

Health and Safety

Report

Worker Health and Safety Branch

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Department of Pesticide Regulation's Human Subjects Protocol Review Process

By

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ABSTRACT

Title 3, California Code of Regulations, Section 6710¹ (3 CCR 6710) codifies the review and approval process for pesticide exposure studies conducted in California that involve human subjects. Per 3 CCR 6710, no person shall conduct any pesticide exposure study in California, which involves human participants, unless the Director of the Department of Pesticide Regulation (DPR) has given written authorization to the study director to conduct the pesticide exposure study according to an approved protocol. This document summarizes the scientific and ethical criteria that pesticide exposure protocols must meet for DPR to grant approval and specifies the protocol submission, review and approval processes for pesticide exposure studies conducted in California.

INTRODUCTION

This document provides guidance to study directors in preparing protocols that meet DPR's scientific and ethical standards and specifies the submission, review and approval processes necessary to receive protocol approval from DPR. The first section of this document explains DPR's protocol submission, review and approval processes. The second section provides guidance in developing pesticide exposure protocols that meet DPR's minimum criteria for scientific and ethical acceptability.

The Worker Health and Safety (WHS) Branch acts on behalf of DPR's Director to review and approve pesticide exposure protocols. 3 CCR 6710 provides regulatory guidance for the submission, review and approval process for pesticide exposure studies. 3 CCR 6000 provides regulatory definitions for institutional review board (IRB), human participant, and pesticide exposure study. These definitions and the text for 3 CCR 6710 are presented in Appendix 1 and are accessible electronically at: http://www.cdpr.ca.gov/docs/legbills/calcode/chapter_.htm.

PROTOCOL SUBMISSION, REVIEW AND APPROVAL PROCESSES

Table 1 outlines the review phases, review processes, and anticipated timeframes for initial protocol review and approval. Study directors should allow a minimum of three months for the entire DPR and IRB review and approval processes. DPR and the Office of Environmental Health Hazard Assessment (OEHHA) may require additional time for review in the following instances:

- The pesticide is not currently registered in California,
- The study is being conducted to meet California registration requirements,
- Evaluation of a new use scenario,
- Scientists have significant concerns about the safety of the pesticide,
- The study includes intentional dosing, or
- Study participants include children.

OEHHA and DPR's WHS conduct a concurrent protocol review. DPR's Human Subjects Review Coordinator (HSRC) compiles the appropriate comments from all reviewers and

includes them in a letter to the study director. WHS conducts the whole review process electronically via e-mail. This includes the protocol submission by the study director, reviews, and protocol approval. In addition to sending electronic versions, WHS sends the study director, via the United States Postal Service, the original signed letters containing the review comments, and DPRs provisional and/or final approval of protocols, protocol amendments and protocol renewals.

Table 1. Review Phases, Review Processes and Anticipated Time Frames for Initial Submissions of Pesticide Exposure Protocols

Review Phase	Review Process	Timeframe
Contact WHS	Call DPR's Worker Health and Safety Branch to obtain contact information for the HSRC.	
Submit Protocol	The study director submits the protocol electronically to the HSRC who acknowledges receipt via e-mail.	1 day
Concurrent Review	The HSRC forwards the protocol to OEHHA and designated WHS scientists for a concurrent review.	1 month
Review Comments	The HSRC compiles the review comments into a letter and sends them electronically to the study director.	2 weeks
Protocol Revision	The study director revises the protocol in response to the review comments.	Varies; depends on the extent of revisions and the study director's response time.
Provisionary Approval	When the revised protocol meets the DPR protocol requirements, WHS grants provisional approval.	1 week
IRB Approval	The study director obtains IRB approval.	1 - 4 weeks depending on the IRB review board schedule, required revisions, consent document translations, etc.
Final Approval	The study director electronically submits the IRB-approved protocol to WHS. The IRB stamp, signature and date must be on each page of the consent documents. Upon granting final approval, DPR will send a letter to the study director notifying him/her of the final approval.	1 - 5 days

Protocol Submission

The process for submitting pesticide exposure protocols to DPR is as follows:

- Contact WHS at (916) 445-4222 between 8 am and 5 pm Monday through Friday (state holidays excepted) to obtain contact information for the HSRC.
- Protocol Submission: The study director electronically submits the protocol package to the HSRC. The package should include the protocol, all consent documents, the Experimental Subject's Bill of Rights, and any related safety or health documents (Material Safety Data

Sheets (MSDS), pesticide product labeling, and participant questionnaires). Also provide documentation of the United States Environmental Protection Agency's (US EPA) Human Subjects Review Board (HSRB) protocol approval if the protocol was submitted to US EPA. WHS prefers the protocol submissions formatted as Microsoft® Word² (Word) documents. WHS also accepts Adobe® Acrobat®³ Portable Document Format (pdf) for documents bearing original signatures, date stamps, or other non-electronic markings. In the e-mail message accompanying the protocol submission, the study director should specifically request a DPR protocol review per 3 CCR 6710.

