California Environmental Protection Agency
Department of Pesticide Regulation

Guidance for Toxicology Study and Data Acceptability in Registration Review and Risk Assessment

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Contents

I. Objective

The Human Health Assessment (HHA) Branch of the Department of Pesticide Regulation (DPR) evaluates a range of toxicity, exposure, and human health data as part of pesticide registration and for human health risk characterization. Toxicology data are reviewed for adequacy in the identification of possible hazards and to support enforcement, mitigation, regulatory, and risk management efforts to protect human health.

This guidance describes the acceptance criteria and the method of evaluation for toxicity studies submitted in support of registration evaluation and for risk determination. It provides a transparent description of HHA's criteria for study and data selection and the suitability of registrant-submitted studies and open literature for specific purposes.[1] This guidance is intended to ensure a transparent and consistent process by which HHA scientists evaluate and accept data for use in determining human health effects of pesticide use and exposure.

II. Introduction

The Human Health Assessment Branch (HHA) is responsible for evaluating the toxic effects of pesticides, what health impacts occur when pesticides are used, and how to protect humans from potential exposure. HHA's core work can be broadly grouped into two areas: the review and evaluation of data submitted for pesticide registration and the assessment and estimation of the risk of adverse human health effects associated with pesticide use and exposure.

DPR requires registrants of certain pesticidal products to submit data on a product's potential chronic, sub-chronic, and acute health effects. HHA scientists review the data for new active ingredients and new products containing currently registered active ingredients, label amendments on registered products including major new uses, and reevaluation of registered active ingredients. Toxicology data are reviewed for adequacy and identification of possible health hazards and combined with exposure monitoring and modeling to assess the adequacy of product labels. Data review activities also include evaluating submitted data to determine if toxicity findings support new uses or label changes, as well as the adequacy of first aid statements, personal protective equipment (PPE), and restricted entry intervals (REIs) to ensure worker health is being protected.

HHA is also responsible for further evaluation of these studies to establish critical endpoints for risk assessment and to propose regulatory targets for risk management consideration. Core assessment work includes development of the toxicology profiles and hazard identification sections in comprehensive Risk Characterization Documents (RCD) as well as more rapid assessments of risk, such as evaluations of illegal pesticide residues on fresh produce for the California Pesticide Residue Monitoring Program (CPRMP), risk determinations of pesticide concentrations in drinking water, and the establishment of Action Levels for cannabis products.

[1] Other guidance documents, either published or in development, provide more detail about HHA's systematic literature review process, the use of epidemiological data in risk assessment, exposure duration definitions, rapid risk determinations for residue in food and drinking water, and the human health risk assessment process. Detailed description of those processes is outside of the scope of this guidance.

These activities are fundamental to supporting the department's mission of protecting human health. Importantly, every pesticidal active ingredient registered in California has been evaluated by HHA for health impacts. Because of the central mission of the branch's activities, it is critical that HHA's recommendations are supported by the best science available. Therefore, this guidance was developed to establish a consistent and transparent process by which acceptability criteria are applied to toxicology and health effects data.

III. Toxicology Data Acceptability for Pesticide Registration

A. Scope

Registrants are required to submit various studies to support registration of new active ingredients and formulated products in California. The data requirements differ depending on the type of new active ingredient (chemical, antimicrobial, biochemical, microbial) and the general use patterns as described in the Code of Federal Regulations. The data requirements consist of studies which are conducted according to either the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA, 7 U.S.C. 136 et seq.) or the Organization for Economic Cooperation and Development (OECD) test guidelines.[2] Pesticide toxicity data requirements are found in Title 40 of the Code of Federal Regulations (40 CFR Part 158.500-158.510) and in Title 3 of the California Code of Regulations (3 CCR) Section 6172.[3]

In addition to the pesticide registration data requirements in 3 CCR 6172, data evaluations are conducted pursuant to the Birth Defect Prevention Act (Food and Agriculture Code Section 13121 et seq.; 27 CCR § 27000). DPR must review toxicology studies supporting the registration of pesticidal active ingredients. Missing or unacceptable studies are identified as data gaps. Toxicity data evaluation also meet requirements found in the Toxic Air Contaminant Code (Health and Safety Code section 39650 et seq.; Food and Agriculture Code Section 14021 et seq.) when a pesticidal active ingredient is being evaluated as a Toxic Air Contaminant. These required evaluations are done pre-registrationally and can be continued and expanded on if a pesticidal active ingredient is prioritized for human health risk assessment (see below).

