Chapter 5. Chemistry

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

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5. Chemistry

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5.1. General Requirements

- The National Institute of Environmental Health Sciences (NIEHS) will typically supply the test article.
- NIEHS will typically provide procedures for test article purity analysis, dose formulation preparation, and dose formulation analysis. Modest modifications may be made to suit existing instrumentation per NIEHS approval.
- For inhalation studies, the development of methods for generation, monitoring, and characterization of the chamber atmosphere shall be the responsibility of the testing laboratory.
- In some cases, the testing laboratory may be required to conduct one or more of the following activities or part of an activity per direction by the contracting officer's representative (COR), including but not limited to procuring and handling the test article, characterizing the test article, including bulk stability; developing a formulation method and developing and/or validating analysis methods; developing and validating biological sample analysis methods; and conducting toxicokinetic studies.
- Toxicokinetic study may be conducted as a part of the toxicology study or as a separate study. The testing laboratory's responsibility is typically limited only to the collection and shipment of biological matrices to a designated analytical chemistry contractor. However, in some cases the testing laboratory shall be required to develop and/or validate analysis methods for quantifying the analyte concentration in biological matrices, analyze the samples, model the data, and provide an interpretation of the results.
- Standard operating procedures (SOPs) shall be prepared for performance of all chemistry activities, including but are not limited to purity analyses, dose formulation preparation, dose formulation analysis, inhalation technology operations, biological sample method development, validation and/or analysis, and toxicokinetic studies.
- The results of all analyses shall be reported to three significant figures unless directed otherwise by the COR.
- The contractor shall refer to DTT Chemistry Specifications[1] for details when applicable.

[1]https://ntp.niehs.nih.gov/howwework/research/chemistry/index.html

5.2. Bulk Test Article

5.2.1. Receipt, Handling, and Storage

The test article(s) and reference standard(s), as well as corresponding storage conditions, will be supplied by NIEHS. Whenever feasible, a sufficient quantity of the test article will be provided so that only one lot of the material will be needed to complete all of the contracted study phases. Testing laboratories shall plan to have adequate storage at the specified condition(s) for bulk test article(s). Upon receipt, the amount received shall be document in a use log. A use log of the bulk test article shall be kept and submitted as part of the raw data at the end of the study.

Upon receipt of each test article, the testing laboratory shall remove samples (typically 15 × 1 gram) to be used as reference samples. The COR will notify the testing laboratory when a smaller amount shall be archived (e.g., in the case of limited test material availability). All reference samples shall be placed in a freezer and maintained at −20°C ± 5°C. In some cases, the storage temperatures of the reference sample may be different depending on the nature of the test article.

The bulk test article shall be stored per directions provided by NIEHS. If appropriate storage conditions for the bulk test article are not provided by NIEHS, it may be possible to use the manufacturer's data to establish the stability and thus the storage conditions for the bulk test article without the need for additional studies by the testing laboratory. If stability studies of the bulk test article are required by the COR, refer to the DTT Chemistry Specifications for details.

5.2.2. Initial Identity and Purity

Methods to confirm the initial identity and purity of the bulk test article upon receipt at the testing laboratory shall be provided by NIEHS and will generally involve up to two identity analyses and one purity determination.

The testing laboratory shall confirm the identity and purity of the test article upon receipt using the method provided by NIEHS. The testing laboratory shall remove one 5-g aliquot of the test article and analyze it with the NIEHS-supplied frozen reference standard. The purity of the bulk test article shall be determined relative to the frozen reference standard.

5.2.3. Chemical Reanalysis

The testing laboratory shall determine the relative purity of the bulk test article against a frozen reference sample taken at the time of receipt. For all studies, this shall be conducted within 30 days prior to start of the study. For studies with an exposure duration >30 days, relative purity of the bulk test article shall be repeated within 30 days after removal of the last animal. For studies with an exposure duration >6 months, relative purity shall also be conducted at 24 ± 2-week intervals throughout the duration of the study. Each frozen reference sample shall only be used for one purity analysis.

The principal investigator shall immediately notify the program COR via telephone or email and in the next monthly progress report of any significant change in purity (e.g., a difference not explained by variability within the analytical procedure used) or appearance of the test article during the study.

5.3. Noninhalation Studies

A summary of the required activities for noninhalation is provided in Table 5-1. Additional information for each activity is provided in the following sections. In some cases, it will be appropriate to refer to the DTT Chemistry Specifications.