- Protocol Package Completeness: Usually within one work week, the HSRC reviews the protocol package to ensure the submission of all essential components, opens the electronic files to ensure they are readable, and that there are no substantial problems with the overall protocol package. Occasionally, the HSRC discovers omissions or substantial problems with the protocol package. In these situations, he/she will contact the study director by phone and/or e-mail to resolve them.
- Concurrent Review:
 - Upon receipt of a complete protocol submission package, the HSRC forwards the documents electronically to both OEHHA and WHS scientists for a concurrent review. WHS generally allows 30 days for completion of these reviews. During the review time, the HSRC may answer any questions.
 - WHS and OEHHA scientists review the protocol package within the context of relevant scientific guidelines. These guidelines include the US EPA's Office of Prevention, Pesticides and Toxic Substances (OPPTS) Testing Guidelines⁴, standards for the ethical conduct of human research studies found in the Common Rule (45 CFR Part 46)⁵, the National Institutes of Health (NIH)^{6,7,8}, and the National Academies of Science (NAS)⁹, as well as the reviewers' professional research and review experience.
- Review Comments: Once the HSRC receives the reviewer comments (30 days after submission for scientific review), he/she compiles the appropriate comments and sends them electronically to the study director (typically within 2 weeks). The reviewer comments address four areas:
 - **General Review**: Is the study design appropriate for achieving the study objectives? The study director must **respond** to the comments under General Review.
 - **Exposure Assessment**: Does the protocol adequately meet DPR data requirements for exposure assessment? The study director must **respond** to the comments under Exposure Assessment.
 - **Worker Protection/Ethical Considerations**: Are the study participants provided with adequate protective equipment? Does the study provide appropriate measures to prevent overexposure of study participants? Does the study provide adequate assurance that the study adheres to ethical principles. The study director must **incorporate** the revisions in the Worker Protection/Ethical Considerations section.
 - **Editorial Comments** - Editorial comments such as misspelled words pertain to any portion of the protocol package. The study director must **respond** to the comments under Editorial Comments, but may use discretion at implementing them.

- **Protocol Revision:** The study director revises the protocol to incorporate and/or address the review comments, and submits the revised documents back to the HSRC for review. A study director may contact the HSRC throughout this review phase to discuss the protocol and any questions regarding the review.

The time required for the study director to complete this phase varies greatly, depending on the amount of revisions and the significance of the revisions. For minor comments, the study director can complete the revisions to the document(s) within a few days. For substantial required revisions, significant registration or safety issues, or for a novel study design, this phase may require weeks to months for the study director to resolve the issues. The HSRC will arrange for telephone conference calls and/or meetings with the study director and pertinent DPR and OEHHA scientists should complex issues need resolution. Study directors can help facilitate the HSRC's review of the revised protocols if they:

- Use Microsoft Word's Review/Track Change function for revisions to the documents. The study director should not adopt the revisions, but leave them visible for the HSRC to review. Upon the HSRC's acceptance of the revisions, the study director can then adopt the revisions.
- Explain the revisions made in response to each review comment.
- For multiple revisions in response to a single review comment, provide the relevant page numbers associated with the revisions.

Upon receiving the revised protocol, the HSRC reviews the protocol revisions to make sure the study director addressed all of the review comments. If the HSRC determines the protocol adequately addresses all of the comments, he/she recommends provisional approval. If the HSRC determines one or more issues have not been addressed, he/she will compile the remaining comments and electronically send them to the study director. The HSRC can typically complete this review within a week.

- **Provisional Approval:** When the HSRC determines the study protocol meets DPR's scientific and ethical standards, DPR grants provisional determination of acceptability of the proposed pesticide exposure study.
- **IRB Approval:** Once the study director receives provisional approval, he/she must obtain protocol approval from an accredited IRB. The IRB must conduct its review in compliance with the Common Rule⁵.
- **Submission of IRB Approved Protocol:** The study director submits the following to WHS electronically, in Word and/or pdf format:
 - The final approved protocol,
 - The consent documents stamped with the IRB's signed and dated approval on each page, and
 - All documentation exchanged between the IRB and the study director related to the review, including documentation of the approval expiration date.
- **Final Approval:** The WHS Branch Chief makes the final decision regarding DPR approval or denial of the protocol and notifies the study director of the decision and the basis for the decision. The HSRC establishes an expiration date for DPR approval not to exceed that established by the IRB. If the study director cannot complete the pesticide exposure study by

the expiration date, he/she shall either discontinue the study or request a protocol renewal from DPR. The study director must wait for DPR to provide a written approval of the protocol renewal before continuing the study.

- HSRB Approval: For study protocols being submitted to the US EPA, HSRB¹⁰ approval is required. Submit the HSRB approval documentation with your protocol package to DPR.

