Chapter 12. Report Formats and Guidance

Specifications for the Conduct of Toxicity Studies by the Division of Translational Toxicology at the National Institute of Environmental Health Sciences

From: Roberts GK, Stout MD, editors. Specifications for the Conduct of Toxicity Studies by the Division of Translational Toxicology at the National Institute of Environmental Health Sciences. Research Triangle Park, NC: National Institute of Environmental Health Sciences; 2023. https://doi.org/10.22427/NIEHS-00

12. Report Formats and Guidance

G.K. Roberts[1], M.D. Stout[1] (Editors)

[1]Division of Translational Toxicology, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, USA

Last Updated: March 2023

12.1. Lab Reports

This section describes the basic requirements for study reports submitted to NIEHS. The overall structure of the reports is flexible and can be determined by the laboratory. In addition to the requirements outlined below, if the study is conducted in compliance with Good Laboratory Practices, additional elements shall be included per 21 CFR Part 58.[1]

12.1.1. Front Matter

Lab reports shall include the following components.

Title Page

- Study title
- Lab study number
- NIEHS study number
- Chemical CASRN
- Date
- Contract number

Summary Table

Information that the study director considers to be toxicologically relevant, including data that are not different from controls but critical to interpret the study (e.g., survival, body weight), shall be included in the summary table. This information may or may not be statistically significant. This table shall not include information that is statistically significant unless it is also deemed to be biologically relevant.

Personnel

- Study director
- Contract principal investigator
- Applicable discipline leaders (e.g., pathology, clinical pathology, DART, quality assurance)
- Data coordinators
- Technical discipline and facility manager(s)

[1]https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-58

12.1.2. Introduction

A brief purpose statement for the study shall be provided. A literature review of the test material uses and potential exposure is not needed.

12.1.3. Materials and Methods

Information listed in this section shall be provided in the body of the report or in contributing scientist reports (CSRs) appended to the study report. In some cases, it will be acceptable to include information in SOPs and facility records, which must be discussed and agreed upon with the contracting officer's representative (COR). Throughout this section, applicable SOPs shall be cited. Where feasible, information shall be tabulated in a summary table; however, if necessary, text can be used to relay this information, but it shall not duplicate what is shown in a summary table.

Chemistry

The below information shall be reported. If information is duplicative of information provided in the prestart chemistry report, that report can be cited instead were appropriate.

Test Article

- Grade or other test article-specific information from the supplier
- Supplier/manufacturer name and address
- Storage conditions for bulk test article
- Lots used, including amount received, date received, dates used for each lot, and color picture of the bulk material compared with a color spectrum
- Test article identity and purity, as follows:
    - Information regarding initial bulk analysis, including name of laboratory performing the analysis, methods used, title of report from lab, and results, with lot number(s) clearly identified
    - Information regarding bulk test article reanalysis, with the applicable SOP used for reanalysis cited
    - A table of results of the initial and subsequent bulk reanalyses for each lot, including dates and analysis results (frozen reference, bulk sample, and calculation of relative purity)
    - A photograph compared with a color spectrum (see Section 12.3 and Figure 12-1 as an example)

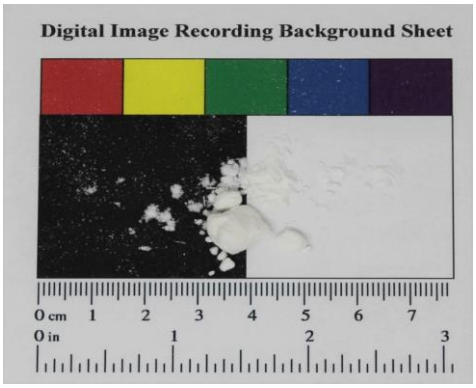

Figure 12-1. Example Color Spectrum Chart

Vehicle

- Vehicle or control article used (e.g., feed, water, corn oil, air)
- Grade/purity/test article-specific information from the supplier
- Name and address of supplier and manufacturer/producer
- Table showing dates and results of purity analyses, citing the applicable SOP used for purity analysis

Dose Formulation Procedure

- Mixing procedure, such as equipment and type of container used and duration of mixing, with the applicable SOP used for dose formulation cited
- Stability and homogeneity information on dose formulation (obtained from analytical lab or performed at testing lab)
- Storage conditions for dose formulations as appropriate for route of administration (e.g., temperature, humidity, protection from light, maximum length of time stored)