Table 5-1. Summary of Chemistry Activities for Noninhalation Studies[a]

Category	Type	Anticipated Frequency	Reporting Requirement
Initial Purity[b]	Identity and purity	Once upon receipt	Prestart chemistry report
	Stability study	Not always required; to be conducted at the direction of the COR	Prestart chemistry report
Chemical Reanalysis	Purity analysis	Within 30 days prior to exposure for all studies; within 30 days of end of exposure for studies with exposure durations longer than 30 days; every 24 ± 2 weeks for studies with durations longer than 6 months	Study report
Vehicle Analyses[b]	Identity and purity analyses	Once upon receipt	Prestart chemistry report
	Purity analysis	Every 24 ± 2 weeks	Study report
	Corn oil analysis, peroxide level determination	Bimonthly	Study report
Method Performance Evaluation for Dose Formulation Analysis[b]	Dose analysis	Once[c]	Prestart chemistry report
Dose Formulation Analyses (Exposure Duration <30 days)	Preadministration dose analyses	Once, prior to study initiation, all batches and each dose	Study report
	Animal room dose analyses	Once, after dose administration, each dose for each sex/species	Study report
	Homogeneity study[d]	Once, prior to study initiation	Prestart chemistry report
Dose Formulation Analyses (Exposure Duration >30 and <90 days)	Preadministration dose analyses	Initial, middle, and final; all batches and each dose for each sex/species	Study report
	Animal room dose analyses	Initial, middle, and final; each dose for each sex/species	Study report
	Homogeneity study[d]	Once, prior to study initiation	Prestart chemistry report
Dose Formulation Analyses (Exposure Duration >90 days)	Preadministration dose analyses	Initial and every 10 ± 2 weeks; all batches and each dose	Study report
	Animal room dose analyses	Initial and every 3rd scheduled formulation room analysis; each dose for each sex/species	Study report

Category	Type	Anticipated Frequency	Reporting Requirement
	Homogeneity study[d]	Once, prior to study initiation	Prestart chemistry report

[a]These activities apply when NIEHS provides the bulk test article to the testing laboratory.
[b]Methods provided by NIEHS.
[c]If concentrations change in subsequent studies, an additional method performance evaluation will be required.
[d]Prior to preparation of formulation designated for dosing; required only for feed and suspension dose formulations; total of three samples from each of three locations.

5.3.1. Dose Formulation

Methods for formulating the test article shall typically be provided by NIEHS.

- Each time an aliquot of the bulk chemical is weighed and formulated with the vehicle, that formulation is defined as a BATCH. For each dose prepared on each formulation day two or more batches might be required.
- An archival sample and an analysis sample of each batch shall be taken at the time of preparation and stored in individually labeled, sealed containers under the same storage conditions as the bulk formulations.
    - The quantities of the archival samples are approximately 50 mL for gavage and drinking water studies, 100 g for feed studies, and 25 mL for dermal studies. The COR will notify the testing laboratory when a smaller amount shall be archived (e.g., in the case of limited test material availability).
    - When a dose analysis of a formulation is planned, an analysis sample shall be used to determine the formulation concentration. Archival sample can be used if a reanalysis is required.
    - Archival and analysis samples that are not used shall be discarded as hazardous waste in accordance with federal, state, and local regulations 90 days or more after preparation.
- To prevent improper dosing of study animals:
    - The containers shall be labeled with the test article name, batch number, storage conditions, other identifying data, and intended species. The inclusive dates that a formulation can be used must appear on the containers.
    - The labels on the containers shall be color coded for different dose groups, species, and sex (if different concentration used for species/sex).
    - Control and dosed formulations shall be stored separately from the bulk test article.
- Formulation shall be aliquoted into dosing bottles (e.g., daily, weekly) as appropriate for study.
- An inventory of each dose formulation shall be maintained. A record shall be kept of the formulation date and the dates/duration the formulation can be used. This record, which shall be signed by the dose formulation supervisor or designee, shall contain information on the quantities of dose formulation prepared and identifying numbers (e.g., lot and/or batch numbers) for both the test article and dosing vehicle.