Protocol Amendments

- The study director may make amendments to the approved protocol provided they do not have any potential health impacts on the study participants. If the potential impact on participants is uncertain, the study director should consult with the HSRC regarding the proposed amendment.
- The study director must request DPR approval for protocol amendments that may impact participant health. Such amendments may include changes to the participant recruitment and consent procedures, and changes to the study design that impact the participant's potential pesticide exposure.
- For any protocol amendments, the study director should submit a written request to the HSRC, preferably electronically. The request should include the proposed amendment, a justification for the amendment, the potential impact on the participants, and any measures proposed to mitigate these potential impacts.
- If the HSRC determines that participant health may be impacted, he/she forwards the proposed amendment and any accompanying documentation to WHS and OEHHA scientists for concurrent review. The review generally takes 2 – 3 weeks. Upon receipt of the review comments, the HSRC provides the comments to the study director. The study director makes any requested changes and submits the revised amendment back to the HSRC.
- DPR grants provisional determination of acceptability after the HSRC receives the revised protocol amendment. The study director must then obtain a review and approval of the proposed amendment from the approving IRB. The study director then submits the approved protocol to the HSRC. The approved protocol must include all documentation exchanged between the IRB and the study director.
- The WHS Branch Chief makes the final decision to approve or disapprove the proposed amendment and provides the study director with the written decision and the basis for the decision. If approved, the study director must conduct the pesticide exposure study in accordance with the amended protocol.

Protocol Renewal

The HSRC tracks current human subject protocol studies in a database. The database shows when the DPR protocol approval expires. Approximately two months prior to the expiration of the DPR protocol approval, the HSRC typically sends the study director a courtesy e-mail, informing him/her that approval will expire shortly. If the study director seeks to renew the protocol approval, he/she must submit study status information to the HSRC by the expiration date. The HSRC shall attach a Pesticide Exposure Study Status and Adverse Health Effects

Information Form to the courtesy e-mail to facilitate reporting of the following required information:

- A statement regarding the status of the study including information concerning the completion, postponement, or cancellation of the study, and
- A report and explanation of any complications or adverse health effects involving the participants and any actions taken.

If the study director wishes to renew the protocol approval, he/she must first obtain a renewal approval from the IRB. After receiving IRB approval, the study director requests a DPR protocol renewal via e-mail to the HSRC. The e-mail should include the following attachments: the protocol, the stamped, signed and dated consent documents, and all documentation exchanged between the IRB and the study director regarding the renewal.

The HSRC reviews the submitted documentation. If DPR approves the protocol renewal request, the WHS Branch Chief will inform the study director in writing. The HSRC establishes a revised expiration date, not to exceed the date established in the IRB's renewal recommendation. The DPR protocol renewal process generally takes 1 week excluding the time required for an IRB to complete their protocol review and renewal process.

Study Conduct

If during the conduct of the study, the study director notes any complications or adverse health effects, he/she must take immediate action to ensure the health and safety of the participants as per 3 CCR 6710. The study director must immediately notify DPR, via the HSRC, of such complications or adverse health effects and the immediate actions taken in response.

DPR or the county agricultural commissioner's staff may inspect the activities of the pesticide exposure study to evaluate compliance with the protocol. DPR or the commissioner may order the study director or participants to cease immediately any pesticide exposure activity that jeopardizes the safety of the participants. DPR may cancel the authorization to conduct the study whenever staff deems it necessary to protect the safety of the participants, the public, or the environment.

Conclusion of the Study

Before the expiration date specified by the IRB, the study director shall submit the following to the HSRC:

- A statement regarding the status of the study including information whether the study was completed, postponed, or cancelled.
- A report and explanation of any complications or adverse health effects involving the human participants and corresponding actions.

PREPARATION OF HUMAN EXPOSURE PROTOCOLS

The remainder of this document provides guidance to study directors in developing protocols that meet DPR criteria for scientific and ethical acceptability. It represents a compilation of DPR policy and “best protocol practices”, based on standards and guidance established by 3 CCR 6710, the US EPA, the Common Rule, the NIH, the NAS, and the reviewers’ own research and protocol review experience. Protocols developed according to this guidance will have the best chance for completing the review process quickly and generally with fewer review and revision comments.

Considerations for Ensuring Scientific Integrity

Purpose

The proposed research should clearly state the aim of the investigation or the study endpoint and should address a regulatory risk assessment issue, present a health or environmental benefit, or likely to produce useful information. It should present clear justification for the participation of human subjects. The protocol should address how the proposed research relates to previous scientific investigations, including relevant field, laboratory and animal studies. If the research is a pilot study, the protocol should discuss how the obtained information might impact future studies so that DPR can assess the potential long-range benefits of the pilot work. If the study involves a new pesticide or device, the study director should provide detailed information about the pesticide or device in an attachment.

Justification for Selecting the Pesticide

The proposed research should clearly state and support the rationale for selecting the pesticide(s) under study. What unique traits led the study director to select the pesticide(s)? Does the research augment previous work conducted for the pesticide(s)? Rationales for the selected pesticide(s) must include supporting data or characterization.

Methods

- The protocol must adequately address relevant testing standards, such as the US EPA OPPTS Testing Guidelines 875 Series⁴. Required elements may include the number of study participants, minimum exposure periods, types of matrices, frequency of sampling intervals, number of sites, etc.
- The study design must be appropriate for the number of variables being evaluated. Protocols submitted to DPR have often proposed to evaluate more variables than can be accomplished by the study design.
- The study protocol should specify an anticipated number of study participants that can provide statistical significance. Relevant testing standards often specify the required number of study participants. If testing standards are not available, the protocol must contain adequate statistical justification to support the number of study participants.
- The study protocol should provide adequate procedural detail to determine the appropriateness of the materials and methods. Since DPR recognizes protocol procedures must have sufficient flexibility to avoid unnecessary deviations, the protocol need not specify

every detail. If the protocol cites specific standard operating procedures (SOPs), include these SOPs in the protocol package.

