necropsy procedure. Similarly, tissue sectioning should be evaluated in the histology lab including functioning of the tissue processor and microtome.

- The collection and processing of the protocol specified tissues will be verified for the on-going study. Also, the expiration dates on various reagents will be checked.

- The archives will be inspected for proper preservation and archiving the wet tissues, blocks, and slides.

/s/_____ 06/01/99
Reviewed by: Robert Cypher Date
Compliance Officer/Toxicologist

/s/_____ 06/01/99
Approved by: Francisca E. Liem Date
Chief, Laboratory Data Integrity Branch

/s/_____ 06/07/99
Approved by: Rick Colbert Date
Director, Agriculture and Ecosystems Division
U.S. Environmental Protection Agency
Office of Enforcement and Compliance Assurance
Office of Compliance

Attachment 1

List of records to be reviewed during the audit of Pathology study records.

ITEM NUMBER	RECORDS	CHECKED		COMMENTS
		YES	NO	
1	Study protocol, amendments and deviations			
2	The applicable SOPs			
3	Final and interim reports			
4	Animal identification			
5	Target organ list			
6	Clinical observation records			
7	Morbidity and mortality records			
8	Incident reports			
9	Animal termination and unscheduled death records			
10	Necropsy records			
11	Residual wet tissue inventory records			
12	Tissue block and slide inventory records			
13	Microscopic pathology records			
14	Statistical analysis			
15	Correspondence file			