The Use of Multi-Criteria Decision Analysis in Performing Alternatives Assessment and Comparative Risk Analysis: The Case Study of Codling Moth Pesticides

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Abstract

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Risk assessment increasingly involves a more systemic evaluation of alternatives and their feasibility, risk, and benefit, in the form of alternatives assessment. However, quantitative, flexible, and standardized methods are still lacking for such analyses. A multi-criteria decision analysis method is proposed here as a framework for comparative risk assessment and alternatives assessment, whereby the feasibility and adoption of alternatives can be assessed and predicted while at the same time evaluating health-health tradeoffs among alternatives. An illustrative case study of occupational exposures to ten different codling moth pesticides is presented. Agricultural consultants to the tree fruit industry were surveyed and interviewed to examine pesticide preferences and the weight of selection criteria. Health impact valuations

were also carried out, as the population of participants is uniquely qualified as well-informed about pesticides and having occupational experience with their application, and with pesticide selection. Decision models were constructed based on these results to attempt to predict pesticide use before and after the paradigm shift resulting from the cancellation of one alternative, azinphos-methyl. Monte Carlo simulation was used to assess probabilistic estimates of doses to handlers of the ten pesticides with a variety of associated potential health outcomes. Toxicological data from the pesticide registration process was used to construct benchmark doses for comparison with human dose estimation, producing a probability of exceeding this limit of acceptable dosing. The fraction exceeding the benchmark was used in a decision analysis model revealing health-health tradeoffs among the alternatives.

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DEDICATION

For the workers who dedicate their time, health, and energy to feeding us all, and for my husband Chris, and my family and friends, in gratitude for their unflagging support,

Chapter 1. INTRODUCTION

As the field of risk assessment moves towards more holistic evaluations, the recognition of forms of analyses which are multidimensional in some way, such as cumulative risk assessment, comparative risk assessment, life cycle assessment, and alternatives assessment has increased.[1] The need for standard, or at least well-described and validated, methods for examining risk based on multiple exposures, routes of exposure, chemical alternatives, endpoints, or chemical fates has also become more apparent. [2] The best methods for these studies will require flexibility in dealing with data gaps, variability, and uncertainty. Such a method would encompass information gathering stages, feasibility assessments for the alternatives under consideration, all current components of risk assessment, and stakeholder engagement, or at the least consultation with members of each layer of the decision process (regulatory to end-user).

1.1 Multi-Criteria Decision Analysis

Multi-Criteria Decision Analysis (MCDA) is a method of decision analysis which, as the name implies, is suited to supporting decision makers who must weigh a number of different factors, or criteria, in informing a choice. Since it is geared towards directly comparing different types of criteria, it seems logically suited to address one of the most problematic criticisms of holistic risk assessments: the lack of suitable comparison methods for a variety of risk types. MCDA methods overcome the comparison problem by using decision maker preferences to assign a quantified relative importance to the various criteria so that they may be placed along a scale and compared even if they are not the same kind of outcome (e.g., health risks and economic risks, or chronic health outcomes and acute health outcomes). The flexibility of utility and preference-based methods also equip MCDA methods well for the feasibility assessment

required for a thorough alternatives assessment. It has been suggested that MCDA provides analysis methods which are more structured and better developed than those for comparative risk and are more grounded through stakeholder input.[3] MCDA has proven popular in various fields like environmental remediation, resource management, and environmental impact assessments, drawing the same advantages from stakeholder involvement in identifying and weighting criteria as comparative risk assessments should but also providing defined quantitative comparison methods.

A true alternatives assessment inherently requires comparison of risks, characteristics, and benefits which may be so different in their nature, value, or severity that they are difficult to compare in a meaningful and equitable way. This problem is exacerbated when characteristics which are difficult to value monetarily are evaluated, for example, human health impacts. Various methods for making these comparisons in a quantitative way have been proposed. The 1998 EPA example uses Quality Adjusted Life Years (QALYs) gained over the baseline per dollar spent, which allows incorporation of health effects and economic impacts into a comparable metric. The QALY system is often criticized, however, on the basis that it undervalues older or disabled individuals, and does not account for the value of the individual and their welfare to others (for instance, the parent supporting children), and critics often associate cost-per-QALY ratios with rationing of care and resources.[4] QALYs based on utility theory assume a given utility of a particular health state without considering that this value may be relative given the patient's current state, which Mooney suggests might be alleviated by basing QALYs on a different philosophy which incorporates relative values of health states [5]. Wong et al proposed another method for quantitatively combining different types of risk information, where a Net Health Impact (NHI) is calculated for any given policy change. The

NHI is calculated based on the change in valued-weighted health impacts across all health endpoints for a population. The weight assigned to a health impact would be a flexible value or distribution of values designed to reflect economic and health -based values. This method has the benefit of flexibility and ability to account for health benefits as well as risks; however, the weighting of health impacts still requires some kind of valuation and the examples provided by the authors include QALYs and life years lost [6]. The need for improved methods of aggregating risks of diverse health impacts is an ongoing obstacle in risk assessment, but also may provide the opportunity for more meaningful stakeholder involvement as such value judgments are the purview of the public as well as expert opinion in MCDA.

These studies will require a wealth of data from various sources, in many cases beyond current regulatory requirements. While this data necessity may be burdensome for the assessor, it also serves to highlight data gaps and weaknesses in established methods, potentially in a systematic way which itself can support updates and reformation of analysis methods.[7-9] The involvement of stakeholders and decision-makers in the research process can serve to supplement data and fill gaps, particularly in the area of the feasibility assessment, further making the case for a method designed around consultation with such individuals. [3]

MCDA methods allow for multiple decision frames of reference with established methods for preference elicitation, and in many cases, existing software which allows real-time assessment of the impact of preferences and criteria or decision-maker weighting.[10] Methods such as PROMETHEE (Preference Ranking Organization METHod for Enriched Evaluation) and its related method, GAIA (Geometric Analysis for Interactive Aid), require only pairwise ranks of outcomes and weights for each criterion [10, 11]. Ranking preferences rather than utility characterization places a lower cognitive burden on participating stakeholders, and requires less

information.[10] Since they do not require complete characterization of a utility function and do not necessarily provide a strict ranking of outcomes or single optimized outcome, PROMETHEE and GAIA methods are often considered for description type multi-criteria problems [11], and so are a good fit for risk analyses that seek to describe various actions and their predicted consequences.

1.2 Agricultural Pesticides

Pesticides used in agricultural operations present a risk assessment scenario which is useful to consider from a systemic perspective. There are typically numerous alternatives for the control of a particular pest species to choose among, and the selection of one compound over another creates differential exposure potential for the pesticide applicators, workers entering treated areas, the surrounding community, and the consumer of the end product. Removal or addition of a product will change the exposure and therefore health impact profile of these populations. Agricultural pesticide products are registered by the Environmental Protection Agency (EPA) following a review process which requires a human health risk assessment and an ecological risk assessment based on information about the product chemistry, environmental fate, human, domestic animal, and non-target species toxicology, and product performance. The efficacy of the pesticide and product performance may be reviewed, but not in all cases.[12] Human health risk assessments are based on toxicological studies in animal models (most often rodents, canines, and non-human primates), paired with estimates of exposure rates for a variety of activities.[13]

The human exposure assessment for pesticide residues in an occupational setting is based on a set of results from field exposure studies specific to each task, maintained by the Agricultural Handler Exposure Task Force (AHETF) and the Agricultural Re-Entry Task Force

(ARTF). These studies are used to produce a summary statistic (an arithmetic or geometric mean) known as an exposure surrogate, describing the rate of exposure per some measure of productivity (for instance, in the case of pesticide handlers, that rate is pounds of active ingredient handled), so that when paired with data on the rate of pesticides used, an estimate of average exposure is produced.[14] This estimate, adjusted by a set of safety factors, can be compared with a No Observable Adverse Effect Level (NOAEL) derived from one of a number of toxicological studies if a hazard is identified for that exposure route, to determine whether the associated risk falls under acceptable limits.[15] The data requirements for pesticide registration result in a large and standardized set of research study results accumulated on the impacts of each individual active ingredient. The availability of this data creates an opportunity to demonstrate the use of MCDA in comparing a variety of alternatives with comparatively few data gaps than many alternatives assessments face for exposure assessment as well as toxicity.[16]

1.3 AZINPHOS-METHYL AND THE CODLING MOTH

In 2006, the EPA announced that the registration of all azinphos-methyl products would be withdrawn due to unacceptable levels of risk to human health discovered in the 2005 registration review. One scenario found to have excessive and non-mitigatable risk was that of pesticide handlers applying the product to tree fruit using airblast sprayers.[17] After the official decision, phase-out of azinphos-methyl in tree fruit lasted until the fall of 2013. Azinphos methyl, an organothiophosphate pesticide and known neurotoxicant, was used for the control of the lepidopteran *cydia pomonella* in pome fruit. *Cydia pomonella*, or codling moth, has a larval stage which feeds on pome fruit and seeds by burrowing through the center. It leaves the fruit to form a *pupal* stage, leaving behind a damaged fruit which is vulnerable to rot and fungal infection. Larvae which bite the fruit but do not burrow leave a wound in the skin called a *sting*.

Both stings and deep entries prevent sale of the fruit. Unchecked codling moth infestation can decimate a harvest.[18] Until the ban on Azinphos-methyl following September of 2013, it was one of the most popular chemicals for codling moth control, and as recently as 2008, 80% of apple growers used it.[19] Because of the high economic stakes in the control of codling moth (the value of the 2014 United States apple crop was estimated at $2.86 billion[20]), an analysis of feasible alternatives and economic impact were completed in the course of the registration decision.

It was projected during the transition from azinphos-methyl that the economic impacts of the decision would be small to the Washington apple industry as a whole, but measurably negative due to the higher cost of the alternative pesticides and the need for their application in greater amounts [19]. The Washington State University working paper on the economic impacts of azinphos-methyl cancellation found that employment costs and apple prices would increase by less than 1%, and apple sales would decline by less than 1%. Although small changes, the authors extrapolated these changes to a net decrease for the apple industry's profits of $16 million, or $101 per acre. These calculations are based on insect controls used in 2007, and the hypothetical insect controls which would have been used if azinphos-methyl were not available in 2007, including pesticides such as chlorantraniliprole and spinetoram which were not actually available in 2007 [19]. The EPA's review of impacts from cancellation in 2012 found that economic losses were less than expected, as costs of azinphos-methyl alternatives are declining and as of 2012, no decreases in crop yield or quality have been experienced [21]. The feasible alternatives included in the analysis were approved based on the above described human health risk assessments, each considered in isolation.

1.4 AZINPHOS-METHYL AND ACETAMIPRID FIELD STUDY

In 2012, the Pacific Northwest Agricultural Health and Safety (PNASH) research center at the University of Washington embarked on a field exposure study designed to assess the exposure of apple orchard pesticide handlers working with azinphos-methyl and acetamiprid. The goal of the study was to assess the acute risks of neurotoxicity to handlers while using the same methods of exposure assessment and risk calculation for each compound. At the time of the study design, in 2009/2010, acetamiprid was one of the most commonly used alternatives to azinphos methyl, with over 50% of growers reporting its use in the previous growing season.[22] While orchards using remaining stocks of azinphos-methyl were plentiful, location of acetamiprid users proved extremely difficult in 2013/2014. Eventually, a sample size of ten was reached for the acetamiprid handlers, collected over the course of two growing seasons. The results from the field study are included in Appendix A of this dissertation. In summary, over-exposure of the azinphos-methyl handlers was confirmed. Were the acetamiprid handlers not wearing extra protective equipment, based on compound deposition measured outside of their garments, they would have also potentially been over-exposed. This finding suggests that the surrogate exposure rate generated by the summary statistics of exposure studies described above may not protect against the range of exposures encountered by workers following the label instructions for pesticide use.

1.5 PURPOSE OF THIS ANALYSIS

An ancillary finding of the field study was that many growers sought out a variety of pesticide alternatives to azinphos-methyl other than acetamiprid, and the days of a single compound dominating the decision space for codling moth control had ended. The purpose of

this study was to more fully explore the trade-offs among the multiple available compounds for codling moth control. The aim of this study was to demonstrate a method which could both describe and predict the selection of pesticide alternatives and explore the reasons for their selection along with the resulting potential for a variety of health impacts. The PROMETHEE variety of MCDA is proposed as a method for this alternatives assessment and comparative risk assessment, and for adoption as a complementary method for the current pesticide regulatory institutions. A comparative risk assessment for the pesticides will be constructed using probabilistic exposure calculation and benchmark dose modeling as an enhancement to the current deterministic methods of pesticide risk assessment.