- If suspensions are to be formulated, the resuspendability and syringeability of the highest concentration formulation shall also be determined after preparation and following storage for at least 24 hours under the recommended storage conditions.
- The dose formulation storage condition and duration of stability/use period typically shall be established by NIEHS. The dose formulations shall not be used beyond their stability period. In some cases, the testing laboratory might need to determine the stability and conditions to mimic dosing and stability prior to study start. In such cases, refer to the DTT Chemistry Specifications for requirements.
- For dosed water studies, water for control groups is to be taken from the identical source and at the same time as the water used for the treated group formulations. The control water and dose formulations are to be stored as specified by NIEHS until it is time to dispense the formulations to water bottles and transport them to the animal rooms. For dosed feed studies, feed for the control groups is to be taken from the identical source and at the same time as the feed used for treated group formulations.
- If the batch sizes required for studies are twofold higher than those evaluated by NIEHS (for feed and gavage suspensions only), or homogeneity is not provided by NIEHS, per COR direction, the testing laboratory shall assess homogeneity of the batch size equivalent to the batch size anticipated for the study at the lowest and highest formulation concentration prior to study initiation. Refer to the DTT Chemistry Specifications for requirements.
- To ensure that homogeneous dosed feed or suspensions are prepared, homogeneity shall be checked prior to initiation of each study or study phase (e.g., 14-day study, 90-day study and 2-year study) at the highest and lowest formulation concentrations, unless blend parameters (size and concentration) have not changed from the previous study.

5.3.2. Formulation Analysis

Formulation analysis methods shall typically be provided by NIEHS. The testing laboratory shall evaluate the method performance prior to study start. If concentrations required for analysis during study phases are outside the qualified/validated range, the testing laboratory shall qualify or validate the method over the proposed range of dose concentrations per the DTT Chemistry Specifications prior to study initiation.

As a quality control check, formulations shall be analyzed periodically by the testing laboratory. The results of analysis for formulations shall be reported using the units specified in the study protocol.

When formulation analyses are required, analyses shall be completed prior to administering the dose formulations per requirements in the DTT Chemistry Specifications.

Determined formulation concentration should be within 10% of target concentration. Values that deviate from the target concentration will be considered out of tolerance/specifications. There may be cases where a 10% tolerance limit cannot be attained; these will be addressed on an individual basis and must be approved by NIEHS. The cause of any deviation from the approved tolerance limit shall be discussed in the monthly progress report. If the dose formulation is out of tolerance, the dose formulation shall not be given to the animals without NIEHS approval. When

NIEHS determines that a re-mix is necessary, it shall be analyzed according to the original procedure. Re-mixes shall be shown to be within 10% of target before they are used for dosing.

The frequency of formulation analysis shall be based on the study duration as given below and in Table 5-1. Each formulation sample shall be analyzed in triplicate.

If NIEHS has directed that the formulations be analyzed by another laboratory, the samples shall be labeled according to the example below, and a sample submittal form (example shown in Figure 5-1) shall be prepared and included with the shipment. The laboratory shall be notified (by email or phone) at least 24 hours prior to arrival of the shipment. Information regarding the carrier and tracking number shall be provided when available. In addition, appropriate return address information shall be included on the package. If the shipment will arrive during nonworking hours or requires special handling or storage conditions, the laboratory shall be contacted at least 48 hours prior to arrival so that arrangements can be made to receive and handle the shipment properly.

Studies with Exposure Durations of Less Than 30 Days

All batches for the initial dose formulations of each dose group shall be analyzed to demonstrate the accuracy of the formulation procedure.

Samples of the formulations shall be taken from the animal room according to the following scheme and analyzed:

- The samples shall only be taken from formulations for which dose formulation samples have already been analyzed.
- The sample shall be taken on the last dosing day prior to the expiration date of the batch.
- The sample shall be taken at the end of the dosing day.
- The sample submitted for analysis shall be the residual formulation in the original dosing vessel. For drinking water studies, the sipper tube assemblies are to be removed and the bottles capped. For dosed feed studies, the contents of the feeders are to be emptied into clear, interferent-free containers. In addition, for dosed feed and drinking water studies, samples of the unused formulation from which feeders or bottles are filled shall be collected and analyzed along with animal room samples in determining animal room sample stability.
- Samples shall be taken from one sex of each species and each dose group (if dose groups for each sex are different, samples must be taken from each sex).
- The quantities of the samples are approximately 50 mL for gavage and drinking water studies, 100 g for feed studies, and 25 mL for dermal studies.

The results of these analyses shall be compared with the results of the original analyses.

