STANDARD OPERATING PROCEDURE		
SOP NO.: GLP-DA-10		Page No.: 1 of 8
Title: **AUDITING GENETIC TOXICOLOGY STUDIES**		
Revision: 1	Replaces: Original	Effective: 06/07/99

1. PURPOSE

To provide guidance and a standard procedure for conducting data audits of genetic toxicology studies conducted 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 genetic toxicology data audits (and/or assisting the Team Inspectors in conducting GLP inspections) 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 final study report is supposed to be a true reflection of the original study records. This fact needs to be verified during the audit. As a preliminary step before the audit, a copy of the final report provided by EPA will be reviewed by the auditor for general content, integrity of the experimental data, consistency of the information presented, and the derived conclusions. A checklist (Attachment 1) can be used to assist the auditor during the conduct of the data audit.

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. Any audit observations 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, 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 Audit Types

Genetic toxicology studies can be divided into two broad categories as follows (most common examples given):

- In Vitro

Host Mediated Assay
Mouse Lymphoma Mutagenesis Assay CHO/HGPRT Mutagenesis Assay
Salmonella typhimurium Mutagenesis Assay (Ames Test)
Chromosome Aberrations Assay
Sister Chromatic Exchange Assay
Unscheduled DNA Synthesis

Cell Transformation Assay
Reverse Mutation Assay

! In Vivo
Rodent Bone Marrow Cytogenistic
Heritable Translocation Assay
Rodent Micronucleus Assay
Chromosome Aberrations Assay
Sister Chromatic Exchange Assay
Rodent Dominant Lethal Assay
Somatic Mutation Assay (Spot Test)

5.2.3 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 as per study requirements. Record keeping, compliance with applicable SOPs and GLPs, the experimental data trail, and mathematical calculations will be checked, and any inconsistencies or other irregularities will be noted. Special attention will be paid to correspondence, and work performed by subcontractors and consultants, if any. Look for evidence of altered data, omitted data or manufactured data. During the course of an audit if any kind of suspicion about the integrity of data arises, inform the Team Inspector about it and devote as much time as possible to gather all relevant information. Don't openly discuss this matter with the facility staff unless the Lead Inspector suggests so. Collect all evidence to support your observation in the audit report. The following specific items will be routinely audited:

- Study protocol, amendments and deviations (if any)- The protocol will be checked to ensure that it contains all essential elements applicable to a particular study (e.g., Rodent Micronucleus Assay, Chromosome Aberrations Assay). Failure to have a protocol is citable under 40 CFR 160.120,

- Test substance receipt, storage, distribution, and tracking,

- Test system (in vitro) supplier, receipt, and subculturing,

- Test system (in vivo) supplier, receipt, quarantine, husbandry, environmental controls, identification, clinical observations, and treatment, feed and water analysis as per study requirements,

- Culture media preparation, lot/batch number documentation, storage conditions, and expiration date,

- Equipment operation - All pertinent equipment records (i.e. Cell Counters, Colony Counters, Image Analyzers, Incubators, Refrigerators, Freezers, Scales, pH Meters, Pipetting aids) used during the study will be reviewed for adherence to the temperature/calibration requirements in the SOP and study protocol,

- Animal necropsy (in vivo) and/or cell harvest (in vitro),

- Microscope slide or petri dish labeling, coding, preparation, and staining,

- Data collection - microscopic slide scoring or automatic/manual colony counting,

- Microscope slide or petri dish archiving procedures (if applicable),

- Complete positive, solvent, and/or negative control data,

- Reagent sources, lot numbers, storage conditions, and expiration dates,

- Mathematical and statistical analysis check will be performed on all computer-generated calculations,

- Correspondence - The correspondence(written and telephone) between the testing facility and the sponsor will be reviewed to assess the data integrity and documentation procedures. Also, the records generated by subcontractors or consultants (if any) will be reviewed.

Particular attention will be paid to any unusual fluctuations of data values, and irregularities or outliers due to calculation

errors in the data, while watching for- the trends. Pertinent study personnel will be interviewed, laboratory procedures reviewed, and adherence to the GLP standards assessed, as necessary. The facility personnel should be given adequate time to respond to the questions. The response given to each observation by the laboratory representative(s) will be recorded, as well as the representative's name and title.

All audit observations will be adequately documented. A photocopy of all the relevant study records will be requested for use as evidence in the audit report. The following general items will also be reviewed during the audit:

- 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. The presence of adequate positive and/or negative control data as well as vehicle control data in accordance with study requirements will be checked. All items merit particular attention when pre-printed work sheets are used by the technical staff. Failure to record raw data or falsification of raw data is citable under FIFRA code §160.130. Failure to retain raw data is citable under FIFRA codes §160.190, and §160.195.

- Standard operating procedures - All the SOPs applicable to the study will be reviewed. It will be verified that SOPs exist for each function or parameter and are reviewed regularly for modification. 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 citable under 40 CFR 160.81 and failure to follow 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 40 CFR 160.35, 160.12, and 160.185 respectively.

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

a. Correct mathematics in the dose preparation calculations,
b. Changes in the study methods not addressed in study protocol,
c. Proper documentation of all test substance usage, including multiple repeat experiments,
d. Proper adherence to the study protocol in reference to cell exposure and incubation times,
e. Correct temperature ranges for the incubators, refrigerators, or freezers used in the study,
f. Qualifications/training of the technical staff performing critical data gathering phases (e.g., slide scoring or colony counting),
g. Insufficient documentation of all experimental phases,
h. Hard copy data trails if real time computer data gatherings performed,
i. Correct performance and interpretation of the statistical analysis,
j. Criteria for a valid test (i.e., positive and solvent controls within the historical ranges stated in the protocol/SOPs),
k. Calibration of any automated data gathering equipment (e.g.. cell counters, colony counters, image analyzers),
l. Erasure marks, white-out or crossed-out data masking the original entries with or without superimposed data,
m. Any change in the writing style or in the ink color of the data recorded during the same day by the same individual probably is suggestive of delayed entry or fraudulent data,
n. Any break in the numbering system of the pages or a signed of possible replacement for the original page(s).

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

5.3 FACILITY WALK-THROUGH

The following laboratory equipment and records will be inspected to assess the proper generation of data:

cell counters	colony counters	image analyzers
incubators	refrigerators	freezers
centrifuges	pH meters	microscopes
water baths	biological hoods	balances
autoclaves	computers	thermometers
	pipettors	

All media preparation and sterilization areas, cell culture laboratories, and data collection stations will be inspected.

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Reviewed by: Robert Cypher Date
Compliance Officer/Toxicologist

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Approved by: Francisca E. Liem Date
Chief, Laboratory Data Integrity Branch

_____ _____

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

Checklist of records to be reviewed during the data audit of Genetic toxicology studies.

ITEM #	RECORDS	CHECKED		COMMENT
		YES	NO	
1	Test Article Receipt & Usage Log			
2	Study Protocol, amendments and deviations			
3	Media/Reagent preparation log			
4	Equipment calibration			
5	Cell culturing log book (in vitro)			
6	Microscopic slide scoring/colony counting			
7	Control data			
8	Equipment temperature/calibration records			
9	Statistical analysis			
10	SOPs relevant to study			
11	The correspondence file			
12	The final report			
13	Test System Husbandry (in vivo)			
14	Training Records (Study and QA Staff)			
15	QA Records (Protocols, Audit Dates, etc.			
16	Master Schedule			