1.6 SPECIFIC AIMS

1) Characterize important decision criteria and preferences for criteria values among pesticide decision makers along with prevalent attitudes and beliefs regarding chemical insecticide use in agriculture.
2) Apply principle component analysis to relate beliefs and attitudes among decision makers to stated preferences and decision criteria for selection of chemical pest control methods.
3) Compare the predicted use of pesticides based on stated preferences with NASS data from before (2005) and after (2011) azinphos methyl phase-out.
4) Estimate probabilistic exposure of pesticide handlers to codling moth control insecticides using AHETF datasets.
5) Construct benchmark dose models from toxicological studies submitted by pesticide registrants to the EPA based on hazard assessments in the EPA Human Health Risk assessment for each compound, and calculate the percent of estimated doses exceeding the benchmark.

6) Use PROMETHEE multi-criteria decision analysis methods to combine the estimates of health risks into a model of health-health trade-offs.

1.7 Chapter Description

The following chapters 2-5 are written as manuscripts for submission to a variety of journals, as described in Appendix B.

2) This paper describes the elicitation of decision criteria, health impact values, and preference functions from the selected population of key informants. The instruments used are included in Appendix C. Figure 2 of the paper shows a sample of the preference functions built for the PROMETHEE models. The remainder are in Appendix D.

3) This paper describes the use of Monte Carlo simulation to estimate probabilistic doses of the ten pesticides selected for this analysis based on the current EPA framework for calculation of a deterministic exposure for pesticide handlers.

4) This paper describes the benchmark dose models for the health impacts used in the EPA occupational risk assessments of the pesticides for which the EPA recognized a hazard. The remaining benchmark doses used in the health-health tradeoff model are included in Appendix E.

5) This paper describes the construction of PROMETHEE models for prediction of pesticide uses over the course of a growing season including 6 potential applications. The health-health trade-off models for the ten pesticides analyzed are also described, and the risk reduction accomplished by the removal of azinphos methyl is examined in the context of predicted pesticide usage rates.

Chapter 2. HEALTH IMPACT VALUATION ELICITATION FROM DECISION-MAKERS WITHIN DECISION PREFERENCE CONVERSATIONS: A CASE STUDY IN PESTICIDE RISK ASSESSMENT.

2.1 ABSTRACT

Alternatives assessment is an area of risk analysis which has become increasingly important in the prevention of occupational exposures. Multi-criteria decision analysis is one method which has been proposed for examination of chemical alternatives. This study demonstrates that multi-criteria decision analysis methods can be used as a framework for the elicitation of preferences and feasibility ranking from decision-makers and end users. The engagement with participants on preferences regarding chemical function is also an opportunity to elicit preferences regarding health impact valuations from a population potentially more directly affected by them. Pesticide selection preferences were used to construct a decision analysis model for codling moth controls which was able to predict stated pesticide preferences collected separately. Preference information on health impacts was collected simultaneously for pesticide-related health impact valuation. Age of the participant and occupational experience were shown by principal component analysis to be associated with differences in the individual's preference rankings.

2.2 INTRODUCTION

Increasing recognition of the value of alternatives assessment and substitution of lower-risk compounds in promotion of occupational health and safety holds great promise but brings increasing challenges due to the information required for human health risk assessments as well

as economic and technical evaluations of multiple chemicals. The goal of preventing "regrettable substitutions" holds considerable allure, but in practice requires significant information on the potential of health outcomes as well as a mechanism for comparison of different types of health impacts and the use of quantified health state values.[23]

Many proposed frameworks for alternatives assessment are available.[23-28] These methodologies vary in their use of exposure assessment, decision analysis or assessment, health state valuation, environmental impacts, depth of economic assessment, treatment of data gaps, and other characteristics.[23] Multi-criteria decision analysis (MCDA) is a broad group of methods which has been proposed and applied as an alternative assessment framework. [3, 23, 29] One advantage of MCDA-based alternatives assessment is that a framework for assessment of a variety of metrics of comparison is built-in and relies on a value-based comparison. The methods for engagement of stakeholders and elicitation of information on feasibility and cost are straightforward and inclusive. These methods are designed to accommodate multiple perspectives and can accommodate and assess variability and uncertainty.[3, 30]

The involvement of stakeholders and decision-makers in the MCDA process is central to its successful application as the source of information on the viability of alternatives and the relative values of decision criteria. The alternatives assessment can also be an opportunity to initiate relationships among stakeholders and conversations about the alternatives and their relative values.[3] It should also be considered an opportunity to engage stakeholders on topics of human health impacts, risks associated with alternatives being assessed, and the risk assessment process in general. MCDA has increasingly been used to evaluate health care and heath interventions from a patient and practitioner perspective.[31, 32] These methods may also provide opportunities to gather preference information on health impacts resulting from environmental

contaminants and chemical exposures. The communication developed with stakeholders and decision-makers for the purpose of characterizing selection criteria could also serve as an opportunity to elicit health state preferences from populations most directly impacted and perhaps with personal experience of the health state in question.

The selection of pest control measures is a scenario where consumers are faced with multiple chemical alternatives with a variety of properties and potential human health implications. In the tree fruit industry, codling moth control has significant importance due to the potentially devastating economic consequences of an infestation.[33] Numerous alternatives are available to control codling moth, including pheromone-based mating disruption, horticultural oils, and a variety of insecticidal treatments typically applied between 1-6 times per growing season using airblast sprayers.[34] The selection among these alternatives for an orchard is often informed or carried out entirely by agricultural consultants licensed by the state to provide pest control recommendations. In many cases, these consultants are also pesticide applicators.

The purpose of this study is to demonstrate the use of MCDA methods in the elicitation of preferences in pesticide selection as well as preference information regarding health impacts of acute occupational pesticide exposure. The popularity of pesticide alternatives will be predicted and compared with stated preferences collected from the consultants, demonstrating the usefulness of these methods in feasibility assessment.

2.3 METHODS

A joint survey and phone interview were implemented to elicit a variety of information from the consultants regarding their information sources, codling moth control preferences, work history, and other factors. The questions included in both instruments were qualitatively evaluated and the text and content were advised upon by two consultants to the tree fruit industry

to improve the relevance and focus of the questions. All research methods and materials were approved by the University of Washington Institutional Review Board.

A list of all licensed crop consultants in Washington state was obtained from the Washington State Department of Agriculture (WSDA). Since the list could not be narrowed by specialty to target only consultants for apple growers, the consultants were filtered based on their address, so that only those consultants in Central Washington based within 25 miles of orchard land were included. A total of 521 consultants were included in the recruitment effort. The survey was distributed first, using both online and postal distribution. Most (86%) of the consultants provided an email address to the WSDA. When possible, email was used to initiate contact with the consultants. Those who did not list an email provided a physical mailing address to which a paper copy of the survey was sent. The initial question asked the consultants to confirm that they worked with the tree fruit industry and provided recommendations specifically regarding codling moth control. Questions in the survey (included in appendix B) focused on demographic and employment characteristics, importance of specific information sources, and frequency of recommendation of chemical and non-chemical codling moth control methods. The items included in the web survey were largely constructed as multiple choice versions of the Likert scale or a similar qualitative rating scale. Questions on agreement with statements reflecting attitudes and beliefs about chemical pesticides and codling moth were included. An open text field was provided for participants to offer any additional information or explanation they wished at the end of the survey. A $5 pre-incentive was included with the survey invitation.

At the end of the survey, participants were asked to indicate if they would be interested in participating in the phone interview portion of the study. Those who responded positively were

contacted immediately to follow up, and the full list of those consultants who had not declined to participate in the study was also used for three rounds of cold-call recruitment. A $25 incentive was offered for completion of the phone interview. Respondents who participated in the phone interview without completing the survey initially were prompted to do so at the end of the interview.

In the phone interview, participants were asked to list factors in their decisions about codling moth control (see supplemental materials for the complete interview script). Following this initial open-ended question, a standard list of potential pesticide characteristics was read with the participant affirming or denying any impact on their decisions. Afterwards, the consultants were asked to name the most important single decision criterion among those factors, either those named spontaneously or identified from the list. The listed factors included efficacy, resistance management, pollinator toxicity, beneficial species toxicity, cost, pre-harvest interval and re-entry interval (beyond observation of the legal limits), protective equipment, length of market availability history, and human toxicity. They were then asked to rank, on a 1-10 scale, the relative importance of each other individual criterion which they reported considering. Based on the selected decision factors, additional questions were asked to elicit preference and indifference thresholds for each factor, for example, the smallest difference in price between two pesticides that would affect the choice between them. Modifying factors for the importance of the selection criteria were also discussed.

After asking participants to identify and rank the decision criteria, even if they did not identify human toxicity as an important decision criterion, they were asked to assign a value on a scale of 1-10 to the importance of prevention of a set of health impact categories in workers. The health impact categories were selected based on types of potential health impacts identified in the

EPA human health risk assessments for ten of the most effective non-organic codling moth pesticides. These health outcomes resulted from animal model toxicological studies, and were used as the basis of the NOAELs for occupational risk assessments. The health impacts on which the NOAEL was based were translated into a more general terminology that would be more meaningful in terms of human health. For each category, a brief explanation and examples were included in the question eliciting a rank, as shown in table 2.1. To avoid implications of hazard and overstatement of evidence of a specific human health impact causation by or association with any specific pesticide, the question was framed in a hypothetical and general fashion:

'I'd like to ask few questions about potential human health impacts of some pesticides and how you feel about their importance.
I'm going to name some health impacts that the EPA investigates as part of the pesticide registration process. I'd like you to tell me, on a scale of 1-10, how important it is, in a hypothetical sense, to prevent each of these impacts in workers exposed to pesticides on the job. Ten is critical to prevent, and one is not at all important to prevent.'

The adoption of this wording was supported by the consultants who provided review of the question text, rather than the original wording based more closely on classic willingness-to-pay verbiage, because it was viewed as significantly less confusing and easier to answer in an interview session. Consultants were also asked more general questions regarding the relative importance of acute or chronic impacts and the highest acceptable probability of an acute or chronic health impact.

The responses to the survey and interview were examined using exploratory factor analysis. Factor analysis was applied to the assigned decision criteria and health impact weights to look for trends in these responses and reduce the weighting scale's dimensions. The criteria of efficacy, secondary pest control, and pesticide persistence were not used in the factor analysis because of lack of any variation in response or a low number of consultants who suggested them

(secondary pest control and pesticide persistence were not listed among the prompts, but were named by a few participants).

Responses on pesticide decision criteria, preference and indifference thresholds, and health impact rankings were used to build a series of decision models for pesticide selection of codling moth using the Preference Ranking Organization Method for Enrichment Evaluations (PROMETHEE) method of decision analysis.[35] Selection criteria values were filled in for each pesticide, using data from the WSU Crop Protection Guide, an economic analysis of the impact of cancellation of Azinphos methyl on the tree fruit industry, and the labels of each pesticide as formulated for use in pome fruit against codling moth. [19, 34, 36-44] The resulting preference ranking for the selected pesticides examined in this study was compared with the stated preferences for pesticide recommendation collected from the survey using Spearman's rho.

2.4 RESULTS

2.4.1 *Survey and Interview Results*

Of the 122 total respondents to the email and mailed survey recruitment (23.4% of the total population), 52 consultants (43%) were eligible for and chose to participant in the survey. Among those, 16 also participated in the phone interview portion of the study. Most respondents (92%) were male and an average age of 51 (ranging from 26 to 68 years old. The majority (77%) had applied pesticides occupationally at some point, and have farmed themselves or had parents who farmed during their childhood. Two-thirds of the responding consultants maintain the additional certification of Certified Crop Advisor in addition to the consulting license, which requires additional continuing education credits each year.

All participants had attained at least some college education, though not all completed a degree program. 64% had either an associate or bachelor's degree, and 23% had attended some

graduate school or earned a graduate degree (master's or doctoral). 58% of respondents worked for a local or national independent consulting firm, and 19% worked for a single grower or a cooperative of fruit tree growers. Only 8% worked for a chemical distributer or manufacturer. The consultants had an average of 21 years of experience in the job (ranging from 2 to 41 years). These characteristics were distributed similarly for the subset of sixteen consultants who participated in the phone interview, except that 38% had completed some graduate coursework or earned a master's degree. 71% of the web survey respondents and 87% of phone interview participants stated that they were usually the main or only decision maker for codling moth controls for their client. Most surveys were completed within 20 minutes, and the interview times ranged from 25 minutes to an hour.