Studies with Exposure Durations of Greater Than 30 Days and Equal to or Less Than 90 Days

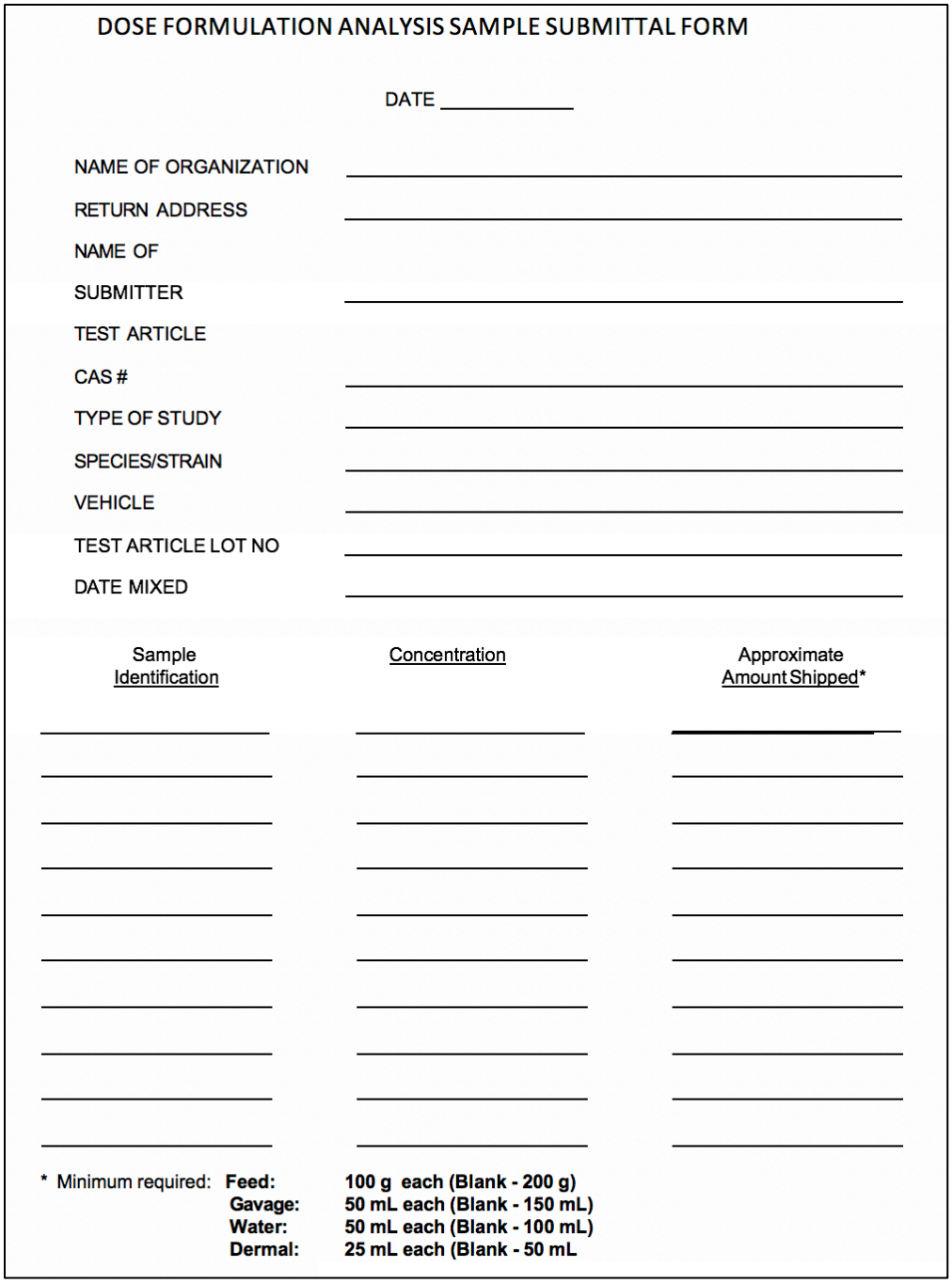
All batches prepared for the initial, midway, and final dose formulations for each dose group shall be analyzed to demonstrate the accuracy of the preparation procedures and analytical methods.

Samples of these same preparations shall be taken and analyzed from the animal room (upon completion of dosing) as stated above.

Studies Greater Than 90 Days in Duration

All batches prepared for the initial set of dose formulations shall be analyzed. Thereafter, these analyses shall be carried out every 10 ± 2 weeks.

Samples of all initial dose formulations shall be taken from the animal room for analysis as described above. Thereafter, similar animal room samples shall be taken during every third scheduled analysis period.



