OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION
WASHINGTON, D.C. 20460

September 8, 2025

MEMORANDUM

SUBJECT: Science and Ethics Review of the Liquid Spray On-Farm Potato Seed Treatment Study Protocol for Exposure Monitoring.

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Petition No.: NA
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REFERENCE: Russell R. (2025) Mancozeb: Liquid Spray On-Farm Potato Seed Treatment Study to Determine Dermal and Inhalation Exposure of Workers to Mancozeb during the On-Farm Treating, Loading, and Planting of Treated Potato Seed Pieces, unpublished protocol dated May 13, 2025, prepared for UPL NA, Inc. 73 p.

Introduction

EPA has reviewed the referenced protocol titled *"Mancozeb: Liquid Spray On-Farm Potato Seed Treatment Study to Determine Dermal and Inhalation Exposure of Workers to Mancozeb during the On-Farm Treating, Loading, and Planting of Treated Potato Seed Pieces"* as well as "*Overview and Justification For New Mancozeb Handler Exposure Study Scenarios*" submitted by UPL Limited to determine if the protocol meets requirements based on current guidelines. The study's protocol was submitted to EPA in June 2025. This protocol is intended to collect occupational exposure measurements to represent potential exposures to mancozeb for three handler scenarios related to "on-farm" liquid pesticide treatment[1] of potato seed pieces (PSPs) and provide more representative exposure data for these on-farm activities, according to the protocol. The following scenarios are to be addressed in the study:

(1) Treating PSPs on-farm with a liquid spray (T-PSP-L-OF),

(2) Loading treated PSPs on-farm into a multi-row potato planter (L-PSP-OF), and

(3) Planting treated PSPs (P-PSP-OF).

Scientific aspects of the proposed research are assessed in terms of the recommendations of the EPA Series 875 Guidelines and of the Human Studies Review Board (HSRB). Ethical aspects of the proposed research are assessed in terms of the standards defined by 40 CFR 26 subparts K and L.

This memorandum was developed in full compliance with *EPA Scientific Integrity Policy for Transparent and Objective Science*, and EPA Scientific Integrity Program's *Approaches for Expressing and Resolving Differing Scientific Opinions.* The full text of *EPA Scientific Integrity Policy for Transparent and Objective Science*, as updated and approved by the Scientific Integrity Committee and EPA Science Advisor can be found here: EPA's Scientific Integrity Policy. The full text of the EPA Scientific Integrity Program's *Approaches for Expressing and Resolving Differing Scientific Opinions* can be found here: Approaches for Expressing and Resolving Differing Scientific Opinions | US EPA.

[1] Seed treatment can be conducted commercially or 'on-farm'. Commercial seed treatment is a much larger-scale operation of treating and storing seeds while on-farm treated seeds are generally loaded and planted directly after treatment (although short-term storage is sometimes necessary).

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1.0 Completeness of Protocol Submission

The submitted protocol was reviewed for completeness against the required elements listed in EPA's human studies regulation. EPA's checklists are appended to this review and can be found in Appendix B. All elements of required documentation are provided in the submitted protocol package and supplementary documentation provided by Advarra Institutional Review Board (IRB).

2.0 Summary Assessment of the Scenario Design

Section 2.1 and 2.2 provide a summary of the scenario and sampling designs of the submitted protocol, respectively. Supporting details are in Appendix A, Section 2.0.

2.1 Scenario Design

The submitted protocol is designed to address occupational dermal and inhalation exposures from workers conducting normal work functions/tasks (*i.e.*, treating, planting, and loading) during on-farm potato seed treatment.

Application formulation: Potato seed pieces (PSPs) will be treated with a liquid product containing the active ingredient (ai), mancozeb (4 lbs ai/gallon).

Application equipment: The study will involve standard/typical on-farm seed treatment equipment such as barrel (fitted with spray nozzles) or linear-style treaters, conveyor/auger loading systems, and tractors with planters attached. Automatic controls are included for regulating the flow of PSPs through the system, agitating spray mixtures, etc. The study will only involve liquid spraying systems with internal and/or shielded spray nozzles. The protocol notes that it is preferable to have variability in equipment within each monitoring area, but that overall, the proposed equipment to be monitored is representative of that which is used in on-farm PSP treatment. *Note: PSPs may have been treated on the farm prior to arrival of the researchers (up to three weeks prior to exposure monitoring) in which case, application rates and treatment process will be monitored and documented as part of the study records. PSPs treated in advance at a commercial facility will not be included as information from the National Potato Council (NPC) indicates that most growers do not utilize commercial PSP treaters.*

Worker activities: As noted, workers will be monitored completing their normal work functions during on-farm PSP treatment. In order to keep the tasks separate and distinct, workers with mixed job functions will not be included in the study. The following work activities are included:

- Treaters (T-PSP-L-OF): activities associated with treating PSPs in preparation for immediate planting or subsequent short-term storage. Activities can include open pouring/mixing test substance, operating treating equipment, adjusting treating equipment, monitoring ancillary treating equipment, cleaning treating equipment, etc.
- Loaders (L-PSP-OF): activities associated with loading or transferring treated seed from trucks or other transport vehicles. Activities can include opening/closing chutes, monitoring conveyors, monitoring the fill level of the planter or planter-loader, operating planter loaders, etc.
- Planters (P-PSP-OF): activities associated with operation or maintenance of the potato seed piece planter. Activities can include driving an enclosed-cab tractor attached to the planter,

occasionally leaving the tractor cab to adjust or unclog the planter or make field repairs to the planter, etc. Cleaning the PSP hopper will not be part of allowed functions for the planter; this would be performed by the loader.

Clothing and Personal Protective Equipment (PPE): The label requires that for PSP treatment, workers wear long-sleeved shirt, long pants, shoes, socks, chemical-resistant gloves and a respirator with a minimum of a NIOSH-approved particulate filtering facepiece respirator with any N, R, or P filter; OR a NIOSH-approved elastomeric particulate respirator with any N, R, or P filter; OR a NIOSH-approved powered air-purifying respirator with an HE filter. The protocol requires that workers wear label-required PPE plus additional PPE including a second layer of clothing (*e.g.*, cloth coveralls) and gauntlet-style gloves when handling test substance or treated seed, or when in contact with treating equipment. Coveralls will be worn by the treater (when handling the formulated product or working with or around the potato seed treater) and by loaders (if they enter a planter hopper (*e.g.*, remove remaining PSPs)). Gauntlet style chemical resistant gloves (*i.e.*, gloves that cover the hand and part of the forearm at least 18 inches in length) will be worn by the treaters (when contact with the test substance is possible), by loaders (at all times while performing tasks), and planters (any time they are outside of the cab of the tractor and exposed to the test substance or treated PSPs). Workers who choose to wear full-face respirators or face shields will not be included in this study. A summary taken from the protocol can be found in Table 2.1 below.

Table 2.1. Summary of Worker Clothing and PPE to be Worn (Protocol, p. 10 of 73)

Personal Protective Equipment	On-Farm Seed Treatment Activity		
	Treater	Loader	Planter
Gauntlet-Style Chemical-Resistant Gloves	During all treating tasks; and during any other task with potential contact with product or treated PSPs	During all loading tasks; and any other task with potential contact with treated PSPs (not allowed to handle product)[2]	When exiting the cab performing any task with potential contact with treated PSPs (not allowed to handle product)
Second Layer of Cloth Clothing	During entire monitoring period	When entering the planter hopper (*e.g.*, to remove remaining treated PSPs; not allowed to handle product)	Never (not allowed to enter the planter hopper or handle product)
Respirator[1]	When opening containers, pouring liquid, or cleaning the treater	During all loading tasks (not allowed to handle product)	Never (not allowed to load treated PSPs, enter the planter hopper, or handle product)

1. Not including full-face respirators.
2. Although not common, at times a worker assigned to one activity may participate in another activity as part of their normal workday (*e.g.*, treaters assisting in loading PSPs). However, for the purposes of this monitoring study, the objective is to have exposure results strictly representing each scenario. Therefore, workers with mixed job functions will not be included in the study.

Workers and Work Locations [Monitoring Units (MUs)]: An MU is a term that represents a single measurement of exposure that comes from one worker performing one PSP-related task on one day. Three MUs will be selected for each job function at each of 7 study locations identified by researchers, resulting in a total of 63 MUs [21 MUs for each activity in 7 monitoring areas]. Details regarding the selection of workers and locations is further described below in Section 2.2.

Amount of Product and Chemical Handled: The amount active ingredient handled (AaiH, typically in pounds) within each monitoring area will be a component of the selection process for all MUs, achieved by selecting for differing rates of application, length of workday, amount of seed treated, and/or acres of PSP planted. Details regarding selection of AaiH can be found in Section 2.2.

Sampling: Dermal and inhalation exposure of the MUs will be measured using the following matrices: inner whole-body dosimeters (WBD), face/neck wipes, hand washes, and personal air sampling pumps. Details regarding sampling methods can be found in Section 2.2.

2.2 Sampling Design

Following contemporary practices for occupational pesticide monitoring studies, the protocol calls for a two-stage selection process to diversify the monitoring data collected for a given scenario. The first stage consists of selecting specific geographic locations and specific farms/sites for monitoring operations. The second stage consists of selecting subjects and other handling conditions within each site to construct a diverse set of data. The selection procedure is primarily non-random but involves some random choice components (*e.g.*, specific timing dependent on weather/climate, soil conditions, etc.). Whenever feasible, random selection of MUs will be used to reduce the possibility of intentional or unintentional selection bias.

In the first stage, monitoring area is defined as a particular geographic area that will contain each set of three new MUs. The process for selecting geographically diverse monitoring areas includes:

1. Restricting each scenario to target U.S. states where the usage of mancozeb-containing liquid products are applied to PSPs on-farm is most common.
2. Partitioning the restricted scenario area into non-overlapping geographic strata.
3. Selection of 7 strata that will contain a single monitoring area per scenario.
4. Locating the specific monitoring area within each stratum. (UPL NA Overview and Justification, p. 25 of 44)

As noted, exposure monitoring is targeted to be conducted on farms in locations representative of potato growing regions. The protocol targets 7 states that were reported to have planted some of the largest quantities of potatoes in 2023 according to the National Agricultural Statistics Service (NASS). The locations are presented in Table 2.2 below.

Table 2.2. Proposed Study Monitoring Areas

State	Acres of Potatoes Planted 2023 (NASS)	EPA Growing Region
Idaho	330,000	XI
Washington	165,000	XI and/or XII
Wisconsin	68,000	V
Colorado	55,000	VIII and/or IX
Maine	53,000	I
Michigan	50,000	V

In the second stage, a set of three MUs is constructed in each area for each scenario based on second-stage diversity selection. This process consists of several steps including:

1. Stratification of amount of active ingredient to be handled based on a practical range for each scenario.
2. Specification of a set of mandatory and preferred similarity restrictions that will be used to enhance within-configuration diversity among MUs.
3. Identification of eligible employers and workers willing to participate.
4. Selection of a diverse (and ideally cost-effective) set of three MUs for each scenario.