Study evaluations are peer reviewed by senior scientists. In addition, registration decisions for new active ingredients are reviewed and approved by the Branch Chief prior to being routed back to DPR's Pesticide Registration Branch for action. DPR can also exercise its regulatory authority to request additional and/or supplemental human health data per Title 3 CCR § 6159 and 6176-6199, et seq., under Supplemental Data Requirements. The same is true for a pesticidal active ingredient which is undergoing formal reevaluation by the department pursuant to 3 CCR 6222.

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[2] Federal Data Requirements for Pesticides are listed in Title 40 of Code of Federal Regulations, Part 158. Available at https://www.ecfr.gov/current/title-40/chapter-I/subchapter-E/part-158. US Environmental Protection Agency Health Effects Test Guidelines (Series 870) and Supplemental Test Protocols are available at https://www.epa.gov/test-guidelines-pesticides-and-toxic-substances/series-870-health-effects-test-guidelines.The OECD Test Guidelines for Chemicals are available at https://www.oecd.org/chemicalsafety/testing/oecdguidelinesforthetestingofchemicals.htm.

[3] See the summary of Department of Pesticide Registration data requirements at https://www.cdpr.ca.gov/docs/registration/regprocess.htm

B. Criteria and Procedures Employed in the Review of Guideline Studies Submitted to Support Product Registration Under FIFRA or OECD

1. Acceptance Criteria

Once the data submissions are received by HHA, the studies are evaluated by branch scientists for adherence to test guidelines, scientific merit, and integrity. Studies satisfying these criteria are deemed to be acceptable. Any study not satisfying these criteria is not acceptable and the submitted data do not support the requested registration action. These data provide HHA the basis for categorizing the toxicity of an active ingredient or formulated product, as well as approving the label language, such as signal words, product specific precautionary label statements, first aid statements, personal protective equipment (PPE), and restricted entry intervals (REIs).

The following criteria must be satisfied for a study to be deemed acceptable:

1. Conduct of the study has been subjected to periodic audits or inspections by the Quality Assurance Unit of the conducting laboratory. This means the reported results accurately reflect the original study data.
2. Study conforms to OECD principles of Good Laboratory Practice (GLP)[4] or FIFRA Good Laboratory Practice standards (40 CFR Part 160) to ensure the quality and integrity of the test data.
3. A signed GLP compliance statement and quality assurance audit record should be included in the study report.
4. Test article employed in the study should be identified
    a. All code names or synonyms need to be defined
    b. Purity, Lot and Batch numbers, and expiration dates must be provided
5. Analysis of dosing solutions or test diets for concentration, stability, and homogeneity should be included in study report. This is important for repeated dose, neurotoxicity, and *in vivo* genotoxicity studies.
6. Justification for dose levels administered determined by a range-finding or pilot study should be submitted. Alternately, the results should be incorporated into the study report.
7. Raw or individual data should be included in the study report in addition to derived and/or summary data.
8. Concurrent or updated positive control data should be submitted for neurotoxicity, developmental neurotoxicity, genotoxicity, and dermal sensitization studies.
9. Historical control data need to be submitted with chronic and oncogenicity studies to allow for comparison between the incidences of nonneoplastic and neoplastic lesions and

[4] The OECD Principles of Good Laboratory Practice (GLP) and GLP Compliance Monitoring are available at https://www.oecd.org/chemicalsafety/testing/overview-of-good-laboratory-practice.htm.

developmental abnormalities (variations and malformations). Historical vehicle and positive controls should be submitted with dermal sensitization studies.

10. In instances where test materials demonstrate persistence of irritation in either primary eye or dermal irritation studies, time points beyond 72 hours must be included in the data in order to determine reversibility of the irritation effects. HHA use these data to properly assign toxicity categories and in the determination of appropriate signal words, precautionary language, first aid statements, and restricted entry intervals on the product labels.