DOSE FORMULATION ANALYSIS SAMPLE SUBMITTAL FORM

DATE _____

NAME OF ORGANIZATION _____

RETURN ADDRESS _____

NAME OF SUBMITTER _____

TEST ARTICLE

CAS # _____

TYPE OF STUDY _____

SPECIES/STRAIN _____

VEHICLE _____

TEST ARTICLE LOT NO _____

DATE MIXED _____

Sample Identification	Concentration	Approximate Amount Shipped*

* Minimum required: **Feed:** 100 g each (Blank - 200 g)
Gavage: 50 mL each (Blank - 150 mL)
Water: 50 mL each (Blank - 100 mL)
Dermal: 25 mL each (Blank - 50 mL

Figure 5-1. Sample Dose Formulation Analysis Submittal Form

5.3.3. Analysis of Dosing Vehicles

The testing laboratory shall perform analyses of dosing vehicles to confirm the identity and purity of the test article. Refer to the DTT Chemistry Specifications for details.

5.4. Inhalation Studies

A summary of activities for inhalation studies is provided in Table 5-2.

Table 5-2. Summary of Activities for Inhalation Studies

Activity	Anticipated Frequency	Phase[a]
Test Material and Analysis		
Receive or procure test material	Once	Prestart
Bulk Chemical Analysis		
Method development	Once	Prestart
Identity and purity analysis	Once[b]	Prestart
Reanalysis	Within 30 days prior to exposure for all studies; within 30 days of end of exposure for studies with exposure durations longer than 30 days; every 24 ± 2 weeks for studies with durations longer than 6 months	Study
Exposure System Design and Characterization		
Exposure system design and schematics	Once[b]	Prestart
Monitor development/qualification	Once	Prestart
Stability in reservoir, generator, and chamber/carousel		
Without animals	Once	Prestart
With animals	At the beginning of study[c]	Study
Identity of test article in reservoir, generator, and high and low concentration chamber/carousel (particulate aerosol)	Once during study (exposure duration <3 months) or annually (exposure duration >1 year)	Study
Evaluation of Aerosol (Vapor Generation from a Liquid)		
Without animals	Once	Prestart
With animals	At the beginning of study	Study
Exposure Concentration/Environment Stability		
Without animals	Once (3-day test generation)	Prestart
With animals	Daily during exposure period	Study
Chamber/Carousel Uniformity		
Without animals	Once	Prestart
With animals	At the beginning of study; every 3 months (studies >3 months)	Study
Chamber Concentration vs. Time Plots		
Without animals	Once	Prestart
With animals	At the beginning of study	Study

Activity	Anticipated Frequency	Phase[a]
Chamber Post-exposure Monitoring		
Without animals	Once	Prestart
With animals	At the beginning of study	Study
Oxygen Determination When Inert Gas Is Used		
Without animals	Once	Prestart
Determine Particle Size (Aerosols)		
Without animals	Once	Prestart
With animals	At the beginning of study, then monthly	Study
Room Air Monitoring	Once	Prestart
Effluent Exhaust Treatment	Once	Prestart

[a]Methods and data shall be presented in the report corresponding to the phase listed.
[b]Preliminary results shall be reported to NIEHS for approval as soon as results are available.
[c]If the test article is to be generated as a particulate aerosol, test article identity shall be confirmed in the generator, distribution line, and high and low chamber/carousel during the prestart effort, once for studies with exposure durations of 1–3 months and annually during the chronic studies.

5.4.1. Test Material and Analysis

The testing laboratory shall either procure or receive the test material from NIEHS. Color photos of the test material compared with a color spectrum shall be generated.

The testing laboratory shall generally be responsible for analytical chemistry, including method development and analysis for the determination of the identity, purity, and as required, physical properties of the bulk test material. If specified by NIEHS, specific assays shall be included (see DTT Chemistry Specifications). In some cases, methods and/or analyses shall be provided by NIEHS.

5.4.2. Exposure System Design and Characterization

Design

Chambers for whole-body inhalation studies or carousels for nose-only inhalation studies can be any design that can be demonstrated to provide uniform and reproducible exposure of all animals to the test article and allows exposure under appropriate environmental conditions. However, the design shall be such that the chamber air supply and the incoming test material will be thoroughly mixed prior to entering the chamber. Schematics of the entire system, including generation, distribution, chambers/carousels, and monitoring system shall be generated.