Selection will utilize "similarity restrictions" (to reduce any potential data correlation thereby increasing the likelihood to capture overall variability) when selecting three MUs within any monitoring area including:

1. No two MUs obtained for the same scenario can utilize the same worker.
2. No two workers in the same monitoring area used for the same scenario can have the same employer.
3. It is preferable that an employer does not contribute a worker for the same scenario to another monitoring area if the employer has previously contributed an MU.
4. It is preferable that no two MUs obtained for the same monitoring area will be in the same AaiH stratum.
5. It is preferable that each set of three MUs in a monitoring area will vary by treater type, loading system, and planter size.

Research staff will refine facility lists into workable geographical areas and contact facilities by phone or in person to explore interest in participating in the study. An eligible farm must:

1. be willing to participate in the study and allow collection of exposure matrices through the workday and agree not to coerce or influence employee's decision to participate in the study in any way;
2. handle potato seed with liquid mancozeb (with specified concentration and application rates);
3. plan to treat, load, or plant potato seed treated on the day of exposure monitoring (up to 21 days of storage permitted after treating); and
4. employ at least one eligible worker whose normal task includes treating, loading, or planting PSPs.

Research personnel will then ask the participating facilities to prepare and post a letter to employees in the workplace stating they have been contacted about a study of the work activities and informing employees that research personnel will visit to speak with employees who may be interested in participating in the study. The research team will also provide a recruitment flyer to post in the workplace (Protocol, pp. 15 to 24 of 73).

To provide additional diversity in general, as well as to facilitate regression analyses, diversification of the AaiH, within each monitoring area will be a component of the selection process for all MUs, achieved by selecting for differing rates of application, length of workday, amount of seed treated, and/or acres of PSP planted. Estimates are based on a minimum 4-hour workday and information from the NPC, state organizations, industry groups familiar with local facilities, etc. The AaiH is stratified with the upper and lower strata having about a 67-fold difference and the middle a 6-fold difference from the lower strata. The amount-handled strata are as follows:

- Treating PSPs with Liquid Mancozeb On-Farm and Loading Mancozeb-Treated PSPs On-Farm (T-PSP-L-OF and L-PSP-OF)
    - 2.3 to 8 lbs
    - 8.1 to 46 lbs
    - 47 to 155 lbs
- Planting Mancozeb-Treated PSPs On-Farm (P-PSP-OF)
    - 1.1 to 3.7 lbs
    - 3.8 to 22.2 lbs
    - 22.3 to 75 lbs

The protocol notes the narrower range for planting is due to the fact that only one worker will be monitored while planting; the high end of AaiH for the treating/loading ranges are based on a worker treating or loading for more than one planting machine operating at the same time.

The AaiH for treating will be based on the amount of product handled by the worker during the monitoring period, even if all product was not applied to the PSPs (*e.g.*, if product is poured into the treater but not all applied to the PSPs, AaiH will be based on the amount poured). Additionally, PSPs treated at a commercial facility will not be used for the loading (L-PSP-OF) or planting (P-PSP-OF) exposure scenarios due to information from NPC indicating that most of their growers do not utilize commercial PSP treaters and if done, utilize similar spray equipment; therefore, it is not expected to limit the ability of locating researchers to locate growers for the study. For logistical and cost reasons it is preferred that growers treat, load and plant on-farm PSPs on the same day, however, because that does not always realistically happen, planting delayed up to three weeks[2] will be permitted; a degradation curve developed from a study conducted by the sponsor[3] will be used to estimate the AaiH (*i.e.*, the potential amount of AaiH the planter is exposed to, days or weeks after treatment) so each P-PSP-OF MU can be fit into an appropriate stratum of AaiH.

As noted in Section 2.1, dermal and inhalation exposure of the MUs will be measured using matrices including inner WBDs, face/neck wipes, hand washes, and personal air sampling pumps. Before beginning work, research personnel will meet with the worker being monitored. Workers will be asked to put on the inner dosimeter under the worker's clothing. The worker's clothing will be inspected for tears or large holes and researchers will trim the inner dosimeter arm and pant cuffs, as needed. If needed, equivalent replacement clothing will be provided by the researchers. Workers will be fitted with a low volume personal air sampling pump. The OSHA Versatile Sampler (OVS) tube will be placed in the worker's breathing zone with the inlet facing downwards, similar to the nasal passage of a worker. Samples will be taken as follows:

- Inhalation samples will be taken upon completion of exposure monitoring period and frozen until analysis.
- The inner WBDs will be collected post-exposure monitoring period, cut into 6 sections (lower arms, upper arms, front torso, rear torso, lower legs, and upper legs), and frozen until analysis.

[2] NPC indicated growers sometimes wait up to three weeks before planting to promote suberization. (UPL Overview and Justification, p. 33 of 44)

[3] The study to develop a degradation curve usually involves sampling from a pile of PSPs on a concrete floor in a cool and ventilated setting, prior to the exposure study.

- Face/neck wipe samples (two sequential) and hand washes will be collected during the exposure monitoring period and frozen until analysis. Samples will be composited and analyzed as one sample for the monitoring period.

In addition, sample matrix fortifications will be prepared and are designed to assess stability of the active ingredient under field storage and transit conditions/during the exposure monitoring periods. The fortifications will involve all four matrices (*i.e.*, air sampling, hand wash, face/neck wipe, inner WBD), each having three fortification levels to be determined at a later date.

3.0 Summary Assessment of the Scientific Aspects of the Study Design

3.1 Statistical design

The primary study objective is to characterize the variability and central tendency of dermal and inhalation exposure measurements, reflecting workers that handle mancozeb (for each activity) in an on-farm PSP treatment. The secondary objective of the study is to provide data that can be used to evaluate the relationship between dermal and inhalation exposure and AaiH for each scenario. AaiH is the default normalizing factor in assessment of occupational pesticide exposures for regulatory purposes as it has been assumed to be generally proportional to resulting exposures.

Three exposure scenarios are proposed, representing three main tasks associated with potato seed treatment: treating PSPs, loading treated PSPs, and planting treated PSPs. Twenty-one MUs for each scenario will be collected based on a "7 areas by 3 MU per area" design. Ranges of AaiH were selected and fit into strata for each activity as described in Section 2.2. The protocol states that these conditions were proposed based on previous work done by the Agricultural Handler Exposure Task Force (AHETF), a pesticide industry consortium that conducted dozens of occupational pesticide exposure monitoring studies over two decades from 2000-2020:

"*Sample sizes are determined based on the experiences of the Agricultural Handler Exposure Task Force (AHETF). The objective of the study is not to obtain purely random samples of workdays from the respective scenario populations; it is to obtain a set of experimental handler-days (i.e., MUs) spanning a diversity of conditions that are expected to influence exposure directly or indirectly*" (UPL NA Overview and Justification, pp. 20 and 21 of 44).

The UPL NA Overview and Justification document notes that "*the AHETF has developed many sets of MUs for various handler scenarios and conducted extensive statistical modeling to establish procedures for determining sample sizes that would meet certain accuracy requirements that would provide sufficient statistical power to evaluate the proportionality with AaiH*." Thus, the specific "7 x 3" sample size configuration was determined using Appendix C of the AHETF "Governing Document" (AHETF, 2010) indicating that "*a combination of 7 locations by 3 MUs/location would be acceptable in terms of statistical power for a given scenario in order to meet the AHETF's primary benchmark objective (i.e., ≤3-fold relative accuracy of important stats when geometric standard deviation (GSD) = 4 and intra-cluster coefficient (ICC) = 0.3)"* (UPL Overview and Justification, p. 23 of 44).

The specific "7 x 3" sample size configuration was determined using Appendix C of the AHETF "Governing Document" (AHETF, 2010) indicating that "*a combination of 7 locations by 3 MUs/location would be acceptable in terms of statistical power for a given scenario in order to meet the AHETF's primary benchmark objective (i.e., ≤3-fold relative accuracy of important stats when geometric standard deviation (GSD) = 4 and intra-cluster coefficient (ICC) = 0.3)"* (UPL NA Overview and Justification, p. 23 of 44).

3.2 Proposed Pattern of Human Exposure

Participants will be monitored using liquid formulated product while they conduct normal work activities including the treating, loading, and planting of PSPs. The participants will handle an amount of the active ingredient, mancozeb, that will fall into lower, mid, and upper strata as described in Section 2.2. The proposed minimum exposure monitoring duration for each MU is described as being representative of a full day of work (generally a minimum of 4 hours).

3.3 Endpoints and Measures

The dermal and inhalation exposure data measured in this study will be used to estimate dermal and inhalation exposure to the active ingredient, mancozeb. The EPA may also utilize this data generically for other pesticides.

Dermal exposure will be measured using WBDs that are to be worn beneath the subject's outer clothing. After the monitoring event, the inner dosimeter will be removed from the subject and cut into 6 sections: lower arms, upper arms, front torso, rear torso, lower legs, and upper legs. In addition, samples via face/neck wipes and hand washes will be taken throughout the exposure monitoring period, composited, and analyzed.

Inhalation exposure will be measured using an OVS tube sample collector connected to a personal sampling pump calibrated and operating at 2L per minute. The air pump will be turned on throughout the monitoring period, including during breaks.

Worker activities throughout the workday will be observed and documented by UPL researchers with a detailed time log. Photographs will be taken of representative study-related activities during exposure monitoring. Additional measures will be detailed such as equipment descriptions (*e.g.*, what equipment, how it is used, etc.). EPA believes that the proposed measures are appropriate and sound for the study design.

4.0 Quality Assurance/Quality Control (QA/QC) Plan

"This study will be conducted in compliance with the U.S. EPA Good Laboratory Standards and will adhere to applicable Testing Facility Standard Operating Procedures (SOPs) and research practices. In-process data and report audits will be performed by the Testing Facility's Quality Assurance Unit (QAU) to ensure compliance with GLP regulations and adherence to this protocol and relevant SOPs. The data package and final report will be audited prior to completion Additional auditing by the Sponsor or Analytical Laboratory QAU may also be conducted" (Protocol, p. 6 of 73).

"*GLP purity analysis for mancozeb will be performed for each available lot of test substance used in the study concurrently with the study conduct. Duplicate samples of each available lot will be collected and shipped to an analytical facility. Documentation of these analyses will be retained in the study raw data*" (Protocol, p. 28 of 73).

