STANDARD OPERATING PROCEDURE		
SOP NO.: GLP-DA-09		Page No.: 1 of 7
Title: **AUDITING GENERAL TOXICOLOGY STUDIES**		
Revision:1	Replaces: Original	Effective: 06/07/99

1. PURPOSE

To provide guidance and a standard procedure for conducting data audits of acute, subchronic, and chronic general toxicology studies intended to be submitted to the Environmental Protection Agency (EPA) to assure compliance with 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 on-site general toxicology data audits to ensure that applicable study records are fully reflected in the final report. 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, 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

5.1.1 The study final report submitted to EPA will be reviewed by the auditor to become familiar with the study design and scope of experimentation including:

- Name of the test substance,
- Species, strain, age, and sex of the test system,
- Route of administration of the test substance,
- Dose levels and number of animals in each group,
- Study initiation and completion dates.

5.1.2 A checklist of the study records to be reviewed during an audit is shown as Attachment 1. Appropriate attention will be paid to any unusual fluctuations (e.g., environmental factors), irregularities, or outliers in the data (e.g., body weight), while watching for the trends.

5.1.3 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 which merit special attention 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 studies will be reviewed.

The laboratory procedures will be reviewed to assess adherence to the GLP standards, as necessary. Any audit observation will be discussed with the Lead Inspector before discussing it with the study director or with the facility staff member(s) responsible for the particular items under scrutiny. The facility staff will be provided adequate time to respond to the questions. 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 guidelines in SOP No. GLP-S-02.

5.2.2 Data and Records Audit

The auditors will check the study records for their completeness, accuracy, and consistency in the raw and calculated data. Inconsistent recording of results can lead to misinterpretation of study outcome or conclusions, therefore pay particular attention to such observations. Adherence to the study performance requirements specified in the protocol and compliance with the applicable SOPs and GLPs will also be checked. Special attention will be paid to correspondence and work preformed by subcontractors and consultants, if any. Look for altered data, omitted data, or manufactured data. Collect all evidences to

support your observations in the audit report. The following general items will be routinely 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 paint, dosed water, etc.). Failure to have a protocol is cited under 40 CFR 160.120.

- The study records will be reviewed to determine the extent of compliance with the protocol and the applicable valid and approved SOPs. Any deviations from study design; unusual fluctuations of body weights, environmental factors, etc.; accidents like equipment malfunction, power failure, etc.: outliers due to calculation errors or excessive mortality in a particular dose group due to an accident; ambiguous statements lacking adequate explanation or factual information; and misinterpretations of factual information need to be highlighted, and their impact on the outcome of the study will be assessed and fully documented.

- The following records and SOPs will be reviewed:

  P Animal receipt (species, strain, sex, number, and receiving date) for accountability of test system and chain of custody,
  P Health check monitoring during the quarantine period and release date of healthy animals for study (Failure to isolate all newly received animals from outside sources until their health status has been evaluated is cited under 40 CFR 160.90(b)),
  P Animal identification, randomization, and group assignment,
  P Animal room environmental conditions (air changes, temperature, relative humidity, and photo period) to check for persistent out-of range values,
  P Feed and water consumption,
  P Health and safety measures and prevention of transmissible diseases,
  P Body weight records to note treatment related or unrelated deaths,
  P Clinical observations, moribundity, and mortality records, to identify any cluster deaths attributable to a particular cause,
  P Clinical chemistry, hematology, and urinalysis records to determine pharmacological or metabolic effects,
  P Serology records for assessment of health status and infections,
  P Target organ list to identify the vulnerable tissues to the treatment with test substance through a specified mode of exposure,

P Incident reports detailing unexpected happenings,
P Animal termination and interim sacrifice records,
P Necropsy records to correlate with clinical findings and histopathology,
P Protocol and SOP deviations and corrective action records (Deviation from the protocol without documentation is cited under 40 CFR 160.120(b)), and
P Correspondence file (including telephone correspondence) to reconstruct the data - gathering.

- Data recording and analysis - The raw data for test start and completion dates, legibility, entries in indelible ink, corrections, omissions, and completion of record book pages will be reviewed. Failure to record raw data or falsification of raw data is cited under 40 CFR 160.130. Failure to retain raw data is cited under FIFRA codes §160.190, and §160.195.
- Standard operating procedures - All SOPs applicable to the study will be reviewed. It will be verified that SOPs exist for each function or parameter and are reviewed regularly. Effective 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 for the entire duration of the study will be requested and evaluated. Failure to maintain SOPs is cited under 40 CFR 160.81 and failure to follow laboratory SOPs without documentation in the raw data is cited 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. The signed and dated QA statement, GLP compliance statement, and the study director's dated signature will be checked and their failure is cited under 40 CFR 160.35, 160.12, and 160.185, respectively.

Generally, the auditor should pay particular attention to the following:

a. Removing the animals from the study without justification,
b. Replacing missing, dead, or accidentally killed animals during the course of the study,
c. Changing the system of randomizing of the animals,
d. Fluctuations or outliers in the body weight data,
e. Continuing the experiment in spite of a noticed mix-up between the test systems or test substance applications,
f. Gaps in the data trail or missing a study document or data

entries for a significant interval,

g. Using off-the-range preparation to dose the test systems without proper documentation of the deviation and action taken.
h. Erasure marks, white-out or crossed-out data with an intention to mask those with or without superimposed data.
i. Any change in the writing style or in the ink color of the data recorded during the same day by the same individual.
j. Any break in the numbering system of the pages or a sign of possible replacement for the original data page(s).

If any of the above listed items has been observed during the audit, thorough investigation should be done with the consent of the Lead Inspector by interviewing the pertinent study personnel to identify the significance of the audit observation.

5.3 FACILITY WALK-THROUGH

Areas for special attention should include:

- The appropriate separation of animal species for different studies, especially supplied by different vendors,
- The maintenance of the proper environmental conditions (air changes, temperature, relative humidity, and photo period),
- The chemical repository for proper labeling, storage, handling of the test substance(s), and adequacy of the receiving and dispensing procedures,
- The dose preparation laboratory and the equipment used for the dose preparations, including the maintenance and use logs of the equipment (e.g., scales, blenders, etc.),
- The body weight recording system, including the calibration and maintenance logs of the scales,
- The clinical laboratory, including the receiving and storage logs of the samples as well as the maintenance and use logs of the equipment (e.g., freezers, pH-meters, analyzers, spectrophotometer, etc.),
- The storage areas of the feed and bedding to ensure the use of proper storage procedures and vermin control measures; the receiving, milling, and use logs of the feed.

/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

Records to be reviewed during the audit of general toxicology study.

ITEM #	RECORDS	CHECKED		COMMENTS
		YES	NO	
1	Study protocol, amendments and deviations			
2	The applicable SOPs			
3	Animal receipt (species, strain, sex, number, and receiving site)			
4	Animal husbandry and care			
5	Animal health check and quarantine			
6	Animal identification			
7	Animal randomization and group assignment			
8	Animal room environmental conditions (air change, temperature, relative humidity and photo-period			
9	Feed consumption			
10	Water consumption			
11	Calibration and use logs of the scales			
12	Body weight records			
13	Clinical observations			
14	Mortality			
15	Clinical chemistry, hematology and urinalysis			
16	Serology records			
17	Target organ list			
18	Incident report			
19	Interim sacrifice and animal termination unscheduled death			
20	Necropsy records			
21	Correspondence file			