11. The appropriate dose-progression factor should be used in the Up-and-Down Procedure (UDP) method in determining the dose levels for acute oral toxicity study. This is especially relevant to chemicals that have steep slopes in their dose response curve.[5]

12. Acute inhalation toxicity studies must include methods and calculations used to determine chamber concentrations of test materials to which the animals are exposed. Particle size analysis of the test material should be performed, and the results submitted with the study report.

2. Types of Deficiencies

Minor Deficiency: A minor deficiency is any deviation from the FIFRA or OECD test guideline that does not impact the overall study outcome. For example, there may be instances when a study was not performed exactly as written in the protocol. However, the deviation from the protocol did not have an impact on the overall study results. This study would still be considered acceptable with a minor deficiency. Specific examples include a slight deviation of animal room temperature or relative humidity levels that are outside the range recommended by the guideline.

Major Deficiency: Any deviation from the FIFRA or OECD test guideline that impacts overall study results. When the study is conducted with a deviation from the protocol that influences or changes the outcome of the study, this would be considered unacceptable with a major deficiency. For example, 1) the number of animals tested is less than the number specified in the guideline; 2) the test was not conducted in species or sex as recommended by the guideline; or 3) the test substance was not administered as per the method specified by guidelines.

3. Study Designation

Acceptable Study: An acceptable study is conducted according to FIFRA or OECD test guidelines and meets the acceptance criteria listed in Section 1 above.

Unacceptable, Not Upgradable Study: This study lacks critical information that impacts the study outcome which cannot be remedied by providing any supplemental information. For

[5] To better support registration decisions for both active ingredients and formulated products, DPR requires that all acute oral toxicity data derived using the UDP methodology in cases of partial survival meet specific submission criteria. More information is available at https://www.cdpr.ca.gov/docs/risk/guidance/up_down_procedure.pdf

example, the number of animals used in the study was less than the number specified by the guideline.

Unacceptable, Possibly Upgradable Study: This is a study that lacks critical information that impacts the study outcome. However, the laboratory that conducted the study or registrant can submit additional information to mitigate raised concerns. If the provided information or justification is sufficient, the study can be reclassified as acceptable.

Supplemental Study: Studies not performed according to test guidelines or failed to include the items listed under Section II above are not acceptable or classified as supplemental data. Journal articles submitted to support registration are considered supplemental data. In addition, studies that fail to assign toxicity categories according to either the US Environmental Protection Agency (US EPA) classification system[6] or the GHS classification system established by the Occupational Safety and Health Administration[7] will also be considered supplemental.

IV. Toxicology Data Acceptability for Quantitative Risk Determination

A. Scope

Because of testing mandates and federal and state data requirements, pesticides are comparatively data-rich chemicals. However, not all data are appropriate to be used to derive quantitative risks estimates. This portion of the guidance applies specifically to the acceptability criteria and evaluation metrics for toxicity data used for risk determinations found in Risk Characterization Documents (RCDs) and in other branch work products such as dietary and drinking water assessments.

HHA uses established best practices in evaluating and recommending reference targets and health protective levels for pesticides. These values must have biological relevancy, empirical consistency, and withstand scientific scrutiny. The differences between the types of toxicity evaluations done on behalf of pesticide registration actions and those done to establish reference targets necessitates different data acceptability standards, as explained below.

B. Toxicity Study Categories

Risk determinations and quantitative risk estimates are based on registrant-submitted guideline and non-guideline studies and studies published in the open literature.