The analytical laboratory will prepare a report detailing procedures used and results obtained during the analytical portion of the study. Field fortification solutions will be prepared and pre-measured into vials by the analytical laboratory and shipped to the research team for field recovery evaluation on all field fortified matrices except OVS tubes. The OVS tubes will be pre-spiked at the analytical laboratory and kept frozen until use in the field. Samples of each matrix will be fortified in triplicate at levels to be determined for the following matrices: air sampling OVS tube, hand wash, face/neck wipe, and inner dosimeter. After fortification, matrices will be exposed to ambient conditions with the exception of the hand wash and neck/face wipes which will be fortified and immediately frozen. Duplicate samples of inner dosimeter sections fortified in the field and duplicate OVS tubes fortified in the laboratory at the highest level (travel spikes) will also be analyzed concurrently with field samples.

5.0 Statistical Analysis Plan

The protocol states that data of each scenario (T-PSP-L-OF, L-PSP-OF, and P-PSP-OF) and exposure route (dermal and inhalation) will be analyzed separately for each evaluation below:

Characterizing the Normalized Exposure Distribution
Estimated statistics of normalized dermal and inhalation exposure distribution will be determined. The estimated statistics include (but are not limited to) the arithmetic mean, geometric mean, standard deviation, and coefficient of variation. Normality of the log(normalized exposure) data will be tested and the expectation is the data will be log-normally distributed. Therefore, statistical methods applicable to lognormally distributed data will be used.

Evaluating the Relationship between Exposure and AaiH
The relationship between AaiH and exposure will be evaluated for each PSP scenario in this study. Linear regression of log exposure on log AaiH will be conducted for total dermal exposure and for total inhalation exposure. The 95% confidence intervals (CIs) of the estimated slopes will be used to judge the proportionality assumption between exposures and AaiH.

6.0 Compliance with Applicable Scientific Standards

This protocol adequately addresses the following elements according to applicable scientific standards:

- Scientific objective
- Experimental design for achieving objectives
- Quantification of the test materials
- Data collection, compilation, and summary of test results
- Justification for selection of test substance and dilution rate
- Justification for sample size

- Fortification levels and number of samples for laboratory, field, and storage stability samples

The objective of determining worker exposures (dermal and inhalation) from mancozeb PSP treatment is clearly defined as well as the experimental design to achieve these objectives including geographic and participant selection, sample size, sampling methods, etc. Fortification levels are not currently provided (*i.e.*, to be determined); however, the methodology is clearly defined. Additionally, the proposal has addressed the technical aspects provided in the applicable exposure monitoring guidelines (*i.e.*, Series 875 Group A and OECD Applicator Guidelines) as well as Good Laboratory Practices (GLPs).

Recommendations:

The EPA provides the following recommendations and comments:

- Revise the protocol to provide information regarding type(s) of potato being treated and how representative the data are for other varieties of potatoes (*e.g.*, Russet, fingerling, Yukon Gold, etc.).
- EPA recommends collecting exposure data that represents workers wearing a single layer of clothes (*i.e.*, no coveralls) in addition to or instead of data representing two layers of clothing for all activities or providing rationale for not monitoring this "single layer clothing" scenario.
- Provide justification for the exclusion of workers who choose to wear full-face respirators.
- Statistical Analysis Plan section in the protocol should also indicate that:
  - "normalized exposure" data is referring to exposure normalized by the amount of active ingredient handled (AaiH) (*i.e.*, *exposure/AaiH)*;
  - mixed-effects model will be used to analyze the log(normalized exposure) data, and GSD, GM, AM, and the 95th percentile of normalized exposure data distribution will be derived/estimated using the statistics estimated from the mixed model;
  - Data adequacy will be determined by:
    - the accuracy (*i.e.*, fold relative accuracy or fRA) of the estimated statistics (GM, AM, and 95th percentile) of normalized exposure will be evaluated, given the study design and the observed data from the study (note that the assumptions GSD ≤ 4 and ICC ≤ 0.3 for PSP exposure data proposed in this study protocol might not be true (*i.e.*, the observed GSD > 4 or ICC > 0.3) and therefore, the fRA might be greater than the objective benchmark fRA of 3); and
    - the width of 95% CI of the estimated slope will used to determine if the post-hoc power to detect proportionality vs. independence between AaiH and exposure is sufficient. Specifically, if the width of 95%CI of the estimated slope is ≤ 1.4, the post-hoc statistical power to detect proportionality would be ≥ 80%.
- EPA recommends that the study not be utilized in the field unless validated methods are incorporated into the protocol prior to monitoring.

EPA Science Conclusions

Provided the protocol is revised to address the noted technical aspects of applicable exposure monitoring guidelines, the protocol is likely to produce scientifically valid and useful data to estimate/assess on-farm potato seed treatment exposure.

7.0 Summary Assessment of Ethical Aspects of the Proposed Research

This section summarizes EPA's evaluation of the ethical aspects of the proposed study based on the protocols submitted by UPL NA Inc., as well as the following additional documents:

- Overview and Justification for New Mancozeb Handler Exposure Study Scenarios
- Flyer dated 13 May 2025
- Employer Letter dated 6 May 2025
- Informed Consent Form dated 6 June 2025
- Research Participants Bill of Rights dated 13 May 2025 Telephone Screening Script – Employer dated 13 May 2025
- Telephone Screening Script – Potential Volunteer dated 13 May 2025
- Advarra IRB Protocol Approval with Modifications dated 11 June 2025
- IRB Correspondence & Associated Documents

This summary assumes that all relevant documents are amended to address all of EPA's comments as outlined below.

7.1 Societal Value of Proposed Research

The purpose of this study is to "*determine dermal and inhalation exposure to the active ingredient mancozeb when workers in farming operations perform activities associated with the on-farm treating using a liquid formulation, and then loading, and planting of potato seed pieces (PSP or seed) that have previously been treated with a mancozeb formulation containing 4 lb a.i./gallon*" (Protocol, p. 5 of 73). Workers will be monitored when performing one of three tasks on the farm – treating potato seed pieces with liquids, loading treated potato seed pieces, or planting treated potato seed pieces. This study is designed to "*generate new data exclusively for potato seed pieces and utilizing treating, loading, and planting equipment that reflect current on-farm practices for potatoes*" (UPL NA Overview and Justification, pp. 18-19 of 44). The data will be submitted to EPA to support the registration review for mancozeb. The "*data [from this study] will provide a better definition of exposure for on-farm uses of liquid mancozeb with PSPs and will also include additional engineering controls, clothing, and PPE that will reduce the potential for workers that handle liquid formulations of mancozeb on-farm*" (UPL NA Overview and Justification, p. 19 of 44). Additional dermal and inhalation exposure data are needed to accurately characterize the exposure potential for workers performing these tasks. EPA will use this data in evaluating the exposure of workers treating, loading, and planting PSPs.

7.2 Subject Selection

A total of up to 63 subjects will be required to conduct the study – three workers per task (nine workers total) in each of seven geographical areas identified in the protocol. Recruitment will occur from farms that agree to allow participation by their employees. The farm selection process will begin with the Study Director compiling a list of farms that perform on-farm potato treating within each of

the seven proposed monitoring areas. This list will be developed with information from various groups, "and may include an informal survey, mass mailing, or phone campaign" (Protocol, p. 16 of 73). Researchers from the study team will speak with potentially qualified employers by phone or in person about the study and site eligibility criteria. Employers must agree to post an Employer Letter and recruitment flyer, allow collection of samples from workers during the workday, and agree not to coerce or influence workers' decisions to participate in the study. The Employer Letter notes who will be conducting the study, that the employer has given permission for the study to be conducted at the farm, that participation is completely voluntary, and that a worker's decision to participate or not will not impact their continued employment or wages.

A recruitment flyer that summarizes the study and outlines eligibility criteria will be posted at the farm with the Employer Letter. This flyer invites interested candidates to contact the research team for more information and/or to attend an informational meeting. Those who call will receive preliminary information about the study. The introductory meetings will involve research personnel outlining the study and explaining the requirement for informed consent. Those who are interested in participating in the study after hearing this information will be invited to attend a private discussion with a member of the research team to go through the consent process.

The protocol limits participation to one person per task per farm. In the event that more than one individual attends the introductory meeting and expresses an interest in enrolling to be monitored for the same task, the protocol indicates that a random selection (*e.g.*, drawing straws) will be made about which individual can move forward with the consent process.

The inclusion/exclusion criteria in the study protocol are as follows, with EPA's recommended additions in red:

Eligibility Criteria

- Males or females at least 18 years old
- Employed by an eligible facility and have at least 5 days experience of the job function that will be monitored
- Willing to perform the monitored tasks in compliance with the label directions and to wear the label and study-required PPE
- Speak English or Spanish
- In good general health
- Allergies or sensitivities to Aerosol OT (the solution to be used to collect hand wash and face/neck wipe samples)
- Free of cuts, abrasions or skin conditions on the hands or face/neck surfaces that could be negatively affected by the Aerosol OT solution
- Willing to be photographed or videotaped
- Not an employee, or related by blood or marriage, to the Sponsor or the research company performing the study
- Willing to present certification of respirator fit testing within the past year as verified by a copy of the respirator fit test certificate or willing to consent to and participate in the medical evaluation and fit testing necessary to wear a respirator

With the EPA's recommendations incorporated, the inclusion/exclusion criteria are complete and appropriate. Pregnant or nursing women, as well as children, are excluded from participation. Females will be asked to confirm that they are not nursing during the screening. Females will be screened for pregnancy or allowed to affirm that they are not capable of becoming pregnant at the start of the monitoring day.

7.3 Risks to Subjects

The proposed test product is a fungicide that contains the active ingredient mancozeb. This product is registered with the U.S. EPA for the uses in this study and undergoing evaluation in registration review. EPA has characterized the risks associated with exposure to these substances in Appendix A, Section 4.1.

The protocol identifies the following potential risks to subjects and describes how they will be minimized:

- Risks associated with exposure to mancozeb
- Risks associated with physical stress or discomfort
- Risks associated with heat stress
- Risks associated with exposure to the diluted Aerosol OT
- Risks of embarrassment associated with disrobing

Subjects will be handling and applying mancozeb. This product's safety data sheet (SDS) notes that it may cause irritation from inhalation and/or eye contact, that it may be harmful if absorbed through the skin and that it may be harmful if swallowed. These risks are minimized by only enrolling subjects with experience performing the tasks to be monitored, by enrolling those who are willing to follow the label and to wear the label-mandated PPE, and by providing additional PPE for subjects to wear during certain tasks. Research staff will review both the label and SDS with the subject during the consent meeting to ensure they are familiar with the instructions and restrictions. Researchers will monitor subject for compliance with the label during the study and will step in if violations are occurring. The subjects will be performing their normal work tasks, so the risks of being exposed to mancozeb should be minimal beyond what the workers would experience during their normal workday.