- The study protocol should have sufficiently detailed methods, sufficiently rigorous study conduct standards (e.g., Good Laboratory Practice Standards [GLP]¹¹), and publicly available references to determine their adequacy for achieving the study objectives.
 - Study Standards – State the pertinent standards, such as OPPTS guidance, GLP, SOPs, etc.
 - Data Analysis – Provide a description of data analysis methods. Briefly explain all non-standard statistical or other analyses.
 - Analytical Methods – DPR and OEHHA scientists have noted that protocols may merely state that the methods have been validated, or that validated methods are available without publicly available references for these analytical methods. A study is only ethically valid if it is also scientifically valid. Exposing study participants is unethical without adequate assurance that the methods are available and appropriate for the research. The protocol must include sufficient detail or references to assure the reviewers that the study uses scientifically sound methods. The methods should minimally summarize such analytical parameters as sample preparation, extraction and analysis procedures, instruments, limits of quantification, mean recoveries from method validation, etc. If the protocol cites methods without providing overview information, the reference should be publicly available or attached.
- Control Measures – The protocol must include and specify sufficient control measures to control bias, ensure for adequate quality control and quality assurance provisions for field activities, analytical and data analyses, and for reporting components of the research.

Considerations for Ensuring Ethical Integrity

Study directors have a fundamental responsibility to safeguard the rights and welfare of research participants. The protocol must include a discussion of the participant protection issues relevant to the proposed research. The principal areas of ethical concern are:

- Minimizing potential risks to the study participants, with additional safeguards for vulnerable populations⁵,
- Equitable and representative participant selection,
- The participant's voluntary informed consent, and
- Maximizing the participant's privacy and confidentiality.

Subject Recruitment

At a minimum, the protocol must specify the following procedures for participant recruitment:

- Who the proposed participants are,
- The rationale for studying this group of individuals, including justification for recruiting vulnerable populations, such as persons who are illiterate, do not speak English as their primary language, minors, the frail or elderly, and persons from lower socio-economic groups. If applicable, specify the appropriate additional safeguards for enrolling potentially vulnerable populations.

- The study director should consider excluding illiterate individuals from participation as they may not understand the true nature of the information by simply hearing it read.
- If participants may be involved in additional studies, the Risks section should present justification and any added risks due to participation in multiple studies (discussed below).
- The total number of participants proposed for the study, the number in each group of the study, and the relevant testing guidance, statistical basis or other rationale for including these numbers of participants.
- The method used to approach potential participants,
- Who will approach the potential participants,
- The setting (location) for recruitment,
- Who will be present,
- The recruitment materials used (e.g., newspaper advertisement, posted signs, and/or video display). Submit a copy of the materials with the protocol.
- Whether the materials will be in more than one language, and
- The selection process the study director will use to select potential participants for the study. Participant selection must be equitable. This section should discuss the screening methods or tests employed to verify eligibility for inclusion in the study (e.g., drivers' license for proof of age, retail urine test kit to evaluate pregnancy status, blood acetylcholinesterase activity, physical exam, etc.).

Subject Consent Process and Documentation

The protocol must provide a detailed discussion of how, when, and by whom consent will be obtained and the proposed consent documentation. If the study will include non-English speaking participants, this section must discuss the participation of translators in the consent process.

Study Procedures

- Specify the location(s) where the study procedures will occur.
- Provide a detailed explanation of the procedures for each participant and compare this with the situation for non-participants. Describe all procedures considered experimental.
- List procedures in the order they will occur. If the study involves screening procedures, mention these first and identify them as tests that will determine participant eligibility.
- If the study involves a standard medical procedure, do not refer to it as "standard" or "routine", regardless of the risk. These terms convey the message that physicians commonly request/perform the procedure. Rather, convey the message of the necessity for this procedure for research purposes and that physicians commonly request/perform the procedure for clinical purposes. Specify the amounts of blood or urine being collected, using lay equivalents (e.g., teaspoons, ounces) for metric terms.
- Describe the frequency and duration of each study procedure, and the total amount of time required for participation in the study.
- Describe the alternatives to participation in the study to the prospective participant should he/she choose not to participate. For example, in a worker exposure study, will non-participants perform their usual tasks, or will they have alternative work available?

Risks and Discomforts

Risks and discomforts may range from physical to psychological to loss of privacy. Describe the risks and discomforts of each procedure.

- Discuss all possible risks and discomforts for participants in the study, and indicate both the severity and the likelihood for each.
- If applicable, discuss the risks of participating in multiple studies or trials.
- Include all possible risks, even unlikely ones.
- In addition to injury resulting from participation in the study, other risks and discomforts of participation may include inconvenience, travel or boredom.
- Consider loss of privacy a risk for participating in research, e.g., participation in research may mean a loss of confidentiality (or privacy). (See the Confidentiality Issues section on page 11.)
- Where appropriate, discuss the methods to minimize these risks, and the actions to take should these risks occur.