2.4.2 *Identified Selection Criteria*

Responses to the initial open-ended question regarding important factors in codling moth control selection were often brief and indicated only one or two decision criteria, therefore a list of prepared criteria suggestions was critical in stimulating additional conversation and characterizing the decision space. Many consultants indicated selection criteria important in the decision of when and whether to treat for codling moth, in addition to what control to treat with. The pest pressure (that is, the degree of infestation) as indicated through monitoring, historic pest presence in the particular location, and the time of year are all factors named by the consultants that are environmental characteristics and first drive the decision of treatment necessity and timing, which in turn may impact the choice of control. The time of year was often mentioned by the participant when discussing modifying factors in the importance of selection criteria. Other responses to this question which were characteristics of the pesticide and therefore more direct decision criteria included whether the orchard was organic, the efficacy of the pesticide, the cost,

the human toxicity, the mode of action, broad or narrow spectrum activity, persistence of residues, the re-entry interval, the pre-harvest interval, and the impact on beneficial orchard species.

The interview participants' responses to the importance of each decision criterion are shown in table 2.2. All participants indicated that efficacy is the most important factor in their decision between codling moth controls. Many offered confirmatory statements during the course of the interview, indicating that using anything less than the most efficacious control (within the confines of the situation) would be risking a greater problem later in the year and would often lead to more pesticide applications and greater overall expense. All participants also indicated practicing some degree of resistance management in their recommendations, so chemicals from the same class would not be used for more than one moth generation within a growing season. Respondents who worked with backyard growers and organic growers reported that because there are fewer approved options for non-commercial or organic use, there may be no choice but to re-use pesticide chemistries that would ideally be rotated. An exception to resistance management principles is granulosis virus, which must be reapplied frequently over the course of the season to maintain sufficient activity to impact the pest pressure.

Other criteria had less consistent responses among all consultants. For example, while pre-harvest interval and re-entry interval are legal restrictions placed on every pesticide use, the degree to which both are minimized beyond the legal requirement as a precaution varies among consultants. The re-entry interval is most important in the early growing season, where such tasks such as blossom and green fruit thinning and branch propping may be required regularly. The pre-harvest interval is progressively more important towards the end of the growing season,

as harvest approaches. Accounting for the REI can be highly variable according to the specific orchard block and the tasks required in the immediate future.

Attitudes toward the importance of minimizing toxicity to pollinating insect species, beneficial orchard arthropods ("beneficials"), and humans varied as well. Most respondents indicated when asked that human toxicity did not factor into their selection since the label-prescribed PPE and handling instructions are designed to ensure safety, and carrying out those instructions is the purview of the applicator and their supervisor or the grower. If pollinators were considered in pesticide selection, they would only be important during bloom and while the pollinating bees were known to be in or near the target spray area. The majority of consultants reported that pesticide applications while bee hives were present were avoided in general, and that the hives would be removed or covered during any necessary sprays. Since only the first insecticidal controls for codling moth are likely to be used during the bloom season, subsequent spray decisions do not consider that criterion.

Although all consultants responded that they consider beneficial species protection to some degree, the range of the rank assigned to that factor ranged from 1-10, and the species named when asked for the most important predators to safeguard varied as well. In order to account for these individualities without assigning to much overall weight to the beneficial species, the assigned criteria weight was divided among all species named by the participant. The species most emphasized by each consultant was included in the decision model (see table 2.2).

2.4.3 *Health Impact Rankings*

The health impact rankings provided by each consultant are listed in table 3. Substantially less variability was present in these rankings within a single respondent's replies in comparison to the pesticide selection criteria ranks. However, most consultants ranked dermal

and ocular irritations as lowest importance, and also ranked dermal sensitization lower to a lesser degree. Developmental impacts were universally ranked highly, as was cancer (no type was specified). Acute neurotoxicity and skin sensitization were ranked with the most variability. In general, reproductive toxicity and sub-chronic organ toxicities were ranked highly, but less consistently high than developmental toxicity. Those scores also tended to cluster together, possibly indicating a lack of differentiation among those impacts by the consultants (table 2.3).

2.5 FACTOR ANALYSIS RESULTS

2.5.1 *Pesticide Selection Criteria*

Three components explained 68.7% of the variance in rankings of pesticide selection criteria (table 4). None of the extraction communalities fell below 0.575. The first component according to the unrotated analysis was associated most strongly with human toxicity, cost, protective equipment, and pollinator toxicity (see table 4). These selection criteria were associated with 33% of the variance. Component 2, which explained an additional 22% of the variance, was associated with resistance management, and was associated with less interest in Pre-harvest interval and Re-entry interval. The third component was associated with market duration, and negatively with beneficial species toxicity. To simplify the interpretation of these factors, as they were not correlated, a varimax rotation with Kaiser normalization was applied. The rotated results showed the first component to be associated with protective equipment, pollinator toxicity, human toxicity, and resistance management. The second component is associated with Pre-harvest interval and Re-entry interval, and the third component again with market duration and negatively with beneficial species toxicity.

The first component represents factors in the pest control which may be occasionally beneficial to minimize, but not essential or always relevant. Although in abstract, these may be

factors which a consultant might consider if no other trade-offs were required, these factors are not often thought of as relevant, since pollinator toxicity can be avoided, and human toxicity is assumed to be prevented through personal protective equipment. Protective equipment itself might be valuable to minimize for worker comfort, but some consultants observed that workers used the same high level of protective clothing regardless of whether it was strictly required, so that changing pesticides would not have an impact on selected PPE. By contrast, component two factors such as cost, pre-harvest interval, and re-entry interval can put concrete limits on the available options.

Little was discovered in clustering of individual component scores. Figure 2.1a shows one potential cluster, where consultants who responded to the paper mailed version of the survey rather than completing it online were more likely to score higher in either component 1 or two, but not both simultaneously. Interestingly, the same pattern is not found in responses on the importance of the internet in information gathering or frequency of internet use in general. The preference for the paper survey may represent some difference in processing information or priorities; however, the limited sample size prevents exploration of this trend. Removal of those participants, leaving n=13, shows no other discernable clusters in the component scores of the small remaining data set.

2.5.2 *Health Impact Rankings*

Eighty percent of the variance in the health impact ranks was explained by three components (see table 2.5). The first was positively associated with non-cancerous organ toxicities (liver, kidney, thyroid) temporary neurotoxicity, hemotoxicity, reproductive toxicity, and carcinogenicity. The second component was associated with ocular and dermal irritation and dermal sensitization. The third was associated with permanent neurotoxicity and developmental

impacts (see table 2.5). These components represent prevention of 1) non-permanent impacts associated with acute or sub-chronic exposures, 2) acute irritations and dermal impacts, and 3) chronic or permanent impacts. Two outliers were present based on components 1 and 2. One participant was the youngest of the consultants by six years, and the other stated after providing the ranks that they did not consider the irritation and sensitization outcomes as health impacts in the sense of the other categories, which are associated with the first component. The factor analysis was re-run without these two responses.

Application of the varimax rotation produces four components which explain 84% of the variance in health impact scores (see table 2.5). The first component is associated with eye and skin irritation, skin sensitization, and acute neurotoxicity. The second is associated with non-cancerous organ toxicity. The third is associated with reproductive and developmental health impacts, and the fourth with cancer and hemotoxicity. Participants who have not applied pesticides occupationally (n=3) tended to cluster with higher scores for component 1. Those of age 50 or greater had positive scores for component 2 for the most part, while those of age less than 50 had negative scores. Participants with shorter duration of experience tended to cluster with lower scores for component 4 with one exception, and patients who strongly agreed that chronic impacts of pesticide exposure are critical to prevent in workers clustered towards the higher values of 4 (figures 2.1b-2.1e).

2.5.3 *Preference Ranking Organization Method for Evaluation Enrichment results and stated preferences*

Two PROMETHEE models were constructed to test against stated preferences. The first model represented selection of a material for use during or just after bloom, for control of the first generation's egg phase. The second model represented selection of a material for control of

the later larval phase of the first generation. Since these models are applicable only to the first generation of codling moth, the criterion of resistance management was not used for this analysis. The selection criteria used for each model are listed in table 2.2. For this model, the selection criteria weights provided by the consultants for pollinator toxicity were adjusted based on the consultants' answers to additional questions about scenarios in which sprays and pollinator activity coincide. This adjustment was accomplished by removing the weight for pollinator protection from the models for consultants who ranked the protection of pollinators at the start of the interview, but stated in the latter part of the discussion that they do not recommend applications for codling moth while pollinators are active in the orchard.

In addition, the toxicity of each compound to beneficial species mentioned by the participants, including aphid predators and mite predators in general, ladybugs, lacewings, parasitoid wasps, and predatory true bugs were applied to the model for each consultant who named them. To avoid over-weighting beneficial species toxicity, the criteria rank was divided evenly among the species for each consultant (see table 2.2). Preference functions using individually stated preference and indifference thresholds were created for each consultant individually. Linear preference functions were set for numeric values, including cost, re-entry interval, and pre-harvest interval, using the indifference thresholds and preference thresholds elicited during the interview. Step functions for criteria with ordinal values, such as ratings of toxicity to pollinators, protective equipment, and human toxicity class, were developed with variable degree of difference in preference depending on the strength of the preference (slight or strong) reported by consultants (see examples in figure 2.2). This model provided rankings of the pesticides which were in most cases similar to the stated individual preferences for each

participant (see figure 2.3). 72% of the 32 models constructed had a Spearman's rho for agreement between the stated preference and the preference ranking of greater than 40%.

2.6 Discussion

This study explored the feasibility of eliciting decision information from a group of professionals involved in selection of agricultural chemicals. While eliciting information on selection criteria for pesticides, information on the valuation of potential health impacts related to pesticide exposure was also explored. The personal experience most participants had and continue to have with pesticide application in an occupational setting and their immersion in the agricultural industry and the ag community coupled with a scientific educational background and occupation make their perspective on pesticide health impacts unique and important to explore.

Some challenges were encountered in carrying out this research. An unusually early spring (a critical time in the production of tree fruit) coupled with historic difficulty in engaging this population of workers made recruitment for the study difficult. Crop consultants work in a variety of settings, and recruitment of those working directly with chemical manufacturing proved difficult, so that the majority of participants worked with independent firms. This difference may result in lack of generalizability of the selection criteria to crop consultants in all settings. Comparison with the responses to the 2009 survey of tree fruit consultants carried out by the pesticide transition management project showed that similar proportions (83% and 78% in this study) recommended azinphos methyl use before the registration was withdrawn. 68% of the PMTP survey participants reported that their parents farmed during their childhood, compared with 73% in this study. 16% of participants in the PMTP project had not completed at least an associate's degree, compared with 8% of consultants in this study. The percentage of female participants was similar (4% in the PMTP and 8% in this study (n=4 of 52 surveyed), and

the age distribution in this study was slightly older than that of the PMTP participants. Overall, despite the relatively small sample size, a similar population appears to have participated in this study when compared to the PMTP study, which reported a participation rate of 60%.[45]

In general, despite issues in recruitment, most participants responded positively to the study and were able to provide responses of some depth and detail to questions about pesticide selection for codling moth. For most consultants, the health impact rating and related questions seemed to pose more difficulty than those more directly about pest control. The feedback provided on this section by the consultants who reviewed the instruments prior to the start of recruitment was invaluable in creating approachable and understandable phrasing for this section. Most commonly, health state preferences are derived from willingness-to-pay, standard gambles, or time trade-off questions, and the standard gamble is the gold standard for utility assessment. However, in evaluation of health states, results can be inconsistent and may be subject to heuristic biases, possibly due to the difficulty in understanding the probabilities associated with these questions.[46] Although rating scales may suffer from bias as well, it has been suggested that the utility and preference data from such scaled questions may be more informative than previously thought.[47] The preference of advising consultants for ranking questions rather than the more complex standard gambles coupled with the desire to limit the time burden imposed on the participants supported the use of the ranking system in this case. Pesticide health impacts are a sensitive topic in many agricultural communities, and emphasizing the hypothetical and general nature of the health impact categories was important to the participants' comfort with the topic. Provision of plain language examples of the health impact categories was helpful given the relatively short time available to complete each interview.