As the intent of the study is to collect workers' exposure, risks of dermal and inhalation exposure will be minimized further through the various residue collection methods utilized in the study. For example, subjects will be wearing inner dosimeters, which will collect test substance that would ordinarily be deposited on subjects' clothing and move through to their skin. Face and neck wipes and hand washes will collect the substance deposited directly on the subjects' skin during their participation in the study. Inhalation exposure will be reduced when the air sampling tube and pump collect the air in the subjects' breathing zone. Furthermore, subjects will be wearing additional PPE beyond what is currently required on the label – gauntlet style chemical-resistant gloves and in some instances coveralls – which will further reduce the risk of dermal exposure.

Subjects may experience minimal discomfort from wearing the inner dosimeter and the air sampling device. Additionally, some subjects will be required to wear a filtering facepiece or respirator during

their study participation. Respirator use can cause physical discomfort and stress. These symptoms can be mitigated through confirming that the subject can safely wear a filtering face piece or respirator (medical evaluation and fit test) or confirming that the subject has a valid test certificate and providing new cartridges or a new filtering face piece for use during the study.

Subjects will be wearing an inner dosimeter, outer clothing, and in some cases coveralls. Wearing additional layers of clothing can increase an individual's potential for heat-related illness. To mitigate the risk of heat-related illness, the research company's Standard Operating Procedure on heat-related illness will be followed. This includes a heat stress education and monitoring program on managing heat stress for both subjects and study staff, as well as monitoring of workers for signs of heat stress and providing a shaded area with cool drinks. This program also requires weather monitoring and establishes conditions for stopping the study under certain conditions and providing medical support services as necessary. The study is scheduled to be initiated in the field early in the season, when the weather is cooler, lowering the likelihood that subjects would experience heat-related illnesses.

To minimize the risks associated with the use of Aerosol OT for hand and face/neck washes, those who have skin conditions on their hands, face, or neck that may be exacerbated by exposure to the wash substance will be excluded from participation.

The protocol proposes to minimize risk of embarrassment by disrobing by ensuring that the donning and doffing of the dosimeter and outer layer of clothing occur in a private area with a member of the study team who is the same gender as the subject.

Additional risks to subjects include the psychological risks of unexpected pregnancy and the risk of unintentional exposure of confidential information. Subjects will be informed about the requirement for pregnancy testing or affirmation of inability to become pregnant for female subjects at the informational meeting and during the consent process. The pregnancy test verification will be conducted in private and the results will not be shared. Female subjects will not be compelled to disclose the results; they will have the option to withdraw from participation or to disclose the results to a female member of the study team.

Information about subjects will be kept confidential by using numbers rather than names to identify subjects in study-related documents, keeping the key linking each subject's name and identifying number separate from other study records and in a locked cabinet, and removing any identifiable facial or other features from subjects in photographs used in study materials.

Stopping rules will be employed in this study to minimize risks to subjects. Examples of circumstances in which the Study Director would remove a subject include when "staying in the study could put the participant at risk, such as a hazardous equipment malfunction, chemical spill, or other hazardous condition; the study is stopped because it gets too hot (heat index of 120^{o}F, or 110^{o}F if working in direct sun) to continue safely; the participant repeatedly fails to or refuses to follow the pesticide label, including use of label-required PPE; and the participant fails to follow the instructions of the researchers, including use of protocol required "additional" PPE" (Protocol, p. 30 of 73).

A member of the research team who holds a valid 2-year Red Cross First Aid certificate will be on site for each study day. Additionally, the study staff will have the address and directions to a nearby medical facility at the start of each test day. In the event of an illness or injury, the research team will either call 911 or transport an injured subject to a medical facility if necessary. All expenses associated with treating a study-related illness or injury that are not covered by insurance will be paid by the sponsor.

7.4 Benefits

This research offers no direct benefits to the subjects beyond the ability to participate.

The study is likely to generate more specific, accurate data that will support the new and ongoing registration of products for liquid treatment of potato seed pieces. The availability of these products will benefit both the registrant and society at large. The study's data will allow regulatory authorities to more precisely assess the risks to workers performing the types of tasks, which will benefit workers and handlers through appropriate protections on pesticide labeling.

7.5 Risk/Benefit Balance

The study monitors activities that the subjects generally perform on a regular basis as part of their normal work duties. It is unlikely that as a result of subjects' participation in this research, they will experience additional risk beyond what they would ordinarily encounter when performing these tasks. With the recommendations of EPA incorporated, the risks to subjects have been thoughtfully and thoroughly minimized in the design of the research. The risks are reasonable in light of the likely benefits to society from new data supporting more accurate exposure assessments for liquid formulation potato seed piece treatment.

7.6 Independent Ethics Review

The protocol, informed consent form, research participant's bill of rights, and recruitment materials were reviewed and approved with modifications by the Advarra IRB on June 6, 2025 (Protocol Approval Letter, p. 1).

This approval letter acknowledges that research may not be initiated until IRB approval is granted following EPA and HSRB review and revisions to address any recommendations.

Advarra IRB is registered with FDA and OHRP (IRB #00000971) and has a Federal-wide Assurance approved by OHRP (00023875). Advarra is fully accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP).

7.7 Informed Consent

Consent meetings will be conducted in either English or Spanish, based on the languages primarily spoken at potato farms in the U.S. Volunteers will be offered the option to have all materials read to

them, which will be noted in the file, and to have family members or friends attend the consent meeting with them.

During the consent process, researchers will work from the IRB-approved consent form to provide a detailed explanation of the study, describe the monitoring procedures, share product labels and safety data sheets with the volunteers, and review the label instructions for PPE that is required by the label as well as the additional PPE required for study participants. Researchers will make clear that subjects in the study have the right to withdraw at any time without giving a reason and without compromising their employment. Subjects will be provided a copy of the Employer Letter. Researchers will allow sufficient time for questions during the discussion. At the end of the discussion and after all questions have been addressed, volunteers will have the option to enroll in the study, not enroll in the study, or to take the materials home to think about whether to enroll.

When a volunteer indicates that they are willing to enroll, the researcher will confirm the volunteer's comprehension of the study and its potential risks by asking a standard set of questions. If the researcher is satisfied of the volunteer's comprehension, they will ask the volunteer to sign the Informed Consent Form and the Research Participant's Bill of Rights. Subjects will receive a signed copy of both documents.

7.8 Respect for Subjects

The study report outlines measures to demonstrate respect for the subjects. The protocol describes measures to protect subjects' privacy, including identifying subjects by number rather than name; maintaining the record linking name and number separately from the other study-related records and in a locked cabinet; not including the subjects' faces in any photos used in study reports; and restricting access to records of the study to the study sponsor, EPA and the IRB. The protocol specifies that pregnancy testing will be conducted in a private location, the results will be verified by a female employee, and provision will be made for discrete disposal of the test, and that females will have the option to affirm that they are not capable of becoming pregnant in lieu of taking a pregnancy test. The process of dressing and undressing in the clothing required for the study will be conducted in a private location with a member of the study team of the same gender as the subject.

All individuals who attend the introductory meeting with the study staff will receive $20, regardless of whether they choose to pursue a consent discussion. All subjects will receive $200 if they enroll in the study, arrive at the worksite, and choose to put on the dosimeter and sampling pump. The remuneration is $200 regardless of a subject's length of participation. All payments will be made in cash at the time the encounter is completed. The compensation is not so high as to unduly influence participants but represents fair remuneration for the subjects' time and inconvenience.

Candidates and subjects will be informed orally and in writing that they are free to decline to participate or to withdraw at any time for any reason, without penalty, at multiple points in the recruitment, consent, and study processes.

The protocol includes adequate precautions to minimize potential for coercion or undue influence. Recruitment materials and interactions with potential subjects will be conducted in English or Spanish,

depending on subject's preference. Subjects will be recruited through flyers posted in the workplace alongside a letter from the employer affirming that the participation or non-participation will not impact the subjects' employment. Researchers will ask individuals whether they would like the materials read to them, ensuring equal access to information for subjects who have difficulty reading. Additionally, consent meetings will be held in private, between the researcher and the potential subject, which will minimize the potential for coercion or undue influence.

8.0 Compliance with Applicable Ethical Standards

This is a protocol for third-party research involving intentional exposure of human subjects to a pesticide, with the intention of submitting the resulting data to EPA under the pesticide laws. The primary ethical standards applicable to this proposal are 40 CFR 26, Subparts K and L. In addition, the requirements of FIFRA §12(a)(2)(P) for fully informed, fully voluntary consent of subjects apply.

A detailed evaluation of how this proposal addresses applicable standards of ethical conduct is included in Appendix B of this review.

EPA Ethics Comments

Before the research is conducted, the documents should be revised as follows and resubmitted for review and approval by the reviewing IRB. This list of comments does not include all typographical and spelling edits, or minor suggestions about wording or language placement:

1. Provide information in the protocol about how subjects' ages will be verified, *e.g.*, affirmation, photo identification, etc.
2. Employer confirmation that employees have undergone a medical evaluation and fit test to wear a respirator is not sufficient to ensure that subjects can safely and appropriately wear a respirator. Revise the protocol and consent form to explain that when respiratory protection is worn, the subject (or their employer) must either provide evidence of a medical clearance and valid fit test certification in order to participate, or consent to undergo those processes prior to their study day and provide appropriate documentation. See this website for more information: https://www.pesticideresources.org/wps-resources/wps-respirator-resources/.
3. Clarify that for any subject who has requested materials and/or the consent process in Spanish, a Spanish-speaking researcher will be on site for the subject's study day and available to answer any questions or to translate any instructions as necessary.
4. Revise the protocol to include a skin check for irritation or disqualifying conditions on the hands, neck, and face prior to the initiation of the study day and at the end of the sample collection process. Indicate who from the research team will conduct this check and how they are qualified.
5. Revise the protocol to include a step at the end of sample collection where the subject is instructed to wash their hands and face prior to leaving the study site in order to minimize the potential for irritation from the wash substance used.
6. Clarify in the protocol what will happen if a subject withdraws and does not agree to allow

the collection of the dermal and inhalation samples. For example, they will be assisted in removing the dosimeters, instructed to wash their hands and face, will receive their remuneration, and free to leave.

7. Clarify the protocol to specify whether subjects will be remunerated separately for the information session and the consent process. Additionally, consider whether additional compensation is appropriate if subjects need to undergo medical evaluation and respirator fit testing in order to be monitored for a task that requires respirator use.
8. Revise the protocol to include specific conditions for the Study Director's ability to withdraw subjects. The Study Director should not have unlimited discretion.
9. Provide information about how incidents or illnesses that occur during the study will be addressed. Who will make an assessment of the severity of the incident or whether it is study-related? What criteria will be used?
10. Provide more information about what steps will be taken if a subject reports experiencing an adverse effect in the follow up call from researchers 14 days after the monitoring occurred.
11. Revise the consent form to include the following:
    a. A concise presentation of key information that is most likely to assist prospective subjects in understanding the reasons why the might or might not want to participate in the research. This should be organized and presented in a way that facilitates comprehension.
    b. One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens: (i) A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject, if this might be a possibility; or (ii) A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.
    c. A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions.
    d. All edits to the protocol corresponding to the consent form.