Dose Formulation Analysis

- Analysis procedure, with the applicable SOP used for analysis cited
- Formulation and analysis schedule for dose preparations and animal room samples
- Tabulated information showing dates that dose formulations were prepared, analyzed, and used; results of analyses (mean ± standard deviation) that include analysis before dosing (% high/low of theoretical), analysis after dosing for unused/stored formulations, and analysis of animal room samples (% high/low of theoretical and % of original formulation); if formulations were out of specification, whether these were remixed or not shall be indicated

Animals and Animal Husbandry

Animals

- Species and strain/stock
- Source of animals (supplier name and address)
- Examinations conducted to assure health of test animals

- Quarantine period
- Randomization procedure (for test group, rack, and cage)
- Animal identification procedure
- Age of animals upon receipt and age and weight of animals when tested
- Serologic analysis performed including sampling dates and results (see format for table of serology results in Section 12.1.

Animal Husbandry

- Description of cages, filters, racks, bedding, feeders, and water bottles or automatic waterers used, including the manufacturer's name and address for each item
- Description of cleaning method for each item listed above and, where applicable, the type of washing equipment and cleaning agent and the manufacturer's name and address for each item
- Schedules for changing cages, chambers, filters, racks, bedding, feeders, water bottles, etc.
- Description of barrier maintenance and disease control procedures
- Description of room sanitization and pest control procedures
- Temperature and humidity ranges, number of room air changes per hour, and type of air filtration used and name of filters (with manufacturer's name and address); light cycle and type of lights used; temperature/humidity excursions, including dates, ranges, and number of hours involved
- Description of study room(s)
- Number of animals per cage, relationship of control and treated group animals (including rack position), rotation of cages on racks, and rotation of racks within the room
- Feed used and storage conditions
- Source of water supply (city or well) and any water treatment used; discuss water analyses performed

Study Design

Design

- Route of administration and frequency of administration
- Number of animals per treatment group, number of groups, and dose levels/exposure concentrations
- Duration of exposure, including specific dates for first and last dose/exposure; details of perinatal dosing (gestation and lactation) for dams and pups for studies with perinatal exposure
- Specific details of special studies performed (e.g., clinical laboratory studies, immunotoxicity studies, neurobehavioral studies, internal dose assessment studies),

including details of tissues/samples taken, sample collection and handling, analysis methods or procedures for conducting special studies, and dates performed

- Identification by title/date all reports submitted under separate cover that are related to these studies (e.g., Prestart Chemistry Reports, Prestart Toxicokinetic Study Reports, Single Administration Toxicokinetic Study Reports, Proficiency Reports for Special Studies)

In-life Observations and Pathological Examinations

- Description and frequency of in-life observations performed
- Specific dates for interim sacrifices and terminal necropsies
- Handling of moribund animals
- Method of euthanasia
- List of tissues collected at necropsy and processed for histopathological evaluation
- Histological processes, preservation, embedding, sectioning, staining, and evaluation scheme (e.g., in the case a read-down is performed in which dose groups are only evaluated to a no-effect level)
- Statistical analyses, if conducted, with short paragraph of methods used

12.1.4. Results

Data for all endpoints described in the study protocol and collected during the study shall be presented in the lab report. In addition to Provantis (or subsequent sponsored data capture system) tables, other tables, figures, and images shall be included as required to provide context and increase the reader's ability to understand and interpret the study findings (see further details below). Findings that are considered related to the test article shall be presented in the main body of the report. Succinct in-text tables shall be created to present toxicity findings, if appropriate. Data for endpoints that were unchanged or not considered related to the test article shall be included in appendices.

For Provantis data, summary tables for all endpoints included in the lab protocol shall be provided in the appendices of the study report or as part of appended CSRs. For non-Provantis data, lab-generated summary tables shall be included in the appendices of the study report or as part of the appended CSRs. In addition, for non-Provantis data, individual animal data that have undergone quality control (QC) review shall be included in the lab report appendices and provided electronically in a machine-readable format. A data transfer and archival process and location shall be discussed with the COR before study initiation for non-Provantis data.

12.1.5. Discussion

A brief summary of salient findings, including biological significance of the data shall be provided. The summary should provide perspective that arises from having conducted the study and include a description of any problems encountered that would affect interpretation of data.

12.1.6. Appendices

In addition to methodology and data included in appendices, appendices shall also include the information below.