1. Registrant-Submitted Studies

[6] US EPA Label Review Manual Chapter 7: Precautionary Statements. US Environmental Protection Agency, Office of Pesticide Programs, Registration Division. Revised March 2018. https://www.epa.gov/sites/production/files/2018-04/documents/chap-07-mar-2018.pdf

[7] Hazard Classification Guidance for Manufacturers, Importers, and Employers. OSHA 3844-02 2016 Occupational Safety and Health Administration, U.S. Department of Labor. 2016. https://www.osha.gov/sites/default/files/publications/OSHA3844.pdf

Pesticide registrants submit studies in support registration of new pesticidal active ingredients, new formulated products, or changes to already registered products. Registrant-submitted toxicology studies generally follow guidelines specified by FIFRA (Title 40, Code of Federal Regulations, Part 158) or OECD and are conducted in laboratories that follow either FIFRA or US Food and Drug Administration (FDA) Nonclinical Good Laboratory Practice standards (40 CFR part 160 or 21 CFR Part 58, respectively).[8] These studies can also be useful for risk assessment because of the high quality and specificity of the data generated. Registrant submitted non-guideline studies conducted with Good Laboratory Practice standards can also be helpful to inform critical endpoint decisions. HHA scientists conduct further expert evaluations of data from guideline studies that are under consideration for use in risk determination as part of Hazard Identification and Dose Response Assessment, to derive or support critical endpoints and points of departure (PODs). Because of these different end-uses, critical PODs used for risk determination may differ from study derived no-observed-effect levels (NOELs) or lowest-observed-effect levels (LOELs) generated for registration decisions.

2. Open Literature Studies

HHA is obligated to review relevant findings of potential human health effects from pesticide exposure published in the open literature. These studies are identified, categorized, and screened for relevance as part of Systematic Review (explained briefly below). In general, HHA's evaluation of peer-reviewed literature is consistent with methods described in US EPA's Guidance for Considering and Using Open Literature Toxicity Studies to Support Human Health Risk Assessment (USEPA, 2012). Studies published in the open literature are designed to address specific research questions and may provide valuable quantitative or qualitative data, such as mode of action or epidemiological data. Such studies may not conform to the Good Laboratory Practice standards mentioned earlier. As such, care must be taken to verify study conclusions that are used for quantitative risk determination purposes, with a particular focus on the conditions under which the study was conducted and the quality and transparency of the data generated from the study (explained further in Acceptance Criteria, below). According to US EPA, when the study results cannot be verified by review of the raw data, the uncertainties of using the data must be explained. Unverified results should be scrutinized against other lines of evidence or similar measures of toxicity to determine the study's reliability (USEPA, 2012).

Additionally, HHA only considers open literature studies published in journals that conduct peer review and adhere to established scholarly publishing standards. Relevant published studies may be identified during a Systematic Review or when submitted or suggested by external reviewers, registrants, or the public.

a) Study Relevance

HHA employs a stringent systematic literature review process to screen and categorize toxicity and health effects data for pesticides. The complete Systematic Review process is reserved for risk determinations that occur as part of the development of a Risk Characterization Document where all available evidence (i.e., the weight-of-evidence) must

[8] FIFRA Good Laboratory Practices Standards are available at https://www.govinfo.gov/content/pkg/CFR-2011-title40-vol24/xml/CFR-2011-title40-vol24-part160.xml. FDA Good Laboratory Practice for Nonclinical Laboratory Studies are available at https://www.fda.gov/media/99828/download.

be considered. The same general process and best practices are also used for human health evaluations with a more limited scope (e.g., for drinking water, fresh produce, cannabis, etc.). In each case, it is critical to maintain transparency and traceability of risk decisions and to document the database used and the completeness of its review.

A brief description of the Systematic Review process is included here because of some overlapping data evaluation elements. In this process, published studies are identified, screened for relevance, and sorted into one of three categorical bins related to relevance using the Population, Exposure, Comparator, and Outcome (PECO) criteria as a guide. Each element of the HHA PECO criteria directly corresponds to one or more of the US EPA Evaluation Criteria (USEPA, 2012) (Table 1). Expert evaluations conducted at this step are documented and reported in a transparent and traceable manner and all reporting documents are subject to peer quality control review.

A study's relevance is based on whether it has information that can be used as part of the weight-of-evidence while its categorical assignment is based on the evaluation of information pertaining to the experimental design, the test system used (e.g., animal model, treatment methods and conditions), data quality, statistical methods and significance, and dose response analysis; both determinations are possible outcomes of the Systematic Review process. The categorical assignment will also determine which studies may be suitable for quantitative and/or qualitative applications (defined below). In most cases, these determinations are made prior to Hazard Identification and Dose Response Assessment. The methods and framework for HHA's Systematic Review will be described in a forthcoming guidance document.