EPA Ethics Conclusions

An IRB-approved protocol addressing all of the necessary elements in 40 CFR 26, Subpart K has been submitted to EPA for review, along with an additional scenario that will be incorporated into the protocol and reviewed by the IRB prior to implementation. EPA has reviewed the protocol and all associated documents, and is consulting with the HSRB about this review. All subjects enrolled in this study will give voluntary, informed consent and be notified about the pesticide to which they will be exposed.

In addition, 40 CFR 26 Subpart L, at §26.1703, as amended effective September 23, 2019, provides in pertinent part: *EPA must not rely on data from any research subject to this subpart involving*

intentional exposure of any human subject who is a pregnant woman (and therefore her fetus), a nursing woman, or a child.

The protocol requires that subjects be at least 18 years old and excludes female subjects who are pregnant or lactating. Thus §26.1703 would not forbid EPA's reliance on a study executed according to this protocol.

If the comments noted above are addressed and the amended protocol is approved by the overseeing IRB, this research is likely to meet the ethical standards of FIFRA §12(a)(2)(P) and 40 CFR 26 subparts K and L.

Appendix A. EPA Protocol Review: Liquid Spray On-Farm Treatment of Potato Seed Pieces

Title: Mancozeb: Liquid Spray On-Farm Seed Treatment Study to Determine Dermal and Inhalation Exposure of Workers to Mancozeb during the On-Farm Treating, Loading, and Planting of Potato Seed Pieces.

Date: May 13, 2025

Principal Investigator (Study Director):
Brian Lange, Lange Research and Consulting, Inc.

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Reviewing IRB: Advarra Institutional Review Board
6100 Merriweather Dr., Suite 600
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1.0 Societal Value of Proposed Research

What is the stated purpose of the proposed research?
The objective of this study is to develop data to determine the potential exposure of workers who treat, load, and/or plant mancozeb-treated potato seed pieces on-farm (Protocol, p. 5 of 73). EPA will use the results of this study to estimate dermal and inhalation exposure for seed treatment activities for mancozeb and likely for a wide range of other agricultural pesticides that are used under these exposure scenarios.

What research question does it address? Why is this question important? Would the research fill an important gap in understanding?
EPA registers new active ingredients, registers new uses of existing active ingredients, and reevaluates existing uses of active ingredients. Currently, EPA has exposure data for on-farm treating/planting

(wheat and potato seed) and loading/planting (wheat and corn seed) which is used to estimate dermal and inhalation exposure via liquid and solid (dust) PSP treatment.

The dermal and inhalation exposure data generated from this study will be used by the EPA in assessing potential exposure and risks to workers engaging in on-farm seed treatment activities.

How would the study be used by EPA?
EPA will consider the dermal and inhalation exposure data from this study in assessing exposures of occupational workers when participating in on-farm seed treatment activities. The data will be used for mancozeb and potentially used generically for other pesticides.

Could the research question be answered with existing data? If so, how?
EPA currently has data that provide dermal and inhalation exposure estimates for different combinations of on-farm seed treatment activities. These data have been considered acceptable and appropriate for human health risk assessment of on-farm PSP treatment; however, EPA has noted that the current dataset may represent a more limited set of conditions. The protocol also proposes an additional type of dermal PPE which has not been measured in previous datasets and therefore, it is unknown how this PPE will impact dermal exposures.

Could the question be answered without newly exposing human subjects? If so, how? If not, why not?
There are no alternative monitoring methods or models that could be used to extrapolate potential dermal and inhalation exposure resulting from the proposed on-farm seed treatment activities.

Is the research likely to produce data that addresses an important scientific or policy question that cannot be resolved on the basis of animal data or human observational research?
Yes. The purpose of this research is to measure exposures of individuals completing their regular workday tasks which includes the use of mancozeb products for on-farm potato seed treatment. In this study, 3 subjects per activity (3) per location (7) will be monitored (63 total MUs). In order to measure exposure from workers, the study needs to be an intentional observational study as the study directors will be requiring additional PPE beyond the label-required PPE for certain activities and requiring workers to wear WBDs and air sampling devices in order to capture exposures. Additionally, monitoring will stop if practices contrary to label requirements are not corrected.

2.0 Study Design

What is the scientific objective of the study? If there is an explicit hypothesis, what is it?
"The purpose of this study is to develop data to determine the potential for exposure to the active ingredient mancozeb that workers might experience when treating, when loading potato seed pieces, and when planting seed that has been treated with a liquid mancozeb product containing 4 lb ai/gallon" (Protocol, p. 8 of 73).

No explicit hypothesis is stated, nor is the study designed to test a hypothesis.

Can the study as proposed achieve that objective or test this hypothesis?
It is likely that the objective can be achieved by the proposed study.

2.1 Statistical Design

What is the rationale for the choice of sample size?
The proposed sample size and study design of 7 areas by 3 MUs per area for each scenario is a sample size configuration based on the size and study designs provided in the Appendix C of the 2010 AHETF Governing Document (AHETF, 2010), where the benchmark objective is for sample estimates of the arithmetic mean and 95th percentile of normalized exposure to be accurate to within 3-fold 95% of the time, given GSD = 4 and ICC = 0.3. The Sponsor believes exposures from each main task (treating PSPs, loading treated PSPs, and planting PSPs) are similar to other AHETF scenarios, and GSD and ICC of each PSP scenario are expected to be similar to other AHETF scenarios. (UPL Overview and Justification, p. 8 of 44)

What negative and positive controls are proposed? Are proposed controls appropriate for the study design and statistical analysis plan?
No positive or negative controls are proposed. This is appropriate for the study design and statistical analysis plan.

How is the study blinded?
The study is not blinded.

What is the plan for allocating individuals to treatment or control groups?
Two stages of selection to allocating areas and MUs are included in this study. The first stage selects seven geographically diverse monitoring areas and identifies targeted potential growers. The second stage is to identify/select workers from among the identified growers, using information of treating/loading/planting condition, to construct a diverse set of monitoring units. It is a requirement that only one MU from each worker is used for each scenario. It is a requirement that only one worker in a monitoring area is used for each scenario. It is preferable to use only one worker from each employer (regardless same or different areas) for each scenario. It is preferable that no two MUs from an area are in same AaiH stratum for each scenario. It is preferable that each set of three MUs in a monitoring area includes some variability for the following characteristics (treater type, loading system, and planter size). While measurement matrices (*e.g.*, dosimeters, OVS inhalation tubes, etc.) have blank/negative control samples, there are no control groups of workers.

Is the proposed research designed in accordance with current scientific standards and practices to include representative study populations for the endpoint in question?
Yes.

Can the data be statistically analyzed?
The data will be assumed to be a true random sample and be statistically analyzed. The results of the data analysis will be conducted and provided in the final report.

What is the plan for statistical analysis of the data?
Data of each scenario and exposure route will be analyzed separately.

Characterizing the Normalized Exposure Distribution

Estimated statistics of normalized dermal and inhalation exposure distribution will be determined. The estimated statistics include (but are not limited to) the arithmetic mean, geometric mean, standard deviation, coefficient of variation. Normality of the log(normalized exposure) data will be tested and the expectation is the data will be log-normally distributed. Therefore, statistical methods for lognormally distributed data will be used.

Evaluating the Relationship between Exposure and AaiH
The relationship between AaiH and exposure will be evaluated for each PSP scenario in this study. Linear regression of log exposure on log AaiH will be conducted for total dermal exposure and for total inhalation exposure. If exposure were directly proportional to AaiH, a slope of 1 would be obtained and if exposure were independent of AaiH, then a slope of 0 would be obtained. In practice, the 95th percentile of the slope estimate will be calculated and if that interval includes 1, but not 0, then the relationship is consistent with proportionality. If the interval includes 0, but not 1, then the relationship is more consistent with independence.

Are proposed statistical methods appropriate to answer the research question?
Yes.

Does the proposed design have adequate statistical power to definitively answer the research question?
The proposed study design of 7 areas by 3 MUs per area for each scenario is one sample size configuration provided in Appendix C of the 2010 AHETF Governing Document, where the benchmark objective in exposure studies is that sample estimates of the arithmetic mean and 95th percentile of normalized exposure are accurate to within 3-fold for 95% of the time, given GSD = 4 and ICC = 0.3. As the exposures from each main task (treating PSPs, loading treated PSPs, and planting PSPs) are expected to be similar to other AHETF scenarios, and the GSD and ICC of each PSP scenario are expected to be ≤ 4 and ≤ 0.3 respectively, the statistical power of the study design to achieve the estimated arithmetic mean and 95th percentile of normalized exposure to accurate to within 3 fold for 95% of the time, *i.e.*, statistical power = 0.95 (Table 5 of Appendix C, 2010 AHETF Governing Document).

Table 15 of Appendix C of the 2010 AHETF Governing Document shows a study design configuration 5 clusters × 5 MUs/cluster (where cluster is a random nesting variable such as region, state, or farm, etc.) would have at least 0.8 power to discriminate a proportional from an independence relationship between exposure and AaiH, given GSD = 4, ICC = 0.3, one-order-of-magnitude-in AaiH range, and great differences of AaiH among MUs within-cluster (*i.e.*, large overlapped AaiH between clusters). Given the proposed study design of 7 clusters × 3 MUs/cluster configuration is close to the 5 cluster × 5 MUs/cluster configuration, and expected GSD ≤ 4 and ICC ≤ 0.3, and the range of AaiH is at least one order of magnitude (please see AaiH strata in 2.2 b), and great overlapped AaiH between clusters/areas, the statistical power to discriminate a proportional from independence relationship between exposure and AaiH would probably be at least 0.80.

Does the investigator propose to conduct the research in accordance with recognized good research practices, including, when appropriate, good clinical practice guidelines and monitoring for the safety of subjects?

This study is proposed to be conducted in accordance with recognized good research practices. This is not a clinical study and therefore good clinical practice guidelines are not applicable.

2.2 How and to what will human subjects be exposed?
The test substance will be products normally used on-farm that includes a liquid mancozeb product containing 4 lb ai/gallon (*e.g.*, Manzate® Max fungicide, EPA Reg. No. 70506-194).

On-farm seed treaters will be exposed to the concentrate and diluted solutions while loaders and planters will be exposed to the diluted solutions on the treated seed pieces.

