STANDARD OPERATING PROCEDURE		
SOP NO.: GLP-DA-11		Page No.: 1 of 7
Title: **AUDITING REPRODUCTIVE/DEVELOPMENTAL TOXICOLOGY STUDIES**		
Revision: 1	Replaces: Original	Effective: 06/09/99

1. PURPOSE

To provide guidance and a standard procedure for conducting data audits of reproductive/developmental toxicology studies to be submitted to the Environmental Protection Agency (EPA), under 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 reproductive/developmental 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.

5. AUDIT PROCEDURES

5.1 PRE-AUDIT PREPARATION

The study final report is supposed to be a true reflection of the original study records. This fact needs to be verified during the audit. A copy of the final report submitted to the EPA will be reviewed by the auditor to become familiar with the study design and scope of experimentation. The accuracy of the calculations will be checked and any deviations from the study protocol, or other contractual requirements will be noted.

A sample of items/documents to be reviewed is given in Attachment 1. 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 their adherence to the GLP standards as necessary. 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 also be checked. Special attention will be paid to

incident reports, correspondence, and work performed by subcontractors and consultants, if any. Watch for the consistency in record keeping practices. Look for altered data, omitted data, or manufactured data. During the course of the audit if any kind of suspicion about the integrity of data arises, gather all relevant supportive evidences to justify the validity of your audit observations. For reproductive/developmental toxicology studies, it is essential to record and keep track of the sequence of events to derive a meaningful conclusion. The following items are significant components of these studies:

S correspondence and phone communication relating to the conduct of the study and the protocol,

S the dates of dosing, mating, and delivery,

S the gestation index,

S the number of offsprings per litter,

S the viability and condition of the offspring and mother at various intervals,

S the lactation index,

S the physical, visceral, and skeletal abnormalities observed in the pups delivered naturally or through Cesarian sectioning,

S the fertility index of the F_0 and F_1 generations, and

S the weight gain or loss patterns.

Subsequent verification of this information requires adequate identification, preservation, and dates of collection of the data and specimens. The following general items will be audited:

! Study protocol including modifications and amendments. The protocol will be checked to ensure that it contains all the essential information contained in 40 CFR 160.120.

! Test substance - The source, identification, receipt, storage, distribution, tracking, preparation in accordance with the study requirements, disposal of the surplus test substance, and the related correspondence between the sponsor and facility staff will be reviewed.

! Test system - The information pertaining to animal supplier, shipping receipt, quarantine, release to the study, identification, body weight, randomization to various groups, housing, animal husbandry and care procedures, dose preparations, dosage administration, clinical observations, sample collection, serology, moribundity, mortality, and disposition will be reviewed.

! The adequacy of the procedures for health and safety, feeding, watering, maintaining the environmental conditions, sanitation, pest and biohazard control, and the quality control steps, where applicable, will be determined.

! Data recording and analysis - The original raw data for test start and completion dates, legibility, entries in indelible ink, corrections, omissions, and completion of record book pages will be reviewed. The presence of adequate positive and/or negative control data as well as vehicle control data in accordance with study requirements will be checked. Statistical and/or mathematical calculations will be verified. All items merit particular attention when pre-printed work sheets are used by the technical staff.

! Standard operating procedures - All studies specific SOPs (e.g., animal mating, determination of the offspring survival index etc.) will be evaluated for adequate content, review, and distribution as well as to their adherence during the conduct of the studies to be audited. SOPs will be verified for each procedure or parameter. Documentation of regular review and appropriate modifications and QA approval will be examined. Study initiation dates, and dates of SOP revisions for the audited studies will be checked and compared with implementation dates contained in the raw data. Failure to maintain SOPs is citeable under 40 CFR 160.81 and failure to follow laboratory SOPs without documentation in the raw data is citeable under 40 CFR 160.81(a).

! Final report - The final report will be compared against 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 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 citeable under 40 CFR 160.35, 160.12, and 160.185 respectively.

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

a. Removing the animals from the study without justification,

b. Replacing missing or accidentally killed animals,

c. Changing the randomization of the animals without legitimate reason or explanation,

d. Continuing the experiment in spite of a noticed mix-up between the test systems or test chemical applications,

e. Excessive mortality without proper documentation leaving insufficient number of animals to draw a valid conclusion of study results,

f. Gap in the data trail or missing a study record or document,

g. Using off-the-range preparation to dose the test systems without proper documentation of the deviation or action taken,

h. Erasure marks, white-out or crossed out data masking the original entries 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 may suggest delayed entry or fraudulent data,

j. Any break in the numbering system of the pages or a sign of possible replacement of the original data page(s).

Study personnel should be interviewed to reconstruct the conduct of the study and to determine the significance of the above observation(s).

5.3 FACILITY WALK-THROUGH

The walk-through should be used as a tool for reconstruction of the studies being audited. Areas for special attention should include:

! Space, equipment, and test material repositories To ensure adequacy for proper conduct of the reproduction/developmental toxicology study, the applicable equipment and facilities will be inspected for test substance/reagent receipt, labeling, weighing, preparation, accountability, storage, and disposal; proper data collection: and health and safety provisions. Applicable calibration, maintenance, and inspection records will be reviewed for equipment such as laminar flow and chemical hoods, ovens, freezers, water baths, refrigerators, autoclaves, microscopes, water purifiers (stills, de-ionizers), pH-meters, ultracentrifuges, and balances.

/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/ _____ 06/09/99
Approved by: Rick Colbert Date
Director, Agriculture and Ecosystem 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 the reproductive/developmental toxicology study records:

ITEM #	RECORDS	CHECKED		COMMENTS
		YES	NO	
1	Study protocol, amendments, and deviations			
2	The applicable SOPs			
3	Animal receipt (species, strain, sex, number and date receipt)			
4	Housing of the animals			
5	Animal room sanitation			
6	Cage and rack sanitation			
7	Cage rotation			
8	Animal identification			
9	Animal room environmental conditions (air changes, temperature, relative humidity, and photo-period)			
10	Feed receipts and storage conditions			
11	Vermin control			
12	Test chemical information records			
13	Dose calculation and preparation records			
14	Body weight records			
15	Dosing records			
16	Mating and delivery records			
17	Gestation index records			
18	Litter records			
19	Clinical observation records of the mothers and offsprings			
20	Lactation index records			
21	Fertility records			
22	Morbidity and mortality records			
23	Serology records			
24	Correspondence Files			