Creation of the decision models based on collected data showed that stated preferences in this case can be modeled with relatively good accuracy based on a short information gathering session (an hour or less). However, the ranks provided by participants without further examination could be misleading, as shown by the contradictions in the importance of pollinator toxicity. Participants who provided a numerical rank revealed through later discussion that the pollinator toxicity of compounds generally had little bearing on decisions since they would be timed for after the bloom season. Although greater participant engagement would be beneficial to the model development and provide opportunities for stakeholder relationship-building, the demands of agricultural production industries, particularly during the growing season, is a barrier to this kind of research. A less time-intensive study structure can still provide valuable information on decision-maker and consumer preferences without burdening participants with limited time for research engagement. As alternatives assessment grows in importance in the field of environmental and occupational health, efficient methods for understanding the selection and utility of product alternatives will likewise be required. This study demonstrates that decision-maker engagement in preference and selection criteria identification can provide valuable information for alternative prediction while also providing the opportunity to discuss and elicit health impact valuations directly from interested populations.

Chapter 3. ADAPTION OF REGULATORY FRAMEWORKS FOR DETERMINISTIC RISK ASSESSMENT TO MONTE CARLO-BASED RISK ASSESSMENT OF OCCUPATIONAL PESTICIDE EXPOSURES.

3.1 ABSTRACT

Implementation of probabilistic analyses in exposure assessment can provide valuable insight into the risks of population extremes and more vulnerable or sensitive subgroups. Incorporation of these analyses into current regulatory methods for occupational pesticide exposures is enabled by the exposure datasets and associated data used in the risk assessment paradigm used by the Environmental Protection Agency. Monte Carlo simulations were performed on exposure measurements from the Agricultural Handler Exposure Dataset and the Pesticide Handler Exposure Dataset along with data from the Exposure Factors Handbook and other sources to calculate exposure rates for four pesticide handling scenarios. Probabilistic estimates of doses for pesticide handlers working with three different neurotoxic compounds were developed and compared with the No Observable Effect Levels used in the EPA occupational risk assessments. It was found that workers using all three compounds exceeded the level of concern by some fraction of the population. This finding has implications for pesticide risk assessment and offers an alternative procedure which may be more protective of population extremes than the current paradigm.

3.2 INTRODUCTION

Probabilistic analyses of hazard and exposure are increasingly used in environmental health in general,[48-52] and particularly in risk assessment of pesticides.[53-58] Probabilistic

exposure assessment has several potential advantages over deterministic methods in utility to risk assessors and managers. The use of distributions instead of summary statistics can be more informative as well as protective of the population at risk. It provides information on the likelihood or degree of a health impact and the shape and dimensions of that likelihood's distribution in a population. Probabilistic exposure assessment can quantify the variability of risk and the uncertainty separately, providing useful information about the quality of data that the deterministic measure is based on as well as the range of potential exposures.

The disadvantage of probabilistic exposure assessment is the amount of data required to characterize the distribution of multiple variables. Probabilistic methods are more difficult to perform than deterministic, and standard procedures for incorporating distributions of risk into regulation are not universal.[59] For this reason, many regulations are based on a deterministic summary statistic from a distribution of exposures, and the value of using probabilistic methods may not be apparent if the average of the distribution is compared with the status quo. Characterization of the population extremes and the probability of excessive exposures may offer the ability to protect more sensitive or highly exposed members of the population, or at least provide an explicit calculation of the possible exposures, doses, or risks that would be deemed acceptable when setting a regulatory level.[58]

The regulation of pesticides is an example of a framework which uses deterministic estimations of exposure and dose to assess human health risks through contact scenarios such as specific occupational tasks. Although most probabilistic pesticide exposure studies have focused on dietary exposures, some occupational studies have been carried out. Phung et. al used Monte Carlo simulation methods to characterize exposure of rice farmers to chlorpyrifos, finding

evidence of potential acute overexposure.[60] Lunchick described a case study of developing exposure distributions for occupational pesticide handlers treating cotton.[58]

The Agricultural Handler Exposure Task Force curates a set of exposure studies which are used to derive average exposure rates in mass of exposure in micrograms (µg) of active ingredient per pound of active ingredient handled during a specific work task.[61, 62] This exposure rate data, an estimate of the amount of active ingredient which deposits on or is inhaled by a person per unit of work accomplished, along with information on specific product application rates and exposure factors from sources such as the Exposure Factors Handbook, is used to calculate the dose (the amount of the active ingredient absorbed into the human body per kilogram body weight per day of work) used in regulation of the pesticide's use.[15] The resulting exposure rates from the AHETF datasets are used for risk assessment-based pesticide regulation by the Environmental Protection Agency, the California Department of Pesticide Regulation, and by the Canadian Pest Management Regulatory Agency. In 2006, the risk of acute neurotoxicity of Azinphos methyl in occupational exposures contributed to the gradual withdrawal of the pesticide from any use in the United States.[63] Azinphos-methyl, an organothiophosphate pesticide, causes neurotoxicity through the inhibition of cholinesterase.[64] One prominent use of Azinphos methyl was the control of codling moth in pome fruit orchards. There are a variety of alternative insecticides and non-insecticidal methods that have taken the place of Azinphos methyl. Some of these alternatives, for example the avermectin benzoate salt Emamectin benzoate and the neonicotinoid acetamiprid, also have the potential to cause neurotoxicity to mammals.[65, 66] According to deterministic estimates carried out during registration, with proper use these pesticides should not create occupational exposures greater than the levels of concern based on the animal studies.

In this analysis, probabilistic methods are used to estimate the exposure, dose and risk associated with the occupational handling of three different neurotoxic pesticides, two of which are currently approved for use in the United States.

3.3 METHODS

Simulations of occupational handler's doses during airblast application to apple orchards were created for three different pesticides. The three pesticides were each assumed to be applied using open-cab tractors, and the handlers were assumed to mix and load the applied pesticides prior to application. The dermal and inhalation doses were calculated following the same framework as is used in EPA occupational risk assessments for the same tasks[62, 67] using the same assumptions where possible.

Exposure was first estimated for the three different mixing and loading scenarios (wettable powder, wettable powder with soluble packaging, and dry flowables) and for the open cab application task using exposure rate data (in micrograms of exposure / pound of active ingredient used) from the Agricultural Handler Exposure Database (AHED) and the Pesticide Handler Exposure Database (PHED). Exposure during mixing and loading of wettable powder with and without soluble packaging was based on data from PHED, and exposure during mixing and loading of dry flowables and application of all formulations was based on data from AHED. The two datasets contain exposure rates that were collected using slightly different methods. AHED is considered the more accurate dataset, but at the time of data analysis, the AHED wettable powder mixing and loading scenarios were in development. The collection methods and sample sizes for the applicable pesticide handling scenarios are summarized in table 3.1.

3.3.1 *Inhalation exposures*

The exposure algorithm indicates that each individual's samples should be normalized by some measure of their task productivity before summarization, for instance using active ingredient applied or time of application[62, 67]. The mass-normalized inhalable mass was estimated according to the exposure algorithm:

For masses collected using powered active air sampling, i.e., with an air pump or impinger (air technology "2" or "3" in the PHED dataset, and all samples in the AHED datasets), normalized inhaled exposure is calculated as

$$\frac{\text{sample mass} * \text{inhalation rate}}{\text{sampling flow rate} * \text{mass active ingredient applied}}$$

For masses collected on filters or respirators where the flow rate is assumed to be driven by the participant's inhalations (air technology "1" in the PHED data for mixing and loading of soluble-packaging wettable powders, n=9), normalized inhaled exposure is more simply calculated as

$$\frac{\text{sample mass}}{\text{mass active ingredient applied}}$$

In order to incorporate variability in inhalation rates, assumed values of which are used in the calculation of inhalation exposure rate, a distribution was fit to the result of the following calculation for each individual observation collected using powered active air sampling:

$$\frac{\text{sample mass}}{\text{sample flow rate} * \text{mass active ingredient applied}}$$

For air samples collected using sampling method 1, the assumed mixing and loading breathing rate of 16.7 L/min was substituted in for the flow rate in the above calculation according to the Standard Operating Manual for the PHED software.[65] The distributions fit to air samples from each scenario are summarized in table 3.2.

The air sample distributions were paired with distributions of breathing rate distributions, estimated differently for mixing and loading or application activities. For application work, breathing rate distributions were estimated to have three possible values, which were toggled between with equal probability. These estimated rates came from the Exposure Factors Handbook's reported rates for outdoor workers working at "slow" rates (a self-reported estimate of effort), both for the category of "essential work" and for all workers in the "slow" category (essential and non-essential). The third estimate of breathing rate is a deterministic value from the NAFTA Technical Working Group on Pesticides recommendation for application task breathing rates.[68] Breathing rates for mixing and loading activities were determined similarly, but using values for "medium" activity levels. The distributions are summarized in table 3.2. For azinphos methyl, which required a respirator during handling tasks, the calculated inhalation exposure was adjusted for an assigned protection fraction for an APF 10 respirator, which includes half-face respirators and filtering facemask respirators commonly used by applicators.[69] The 2010 review article by Nicas summarized estimated protection factors for half-face respirators from seven studies [70]. Lognormal distributions were established according to reported geometric means and standard deviations from each study, see table 3.2. These distributions and the deterministic value of 0.1[69, 71] were sampled with equal probabilities to create a distribution of protection factors where the deterministic value is sampled with 1/8 probability.

3.3.2 *Dermal Exposures*

Dermal exposures were estimated using distributions based on normalized exposure measurements (mass of active ingredient exposure divided by pounds of active ingredient handled), and either were a total mass per body area, or a mass per area rate for a given body

part, depending on whether a rinse, wipe, or cotton garment or patches were used to measure exposure.

3.3.2.1 Hands

In all scenarios, a mass amount removed from both hands rather than a mass/area rate was reported and used. The measurements of dermal exposure to the hands were all taken with pesticide handlers who wore gloves during the tasks. Samples were taken by removing all available mass from the full surface of both hands after the gloves were removed. In the case of the three pesticides of interest, gloves are required for handling, so no adjustments for protection were made for the hands.

3.3.2.2 Faces

For face, neck, and head measurements, a variety of methods were used, including patches and wipes, so the distribution was fit to mass/area or mass values depending on the scenario. In the application scenario, measurements were taken of the head exposure with an external patch dosimeter and an internal patch dosimeter underneath a chemical resistant hat. Face and neck wipes were also taken, so in this scenario multiple distributions were fit for the head and neck exposure. The calculation of exposure to the head must take into account the possibility of using a chemical resistant hat, eye protection, and/or a respirator. For the respirator, it was assumed that the half-face would cover 20% of the total facial surface area (based on the typical 135 cm^2 surface area of a particle respirator [72], and for the goggles, 10%. The chemical-resistant hat was assumed to cover all of the head except the face and front of the neck, so that the exposures could be adjusted by the proportion of the head surface area covered.

It was assumed that the face/neck exposure was unchanged by the presence of a chemical-resistant hat.

3.3.2.3 Body

In the wettable powder and soluble-packaged wettable powder mixing and loading tasks, dermal loads for body sections were calculated based on measurements taken from the PHED sets, which used patches. The lower leg section was represented by the shin, ankle, or calf (or an average of them if more than one of those three was taken). Upper arm samples were taken from the upper arm or shoulder (or an average if both were taken). For bilateral measurements, the sum of the loads was used to fit the distribution, and was paired with half of the surface area value for both body parts. The body surface areas were derived from the Exposure Factors Handbook measurements of the body surface area of males aged 21 and over[73]. The chest and back and neck are combined in those estimates. To divide the neck with the head instead, the surface area of the neck was subtracted from the torso and added to the head. The face and neck surface area was composed by adding half of the neck area to the face area, defined as one-third of the head surface area. Distributions of surface area were fit based on the means and 95th percentiles of each part. The other scenarios, using the newer AHED data (application and dry flowable mixing and loading) were measured using full-body dosimeters, and were reported as masses per body part rather than masses per area rates, therefore not requiring the addition of skin surface area parameters to calculate the deposition per body part.