What is the rationale for the choice of test material and formulation?
"Mancozeb is a broad-spectrum multi-site contact fungicide with a unique mode of action and no known resistance.

The study is being conducted to support the continued registration of an on-farm liquid mancozeb-based product for use on potato seed pieces. In addition to quantifying exposure to mancozeb, study data may ultimately be used to generically estimate chemical exposure to agricultural workers who treat, load, and plant potatoes treated with similar seed treatment formulations" (Protocol p. 11 of 73).

What is the rationale for the choice of dose/exposure levels and the staging of dose administration?
"The sponsor has determined a practical range in AaiH for each scenario taking into account the concentration of liquid mancozeb products, mancozeb use rates, treating capacity in terms of weight of PSPs, number of planters working at a time, acres planted in a day, etc. The ranges have then been split into three strata with the center strata being rather large" (Protocol, p. 16 of 73).

Proposed AaiH Strata for T-PSP-L-OF and L-PSP-OF:
From 2.3 to 8 lb.
From 8.1 to 46 lb. (6x)
From 47 to 155 lb.

Proposed AaiH Strata for P-PSP-OF:
From 1.1 to 3.7 lbs.
From 3.8 to 22.2 lbs (6x)
From 22.3 to 75 lbs. (pp. 16 to 19 of 73)

What duration of exposure is proposed?
Workers will be monitored during a period of time representative of a full day's work, generally a minimum of 4 hours. Dosimeters will be donned prior to starting work activities and the air pump will be turned on when the worker begins work and shall remain on, even during breaks, throughout the exposure monitoring period (*i.e.*, end of day).

2.3 Endpoints and Measures

What endpoints will be measured? Are they appropriate to the question(s) being asked?
UPL proposes to measure dermal and inhalation exposures resulting from tasks associated with liquid on-farm PSP treatment activities. Dermal and inhalation exposure will be measured using inner whole-

body dosimeters (WBD), face/neck wipes, hand washes, and personal air sampling pumps. The personal air samplers will collect residues from the breathing zone with the sampling cartridge facing downwards (mimicking nostrils). An OSHA Versatile Sampler (OVS) will be used to collect inhalable particles. Flow rates will be approximately 2 L/min for each of the samplers (Protocol, pp. 37-38 of 73).

EPA finds these endpoints appropriate for the study objective.

What steps are proposed to ensure measurements are accurate and reliable?
"This study will be conducted in compliance with the U.S. EPA Good Laboratory Standards and will adhere to applicable Testing Facility Standard Operating Procedures (SOPs) and research practices. In-process data and report audits will be performed by the Testing Facility's Quality Assurance Unit (QAU) to ensure compliance with GLP regulations and adherence to this protocol and relevant SOPs. The data package and final report will be audited prior to completion Additional auditing by the Sponsor or Analytical Laboratory QAU may also be conducted" (Protocol, p. 6 of 73).

"The analytical laboratory shall prepare a report detailing procedures used and results obtained during the analytical portion of this study. The report will be signed by the Analytical Investigator and will include a statement of GLP Compliance and a Quality Assurance Statement" (Protocol, p. 44 of 73).

What QA methods are proposed?
"This study will be conducted in compliance with the U.S. EPA Good Laboratory Standards and will adhere to applicable Testing Facility Standard Operating Procedures (SOPs) and research practices. In-process data and report audits will be performed by the Testing Facility's Quality Assurance Unit (QAU) to ensure compliance with GLP regulations and adherence to this protocol and relevant SOPs. The data package and final report will be audited prior to completion Additional auditing by the Sponsor or Analytical Laboratory QAU may also be conducted" (Protocol, p. 6 of 73).

How will uncertainty be addressed?
In general, field measurements are adjusted based on the recovery from the fortification sample.

"Correction for loss of residues on sampling matrices will be accounted for by using field fortified samples that are exposed to ambient conditions [inner dosimeter sections and OVS tubes] for the duration of exposure or immediately frozen [hand wash and face/neck wipes]. These field recovery samples will be packaged, stored, and shipped similarly to the corresponding study samples. Therefore, these field recovery results will correct for all phases of potential losses. Two control (blank) samples for each matrix will also be processed with the field recovery samples. Field fortification levels (in triplicate) will be provided" (Protocol, pp. 39-40 of 73).

"Sample matrix fortifications are designed to assess stability of the active ingredient under field storage and transit conditions in or on the sampling materials (inner dosimeter, hand wash solution, face/neck wipe, and OVS tube) and will take place during exposure monitoring at logical intervals throughout the study, capturing typical weather conditions experienced at different times during the study and spaced temporally throughout the study period. Ideally, at least one set of field recovery samples will be prepared at each monitoring area used in the study" (Protocol, p. 39 of 73).

The evaluation of accuracy of estimated statistics (GM, AM, or 95th percentile of normalized exposure) or precision of estimate slope in the proportionality analysis were not mentioned in the Data Analysis section in the protocol or the justifications document (see Section 6.0 of the review memo for EPA's recommendations).

3.0 Subject Selection

3.1 Representativeness of Sample

What is the population of concern? How was it identified?
On-farm workers who are treating, loading, and planting potato seed pieces with liquid pesticide formulations are the target population of this study. "*The study is being conducted to support the continued registration of on-farm liquid mancozeb-products for use on PSPs* (Protocol, p. 11 of 73).

From what populations will subjects be recruited?
"Mancozeb liquid formulations containing 4 lb a.i./gallon are available for use in the potato growing areas of the United States. Exposure monitoring will be conducted on farms located in representative potato growing regions where on-farm seed treatment is commonly employed. The study is targeted to be conducted in the following seven monitoring areas within the United States which are the seven states with the largest acreage of potatoes planted in 2023 according to National Agricultural Statistics Service (NASS).

Idaho (EPA Region XI)
Washington (EPA Region XI and/or XII)
North Dakota (EPA Region VII and/or V)
Maine (EPA Region I)
Colorado (EPA Region VIII and/or IX)
Michigan (EPA Region V)
Wisconsin (EPA Region V)

Diversification of AaiH within each monitoring area will be a component of the selection process for all MUs (e.g., differing application rates, length of workday, etc.). In addition, similarity restrictions will be imposed during the site selection process (e.g., equipment similarity, ai stratum, etc.)" (Protocol, pp. 15-16 of 73).

Are expected participants representative of the population of concern? If not, why not?
The objective of this study is to quantify exposures (dermal and inhalation) of workers performing on-farm PSP treatment activities (treating, planting, and loading) using liquid pesticide formulations. After facilities (farms) are identified through the selection process, eligible workers will be recruited through the workplace/employer. All materials will be available in both English and Spanish (Protocol, pp. 24 and 25 of 73).

Therefore, EPA expects that the participants will be representative of the population of concern (*i.e.*, workers performing on-farm PSP treatment activities).

Can the findings from the proposed study be generalized beyond the study sample?
It is expected that the activity exposure data collected will be generically applicable to on-farm seed treatment activities via various liquid pesticide formulations.

3.2 Equitable Selection of Subjects

What are the inclusion/exclusion criteria? Are they complete and appropriate?
The eligibility criteria are complete and appropriate, with EPA's recommendations (indicated with red text) incorporated.

- Males or females at least 18 years old
- Employed by an eligible facility and have at least 5 days experience of the job function that will be monitored
- Willing to perform the monitored tasks in compliance with the label directions and to wear the label and study-required PPE
- Speak English or Spanish
- In good general health
- No allergies or sensitivities to Aerosol OT (the solution to be used to collect hand wash and face/neck wipe samples)
- Free of cuts, abrasions or skin conditions on the hands or face/neck surfaces that could be negatively affected by the Aerosol OT solution
- Willing to be photographed or videotaped
- Not an employee, or related by blood or marriage, to the Sponsor or the research company performing the study
- Willing to present certification of respirator fit testing within the past year as verified by a copy of the respirator fit test certificate or to consent to undergoing a medical evaluation and fit test prior to wearing a respirator in the study

What, if any, is the relationship between the investigator and the subjects?
There is no relationship between the investigator and subjects. Employees and relatives of employees of the sponsor and research company conducting the study are excluded from participation as subjects.

Are any potential subjects from a vulnerable population?
The protocol does not call for targeting recruitment to a vulnerable population. However, individuals may be enrolled who cannot read. To ensure that all subjects have access to the information in the materials presented, the researchers will offer to read all materials to individuals during the consent meeting.

The protocol contains adequate precautions to minimize any potential for coercion or undue influence. Recruitment materials and interactions with potential subjects will be conducted in English or Spanish, depending on subject preference. Employers will be required to affirm that they will not impact workers' decision not to participate and to post a letter about the study and individuals' freedom to enroll or not without affecting their employment. Subjects will be recruited through posted signs in the workplace, rather than through contact by their employer to minimize the potential for coercion or

undue influence. In addition, the compensation is not so high as to unduly influence participants, but represents fair remuneration for the subjects' time, travel, lost employment opportunity, and inconvenience.

What process is proposed for recruiting and informing potential subjects?
Potential subjects will be recruited through a study flyer and employer letter posted at the farm. All recruitment will be done in English and Spanish, depending on each individual's preference. A member of the study team (including a bilingual researcher, if necessary) will conduct an introductory meeting for all interested individuals at the farm or at another agreed upon location, describing the study, outlining the eligibility criteria, and affirming that there will be no penalty from the employer for individuals regardless of whether they decide to enroll in the study or not to enroll. Subjects will be free to ask questions during the introductory meeting.

Individuals who are interested in enrolling in the study will be invited to meet one on one with a member of the study team. During the consent meeting, the researcher "*will provide each potential participant with a full explanation of the study, including study requirements, eligibility criteria, potential risks and benefits. The exposure monitoring procedures will be explained in detail. The Investigator will provide product labels and MSDSs to the potential participant, and review label instructions for PPE that is required by the label and study protocol during various seed treatment, loading, and planting activities, as described in section 7.D.3, above. The IRB-approved Informed Consent Form will be presented and all sections discussed in detail. Potential participants will be advised of their right to withdraw from the study at any time and for any reason without jeopardizing their normal position with their employer. Each potential participant will be provided a copy of the Employer Letter which states they will not suffer any consequence if they decide not to participate. Ample time will be provided for questions during the recruiting and informed consent discussion, and the Investigator will answer questions and provide additional information or clarification as requested*" (Protocol, p. 25 of 73).

Potential subjects will be permitted to take the consent form home to read, discuss with friends and family members, and consider whether to participate. Before completing the consent process and enrolling, a member of the research team will ask a standard set of questions to ensure that the potential subject comprehends the consent materials. Once comprehension is confirmed, the subject will proceed to sign the consent form.