Table 1. General DPR PECO Criteria with Corresponding US EPA Criteria

PECO Criteria	US EPA Evaluation Criteria
Population: The animal models used in the study (i.e., the population of the study).	*Test organism; The number of organisms tested per concentration and the number of concentrations or dosage levels evaluated; Husbandry conditions*
Exposure: AI, synonyms, and relevant metabolites, and/or derivatives.	*Nature of the test substance (percent active ingredient); Exposure method, route, and frequency of administration and length of the treatment period*
Comparator: The controls required for study consideration.	*Controls*
Outcome: The study outcomes of interest.	*Performance of test species; Macroscopic observations of the test animals; Microscopic observations of the test animals; The toxic effects must be able to be attributed to exposure from the chemical*

C. Toxicity Data Categories

As mentioned above, pesticides are data-rich chemicals with well-established databases conforming to federal and state registration requirements. Because the data requirements have evolved over time, older pesticides may lack some types of toxicity data. In general, the following data are available for most pesticides:

- acute oral, dermal, and inhalation toxicity
- primary eye and dermal irritation
- dermal sensitization
- acute neurotoxicity
- subchronic oral, dermal, and/or inhalation toxicity
- subchronic and/or delayed neurotoxicity
- chronic oral toxicity
- carcinogenicity - two rodent species (or combined chronic and carcinogenicity bioassay)
- prenatal development
- reproduction and fertility effects
- developmental neurotoxicity
- mutagenicity testing (in vivo and in vitro)
- metabolism and pharmacokinetics
- immunotoxicity

In addition, other studies such as those reporting novel modes/mechanisms of action (MOAs/MoAs), Adverse Outcome Pathways (AOPs), pharmacokinetic-pharmacodynamic (PBPK) models, clinical case studies, and population-based studies may be available as non-guidelines studies or in the open literature.

D. Quantitative versus Qualitative Data Applications

As part of the human health risk assessment process, HHA scientists review and summarize relevant studies for a pesticidal active ingredient. This includes studies that are used to determine critical PODs as well as studies providing weight-of-evidence or supporting information. Quantitative data are the basis for establishing the hazard that can then be combined with data for exposure scenarios to calculate risk. Applying acceptability criteria to quantitative data is a critical step in maintaining the scientific robustness and integrity of a risk determination. However, qualitative data that more broadly describe a hazard are also useful, especially as weight of evidence in supporting a conclusion based on quantitative data. Qualitative data can also be valuable in justifying any deviation from a default uncertainty factor, supporting the use of additional extrapolation factors, in risk appraisal discussions, and/or providing context for regulatory or mitigation activities. HHA generally follows the US EPA criteria for determining whether a scientifically valid study should be considered quantitative or qualitative (USEPA (2012); see Table 2 below) and evaluates each study for utility on a case-by-case basis using best professional judgment. The special cases of genotoxicity and population-based data are explained below.

1. Genotoxicity Studies

Genotoxicity Studies (in vitro, in vivo, and ex vivo) are used to establish evidence for a genotoxic mode of action. These data are used in qualitative manner to make a yes or no determination. The evaluation of a pesticide's genotoxic potential is critical for supporting quantitative cancer risk estimation. As such, unnecessarily high levels of uncertainty may be introduced by using data from studies not meeting the study and data acceptance criteria. A

recent genotoxicity data acceptability evaluation can be found in the Final Risk Characterization Document for Fipronil (Appendix V. Published Studies Excluded from the Fipronil Genotoxicity Assessment in) (DPR, 2023).