For each body section, the label-prescribed clothing and protective equipment was used to apply protective factors. For those pesticides which required long sleeves and pants, a single layer of work clothing was assumed for the upper and lower arms and legs and the chest and back. The measurements for all scenarios except the packaged wettable powder scenario were

taken underneath a single layer of clothes, and so no adjustment was made for work clothes in those tasks. If the label called for chemical-resistant clothing, an additional factor was applied to the same body areas. If the label called for chemical-resistant clothing and/or a hat, an additional protective factor was applied to the same body sections and head minus the surface area of the face. The values used for the clothing protective factor sample with equal probability between distributions based on Keeble et al [74], two distributions from Driver et al for airblast application and wettable powder mixing and loading [75], and deterministic values of 0.1 from CDPR assumptions [76] and 0.5 from EPA assumptions [77]. The chemical-resistant factor was drawn from sampling equally between the CDPR assumption of 0.01 [76], and distributions based on data for Tyvek and PVC-coated cloth from Keeble et al [74].

3.3.3 *Exposure data structure and interpolation*

A number of both the dermal and inhalation exposure measurements in PHED are below the limit of quantification (see table 3). The protocol for those values in the EPA exposure algorithm is to substitute ½LOQ. However, it is suggested that interpolation is more robust than such single value substitutions, especially when more than 10-15% of the data are missing.[78] For each sampled skin section and for the mass collected with air sampling, as listed in table 3.3, the missing values were estimated via interpolation. The interpolation was accomplished by log-transforming the non-missing values, assigning a distribution to the transformed values with the fitdistr function of the R package fitdistrplus, and generating 5000 values from the distribution using bootdist from the same package. The trial values were then back-transformed. Values below the LOQ for the study were used to replace the missing values. The pre-interpolation and post-interpolation distributions are compared in table 3.3. Comparison of the interpolated data

set with the result of the ½ LOQ substitution showed similar or lower geometric means and greater variability in the interpolated set, highlighting the advantage of this method in describing variability among the lower tail of the distribution (see supplemental data). The application dataset from AHED had very limited numbers of samples below the LOD or LOQ for any particular sample type and location. Because of this, the ½ LOD or ½ LOQ substitution method as used in the original analysis was also used in this study. The dry-flowable mixing and loading scenario did not report any samples below the LOD or LOQ, and so did not require any substitutions.

All exposure studies from AHED and PHED are composed of samples that were collected on multiple days, from orchards in different parts of the United States. This sampling structure improves the generalizability of the dataset but also creates the possibility that the dataset will have differences in variability among samples from the same sampling location which can distort differences between samples from different locations. If this hierarchical structure exists in the data set, it must be accounted for in fitting the distributions. If not, the true variability among pesticide handlers may be incorrectly estimated. The AHETF monographs on the AHED scenarios include the evaluation of the data for such clustering by presenting the result of fitting a mixed-model regression and a normal linear regression to the dataset. The general finding was that there is some effect on the estimates of variability if the study clusters are not accounted for in the dry-flowable and liquid mixing and loading scenarios, but not in the open-cab application scenario. [62, 79, 80]

To check the effect of including the study as a clustering variable, distributions were fit to the body area sections using the un-clustered data from each scenario and comparing that distribution to a clustered distribution. The clustered distribution was created by fitting

distributions to the data from each study within each scenario, and sampling from those distributions with a probability corresponding to the percent of the total scenario sample size that the study contributed using the *mcprobtree* function of the mc2d package[81]. Two studies (30 and 432) in the liquid and wettable powder mixing and loading scenarios had an n of 2, in which case a distribution was not fit, but the geometric mean and the geometric standard deviation of the available values were used to specify a distribution instead. Distributions were compared using quantile-quantile plots and the Kolmogorov-Smirnov test.

3.3.4 *Dose calculations*

Inhalation exposures were assumed to be completely absorbed and available to target systems, so no adjustments to the exposure amount were required. The dermal exposures estimated to reach the skin were reduced by a percentage estimate of dermal availability from the registrant submitted studies for each pesticide.[82-84] Assumption of fixed fractional dermal absorption is traditional in pesticide exposure assessment, but has significant limitations. It is adopted here for simplicity and comparability with prior analyses.

To calculate the body weight, two distributions were sampled from with equal probability: the body weights of participants in the AHETF studies and body weights of adult males from the Exposure Factors Handbook[73]. All variables were combined to calculate dose and margin of exposure in a Monte Carlo simulation and distributions of 10,000 doses were simulated 1,000 times for each pesticide using the mc2d package. Margins of exposure were calculated as the ratio of the No Observable Adverse Effect Level (NOAEL) from each neurotoxicity study to the calculated dose. [85-87]

3.4 RESULTS

3.4.1 *Exposure rates*

The probabilistic estimates of exposure rates in µg per pound of active ingredient were compared to the rates published in the Occupational Pesticide Handler Unit Exposure Surrogate Reference Table, which are used in the calculation of doses for risk assessment. The distributions and deterministic factors are plotted for the four inhalation and four dermal scenarios used in figures 3.1 and 3.2. For open cab inhalation, 16% of the distribution of inhalation exposure rates and 18% of the dermal exceeded the deterministic value. Dry flowable and packaged wettable powder mixing and loading scenarios were also similar, with 25% of the inhalation and 22% of the dermal rates exceeding the deterministic values for dry flowables and 43% of both dermal and inhalation rates for packaged wettable powders. For unpackaged wettable powders, 23% of the inhalation distribution and 66% of the dermal distribution exceeded the deterministic rates.

3.4.2 *Exposure distribution clustering*

Distributions of exposure rates were created from all studies combined and for comparison, from individual studies combined by weighted sampling from each according to sample size into a single "nested" distribution. The quantile-quantile plots of the clustered and non-clustered distributions produced for each scenario and exposure rate are shown in figure 3.3. Kolmogorov-Smirnov p-values are shown in table 3.4. In all scenarios, one or more body section showed significant differences between the clustered and non-clustered distributions. Dry flowable mixing and loading showed the least differences between the distributions, but the upper arms and head still had some divergence in the higher percentiles of the distributions for

that scenario. In all cases, the differences between clustered and non-clustered distributions were most apparent at the higher range of the quantiles. Clustered distributions tended to have higher maximums, but this finding was not universally true. Despite these differences, the distributions of the margins of exposure produced were not significantly different for these three pesticides whether clustered or non-clustered distributions were used in their construction.

3.4.3 *Dose*

The estimated dose distributions, repeated 1,000 times for 100,000 total simulated doses, are summarized in table 3.5 and illustrated in figure 3.4 along with the deterministic values used in the EPA human health risk assessments for tree fruit applicators and mixer-loaders. Distributions of dose, which converts from exposure using dermal absorption and body weight, were lognormal. Total doses for handlers of azinphos methyl ranged from 5.27 ng/kg/day to 3.34 mg/kg/day, with a geometric mean of 2.73 µg/kg/day (GSD = 5.8). The dermal dose was an average of 97% of the total dose, ranging from 30% to 100%. Emamectin benzoate doses ranged from 11.31 pg/kg/day to 0.12 mg/kg/day, with a geometric mean of 0.043 µg/kg/day (GSD = 8.0). The dermal dose of Emamectin benzoate ranged from 0.01% to 100% of the total dose, and averaged 65% of the total. The doses calculated for acetamiprid handlers ranged from 13.19 ng/kg/day to 3.36 mg/kg/day and had a geometric mean of 5.05 µg/kg/day (GSD 6.2). The Acetamiprid dermal dose ranged from 18% to 100%, mean of 87%, of the total dose. All estimated dose distributions overlapped with the corresponding deterministic value from the registration assessment, but at least 13% of the distribution of computed estimates exceeded that value for each compound (table 3.5).

3.4.4 *Margins of Exposure*

Computed distributions of margins of exposure (MOE) generated from comparison of the NOAEL and total dose distributions are shown in figure 3.5. MOE were also calculated for separate inhalation and dermal doses as shown in table 3.5. The MOE for azinphos methyl ranged from 0.1 to 116,556, with a geometric mean of 83 (GSD=6). One percent of the margin of exposure distribution was less than 1, indicating doses higher than the NOAEL dose. The MOE range of acetamiprid was calculated between 3 and $2.1*10^6$, with a geometric mean of 1,979 and GSD of 6. The range of emamectin benzoate MOE was 0.6 to $5.1*10^9$, with a geometric mean of 763 (GSD=8). All three pesticides exceeded the level of concern indicated in the EPA human health risk assessments through both inhalation and dermal doses (see table 3.5) for some fraction of the pesticide handler population.

3.4.5 *Sensitivity Analysis*

Sensitivity analysis of both variability and uncertainty loops was performed using Spearman's correlation coefficients to compare the input variables with the output of dose for each compound (see supplemental). The variability inputs with the strongest correlation were variables related to air concentration (breathing rates for both mixing and loading and application, the air concentration normalized to sampling rate and active ingredient for mixing and loading), and the variables which determine the active ingredient handled (acres of application and rate of application), and the dermal deposition for all body parts during application. Dermal depositions during mixing and loading were often less correlated. The variability component of dermal absorption was least correlated with the dose of all variability inputs.

Among the variables assigned to uncertainty, the strongest correlation was associated with error in application rate. The uncertainty variables used in sampling among variability inputs were next highest in degree of association, depending on whether the variable in question was included in the dose (for example, respirators were only relevant in calculation of azinphos methyl). The dermal absorption uncertainty again had the smallest correlation. The assignment of dermal absorption as variability or uncertainty, or as both, heavily influences the correlation coefficient calculations, although the dose calculation result and the margins of exposure do not change significantly depending on the assignment.

3.5 Discussion

Exposure datasets used to generate summary statistics for occupational risk assessments of pesticide handlers were successfully applied to create probabilistic estimates of exposures for the same tasks. The same exposure formulae used in in the EPA assessments were followed as a framework, with addition of variability and uncertainty where possible. The exposure distributions were translated to doses which could be compared to the NOAELs elicited from neurotoxicity studies and used as the basis for the levels of concern, producing a distribution of risk estimates. Although differing distributions resulted from accounting for the clustering of exposure measurements between studies, the margins of exposure estimated were not materially changed. In the case of these pesticides, the additional structure is not relevant to risk management decisions; however, this finding is not guaranteed in other pesticide handling scenarios, and the effects of impacts on exposure variation should be investigated in each scenario during the development of probabilistic estimation.

The dermal route of exposure contributed the majority of the total doses most of the time, but in some fraction of the simulated cases for all three pesticides, dermal was exceeded by the

inhalation dose. Emamectin benzoate, which was the compound with the lowest dermal absorption fraction, had the highest percent of simulations where inhalation was the dominating exposure route. In all three pesticides, both the dermal and inhalation doses separately exceeded the level of concern by some percent of the population, which highlights the importance of protecting against both routes of exposure and evaluation of both in occupational risk assessment. The nature of deterministic calculation of risk does not always provide this kind of insight, showing only the average result. In these three cases, the average result indicates that dermal exposure is the route of the majority of the dose. In comparison with deterministic exposure rates, where the dermal exposure rates were consistently higher for these pesticides' scenarios, these estimations showed that the relative contribution to dose between dermal and inhalation exposure is variable.

Of the three pesticides, azinphos methyl's distribution of MOEs fell most often over the level of concern (below 100), and the estimates of dose overlapped with the biomonitoring data cited in the updated occupational risk assessment released by the EPA in support of azinphos methyl's cancellation[88] although the calculations in this analysis are based on PHED and AHED data. For acetamiprid and emamectin benzoate, no biomonitoring data is available for comparison. Although the percent of the estimates which exceed the level of concern for those pesticides is lower than for azinphos methyl, they represent a potential for over-exposure in the normal course of performing pesticide handling activities. The use of deterministic estimates based on a mean, a common strategy in regulation, implicitly allows for these exceedances, but this analysis demonstrates that estimating the probability of these high exposures is feasible where exposure datasets exist, opening up other options for calculation of regulatory limits such as a higher percentile.