If any subjects are potentially subject to coercion or undue influence, what specific safeguards are proposed to protect their rights and welfare?
See the response above. Allowing employees to proactively identify an interest in the study by responding to a posted Recruitment Flyer or voluntarily attending an introductory meeting reduces the potential for coercion and undue influence exerted on the workers by peers or the employer.

3.3 Remuneration of Subjects

What remuneration, if any, is proposed for the subjects?
The protocol proposes to compensate individuals $20 for attending the introductory meeting and $200 for participating in the study by putting on the dosimeters. Remuneration is not conditioned on

consenting to participate in the study nor is it affected by an individual's decision to withdraw after monitoring has begun.

Is the remuneration consistent with the principles of justice and respect for persons?
Yes. The proposed payment amounts are fair and reasonable compensation for the subjects' time, factoring in their experience and inconvenience.

Is proposed remuneration so high as to be an undue inducement?
No.

Is proposed remuneration so low that it will only be attractive to economically disadvantaged subjects?
No.

How and when would subjects be paid?
Compensation will be paid in cash at the end of the introductory meeting and when subjects leave the study site.

4.0 Risks to Subjects

4.1 Risk characterization

Is adequate information available from prior animal studies or from other sources to assess the potential risks to subjects in the proposed research?
As noted in Section 1.0(d), EPA currently has data that provide dermal and inhalation exposure estimates for different combinations of on-farm seed treatment activities and seed. This data has been considered acceptable and appropriate for human health risk assessment of on-farm PSP treatment; however, EPA has noted that the current dataset is limited due to the number of studies available at this time. The protocol also proposes an additional type of dermal personal protective equipment (PPE, *e.g.*, gauntlet gloves) that has not been measured in previous datasets and therefore, it is unknown how this PPE will impact dermal exposures.

What is the nature of the risks to subjects of the proposed research?

"The study, which will observe and collect samples from workers during the course of a normal workday, is not expected to markedly increase or decrease the occupational risk of participating workers" (Protocol, p. 13 of 73).

The protocol acknowledges several instances of potential risk to subjects including:

- risks associated with exposure to mancozeb;
- risks associated with physical stress or discomfort;
- risks associated with heat stress;
- risks associated with exposure to the diluted aerosol OT; and
- risks of embarrassment associated with disrobing.

EPA has identified additional risks, including the psychological risk of unexpected pregnancy testing results and the unanticipated loss of confidentiality.

How do proposed dose/exposure levels compare to the established NOAELs for the test materials?

This study is developed to expand the understanding of dermal and inhalation exposures (*i.e.*, dermal and inhalation exposures from the current dataset) associated with seed treatment activities. As noted, the current exposure data is sufficient for risk assessment; however, there is a possibility that the current unit exposures represent a more limited dataset, potentially overestimating actual exposure for on-farm PSP treatment activities. The proposed study is designed to collect typical workday exposure for one day at currently-labeled application rates. Unlike the existing data, the proposed study will distinguish between distinct activities – treating PSP, loading PSP, and planting PSP – by collecting separate data for each type of activity. The existing data are based in part on commercial seed treatment activities, while the proposed study will be conducted to measure on-farm PSP activities specifically. The proposed study calls for subjects to wear PPE beyond that which is currently required on registered labels. "*The risk is no greater than that of a normal workday, since workers will be performing their job the way they normally would, in fact the risk is mitigated by use of clothing/PPE and additional engineering controls for treatment equipment*" (Protocol p. 13 of 73).

Due to the clothing and PPE requirements, dermal exposures to mancozeb in the study should be negligible. Treaters and loaders will be required to wear respirators, which will limit inhalation exposures. The dosimeter, hand washes, and OVS sampling devices will capture any residues that the PPE did not intercept. The exposures (dermal and inhalation) will then similarly be compared to established NOAELs.

Does the research proposal adequately identify anticipated risks to human subjects and their likelihood of occurrence? How was this likelihood estimated?

Section 4.1(c) outlines risks anticipated for participants. Specifically, the protocol notes the following regarding potential instances of risk:

- Risks associated to the test product be no different than a typical workday since workers will be performing their job in the way that they normally would.
- Risks associated with physical stress of performing seed treatment activities should be similar to normal activities while there may be discomfort associated with wearing an air sampling device; however, this is similar to wearing a portable radio which would essentially be negligible.
- There is marginal additional risk of heat-related illness due to the long underwear the workers will be wearing. However, the garment is a thin and breathable material, the study will be conducted early in the season, and there will be a heat stress education and monitoring program. Workers are able to take breaks at any time and moved to a shaded/cooled area if researchers observe signs of heat-related illness.
- Risks associated with exposure to a 0.01% Aerosol OT should be minimal as workers have existing abrasions or skin conditions that reduce barrier properties of the skin (*e.g.*, eczema) will be excluded from the study.

- Risks associated with disrobing embarrassment is low as the researcher will be the same sex, they are experienced in worker risk assessments studies, and participants will always remain in their own undergarments (Protocol, pp. 13-14 of 73).

If any person with a condition that would put them at increased risk for adverse effects may become a subject in the proposed research, is there a convincing justification for selection of such a person and are there sufficient measures to protect such subjects?

The eligibility criteria for participants excludes subjects who have conditions that would put them at increased risk of adverse effects, *i.e.*, people who are not in good health, people who have skin issues that would be exacerbated by exposure to Aerosol OT, people with known allergies to Aerosol OT.

4.2 Risk Minimization

What specific steps are specified in the protocol to minimize risks to subjects?

The protocol notes that risks to subjects will be minimized as follows:

- Selecting workers that consider themselves to be in good health with no physical or medical conditions (*e.g.*, skin abrasions, conditions that reduce the skin barrier such as eczema, etc.) which would preclude participation in the study.
- Selecting workers that have not had or have reason to believe they will have an allergic reaction to Aerosol OT, a 0.01% soap solution used in collection of hand wash and face/neck wipe samples.
- Selecting workers that are willing to perform potato seed treating, seed loading, or planting tasks in compliance with the labeled directions for use, wearing the label and study-required PPE.
- Monitoring workers with experience and only while performing their normal workday activities.
- Reminding workers that they are free to take breaks as needed throughout the day.
- Checking subjects' skin for conditions that would disqualify them from participation.
- Implementing a heat stress education and monitoring program for subjects.
- Ensuring the study staff are familiar with identifying and treating heat-related illnesses and monitoring weather conditions to stop the study if certain heat index-related conditions are met.
- Identifying subjects by number and ensuring photographs and videos do not show any identifying information.
- Maintaining study-related records in a secured location with limited access.
- Having a researcher of the same sex in the changing room to assist the worker with donning and doffing the dosimeters.

What stopping rules are proposed in the protocol?

In the protocol there are several instances noted in which the study will be stopped. These instances include but are not limited to:

- If staying in the study could put the participant at risk, such as hazardous equipment malfunction, chemical spill, or other hazardous conditions (Protocol, p. 26 of 73)
- It is too hot to continue working safely (heat index of 120°F or 110°F if working directly in the sun) (Protocol, p. 27 of 73)
- The participant repeatedly fails to or refuses to follow the pesticide label (including label-required PPE) (Protocol, p. 27 of 73)
- The participant fails to follow the instructions of the researchers, including use of protocol required additional PPE (Protocol, p. 27 of 73)

How does the protocol provide for medical management of potential illness or injury to subjects?

"A nearby medical facility will be selected prior to each day's monitoring, and the address and directions to the facility will be available to all on-site study personnel in case of emergency. If a subject is injured during their participation in the study, the worker will be transported by study personnel to the medical facility for care, and the Sponsor will pay for needed medical treatment that is not paid for by the subject's own insurance or by someone else's insurance that covers them. If needed, researches [sic] *will call 911 for assistance"* (Protocol, p. 30 of 73).

How does the protocol provide for safety monitoring?

In addition to identifying and providing transportation to medical facilities, researchers will be observing subjects throughout their participation and will be looking for signs of fatigue, adverse effects from exposure to the test substance, and heat stress.

How does the protocol provide for post-exposure monitoring or follow-up? Is it of long enough duration to discover adverse events which might occur?

"Research personnel will follow up with a telephone call to each worker within 14 days following exposure monitoring to ask if the worker experienced any adverse effects from the study" (Protocol, p. 15 of 73).

EPA expects that any adverse reactions would appear during or shortly after participation in the study, so the proposed follow up period is sufficient.

How and by whom will medical care for research-related injuries to subjects be paid?

The sponsor will pay for medical treatment for study-related illnesses or injuries that are not paid for by the subject's own insurance or by someone else's insurance that covers them.

5.0 Benefits

What benefits of the proposed research, if any, would accrue to individual subjects?

There are no direct benefits to the subjects of participating in this research study.

What benefits to society are anticipated from the information likely to be gained through the research?

As a result of the data from this study, society will benefit from *"the continued availability of conventional pesticides used to increase yield and quality of agricultural commodities. Seed-applied pesticides more effectively control certain pests and diseases and do so at lower use rates than soil or foliar products, thereby reducing the total amount of pesticide used. These data will improve the completeness and accuracy of the EPA's worker exposure risk assessments for on-farm potato seed treating, seed loading, and planting situations and may allow assessment of other chemicals proposed for use in similar ways"* (Protocol, p. 14 of 73).

How would societal benefits be distributed? Who would benefit from the proposed research?

Registrants are the primary beneficiary of this research. Registrants of seed treatment pesticides will benefit because they will provide EPA with data on exposure that may aid in maintaining existing pesticide registrations and in registering new pesticides. EPA will benefit from the submission of data that reduces uncertainty around the exposure experienced by workers using these products, allowing for more precise risk assessments. Farmers will benefit from the continued availability of conventional pesticides used to increase yield and qualify of agricultural commodities. EPA will benefit from the submission of data that reduces uncertainty around the exposure experienced by workers using these products, allowing for more precise risk assessments. Registrants of seed treatment pesticides will benefit because they will provide EPA with data on exposure that may aid in maintaining existing pesticide registrations and in registering new pesticides.

What is the likelihood that the identified societal benefits would be realized?

The research is likely to produce accurate and reliable information concerning dermal and inhalation exposure, with resulting societal benefits in the form of more accurate and confident assessments of exposure and risk.

6.0 Risk/Benefit Balance: How do the risks to subjects weigh against the anticipated benefits of the research, to subjects or to society?

"The benefit of improving the completeness and accuracy of the data used by EPA to assess exposure to mancozeb-based potato seed treatment products and possible other seed treatment products in this use pattern outweigh any incremental risks to study participants" (Protocol, p. 15 of 73).

7.0 Independent Ethics Review

What IRB reviewed the proposed research?

Advarra IRB.

Is this IRB independent of the investigators and sponsors of the research?

Yes.

Is this IRB registered with OHRP?

Yes.

Is this IRB accredited? If so, by whom?