Treatment and Compensation

The protocol should discuss compensation and/or medical treatment for participants if a research-related injury or illness occurs, who pays the cost for immediate and future medical treatment, the name of the medical facility providing care, and who provides the transportation for medical treatment.

Benefits

Discuss the anticipated benefits, if any. If the participants receive no direct benefits from the study, state this. If the study provides general scientific benefits such as a greater understanding about safety working around the pesticide, indicate that these benefits may accrue.

Alternatives

State the alternatives, if any, to participating in the study. Generally, this means the individual does not participate and performs his/her usual job.

Confidentiality Issues

Avoid using legal statements concerning study participant access to records and personal identifiers. The protocol should state the degree of protection for personally identifiable information by addressing the following:

- Record retention periods: If no specific standard applies, such as GLP¹¹, indicate the length of the retention period as either permanently or indefinitely.
- Specify the conditions for release of personal identifiers and personally identifiable information. If the study includes the making of video or audio tapes, address their disposition.
- Will the study participants have access to their study results? If so, describe the arrangements for their access. Although not mandatory that the study director provide the results to the participants, many protocols state that study director will provide the results to participants who provide their contact information. Attach any forms used to record such information.

Amendments and Deviations

The protocol must discuss the procedure to address and document protocol (and SOP) amendments and deviations made after DPR and IRB approval. Additionally, per 3 CCR 6710¹, specify that any protocol changes involving potential health impacts to participants must receive **approval** by **both** DPR and the IRB.

Qualifications of the Investigators

Note the academic qualifications, faculty status, if applicable, and the length of applicable experience of the principal and co-investigators. For studies employing procedures that require specialized skills on the part of the study personnel, provide a brief summary of relevant information on the investigator's background, explaining his/her qualifications to perform these procedures. Do not submit a complete curriculum vitae.

References

If the protocol cites books, articles, methods, SOPs or other publications, list them in a bibliography. Include with the protocol any references not published in the open literature or available to the public on the internet.

Preparing the Informed Consent Form (ICF)

The study director (or study staff) may contact prospective participants in writing or by personal oral communication. He/she must inform the potential participant about the purpose, procedures, risks and benefits of that study, the participant's rights, and the freedom to decline to participate without any jeopardy. If applicable, explain any alternatives to the participant. The study director must give the potential participant the opportunity to obtain further information and have study-related questions answered. The ICF serves as a written summary of the exact information presented to prospective participants before they agree to participate in the study and provides a useful reference for both the participant and the study director. The ICF serves as a legal record to document the complete consent process.

Write consent forms in simple, non-technical language. For vulnerable populations, aim for a fourth to sixth grade reading level. For non-vulnerable populations, aim for a tenth grade reading level. Avoid using "I understand" or "You understand" language. Write the body of the ICF in the second person; write the consent section in the first person.

To make the ICF easier to understand, present the information under section headings. As a record-keeping aid to the participant, include the sequential page number in the ICF header or footer, e.g., page 3 of 7.

Include the following elements in a consent form:

- Study Purpose - Explain the purpose of the study, the expected duration, and the approximate number of participants involved in the study.

- Test Substance - Identify the test substance as a pesticide. Indicate the availability or provision of pertinent safety information (e.g., pesticide labels, MSDSs) to the study participants.
- Procedures - To emphasize the voluntary nature of participation in the study, this section should begin with the following or similar phrase: “If I agree to participate in this study, the following will happen”. Include all statements to which the participant must consent. Completely describe the procedures the participant must follow. Describe alternative procedures, if available.
- Risks and Discomforts - In lay language, describe all reasonably foreseeable study-related risks and discomforts to the participant. If applicable, include risks to the participant for participating in multiple studies or trials. Disclose all risks include remote, but serious ones. Avoid downplaying potential risks and discomforts. Include a statement of the possibility of unknown risks and discomforts.
- Alternatives – Specify and discuss the alternatives available to potential participants should they choose not to participate in the study. At the minimum, provide a brief paragraph clearly stating the possible alternate choices. Many ICFs merely state that the alternative is to not participate, or, for a worker exposure study, that non-participants will perform their usual work tasks.
- Exclusion Criteria - State the participation exclusion criteria, if any, such as age, gender, illiteracy, pregnancy, etc. State how the study director (or study staff) will evaluate the exclusion criteria (e.g., documentation of minimum age, how and when to conduct pregnancy testing and interpretation of testing results).
- Benefits – Describe possible direct or general benefits, if any, to the participant and others; indicate that benefits are not guaranteed. If study participation provides no individual benefits, but that the research may further the general knowledge of pesticide exposure, state such. Exclude a discussion of payment for participation from this section.
- Costs to the Participant – Clearly state in the consent form any expected cost the participant may incur while participating in the study. For example, will the participant bear the costs of travel to the study site? If so, this needs to be stated. When the participant will incur no costs for participating in the study, state this clearly.
- Payment for Participation – Researchers often pay individuals for participating in studies. The payment must adequately offset the participants’ time, travel and inconvenience, but not great enough to induce participation solely for the payment alone. State the total amount of payment for participation, the frequency of payment, and the form of payment. When discussing payment for participation, do not use the following terms: “compensation”, which designates compensation for injury, nor “reimbursement”, which connotes money provided for an accounting or tax purpose. Specify any conditions attached to the payment (e.g., pro-rated) if a participant does not complete the entire study. Alternatively, state that the participant will receive full payment regardless of the length of their participation in the study. Provide a payment schedule, if appropriate.
- Confidentiality – Briefly describe the procedures to protect participant confidentiality, i.e., coding of records, limiting access to the study records, not using personal identifiers in publications or reports.