The results presented here show that the current deterministic framework for pesticide risk assessment, which necessarily does not elucidate the variability present in occupational doses, is problematic. Comparison of a single summary value against a reference value to determine whether a task is safe or unsafe leads to inequity in protection between chemicals as seen in this analysis. It also obscures the true decision being made: what proportion of the worker population exceeding the reference level should be considered unacceptable? Dietary pesticide doses are evaluated based on the 99.9th percentile among multiple age groups, even for acute exposures,[89] and yet among the occupationally exposed measures of central tendency are accepted. The potential for compounded conservatism[90] by using upper bounds of assumptions other than exposure rate does not result in a highly conservative estimate of dose or risk in these cases, leaving portions of the population unprotected. While this strategy reflects the common perception that occupational exposures are more acceptable than residential or dietary due to assumptions of risk and compensation, this decision to use a deterministic summary value and the risk implications are not transparent to those undertaking the risks. This analysis shows that additional information is available for use in regulation of occupational exposures and in some cases a greater proportion of workers could be protected.

For the potential of probabilistic assessment in support of regulation to be realized, standardized collection of exposure data from specific tasks and task groups on a large scale would be required to provide the basis for the estimates. In the specific case of pesticides, exposure datasets curated by a task force supply a standard dataset and the tasks are well-defined. This analysis demonstrates calculations implemented using freely available open-source software. It may be that other occupational exposure datasets exist that could be used in a

similar fashion to thoroughly examine the effects of a variety of regulatory limits on population exposures.

Chapter 4. USE OF THE BENCHMARK DOSE MODELS IN RISK ASSESSMENT FOR OCCUPATIONAL HANDLERS OF EIGHT DIFFERENT PESTICIDES USED IN POME FRUIT PRODUCTION.

4.1 ABSTRACT

The benchmark dose has been frequently recommended for the creation of points of departure for regulatory dose limits, but many regulations, including pesticide risk assessment and registration in the United States, continues to rely on NOAEL methods as the OECD toxicological standard methods recommend. This study used data from studies in support of pesticide registration for eight different compounds to build dose-response models and calculate benchmark doses and confidence limits. The results were compared to the NOAEL of the same study. A probabilistic estimate of dose was compared with all points of departure to demonstrate differences in the protective ability of each different selected limit. While neither the BMD/BMDL nor the NOAEL was consistently more protective, the advantage of using the BMD in quantifying the uncertainty of the point of departure is highlighted, and the feasibility of using current OECD-guideline studies for derivation of a BMD is demonstrated in these cases.

4.2 INTRODUCTION

Despite a decades-old and often-echoed recommendation to adopt benchmark dose modeling as the default basis for regulatory limits [91-94], the method has had slow acceptance and the No Observable Adverse Effect Limit (NOAEL) is still the standard procedure for derivation of a regulatory limit in many cases, including the OECD testing guidelines. The limitations of the NOAEL approach have been described [94, 95], and one of the most telling is that the identified point of departure must be among one of the pre-selected dose groups used in the study. Because of this limitation, there may be very little biological basis behind the specific dose chosen, particularly if the test is designed in the absence of existing toxicology studies, despite the regulatory meaning assigned and the use of the NOAEL in quantification.

Travis et al [95] described a number of reasons why the benchmark dose (BMD) methods have not been adopted with greater speed and why the NOAEL should remain the predominate tool in determining the point of departure (POD). The authors suggested that the NOAEL is more intuitive, easier to verify and understand, that quantal outcome BMDs cannot accurately reflect the same kind of outcome in human populations since they are based on variability which may not correspond across species, and that the BMD is too sensitive to the model type selected. However, the intuitive appeal of the NOAEL may lead to a false sense of safety and the applicability of the NOAEL estimation may also suffer from differences in variability between human and animal populations. [96] Simplicity of method is not a benefit if it limits the scientific basis and use of the result. The BMD method is easier to reconcile with uncertainties in dose estimates, and the resulting values more useful in probabilistic assessments of risk [97]. Wignall et al discuss the lack of transparency and consistency in the BMD approach, and suggest that a 1

standard deviation or 10% critical effect basis could be the basis for unified benchmark dose modeling of large sets of toxicological data in an efficient analysis.[98]

Pesticide regulation in the United States is based on toxicological studies performed in accordance with OECD guidelines, and is one area of chemical risk assessment where the NOAEL, along with some uncertainty factors, is the basis of the regulatory limits. Numerous tests are required for registration of an active ingredient, assessing potential human and ecological impacts of any proposed uses. In the assessment of these studies, where a hazard is deemed present, one or more NOAELs are chosen to pair with residential, dietary, and occupational doses to humans based on the length of the exposure, sensitivity and specificity of the study and outcome, and the route of exposure. The NOAEL is divided by an estimate of the dose to calculate the Margin of Exposure (MOE), which must be above a Level of Concern (LOC), usually 100 for occupational exposures. [99] Substitution of a benchmark dose into this existing paradigm should be feasible if the existing studies can be used to generate dose-response curves. A further advantage of this method is that integration of new approaches involving PBPK model development can be integrated with the dose-response models used in production of the BMD. [100]

The purpose of this paper is to demonstrate the feasibility of using OECD guideline toxicology studies completed for the purpose of producing NOAELs for a variety of pesticides for production of dose-response models and benchmark doses with associated lower confidence limits. The effects of using a variety of critical effect sizes in continuous data will be explored.

4.3 METHODS

Eight pesticides with a variety of potential acute or sub-acute health impacts as identified by their respective EPA human health risk assessments were selected for this analysis: azinphos

methyl, acetamiprid, emamectin benzoate, methoxyfenozide, novaluron, phosmet , spinetoram, and thiacloprid [65, 66, 88, 101-106]. These pesticides are currently or formerly used in the production of pome fruit. The one-day dose of a pesticide handler mixing, loading, and applying each pesticide using open cab airblast methods was calculated probabilistically as described previously (in review). In brief, exposure data from the Agricultural Handler Exposure Dataset (AHED) and the Pesticide Handler Exposure Dataset (PHED) were used to construct probabilistic exposure rates similar to those deterministic rates used in official calculations. These rates were paired with distributions of other factors, including cloth protection factors, application rates and areas, and anthropometric variables [62, 73, 107]. In the EPA human health assessments, occupational exposures to methoxyfenozide and spinetoram were calculated for the inhalation route only, as there was not considered to be evidence of a hazard via the dermal route based on acute dermal studies [108, 109]. To remain consistent with the EPA methods, only the dose from the inhalation route was included in the probabilistic dose estimates for spinetoram and methoxyfenozide. A separate probabilistic estimate of dermal dose with dermal absorption fraction accounted for was also completed and compared with the points of departure derived in this analysis.

Data from the same study used to select a NOAEL for use in EPA occupational risk assessments was used to construct multiple benchmark dose models for each pesticide. The nine studies, identified by MRID in table 4.1, were obtained via Freedom of Information Act request. Using the EPA Benchmark Dose Software (version 2.6.0.1), available models were fit to the dataset, according to whether the endpoint was quantal or continuous. Quantal models were fit using gamma, logistic, log-logistic, log-probit, probit, Weibull, and quantal-linear equations. Continuous models included exponential, hill, linear, polynomial, and power equations. The

BMD Software uses maximum likelihood methods in the calculation of equation parameters, and the confidence interval of the benchmark dose is calculated using profile likelihood methods.[94] A 10% effect level was used for all quantal models to permit the most comparability among models and among health outcomes. A benchmark response level was chosen for each continuous outcome as shown in table 4.2.

The response or critical effect size was based on levels specified in a survey of experts on the commonly recommended effect size for a variety of outcomes [110]. For all endpoints except cholinesterase depression, which was assigned 20% as a toxicologically relevant effect size, this level was 10% relative deviation from the control group. Phosmet and azinphos methyl were therefore modeled with both 10% and 20% depression as the critical effect size. In addition, since phosmet risk assessment was based on a combination of data from an oral and dermal toxicological study, the dermal dose will be compared to the points of departure from dermal study without the inhalation dose. Based on the recommendation of EPA benchmark dose modeling guidelines, the 1 standard deviation effect size was also examined for the continuous impacts. [111]

Each possible model was assessed for goodness-of-fit using qualitative evaluation of the dose-response graph and the p-value of the X^2 goodness-of-fit test. Models were compared within each toxicological endpoint using the qualitative fit of the curve, the Akaike Information Criterion, and the residuals. The 95% confidence limit was calculated The resulting benchmark dose (BMD) and the lower confidence limit of the benchmark dose (BMDL) are compared with the NOAEL from the same study and the deterministic dose used in the EPA human health assessment for the same pesticide application scenario. The estimated dose distribution was also

compared with all three points of departure (BMD, BMDL, and NOAEL) using the calculated exceedance fraction, computed using the *efraction.exact* command of the R package STAND. [112]

4.4 RESULTS

The toxicological studies, endpoints of interest, critical effect size used, and associated NOAELs for each pesticide are described in tables 4.1 and 4.2. Although each compound had multiple studies which yielded toxicological endpoints potentially useful in creating a benchmark dose, the studies presented here are those used in the EPA's human health risk assessment for pesticide handlers to explore the impact of use of a benchmark dose in place of a NOAEL. Goodness of fit values and the resulting BMD and BMDL for each possible model fit to the eight pesticides' outcomes can be found in the supplemental material. The graphs for the selected models are shown in figure 4.1. Parameters for the chosen equations are listed in table 4.3.

4.4.1 *Selection of toxicological outcomes and benchmark dose models*

4.4.1.1 Acetamiprid

Acetamiprid symptoms of developmental neurotoxicity were recorded in rats through the functional observation battery of neurotoxicity testing in offspring of dosed dams. The most useful acetamiprid outcome was recorded changes in the auditory startle reflex amplitude maximum in males at post-natal days 20 and 60. Other outcomes observed in this study were not able to produce a dose-response model due to variability in the control animals. These outcomes (including reductions in pup viability and alterations in weight gain) were also non-specific to neurodevelopmental impacts. PND 20 was selected for this analysis as the dose-response effect was more evident than at PND 60. Of the models assessed, similar results for goodness of fit and residuals were generated, and the Hill model had the lowest AIC.

4.4.1.2 Azinphos methyl

The outcome of interest for assessment of azinphos methyl neurotoxicity was identified *a priori* as cholinesterase depression. Erythrocyte, plasma, and brain cholinesterase were measured at varying time points during the 1-year study performed with dogs, and at 13 weeks, significant depressions in all three cholinesterases' activity were recorded. Although acute studies assessing cholinesterase inhibition in animals and in humans were available, this study was judged by the EPA to be the most protective and appropriately conducted for comparison with biomonitoring dose measurements of pesticide applicators. The erythrocyte cholinesterase provided the most protective result, and had the advantage over the brain cholinesterase measurement in that it had been checked at 4 weeks after baseline as well. This 4-week time point in males was used as the basis for the dose-response as it was closer to the length of exposures expected in an occupational setting. However, the results from the 13-week measurement produced a lower benchmark dose (at 10% effect size, 0.23 mg/kg/day compared with the 13 week's 0.07 mg/kg/day), although the same NOAEL would be selected based on either time point.

4.4.1.3 Emamectin benzoate

The emamectin benzoate study of acute (15-day) neurotoxicity in mice was used to find the most protective NOAEL for occupational risk assessment. Several endpoints indicative of neurotoxicity were recorded; tremors were the first frank symptom to be observed, followed by ptosis, gait and posture abnormalities, decreased activity, urine staining, and labored breathing. At necropsy, some animals in the highest dose groups had sciatic nerve degeneration. Since tremors appeared first and at the lowest doses of all symptoms, they were regarded as the most sensitive indicator and selected for this analysis and by the EPA for derivation of the NOAEL. All dichotomous models were successfully fit, passing goodness of fit testing and with

satisfactorily low residuals (considered to be residuals less than |2.0|). The AIC values were similar, with the lowest being the quantal-linear model. This model also was the best fit after visual assessment of the curve.

4.4.1.4 Methoxyfenozide

Occupational exposures to methoxyfenozide were assessed only for inhalation by the EPA, as acute dermal toxicity studies did not indicate a hazard according to the EPA human health risk assessment for this compound. Although various other outcomes were investigated, the hematological impacts shown in a two-week study of dogs were selected to derive the NOAEL used in the occupational risk assessment. This study included only two animals per sex per dose group; however, similar hematological toxicity was observed at 3 months in the 1-year study with a sample size of 4 per group. This study was therefore used to derive the benchmark dose model. The authors of the study noted the symptoms but did not believe them to be treatment related. However, dose-responsive patterns were found in the male treatment groups. The outcome, among platelet count, red blood cell count, hematocrit, and methemoglobin, for which models were fit successfully was the three-month measurement of red blood cell count. All continuous models showed satisfactory fit, and the exponential 4 model was selected based on a marginally lower AIC.