Advarra IRB is accredited by the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP).

Does this IRB hold a Federal-Wide Assurance from OHRP?

Yes.

Are complete records of the IRB review as required by 40 CFR 26.1125 provided?

Yes.

What standard(s) of ethical conduct would govern the work?

This is a protocol for third-party research involving what EPA has interpreted to be intentional exposure of human subjects to a pesticide. The study is being conducted with the intention of submitting the resulting data to EPA under the FIFRA. Thus, the primary ethical standards applicable to this proposal are 40 CFR 26, Subparts K and L. In addition, the requirements of FIFRA §12(a)(2)(P) for fully informed, fully voluntary consent of subjects apply.

8.0 Informed Consent

Will free and fully voluntary informed consent be obtained from each prospective subject?

Yes.

Will informed consent be appropriately documented, consistent with the requirements of 40 CFR §26.1117?

Yes.

Do the informed consent materials meet the requirements of 40 CFR §26.1116, including adequate characterization of the risks and discomforts to subjects from participation in the research, the potential benefits to the subject or others, and the right to withdraw from the research?

Yes.

What is the literacy rate in English or other languages among the intended research subjects?

The ability to speak English or Spanish is specified as a criterion for inclusion in the study. There is no minimum literacy rate for subjects. Subjects will have the option to have all study-related materials read to them.

What measures are proposed to overcome language differences, if any, between investigators and subjects?

The research team will include a Spanish-speaking member who has appropriate ethics training. For those who speak Spanish, the Spanish-speaking member of the team will conduct the meeting and consent session. All materials will be available in English and Spanish.

What measures are proposed to ensure subject comprehension of risks and discomforts?

All written recruitment, consent, and risk communication materials will be available in both English and Spanish. The research team will offer to read materials aloud to ensure that the information is accessible to all potential subjects. During the private consent meeting, the researcher will provide each volunteer with a full overview of the study, participation requirements, any potential risks and benefits, and alternatives to participation. Subjects will have the opportunity to ask questions throughout the consent process. Before the potential subject is asked to sign the consent form, the researcher conducting the meeting will ask a standard list of questions to confirm that the potential subject understands the study, including its potential risks and benefits.

What specific procedure will be followed to inform prospective subjects and to seek and obtain their consent?

See section 3.2 above for a full description. The protocol describes the recruitment and consent processes on pages 15-26. The researchers will solicit and enroll eligible facilities. Then the researchers will post an employer letter and information about the study in a central location on the farm. Individuals will be invited to attend an informational meeting, and if interested in enrolling to attend a one-on-one consent meeting.

What measures are proposed to ensure fully voluntary participation and to avoid coercion or undue influence?

Recruiting of subjects will take place through flyers and employer letters posted at qualified and enrolled farms. The employer letter explains that the employer has consented to the study and that employees will not be penalized if they decide to participate or not participate in the study.

The researchers will confirm that subjects' participation is voluntary, stressing the importance of voluntary participation and the absence of penalties for enrolling, not enrolling, or withdrawing, during the introductory meeting, consent meeting, and at the start of the test day.

9.0 Respect for Subjects

How will information about prospective and enrolled subjects be managed to ensure their privacy?

Information relating to each subject will be tracked through a subject identification number rather than by the subjects' names. Names and personal identifiers will be kept confidential. Photographs and video used in the study report will not show the subject's face or any recognizable image of the subject.

How will subjects be informed of their freedom to withdraw from the research at any time without penalty?

The protocol notes that subjects will be informed by the research staff orally and in writing at multiple points about their freedom to withdraw from the study at any point without penalty. This will occur through recruitment flyer and employer letter posted in the workplace, during the introductory and consent meetings, in writing on the consent form, and at the start of the test day.

How will subjects who decline to participate or who withdraw from the research be dealt with?

Subjects who decline to participate will not experience any penalty from their employer or the study team.

Subjects who withdraw after they have donned the dosimeters will be paid $200 cash and allowed to withdraw without penalty. If any monitoring has occurred prior to the subject's withdrawal from the study, the Study Director will ask whether the monitoring samples (dermal and inhalation) can be collected. If the subject agrees, the samples will be collected and the subject will be free to leave the study.

Appendix B. Study Criteria Checklists

§ 26.1111 Criteria for IRB approval of research

Table B-1. § 26.1111 Criteria for IRB approval of research ***Liquid Spray On-Farm Potato Seed Treatment Study Protocol***		
Criterion	**Y/N**	**Comment/Page Reference**
(a)(1)(i) Risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk.	Y	Protocol pp. 13-15
(a)(1)(ii) Risks to subjects are minimized, whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.	n/a	
(a)(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (*e.g.*, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.	Y	
(a)(3) Selection of subjects is equitable, taking into account the purposes of the research and the setting in which it will be conducted, and being particularly cognizant of the special problems of research involving vulnerable populations, such as prisoners, mentally disabled persons, or economically or educationally disadvantaged persons.	Y	
(a)(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §26.1116.	Y	Protocol, pp. 24-26
(a)(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by §26.1117.	Y	
(a)(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.	Y	
(a)(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.	Y	
(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, additional safeguards have been included in the study to protect the rights and welfare of these subjects.	Y	Employer letter Protocol pp. 21-22

§26.1116 General requirements for informed consent

Table B-2. §26.1116 General requirements for informed consent ***Liquid Spray On-Farm Potato Seed Treatment Study Protocol***			
Criterion		**Y/N**	**Comments**
Before involving a human subject in research covered by this subpart, an investigator shall obtain the legally effective informed consent of the subject.		Y	
An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence		Y	
The information that is given to the subject or the representative shall be in language understandable to the subject or the representative		Y	All materials in English and Spanish
The prospective subject must be provided with the information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information.		Y	
Informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension.		N	EPA recommendation to add.
Informed consent as a whole must present information in sufficient detail relating to the research and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's understanding of the reasons why one might or might not want to participate.		Y	
No informed consent may include any exculpatory language through which the subject is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence		Y	
(a) In seeking informed consent the following information shall be provided to each subject	(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental	Y	
	(2) A description of any reasonably foreseeable risks or discomforts to the subject	Y	
	(3) A description of any benefits to the subject or to others which may reasonably be expected from the research	Y	
	(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject	n/a	
	(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained	Y	
	(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained	Y	
	(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject	Y	
	(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled	Y	

	(9) One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens: (i) A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject, if this might be a possibility; or (ii) A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.	N	EPA recommendation to add
(b) When appropriate, one or more of the following elements of information shall	(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject may become pregnant) which are currently unforeseeable	Y	
	(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent	Y	
	(3) Any additional costs to the subject that may result from participation in the research	Y	
	(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject	Y	
	(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject	n/a	
	(6) The approximate number of subjects involved in the study	Y	V2:177-186
	(7) A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit	n/a	
	(8) A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions	N	EPA recommendation to address
	(9) For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (*i.e.,* sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen)	n/a	
(h) If the research involves intentional exposure of subjects to a pesticide, the subjects of the research must be informed of the identity of the pesticide and the nature of its pesticidal function.		Y	V2:177-186

§26.1117 Documentation of informed consent

Table B-3. §26.1117 Documentation of informed consent ***Liquid Spray On-Farm Potato Seed Treatment Study Protocol***		
Criterion	**Y/N**	**Comments**
(a) Informed consent shall be documented by the use of a written consent form approved by the IRB and signed (including in an electronic format) by the subject. A written copy shall be given to the subject.	Y	
(b)(1) A written informed consent form that meets the requirements of § 26.1116. The investigator shall give the subject adequate opportunity to read the informed consent form before it is signed; alternatively, this form may be read to the subject.	Y	
(b)(2) A short form written informed consent form stating that the elements of informed consent required by § 26.1116 have been presented orally to the subject, and that the key information required by § 26.1116(a)(5)(i) was presented first to the subject, before other information, if any, was provided. The IRB shall approve a written summary of what is to be said to the subject. When this method is used, there shall be a witness to the oral presentation. Only the short form itself is to be signed by the subject. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary must be given to the subject, in addition to a copy of the short form.	n/a	

§26.1125 Prior submission of proposed human research for EPA review

Any person or institution who intends to conduct or sponsor human research covered by §26.1101(a) shall, after receiving approval from all appropriate IRBs, submit to EPA prior to initiating such research all information relevant to the proposed research specified by §26.1115(a), and the following additional information, to the extent not already included:

Table B-4. §26.1125 Prior submission of proposed human research for EPA review ***Liquid Spray On-Farm Potato Seed Treatment Study Protocol***			
Requirement		**Y/N**	**Comments**
Copies of all of the records relevant to the research specified by § 26.1115(a) to be prepared and maintained by an IRB	(1): Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.	Y	IRB Correspondence Volume
	(2): Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; a written summary of the discussion of controverted issues and their resolution.	N	EPA has requested directly from Advarra
	(3): Records of continuing review activities, including the rationale for conducting continuing review of research that otherwise would not require continuing review as described in §26.1109(f)(1).	n/a	
	(4): Copies of all correspondence between the IRB and the investigators.	Y	
	(5): A list of IRB members in the same detail as described in § 26.1108(a)(2).	Y	
	(6): Written procedures for the IRB in the same detail as described in § 26.1108(a)(3) and (4).	Y	Provided to EPA by Advarra
	(7): Statements of significant new findings provided to subjects, as required by § 26.1116(c)(5).	n/a	
	(8): The rationale for an expedited reviewer's determination under §26.1110(b)(1)(i) that research appearing on the expedited review list described in §26.1110(a) is more than minimal risk.	n/a	
	(9): Documentation specifying the responsibilities that an institution and an organization operating an IRB each will undertake to ensure compliance with the requirements of this subpart.	Y	
(a)(1): The potential risks to human subjects		Y	
(a)(2): The measures proposed to minimize risks to the human subjects		Y	
(a)(3): The nature and magnitude of all expected benefits of such research, and to whom they would accrue		Y	
(a)(4): Alternative means of obtaining information comparable to what would be collected through the proposed research		Y	
(a)(5): The balance of risks and benefits of the proposed research		Y	
(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.		Y	

Table B-4. §26.1125 Prior submission of proposed human research for EPA review ***Liquid Spray On-Farm Potato Seed Treatment Study Protocol***		
Requirement	**Y/N**	**Comments**
(c): Information about how subjects will be recruited, including any advertisements proposed to be used.	Y	
(d): A description of the circumstances and methods proposed for presenting information to potential human subjects for the purpose of obtaining their informed consent.	Y	
(e): All correspondence between the IRB and the investigators or sponsors.	Y	
(f): Official notification to the sponsor or investigator, in accordance with the requirements of this subpart, that research involving human subjects has been reviewed and approved by an IRB.	Y	