- Medical Records - List any parties that may inspect the participant's medical records, if applicable. (Some IRBs have developed standard language that incorporate the listed parties into the protocol). Include an authorization to release medical records to all of the listed parties, if applicable. Otherwise, state that no one else has authority to inspect the medical records.
- Medical Treatment - Discuss compensation and/or medical treatment for participants if a research-related injury or illness occurs, who pays the costs for immediate and future medical treatment, the name of the medical facility providing care, and who provides transportation for medical treatment. The sponsor will arrange for transportation and pay costs associated with medical treatment for research-related injuries or illnesses.
- Subject Rights - Include a statement that the consent form does not waive participant's rights. Avoid language that suggests any participant waiver of rights or investigator release from liability. Avoid wording that may seem overly coercive or overly reassuring to a potential participant.
- Contact Persons - List at least one researcher and his/her telephone number as the contact person for participants to obtain information on research-related questions or research-related injury. For the participant's benefit, list the researcher's hours of availability. List the IRB as the contact for participant's rights. For their benefit, list the IRB contact, telephone number, and hours of availability.
- Voluntary Participation - Prospective participants must feel free from both coercion and inducement and must voluntarily decide to participate. Include a statement of voluntary participation and withdrawal, indicating that the participant may refuse to participate or may end participation at any time without penalty.
- Participation Termination Criteria - State the participation termination criteria: At a minimum, specify that the study director may end the individual's participation, for any reason, without his/her consent.
- New Findings - Include a statement that the study director will provide the participant with any significant new findings developed during the research that may affect the participant's willingness to continue in the study.
- Participant Copies - Include a statement that the participant will receive a copy of their signed and dated consent form and a copy of their signed and dated *Research Participant Bill of Rights*, in the appropriate language(s). Many IRBs have developed their own Bill of Rights. As examples, see the attachments for DPR's Bill of Rights, in both English and Spanish.
- Consent Statement - Include a statement of consent to participate, at the end of the form, near the signature section. This section should state that participation in the research is voluntary, and explain the individual's right to decline to participate, or to withdraw from the study at any time. If the study includes employees as participants, consider adding a phrase indicating that refusal or withdrawal from the study will not jeopardize their job.
- Assent Statement - If age criteria apply, include an assent that the participant meets the required minimum age, e.g., 18 years of age.
- Signature and Date Blocks - Include appropriate signature and date lines. At a minimum, include lines for the participant and the study director (or study staff) conducting the

informed consent discussion. If the study director uses the services of a translator to obtain consent, add a line for the translator to sign the form.

ICF Translation

The study director must provide the ICF in the appropriate languages for the participant population under recruitment. Many IRBs will develop and/or translate the consent form into the appropriate languages.

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11. Title 40 Code of Federal Regulations (Protection of Environment), Part 160 (FIFRA Good Laboratory Practice Standards) (1999 et seq.). Text available at: http://www.access.gpo.gov/nara/cfr/waisidx_02/40cfr160_02.html
Assistance available from US EPA at: <http://www.epa.gov/compliance/monitoring/programs/fifra/glpqanda.html>

Appendix I
California Department of Pesticide Regulation
RESEARCH PARTICIPANT BILL OF RIGHTS

The rights below are the rights of every person who is asked to be in a research study. As an experimental subject I have the following rights:

1. To be told what the study is trying to find out.
2. To be told what will happen to me and whether any of the procedures, pesticides, or devices is different from what would be used in standard practice.
3. To be told about the frequent and/or important risks, side effects, or discomforts of the things that will happen to me for research purposes.
4. To be told if I can expect any benefit from participating, and, if so, what the benefit might be.
5. To be told the other choices I have and how they may be better or worse than being in the study.
6. To be allowed to ask any questions concerning the study both before agreeing to be involved and during the course of the study.
7. To be told what sort of medical treatment is available if any complications arise,
8. To refuse to participate at all or to change my mind about participation after the study is started. This decision will not affect my status with my employer or my right to receive the care I would receive if I were not in the study.
9. To receive a copy of the Research Participant's Bill of Rights and the signed and dated consent form.
10. To be free of pressure when considering whether I wish to agree to be in the study.

Additional information regarding this research study is available either before or during the course of this study. If you have any questions or research-related side effects or injury, you should contact the California Department of Pesticide Regulation (DPR), Worker Health and Safety Branch, at (916) 445-4222, from 8 AM to 5 PM (Pacific Time), Monday-Friday, or by writing to the DPR, Worker Health and Safety Branch, 4th Floor, 1001 I Street, Sacramento, California, 95814.