4.4.1.5 Novaluron

The NOAEL used for occupational risk assessment of Novaluron handlers was drawn from the 90-day feeding study performed in rats which assessed a variety of hematologic parameters. Like other compounds with impacts on this system, red blood count, hematocrit, and hemoglobin were all influenced in the higher dose groups. In addition, spleen and liver pigmentation and splenic hematopoiesis were observed, and all of these impacts combined led to the derivation of the NOAEL from this study. With the exception of red blood cell counts and

hematopoiesis, the dose-response for these impacts was irregular and non-significant, resulting in poor model fits. The outcome of reduced blood cell count was therefore used in the calculation of the benchmark dose. Models for both the red blood cell count and spleen hematopoiesis passed the goodness of fit and variance tests, and had comparable AIC among them. Either endpoint could be used, but the dose-response is clearer in the RBC data. The exponential 4 model of RBC was selected based on AIC and visual evaluation of the model fit.

4.4.1.6 Phosmet

Like azinphos methyl, phosmet is known to act as a cholinesterase inhibitor, so that the outcome of cholinesterase activity was measured in acute toxicity studies. In the case of phosmet, a dermal and oral study were both used to generate a separate NOAEL for the routes of exposure, since there was no human biomonitoring data as for azinphos methyl. Dose-response curves were constructed using both dermal and acute oral data, for plasma ChE in the dermal study and red blood cell cholinesterase in the oral study, which proved to be the most sensitive measures. For both the dermal and oral models, the Hill equation provided the best fit and lowest AIC. The model for the oral exposure was a better fit based on the results of the X^2 goodness-of-fit test as well as providing a lower benchmark value, as expected.

4.4.1.7 Spinetoram

As with methoxyfenozide, insufficient evidence of dermal toxicity in the short or intermediate term was found in the EPA human health risk assessment to warrant risk assessment of that exposure route. The outcomes used in the derivation of the NOAEL for the inhalation route of exposure were also hematologic, drawn from the sub-chronic feeding study performed with dogs. Blood cell and hematocrit levels were significantly affected, and anemia, arteritis and bone marrow necrosis were observed. The anemia and lowered platelet counts observed were

believed to be secondary to the bone marrow necrosis, so the arteritis and bone marrow necrosis were both evaluated. Since all animals in the control and lowest dose group were free of arteritis and all animals in the higher dose groups developed it, the dose-response in that case was of limited use and the bone marrow necrosis was used to derive the benchmark dose. The dose-response curves for necrosis were similar overall with respect to AIC and residual values, but the logistic regression offered the best fit qualitatively for both the dose-response curve and the 95% confidence interval.

4.4.1.8 Thiacloprid

The normal battery of toxicological evaluations showed a number of potential impacts of thiacloprid dosing. Occupational doses were evaluated using a NOAEL derived from liver and thyroid impacts observed in the subchronic and chronic feedings studies of rats. A variety of liver impacts were recorded, including enzymatic induction (N-demethylase, O-demethylase, and CYP450), and hepatocellular hypertrophy. Thyroid hypertrophy was also noted. Of the two organs, the liver impacts were evaluated at lower doses. Thiacloprid is also classified as a likely human carcinogen, but as the occupational risk assessment was based on organ toxicities as the more protective outcomes, a cancer risk assessment was not performed in this analysis.

The liver enzyme induction impacts in general produced model fits which identified significant dose responses and passed goodness-of-fit tests for the mean, but in many cases the dose-response was inconsistent in the low-dose groups leading to a poorer model fit, particularly at the low doses. The model which was selected was the log-logistic model of hepatocellular hypertrophy, which provided a more consistent fit to the data at low doses (based on visual inspection of the curve), passed the goodness-of-fit test, and had satisfactory residual values.

4.4.2 *Benchmark doses and NOAELs in comparison to deterministic dose*

The ratio of the benchmark dose to the associated lower 95% confidence interval ranged from 1.12 to 5.76, with an average of 3.3 (table 4.4). Three of the benchmark doses were lower than the NOAEL from the same study, and five of the lower benchmark dose confidence limits were lower than the NOAEL (figure 4.2).

NOAELs for acetamiprid, novaluron, and phosmet were above the BMD for the same study, indicating that in those cases the NOAEL is less sensitive than the BMD method. The NOAEL for azinphos methyl, spinetoram, and emamectin benzoate fell below the below the BMDL, so that in those cases, the NOAEL was more protective than the BMD. In the remaining cases of methoxyfenozide and thiacloprid, the NOAEL fell between the BMD and BMDL (figure 4.2). The ratio of the BMD to the NOAEL ranged from 0.17 to 12.15, and averaged 2.8 (table 4.4).

The comparison of the NOAEL and dose used in the EPA risk assessments supports the findings of those assessments (table 4.3). The only ratio which falls below the LOC, or level of concern (100 for all occupational doses except emamectin benzoate, which has an LOC of 300), is that of azinphos methyl, as well as phosmet depending on the method of calculation and data source. For the most part, the ratio of the BMD to the dose produces the same conclusion, except in the case of acetamiprid. If the BMDL were used, azinphos methyl and acetamiprid would both produce a ratio less than 100 and therefore of concern, but all other chemicals would still be on average dosed below the level of concern.

4.4.3 *Probabilistic dose comparisons with BMD and NOAEL*

Comparison of the probabilistic dose estimations with the various points of departure allows estimation of an exceedance fraction, the proportion of the estimated potential doses which are above the deterministic level of concern. Table 4.5 shows this fraction for the

NOAEL, BMD, and BMDL point estimates divided by 100 (300 in the case of emamectin benzoate) to account for uncertainty factors. Exceedance fractions varied, depending on chemical and point of departure selected. Exceedance of the NOAEL ranged from 0.005 % in the case of Methoxyfenozide to 72.2% for azinphos methyl. Azinphos methyl doses had the highest fraction exceeding all of the points of departure. Exceedance fractions for methoxyfenozide and spinetoram were increased by a minimum of 40 times by the addition of the estimated dermal doses. The exceedance fractions for azinphos methyl and phosmet varied depending on the choice of point of departure and the source of the dose-response data (oral vs dermal). The ratio of the exceedance fractions of the BMDL and the BMD are a crude relative measure of the uncertainty in the benchmark dose measurement. These ratios ranged from 1.1 to 8.4. By comparison, the ratio of the exceedance fraction of the BMD to that of the NOAEL ranged from 0.1 to 5.0, and averaged at 1.2, indicating the relative protective ability of the two points of departure. There was no correlation between the two ratios.

4.5 Discussion

This analysis shows that studies designed for the production of a NOAEL according to OECD guidelines can be used to generate a dose-response curve and derive a benchmark dose and the associated confidence interval. With the exception of azinphos methyl, there are not existing benchmark dose models to compare these results to. In the case of azinphos methyl, the 20% BMD and BMDL in male rats found here (0.50 mg/kg/day and 0.35 mg/kg/day) are similar to the values reported by the ATSDR benchmark analysis (0.48 and 0.30 mg/kg/day), which used the same data, although different models were selected.[113] This analysis also showed that benchmark dose methods do not produce inherently more (or less) conservative or protective

dose limits than the NOAEL method, as the NOAEL for many of the compounds was lower than the BMD, and in some cases less than the lower confidence limit.

The degree of uncertainty in the BMD estimates shown here varies, and in some instances health outcomes were observed in the study which could not be used to build a dose-response model, either due to infrequent observation, lack of significant dose-response, or, non-monotonic or inconsistent dose-response. Although a successful dose-response model was fit in the case of each pesticide in this study, it is likely that in other instances, particularly where the compound is of relatively low toxicity and therefore responses will not be measured at lower doses, the OECD guidelines will not produce a study with sufficient data to create a model. An increase in the number of dose groups required could help produce studies more amenable to a benchmark dose analysis, as suggested by Wout Slob in 2002.[114] It is important to recognize that a NOAEL is as likely as the BMD to be unreliable or impossible to determine in cases where the dose-response is uncertain or variability in the controls is high.[115] The advantage of dose-response modeling and the benchmark dose is that some measure of the point of departure's uncertainty is available and expressed relatively simply as a confidence interval, whereas the uncertainty in estimation of a NOAEL is potentially the same but left opaque if the number is taken at face value.

A further advantage of the dose response method is also illustrated through the comparison of the results of the cholinesterase inhibition models. The use of a continuous endpoint in the NOAEL paradigm may require only a statistical difference in the outcome to determine the target value. No biological justification or clinical significance is necessarily required. While this method may arguable be more sensitive to small changes in a measure, it is not guaranteed to be more protective, and does not necessarily lead to a result which is useful in risk management. Since the benchmark dose method requires that an effect size be specified, the

model is more flexible and the impact of selection of varying effect sizes can be investigated. In the case of azinphos methyl, use of 20% inhibition rather than 10% inhibition of cholinesterase decreases the proportion of the workers receiving doses over the level of concern from 80% to 56%. However, for phosmet, the same decision changes the proportion from 14% to 9%. The impact of these kinds of differences on a risk management decision is not clear, but the potential for evaluating the sensitivity of the population's level of concern to the effect size chosen has great value in increasing the flexibility and transparency of risk management. Potentially, increased data availability on the assessment of dichotomous outcomes and the effective critical effect size decision-making they imply (as described by Slob and Pieter[97]) could allow for sensitivity analysis for the designation of outcomes usually considered quantal, for example, cellular hypertrophy.

The potential dependence of the benchmark dose on the choice of critical effect size has been described as a weakness of the method [95]. This study demonstrates that while effect size may have a large or small impact on the benchmark dose, consistency of reporting the process and results of benchmark dose modeling at these different possible effect sizes can provide transparency and make this weakness an advantage. Biological basis and transparency in the choice of critical effect size may be a more sound basis for developing a consistent BMD methodology than choosing on effect size as the basis for consistency.

In summary, this analysis demonstrates the use of existing OECD guideline studies to build a benchmark dose model and derive points of departure for risk assessment. The use of the benchmark dose compared to the NOAEL may or may not substantively impact the risk assessment outcome, but is able to provide a quantification of the uncertainty around the selected point of departure which is absent in the reports of NOAELs from the same studies. Benchmark

doses provide transparency and flexibility and can be performed with existing study guidelines, despite room for improvement in study design. Consistency in the process of modeling and reporting can provide the standardization necessary for the adoption of these measures into standard operating procedures for official risk assessment.

4.6 Declaration of conflicts of interest

The authors report no conflicts of interest. Funding in support of this analysis was provided by the NIEHS Environmental Toxicology and Pathology training grant and the CDC/NIOSH Cooperative agreement U54 OH007544.

Chapter 5. THE INTEGRATION OF TECHNICAL FEASIBILITY AND HUMAN HEALTH RISK ASSESSMENT FOR ALTERNATIVES ASSESSMENT USING MULTI-CRITERIA DECISION ANALYSIS METHODS IN THE CASE OF CODLING MOTH PESTICIDES.

5.1 Abstract

Alternatives assessments and the components of a complete assessment, such as comparative health risk assessment, require quantitative methods of trade-off evaluation which can balance very different characteristics that may be difficult to assign an economic value. The Preference Ranking Organizational Method for Evaluation Enrichment (PROMETHEE) method of multi-criteria decision analysis (MCDA) provides a framework which can assess a variety of qualitative and quantitative dimensions of a decision space. This study uses the PROMETHEE method to evaluate the comparative risk case study of codling moth pesticides used in tree fruit production. Decision criteria were elicited from industry consultants who recommend pest control methods through semi-structured interviews. In the same interview, valuations of potential health impacts associated with occupational pesticide exposure were also discussed. PROMETHEE models were constructed to attempt to predict pesticide usage before and after a major codling moth control paradigm shift which occurred with the cancellation of azinphos-methyl. In addition, health impact trade-off models were constructed using the same framework, based on the population exceedance fraction of a benchmark dose level. While predictions of pesticide preference did not perfectly match usage records, useful information on tradeoffs between acute and subchronic health impacts among ten different pesticides was gained.