2. Population-based Studies

The utility and application of epidemiology data in risk assessment has received considerable attention in recent years. For some pesticides, there is a growing number of population-based studies that may inform a human health risk assessment. However, there are challenges to incorporating epidemiological results into quantitative risk assessment. Not all epidemiological studies that investigate associations between pesticide exposure and adverse health outcomes have quantified exposure or contain sufficient data regarding the relationships of exposure to effect. However, the lack of these data does not necessarily preclude the use of data from human observational studies in risk assessments. This was the case with the analysis of population-based studies in the Final Toxic Air Contaminant Evaluation of Chlorpyrifos (DPR, 2018). Epidemiological data were used as weight of evidence to inform on the consistency of effects seen in human populations and test species and for establishing the developmental neurotoxicity of this active ingredient (DPR, 2018).

Evaluating epidemiological and observational data is important to the completeness and transparency of the risk assessment process. Considering the potential associations documented in epidemiological studies helps to inform the weight of evidence for a particular effect. A guidance that describes the use of population-based studies in HHA human health risk assessment process is currently in development. In the interim, the US EPA's Office of Pesticide Program Framework for Incorporating Human Epidemiologic & Incident Data in Risk Assessments for Pesticides is used as a guide (USEPA, 2016).

Types of data, their application within the risk determination process and their quantitative or qualitative nature are summarized in Table 2.

Table 2. Data Types and Applications and Data Categories for Risk Determination

Data Type and Application	Data Category
Health effects (endpoints) related to treatment	Quantitative
Exposure levels for corresponding points-of-departure (PODs) for threshold effects (non-cancer and cancer)	Quantitative
Slope factors for non-threshold effects (cancer)	Quantitative
Uncertainty factors (UFs) or extrapolation factors used to determine target risk levels	Quantitative
Quantitative support for quantitative parameters	Quantitative
Evidence of genotoxicity	Qualitative
Qualitative support for quantitative parameters	Qualitative

Table 2. Data Types and Applications and Data Categories for Risk Determination

Data Type and Application	Data Category
Identification of relevant mechanisms, modes of toxicity or adverse outcome pathways	Qualitative

E. Acceptance Criteria

Open literature studies that have been screened for relevance and categorized based on their study designs, data, and potential for quantitative and/or qualitative applications are evaluated for acceptance using the principles described in this guidance. Relevant studies with data that may be suitable for quantitative and/or qualitative applications are analyzed for details such as reporting, experimental design and methods, the test system (e.g., animal model, treatment methods and conditions), data quality, statistical methods, and journal quality. The study or data acceptability determination does not pertain to the selection of parameters used to calculate risk (e.g., endpoints, PODs, uncertainty factors (UFs), and cancer slopes). Risk calculations are ultimately incorporated into branch work products such as rapid human health determinations of pesticide residues in drinking water and fresh fruits and vegetables, to assist with determining risk after accidental releases or drift incidents, and in the development of more complex human health risk and exposure assessments.

HHA uses established best practices in evaluating and recommending health protective levels for pesticides. Examples of recent HHA determinations where data acceptability was specified include in the supporting documents for the Pesticide Contamination Prevention Act review process for imidacloprid (DPR, 2022) and the final Risk Characterization Document for Fipronil (DPR, 2023). The study or data acceptability determination does not pertain to the selection of parameters used to calculate risk (e.g., endpoints, PODs, uncertainty factors (UFs), and cancer slopes) that is conducted during the Hazard Identification and Dose Response Assessment processes. Table 2 provides more detail on the specific data and study acceptance criteria used by HHA for its risk determinations. A determination of acceptability requires a complete evaluation using all of the criteria listed below.

1. Journal Quality

HHA follows established criteria for identifying predatory journals and publishers (Laine and Winker, 2017; Elmore and Weston, 2020). The most reputable biomedical journals are indexed in MEDLINE, the premier bibliographic database for journals on life sciences and biomedicine (https://www.nlm.nih.gov/medline/index.html). HHA scrutinizes and/or flags journals with articles in PubMed that are not indexed in MEDLINE. HHA further evaluates these journals using the following minimum criteria as a guide:

- Peer-review process is available and clearly stated
- Article publishing fees are clearly stated
- Editor is clearly identified

- Academic information is provided regarding the editor, editorial staff, and review board members
- It is easy to contact the publisher
- The name of the journal is consistent with its name (e.g., a journal with “British” in the title has some connection to British institutions)
- The journal has a clean record with regards to plagiarism
- The journal has clear rules in place for the purpose of preventing author misconduct including plagiarism

If any of these journal criteria is not met, studies published in that journal may be considered unacceptable.