If I have questions about my rights as a research participant, I may also contact the Independent Investigational Review Board, which is concerned with protecting the rights and welfare of research volunteers. I may reach them by calling (877) 888-4472, from 11:00 AM to 8:00 PM (Pacific Time), Monday-Friday.

Signature of Person Asked to Participate as a Research Subject Date

Signature of WHS Staff Date

A Spanish version is also available.

Departamento de Reglamentación de Pesticidas de California
CARTA DE LOS DERECHOS DEL PARTICIPANTE EN UNA INVESTIGACIÓN
CIENTÍFICA

Los derechos mencionados a continuación, constituyen los derechos de cada persona a quien se le pida que tome parte de un estudio de investigación científica.

En calidad de sujeto experimental, yo tengo los siguientes derechos:

1. Que se me informe que es lo que el estudio está tratando de averiguar.
2. Que se me informe que me sucederá y si algunos de los procedimientos, pesticidas o dispositivos, son diferentes a los que se usan en la práctica normal.
3. Que se me informe acerca de los riesgos, efectos secundarios [colaterales], o molestias, frecuentes y/o importantes, de las cosas que me sucederán para los propósitos de la investigación científica.
4. Que se me informe si puedo esperar algún beneficio por participar y, si es así, cuál sería el beneficio.
5. Que se me informe acerca de otras opciones que tengo y acerca de como ellas pudieran ser mejores o peores que estar en el estudio.
6. Que se me permita hacer cualquier pregunta(s) relacionadas con el estudio, tanto como antes de acceder a participar, así como durante el transcurso del estudio.
7. Que se me informe que tipo de tratamiento médico se encuentra disponible, si surgiese cualquier complicación(es).
8. Rehusarme a participar en absoluto o cambiar mi parecer acerca de la participación, después que el estudio haya comenzado. Esta decisión no afectará mi derecho de recibir la atención que yo recibiría, si no estuviese en el estudio.
9. Recibir una copia del formulario de consentimiento firmado y fechado.
10. Estar libre de presión cuando esté tomando en consideración si deseo acceder estar en el estudio.

Si tengo cualquier otra pregunta(s), yo debería preguntarle al investigador. Además, puedo ponerme en contacto con la Rama de Salud y Seguridad del Trabajador, del Departamento de Reglamentación de Pesticidas de California, la cual se ocupa de la protección de los voluntarios en proyectos de investigación científica. Yo puedo ponerme en contacto con ellos llamando gratis al (916) 445-4222, desde las 8:00 a.m. hasta las 5:00 p.m., de lunes a viernes, o escribiéndole al Departamento de Reglamentación de Pesticidas, Department of Pesticide Regulation, Worker Health and Safety Branch, 1001 I Street, Sacramento, California, 95814.

Firma de la Persona a la que se le Pidió que Participara

Fecha

Firma del personal de WHS

Fecha

Appendix II
TEXT OF CALIFORNIA REGULATIONS

TITLE 3. CALIFORNIA CODE OF REGULATIONS
DIVISION 6. PESTICIDES AND PEST CONTROL OPERATIONS
CHAPTER 1. PESTICIDE REGULATORY PROGRAM
SUBCHAPTER 1. DEFINITION OF TERMS
ARTICLE 1. DEFINITIONS FOR DIVISION 6

Amend section 6000 by adding, in alphabetical order, the following definitions:

6000. Definitions.

"Human Participant" means a living person who participates in a human pesticide exposure study conducted in order to obtain (1) data through intervention or interaction with the participant, or (2) identifiable private information. Intervention, as used in this definition, includes both physical procedures by which data are gathered and manipulations of the participant or the participant's environment that are performed for research purposes. Interaction, as used in this definition, includes communication or interpersonal contact between the investigator and human participant. Private information, as used in this definition, includes information about behavior that occurs in a context in which a participant can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by a participant and which the participant can reasonably expect will not be made public. Private information must be individually identifiable in order for the acquisition of that information to constitute research involving human participants. Individually identifiable means that the identity of the participant is or may readily be ascertained by the investigator or associated with the information.

"Institutional Review Board (IRB)" means an objective committee whose purpose is to review protocols of human pesticide exposure studies to ensure the safety and general welfare of the human participants, and to guarantee that their human rights are not violated. The Institutional Review Board shall meet the requirements as specified in Title 40 Code of Federal Regulations, (Protection of Environment), Part 26, (Protection of Human Subjects), when conducting a review of a protocol.

"Pesticide exposure study" means:

- (a) A data gathering project that meets one or more of the following criteria:
- (1) Human participants are to be directly exposed to the pesticide for the purpose of determining its pharmacokinetics or pharmacodynamics;
 - (2) Human participants are monitored and the use of the pesticide is not consistent with current accepted labeling or current regulations;
 - (3) Humans are exposed as the result of a contrived application in order to monitor exposure without routine pest control being a significant objective;

- (4) Human participants are monitored for the purpose of satisfying initial or continuing registration requirements of the U.S. Environmental Protection Agency or the department; or
 - (5) Human participants are monitored to develop or contribute knowledge of pesticide exposure to be generalized to other populations.
- (b) "Pesticide exposure study" does not include the following:
- (1) Data collected for the purpose of satisfying an existing health standard for exposure monitoring or if it is understood that routine monitoring is a condition of employment;
 - (2) Unscheduled monitoring of persons in response to a medical emergency to identify possible sources of exposure;
 - (3) Monitoring conducted by a government agency or by an employer, to determine the workplace exposure of his or her employees.
 - (4) Monitoring requested by an individual or group of individuals to determine personal exposure levels.
 - (5) The analysis or evaluation, after the human participant involvement has ceased, of existing or previously collected data, documents, records, specimens, or samples, if these sources are publicly available or if the information is recorded by the study director in such a manner that the human participants cannot be identified, directly or through identifiers linked to the participants.