The testing laboratory shall develop methodology for exposure generation and monitoring exposure concentrations, including calibration of the online monitoring system. The specificity, precision, linearity, absolute recovery, measurement limits, and relative error shall be established for the online monitoring method, along with appropriate methods of calibration.

The concentration of test article in the treated and control chambers/carousels must be monitored and recorded once per hour at minimum, and preferably continuously using a monitoring method from a single representative port.

If an aerosol is being generated, then the vapor (if present) as well as aerosol concentration shall be determined. Once the ratio of aerosol to vapor concentration has been calculated for each exposure concentration, only the aerosol concentration needs to be monitored on a daily basis. (The vapor concentration monitoring methodology developed by the testing laboratory shall be able to quantitate vapor at a level of 1% of the targeted aerosol concentration.)

Characterization

All evaluations with animals shall occur at the beginning of the studies, with a maximum load of animals in the chambers/carousels.

Aerosol Particle Size

If the test atmosphere is an aerosol, the particle size distribution shall be controlled and monitored. The measurement method must provide the mass median aerodynamic diameter (MMAD) and the geometric standard deviation for the distribution. The initial particle size distribution determination shall be done by impactor and shall have a MMAD of <3 microns and a sigma g of <3.

Evaluation for Potential Degradation Products

The testing laboratory shall develop methods for analysis of known or suspected degradation products or impurities. The studies shall be carried out at the lowest and highest exposure concentrations during developmental work without animals in chambers/carousels and at the beginning of each study with animals in chambers/carousels. Methodology developed by the testing laboratory must be sensitive enough to detect the degradation products down to a level of 0.1% of the chamber/carousel concentration target. Stability/degradation studies to confirm the integrity of the generated chemical atmosphere shall be conducted by

1) Establishing there is no degradation of test article in the reservoir during the expected residence time in the reservoir. The reservoir sample shall be taken at the end of an exposure day. If the reservoir is not refilled daily, the sample shall be taken immediately before a refill. This sample shall be compared with a sample collected from the container of test article used to fill the reservoir or an analytical standard collected after receiving the test material, if it is necessary to avoid repeated opening of the vessel.
2) Establishing the generation system does not cause degradation of the test article prior to introduction into the inhalation chamber/carousel. The distribution line sample shall be taken at a point after generation but prior to final dilution of the chemical stream before introduction into the exposure chamber/carousel.
3) Determining to what extent, if any, the test article is degraded after introduction into the chamber/carousel atmosphere. The chamber/carousel sample to be tested shall be taken during the first and last hours of the exposure. The testing laboratory shall establish a generator/reservoir change-out schedule.

The testing laboratory shall establish a generator/reservoir change-out schedule and develop operating procedures covering the maintenance of the generator/reservoir based on these stability studies.

Evaluation for Aerosols

When the test atmosphere of a liquid (at standard temperature and pressure) test article is to be generated as a molecular vapor of that test article rather than as an aerosol, the testing laboratory shall demonstrate by photometric (or other appropriate means) that the test atmosphere does not contain aerosolized test article.

Exposure Concentration/Environment Stability

The method of generation of the test atmosphere shall be reproducible so that the daily average chamber/carousel concentration does not vary by more than ±10% from the target concentration from exposure period to exposure period. The daily relative standard deviation (RSD; standard deviation divided by the mean, expressed as %) of chamber concentration shall not vary by more than ±10%. Daily average chamber/carousel concentrations, relative error (RE), and RSD shall be reported. For certain test materials, low exposure concentrations, nose-only exposures, and others, it may be necessary to broaden the RE/RSD limits, which will be determined on a case-by-case basis.

The stability of environmental parameters (temperature, relative humidity, air flow, and vacuum) and of exposure concentrations must be established for a period of the daily exposure duration to be used in the studies, plus T_{90} (for whole-body studies) for 3 days. All the data shall be obtained in the same exposure room and under identical conditions that will be used during the animal exposures.

Exposure Uniformity

The uniformity (homogeneity) of the exposure concentrations in the chambers/carousels shall be demonstrated to confirm that the challenge to each animal is the same. Total port variability consists of within port and between port variability (WPV and BPV, respectively). WPV and BPV shall not exceed 5% RSD.