Table 3. Study and Data Acceptance Criteria

Criteria	Description
The toxic effects are in an appropriate test system	The appropriateness of a test system (organism) used in a study should consider species, sex, age, life-stage, health status, and overall performance under test conditions. This is applicable to *in vivo* and *in vitro* studies.
Treatment(s) are relevant to human exposure	The relevance of a dosing solution should consider its potential effects on absorption, distribution, metabolism, or the elimination (ADME) of the pesticide and general effects on the test system used. This applies when solvents and/or detergents are used in gavage solutions. Dosing modalities must also be relevant to human exposures. Additional scrutiny will be applied to non-traditional toxicological dosing methods such as intraperitoneal and intramuscular injection.
Treatment(s) are compared to acceptable controls	A study should include concurrent controls treated under comparable conditions (e.g., solvent vehicle controls). Test system health status should be considered (e.g., > 10% mortality in a concurrent control group maybe cause for invalidation.
Experimental design and/or conditions are adequate for extrapolation to human exposures	A study design should be appropriate for the purpose of providing data that can be used to estimate human risk. This includes dose levels, group sizes, and experimental endpoints that are adequate for providing robust data that can be used as a surrogate for human exposures. This includes conduct under well-controlled conditions with regards the laboratory environment, animal husbandry, and technical competence. Potential experimental confounders should be considered.

Table 3. Study and Data Acceptance Criteria

Criteria	Description
Adequate data on the chemical tested are provided	A test substance should be well characterized with regards to source, purity, and nature. Analytical data should be complete for this purpose, if included.
The toxic effects must be able to be attributed to exposure from the chemical	Study results where effects observed in either in vivo or in vitro test systems must be attributed to the pesticidal active ingredient, not other study conditions or variables.
The study was adequately reported	The study report should provide sufficient and accurate information to evaluate its design, in-life conduct, and results so that it can be interpreted and evaluated for both relevance and acceptability. This includes compete and accurate descriptions of methods, endpoint data, and methods used for data analysis (i.e., statistical tests). Inconsistencies and errors in conduct or reporting should be considered. Any uncertainty in observation or conclusion must be explained.
Reporting journal and/or author do meet minimum quality standards	The study must meet minimum journal and authorship criteria (see above).

Examples of study deficits that are frequently encountered are provided below:

No information on purity of test article – In determining evaluating the toxicity of a pesticide, it is critical to know the purity as it determines the dose given to experimental animals. Without this information, it is also not possible to attribute the observed effects to the pesticide when they may have been caused by a toxic contaminant.

Introduction of solvents to test article – For example, studies that use the organic solvent dimethyl sulfoxide (DMSO) or the detergent TWEEN-20 in oral dosing solutions would be scrutinized because the introduction of either can affect the oral bioactivity of a compound and spuriously alter or modulate a compound's toxicity. This precludes the use of such findings to establish a critical POD.

Lack of dose-response or statistical significance – PODs derived from endpoint data lacking a dose response or statistically significant differences between treated and control groups, or from studies only examining a single dose level are associated with unacceptable uncertainty.

Confounding experimental condition – For examples, if effects were only seen in groups of animals fed a high-fat diet, and not in animals receiving standard lab diet. This is a confounding condition of treatment and not relevant for studies that are used as surrogates for human health effects.

V. Conclusion

DPR is committed to ensuring public confidence in its efforts to protect human health by establishing and maintaining a transparent system by which pesticide data is evaluated. This guidance provides a description of the data acceptance criteria that are applied to registrant-submitted studies and open literature publications and how HHA scientists evaluate data quality for both pesticide registration and risk determination purposes. Central to HHA's efforts is the independent scientific review of data on pesticide impacts to human health. Data used in scientific decision making must be judged for their quality and relevance. Only those data that meet the acceptance criteria described herein should be used to support pesticide evaluation and risk determination activities.

VI. References

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