"Study director" means the individual responsible for the overall conduct of a research project.

NOTE: Authority cited: Sections 11456, 11502, 12111, 12781, 12976, 12981, and 14005, Food and Agricultural Code. Reference: Sections 11408, 11410, 11501, 11701, 11702(b), 11704, 11708(a), 12042(f), 12103, 12971, 12972, 12973, 12980, 12981, 13145, 13146, and 14006, Food and Agricultural Code.

6710. Pesticide Exposure Studies Involving Human Participants.

- (a) No person shall conduct any pesticide exposure study in California, which involves human participants, unless the Director has given written authorization to the study director to conduct the pesticide exposure study according to an approved protocol.
- (b) The study director shall submit the protocol to the Director for review and provisional determination of acceptability.
- (c) The Director shall forward a copy of the protocol and review documentation to the Office of Environmental Health Hazard Assessment for concurrent review.
- (d) The Director shall provide comments to the study director on the basis of Department of Pesticide Regulation review and any comments from the Office of Environmental Health Hazard Assessment. The study director shall make any changes deemed necessary by the Director. Upon receipt of the Director's provisional determination of acceptability, the study director shall obtain a review and approval from an Institutional Review Board (IRB). The IRB must conduct its review in compliance with Title 40 Code of Federal Regulations (Protection of Environment), Part 26 (Protection of Human Subjects).
- (e) The study director shall submit to the Director the IRB's approval of the protocol and all documentation exchanged between the IRB and the study director related to the review.
- (f) The Director shall make the final decision regarding approval or denial of the protocol based on the information required in subsection (e), other relevant available information available

to the Director. The Director shall notify the study director in writing of the decision and the basis for the decision.

- (g) The Director shall establish an expiration date for the approved protocol. In no instances shall the expiration date exceed that established by the IRB. If a pesticide exposure study is not completed by the expiration date established by the Director, the study director shall not continue the pesticide exposure study until the Director has approved the renewal of the protocol in writing as required in subsection (i).
- (h) Protocol Amendment. The study director shall not make an amendment to the approved protocol that may impact the health of the human participants without approval from the Director. For amendments where participant health is potentially impacted, the study director shall make the request in writing. The proposed amendment, justification, potential impact on study participants, and any measures proposed to mitigate potential impacts shall accompany the request. The Director shall forward a copy of the proposed amendment and any accompanying documentation to the Office of Environmental Health Hazard Assessment for concurrent review. The Director shall provide comments to the study director on the basis of Department of Pesticide Regulation review and any comments from the Office of Environmental Health Hazard Assessment. The study director shall make any changes deemed necessary by the Director. Upon receipt of the Director's provisional determination of acceptability, the study director shall obtain a review and approval of the proposed amendment from an IRB as required in subsection (d). The study director shall submit to the Director the protocol and all documentation exchanged between the IRB and the study director. The Director shall notify the study director of the decision and the basis for the decision. If approved by the Director, the pesticide exposure study shall be conducted in accordance with the approved amended protocol. In the event that the potential impact on human participants is uncertain, the study director shall consult with the Director.
- (i) Renewal of Protocol. The study director shall obtain approval of renewal from an IRB as described in subsection (d) prior to requesting the Director's approval to renew the protocol. The study director shall submit, to the Director, the protocol and all documentation exchanged between the IRB and the study director regarding the renewal. After reviewing the documentation, if the Director approves the request for protocol renewal, the Director shall establish a revised expiration date. The revised expiration shall not exceed that date established in the IRB's renewal recommendation.
- (j) In the event of any complications or adverse health effects identified during the conduct of the study, the study director shall take immediate action to ensure the health and safety of the human participants. The study director shall immediately notify the Director of such complications or adverse health effects and the immediate actions taken.
- (k) The study director shall submit the following information to the Director by the expiration date:
 - (1) A statement regarding the status of the study including information as to whether the study was completed, postponed, or cancelled.
 - (2) A report and explanation of any complications or adverse health effects involving the human participants and what actions were taken.
- (l) The Director or agricultural commissioner of the county where the study is taking place may inspect the pesticide exposure study activities to evaluate compliance with the protocol. The Director or commissioner may order the study director or human participants to cease immediately any human pesticide exposure activity conducted during the study to protect the safety of the human participants. The Director may cancel the authorization to conduct the

pesticide exposure study whenever it is deemed necessary to protect participant safety, public safety, or the environment.

NOTE: Authority cited: Sections 12976 and 12981, Food and Agricultural Code.

Reference: Sections 12980, 12981, 12987 and 12988, Food and Agricultural Code.