Build-up and Decay

Chamber concentration versus time plots shall be developed for each chamber. These data will be used to evaluate: the time necessary to reach the target concentration; the ability of the generation system to maintain a stable concentration over a full exposure period; the length of time necessary to clear the chamber of test article; the times necessary to reach 90% of the target concentration at exposure initiation (T_{90}) and to reach 10% of the target concentration (T_{10}) after exposure termination shall be estimated from chamber concentration versus time plots and compared with the theoretical T_{90} and T_{10}, respectively. The T_{90} shall be added to the nominal daily exposure duration (e.g., 3 or 6 hours).

Post-exposure Monitoring

The residual concentration of test article in the high chamber atmosphere shall be monitored overnight or until the concentration for two consecutive hours is <1% of the target concentration. The overnight monitoring period shall begin immediately after exposures are completed. If possible, opening and servicing of chambers shall be delayed until the concentration has decayed to <1%.

Oxygen Determination

If an inert gas (e.g., nitrogen) is used to generate or transport the test article to the inhalation chamber/carousel, the oxygen content in each exposure chamber/carousel shall be measured. A minimum oxygen concentration of 19% is required.

Room Air Monitoring

Method(s) of room air monitoring shall be developed and evaluated at exposure concentrations used in the studies in all chambers/carousels under exposure conditions. The lower limit of detection of the monitoring method(s) shall be defined. It shall be documented that this level provides an adequate safety margin for personnel.

Effluent Exhaust Treatment

Method(s) for effluent treatment shall be developed and tested at protocol-required concentrations in all chambers/carousels under exposure conditions. The effectiveness of the exhaust treatment unit immediately after the effluent treatment unit and at the point of exhaust from the building shall be demonstrated. The percent efficiency of the exhaust treatment shall be determined. The effluent exhaust treatment must be effective in removing the test material to an acceptable concentration, that is, >90% efficiency of removal by the treatment system and <50% of the threshold limit value (TLV), if a TLV exists; otherwise, written documentation for a waiver from the appropriate air regulatory agencies must be provided. The lifetime expectancy of any proposed filtration/treatment units and amount of treatment media required shall be determined. It shall be confirmed that none of the exhausted test material is re-entrained.

5.5. Completion of Test Article Program

5.5.1. Exposure System Closeout

The exposure system for a specific test article may be used for one or more studies. Following completion of the testing program for a given test article, the exposure system shall be decommissioned. All consumable/disposable materials shall be removed and disposed of according to the appropriate guidelines (see Chapter 3 [Health and Safety], Section 3.7. Waste Disposal/Test Article Shipment). If reusable, the materials or equipment shall be sent through a cage wash if appropriate (e.g., will not cause damage to equipment based on water temperature, detergents).

Test article requirements could stipulate that some studies have additional provisions, such as for wipe samples or air sampling, aimed at ensuring proper cleaning has occurred so that no additional hazards are present on the materials or equipment or in the study rooms.

5.5.2. Disposition of Surplus/Residual Test Article

Thirty days prior to the shipment of the test article, the testing laboratory shall notify NIEHS of its intention to ship surplus or residual chemical, including the amount to be shipped. Shipment is to be made within 30 days after the terminal sacrifice for the last study for that test agent. (See Section 3.7 for complete details.)

A completed surplus test article aliquot transmittal form (example in Figure 5-2) shall accompany shipments of aliquots and surplus test article. In addition to the surplus chemical, a

100 g aliquot of each batch of chemical shall be reserved and shipped. The chemistry support contractor shall be notified (by email or phone) at least 24 hours prior to arrival of the shipment. Information regarding the carrier and tracking number shall be provided when available. In addition, appropriate return address information shall be included on the package. If the shipment will arrive during nonworking hours or requires special handling or storage conditions, the laboratory shall be contacted at least 48 hours prior to arrival so that arrangements can be made to receive and handle the shipment properly.

SURPLUS TEST ARTICLE TRANSMITTAL FORM

DATE _____

NAME OF ORGANIZATION _____

RETURN ADDRESS _____

NAME OF SUBMITTER _____

TEST ARTICLE* _____

CAS# _____

Provide information below for each lot used.

Lot #	Date lot received	Temperature lot stored	Amount of Test Article Returned	List study types for which lot used

* Use full NTP test article name.

Figure 5-2. Example Surplus Test Article Submittal Form

5.6. Peer Review

The Division of Translational Toxicology (DTT) conducted a peer review of chapter 5 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 chapter 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 5: Chemistry
2. Comment on the completeness of each chapter.

DTT carefully considered reviewer comments in finalizing this document.

Peer Reviewer

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