- Feed information, including sample feed tag, irradiation certificate, and table with lots used in the study, milling date, and date of initial use
- Temperature and humidity recordings for study room(s) (presented by study week) that include minimum and maximum readings for temperature and humidity, the number of readings within specification, and total readings for temperature and humidity
- Copy of work assignment and modifications
- Copy of laboratory protocol, deviations, and summary of amendments
- Lab reports generated by a subcontractor
- Individual animal data that cannot be collected in Provantis (also to be provided electronically)
- SOPs for nonstandard aspects of the studies, if requested by the COR

12.2. Prestart Chemistry Report

Before starting noninhalation toxicity studies, a prestart report is to be submitted that includes the following items (where applicable for individual test articles).

- Information on the source of the bulk chemical as well as manufacturer stability, storage requirements, and a color picture of the bulk material compared with a color spectrum
- Identity and purity data along with representative chromatograms and spectra
- Stability of the bulk chemical using methods developed by NIEHS or the testing laboratory as well as copies of the SOPs for the purity analysis methods
- Data on preparation, handling, stability (if performed by the testing laboratory), homogeneity, and dose formulation analysis as well as SOPs for formulation preparation and analysis methods
- Method performance evaluation procedures and validation data for dose formulation analysis, including representative chromatograms or spectra (see Chapter 5 [Chemistry], Section 5.3.2. Formulation Analysis)
- Health and safety procedures

Animals shall not be dosed until this report has been received and approved by the program COR.

12.3. Prestart Inhalation Report

A prestart inhalation report describing chemistry, exposure system, and health and safety methods and results shall be prepared and submitted before starting inhalation studies. Only one report shall be provided for a given exposure duration. For example, one report would be

provided for a 3-month study in rats and mice. This report shall include the following, as applicable for individual test articles.

- Information on the source and receipt of the bulk chemical as well as the manufacturer description of the bulk material, stability, storage requirements, identity, and purity data (including particle size and milling information if appropriate); study laboratory description and color photograph of the bulk material compared with a color spectrum (see Figure 12-1); the amount of test material remaining for conducting the study; and the intended disposition of the material at the end of the study.
- Methods, results, data, and conclusions, as appropriate, for the following:
    - Identity and purity, including representative chromatograms or spectra of the test article and reference material, if used; stability and physical properties (e.g., density, dimensions, surface area) of the bulk test material, if required
    - Description and schematics of overall exposure system (including exposure suite, chamber or carousel, generation, distribution, and monitoring systems) and exposure operations
    - Exposure concentration monitoring validation, including demonstration of performance of the method, sample collection efficiency/stability, calibration of online monitor, specificity of online monitor, accuracy/precision of online monitor, linearity of online monitor, and detection/quantitation limits of the online monitor
    - Test chemical purity and stability in the exposure system (reservoir, distribution line, chambers/carousels); evaluation of aerosol in exposure chambers (for vapors generated from liquids); exposure concentration and environmental stability over 3 days of exposure; exposure concentration uniformity; exposure concentration versus time; post-exposure monitoring; measurement of oxygen levels in exposure chambers/carousels (when inert gas used for distribution)
    - Concentration monitoring in the exposure room methodology, strategy, frequency, and results; effluent exhaust treatment monitoring methods/data and percent efficiency of the effluent exhaust treatment
    - Health and safety procedures (refer to appropriate section of specifications).
    - SOPs for test article identity and purity reanalysis; characterization, operation, and maintenance of the exposure, distribution, and monitoring systems; concentration monitoring in the exposure room and effluent exhaust monitoring; other SOPs specific to the test material

All corresponding data performed during the in vivo study shall be included in the respective study report.

12.4. Peer Review

The Division of Translational Toxicology (DTT) conducted a peer review of chapters 1, 2, 3, 4, 11, and 12 within the draft *Specifications for the Conduct of Toxicity Studies by the Division of Translational Toxicology at the National Institute of Environmental Health Sciences* by letter in

February 2022 by the expert listed below. Reviewer selection and document review followed established DTT practices. The reviewer was charged to:

1. Peer review the following chapters within the draft Specifications for the Conduct of Toxicity Studies by the Division of Translational Toxicology at the National Institute of Environmental Health Sciences.
    - Chapter 1: General Personnel Requirements
    - Chapter 2: Facilities
    - Chapter 3: Health and Safety
    - Chapter 4: Quality Program
    - Chapter 11: Data Collection and Submission
    - Chapter 12: Report Formats and Guidance
2. Comment on the completeness of each chapter.

DTT carefully considered reviewer comments in finalizing this document.

Peer Reviewer

Catherine Spong, M.D.
Professor and Chair, Department of Obstetrics and Gynecology
Chief of Maternal Fetal Medicine
UT-Southwestern Medical Center
Dallas, Texas, USA