5.2 INTRODUCTION

As the field of risk assessment progresses with the consideration of hazards in a more holistic fashion, cross-disciplinary frameworks such as life-cycle assessment and alternatives assessment are increasingly important in research and regulatory decision making. These methods incorporate the principals of comparative risk assessments, despite the decline in popularity of comparative risk use in priority setting and policy making. Alternatives assessment requires the identification, comparison, and selection of safe alternatives to a given chemical of concern on the basis of hazards, performance and feasibility, and economics.[116] A variety of frameworks has been proposed for use in alternatives assessments and a useful methodology should include feasibility and economic assessments, methods for incorporating variability and uncertainty, and human health risk assessment methods including robust exposure and toxicity assessments.[23] Comparative risk principles can be applicable in particular for the hazard assessment component of such analyses, but are limited in their incorporation of feasibility and economic information.[117] Multi-criteria decision analysis (MCDA) is a branch of methods which is designed to include a variety of information types, both qualitative and quantitative, through the equalizing lens of preference and utility.[3] This flexibility in information type and in the incorporation of multiple stakeholder perspectives makes MCDA ideal for alternative assessment.

There are a number of different multi-criteria decision analysis methods available. The choice of method depends largely on the desired outcomes of the project and the type of question the analysis is meant to address. Decision problems have been broken down into four main types, or *problematiques*: choice problems, sorting problems, ranking problems, and description problems.[11] Some methods, such as multi-attribute utility/value methods (MAUT/MAVT) and

simple additive weighted (SAW) methods, require complete characterization of utility functions for each outcome and produce a complete ranking of alternatives. Utility methods also frequently require complete tradeoffs between characteristics, so that a strong scoring in one criterion may outweigh low or zero scores in other criteria, so any single criteria may not have a threshold acceptable value. This assumption may be problematic; for example, if one chemical alternative were significantly more effective than all other alternatives, it might still be ranked as the optimal decision even if it also has unacceptably high toxicity towards humans, although this may be accounted for using additional thresholds of acceptability in other parts of the analysis.

Outranking methods such as analytic hierarchy process (AHP) do not use weights to compare criteria along a single scale, but to provide rank of importance, allowing ranking of alternatives according to stakeholder values based on pairwise comparisons.[10, 118] Other methods, such as PROMETHEE (Preference Ranking Organization METHod for Enriched Evaluation) and its related method, GAIA (Geometric Analysis for Interactive Aid), require only pairwise ranks of outcomes and weights for each criterion.[10, 11] Since they do not require complete characterization of a utility function and do not necessarily provide a strict ranking of outcomes or single optimized outcome, PROMETHEE and GAIA methods are often considered for description type multi-criteria problems[11], and so are a good fit for risk analyses that seek to describe various actions and their predicted consequences. These methods are also the most supported with available software.[10, 16]

Pesticide use in the tree fruit industry provides a useful case study for the application of MCDA as a framework for alternatives assessment. In 2015, Washington state orchards produced 5.9 billion pounds of apples, harvested from 148,000 acres of land.[119] In 2008, 7.28 million pounds of insecticide active ingredient were used on apples in the United States.[120]

Many growers engage pest management consultants, or crop consultants, to provide recommendations on the application of pesticides along with other technical production issues (soil quality, fruit thinning, etc). A 2010 survey of the crop consultants for the tree fruit industry in Washington State found that the most unacceptable damage in apples was caused by the codling moth, and 67% of respondents stated that if no controls for this pest were used for a year, more than 10% crop injury would result.[45] As a result, growers will ordinarily apply insecticides for codling moth between one and six times per growing season, although these applications have been reduced by the widespread use of pheromone-based mating disruption.[18] A wide variety of insecticides and growth regulators are available for codling moth control, although not all are commonly used. In 2006, it was announced that azinphos methyl, an organophosphate which was formerly the most commonly used pesticide for codling moth, would be withdrawn. A phase-out period of 6 years followed, and the use of various alternatives increased in frequency (see figure 1). The fluctuations in pesticide use year-to-year over the last decade have likely been influenced by this large change in pest management practice, other product withdrawals, mating disruption use, and other factors.

The viability of the codling moth control pesticides and their popularity has implications for the occupational exposures of pesticide handlers, re-entry workers, and the dietary and environmental exposures of the population as a whole. Pesticide registration requires a battery of toxicological testing in animal models and comparison of the results of these studies, in the form of a No Observable Adverse Effect Level (NOAEL) with estimates of human exposure for various scenarios. A dataset of occupational exposure field studies is managed by the Agricultural Handler Exposure Task Force and used to generate exposure rates (mass per pound of active ingredient) for pesticide-handling tasks. These data and analysis requirements create a

systematic, publicly-catalogued source of information that could fill in many of the data gaps which alternatives assessments are subject to in terms of human health impacts. The cancellation of azinphos methyl and subsequent changes in pesticide usage creates an opportunity to evaluate the ability of MCDA to predict the feasibility and therefore popularity of use of pesticides as different alternatives come and go. The wealth of human exposure and toxicity data available for pesticide exposures also provides an opportunity to complete an alternatives assessment from a human health perspective, incorporating exposure and hazard assessment based on an already-existing protocol.

The purpose of this study is to evaluate ten potential codling moth insecticides by constructing a decision analysis model for selection probability, and to expand the model to compare health-health tradeoffs among these alternatives, before and after the cancellation of azinphos methyl. The selected alternatives included azinphos methyl and the nine other most efficacious insecticides recommended for codling moth as identified by the Washington State University Tree Fruit Research and Education Center's Crop Protection Guide from 2013.[34] The nine pesticides were acetamiprid, chlorantraniliprole, emamectin benzoate, methoxyfenozide, novaluron, pyriproxyfen, phosmet, spinetoram, and thiacloprid.

5.3 METHODS

5.3.1 *Preference elicitation*

Selection criteria for pesticides used against codling moth were identified and discussed with sixteen crop consultants who work with the pome fruit production industry in Washington State. The identification and recruitment of the participants is described in additional detail in Pouzou et al (chapter 2). Phone interviews focused on the nature and relative importance of

selection criteria were carried out with each participant following an initial web survey. The interview time ranged from 25 to 60 minutes. Participants were asked to describe the factors important in their selection, and to identify any not already mentioned from a pre-set list of pesticide characteristics which included efficacy, resistance management, pre-harvest interval, re-entry interval, cost, pollinator toxicity, human toxicity, beneficial species toxicity, duration on the market/length of experience with the chemical, and protective equipment required by the label. The consultant was asked to identify the importance of each selected criterion and any additional named criteria on a scale of 1-10 in comparison with the most important criterion (designated as the reference for a rank of 10). Based on the selected decision factors, additional questions were asked to elicit preference and indifference thresholds for each factor, for example, the smallest difference in price between two pesticides that would affect the choice between them. Modifying factors for the importance of the selection criteria were also discussed.

After asking participants to identify and rank the decision criteria, even if they did not identify human toxicity as an important decision criterion, they were asked to assign a value on a scale of 1-10 to the importance of prevention of a set of health impact categories in workers. These categories were drawn from human health risk assessments performed for each of the 10 pesticides examined in this analysis. Any health impact which was reported as significantly dose-responsive and treatment-related was included in the questionnaire, although not all were incorporated in the final analysis as relevant to occupational exposure durations. For each category, a brief explanation and examples were included in the question eliciting a rank, as shown in table 5.1. To avoid implications of hazard and overstatement of evidence of a specific

human health impact causation by any pesticide, the question was framed in a hypothetical and general fashion.

5.3.2 *Decision analysis modeling and estimation of pesticide usage*

Two decision models were constructed based on the selection criteria and preference details collected in the interviews. Because the PROMETHEE model was used in these analyses, removal or addition of an alternative requires the construction of a new model, since the preference and resulting rankings are dependent on the available alternatives.[16] One model contained only alternatives that were available in 2005, before the phase-out of azinphos methyl was announced. Those alternatives include acetamiprid, azinphos methyl, methoxyfenozide, pyriproxyfen, phosmet, and thiacloprid. The second model contained alternatives available in 2011, the most recent year which pesticide use data in apples is available from the National Agricultural Statistics Service for comparison, and close to the end of the permissible use of azinphos methyl. This model included azinphos methyl and nine possible alternatives: acetamiprid, chlorantraniliprole, emamectin benzoate, methoxyfenozide, novaluron, phosmet, pyriproxyfen, spinetoram, and thiacloprid.

The decision models were constructed separately for each individual participant to allow customization of the preference functions. The type of preference function used for each criterion was the same for all participants, and was selected from among the six preference functions proposed by the creators of the PROMETHEE method[35] based on the variable type. Numeric/integer variables were matched with linear and v-shape linear functions. Categorical variables were fit to level functions, since differences between categorical variables could only result in a few finite options. Indifference and preference thresholds were applied according to individual interview responses to questions about each decision criterion.

The relative rankings calculated from the decision modeling results were converted to a probability of selection by taking the anti-log of each percentage over the total sum of the anti-logs of each ranks. The probabilities of selection were then used to construct a decision tree of sequential probabilities of use over six pesticide applications by pairing them with percentages of repeated application for each pesticide by Washington State growers based on a 2008 and 2010 survey from the Pesticide Management Transition Project (table 5.2). The probability of selection during the growing season was multiplied by the number of acres worked by each consultant and the percent of the total calculated. This percent of acreage to which each compound was applied was compared to the same value for the NASS data of 2005 and 2011.

5.3.3 *Probabilistic Exposure Assessment*

The one-day dose of a pesticide handler mixing, loading, and applying each pesticide using open cab airblast methods was calculated probabilistically as described previously (J. Pouzou et al, see chapter 3). In brief, exposure data from the Agricultural Handler Exposure Dataset (AHED) and the Pesticide Handler Exposure Dataset (PHED) were used to construct probabilistic exposure rates similar to those deterministic rates used in official calculations. These rates were paired with distributions of other factors, including cloth protection factors, application rates and areas, and anthropometric variables[62, 73, 107].

5.3.4 *Hazard assessment and benchmark dose modeling*

The human health risk assessments prepared by the Environmental Protection Agency based on review of the toxicological studies submitted for registration were used as the basis of hazard assessment for this analysis. Any health impact identified in the human health risk assessment which was potentially associated with a subchronic or acute exposure time-frame, or

with a developmental impact, was included in the analysis. In one case, chlorantraniliprole, a chronic endpoint was used as no other study described in the human health risk assessment showed any health impacts. The study from which each endpoint was observed was requested via Freedom of Information Act request from the EPA. The identified endpoint and any other observed symptoms indicative of the health impact category were used to construct benchmark dose models. The endpoint which provided the best model fit for each health impact category was selected. In cases where model fits were comparable among outcomes from the same study, the endpoint which provided the lowest benchmark dose was used. The details of dose-response model construction and benchmark dose selection procedure are described previously (J. Pouzou et al, see chapter 4).

5.3.5 *Comparative assessment*

The probabilistic dose distributions were compared with the benchmark doses calculated for each health impact, resulting in an exceedance fraction as calculated using the *efraction.exact* command of the R package STAND.[112] This exceedance fraction was input into a PROMETHEE decision model for each consultant where the selection criteria were the health impact categories ranked by the crop consultants during the interview. The differences in preference associated with difference in percent of the population beyond the Benchmark Dose multiplied by 100 were fit to a linear preference function, with the preference threshold set to the maximum probability of any health impact acceptable to the participant. The indifference threshold was set as zero in all cases, so that a difference in exceedance fraction of 1% corresponds to a 0.01 difference in preference in the same direction. Multiple models were created to explore health impact trade-offs: all health impacts were included in models with and without azinphos methyl, and models containing only impacts from acute or developmental

doses were constructed with and without azinphos methyl. The same models were constructed using halved weights for subchronic/chronic outcomes for comparison. Although sub-chronic toxicological studies may be useful for acute human exposures, and the EPA human health risk assessments for pesticide handlers of novaluron and methoxyfenozide use NOAELs from subchronic studies,[105] this down-weighting is a simple method of acknowledging the potential uncertainty produced by pairing different duration of exposure and dose-response. This adjustment will place double the emphasis on acute and developmental toxicity relative to impacts seen in sub-chronic and chronic testing in the calculation of the relative value of each compound in terms of minimizing health impacts.

5.4 RESULTS

5.4.1 *Decision models*

The selection criteria and their respective weights used in construction of the PROMETHEE models are previously reported (Pouzou et al – see chapter 2). Tables reproducing the pertinent values are reproduced in supplemental materials. The preference functions constructed for each decision criterion as customized for each participant are shown in figures 5.2a-h. Participants responded with variable thresholds of indifference strict preference for all numerical criteria except for duration of the compound on the market. All consultants stated that compounds must have been in trial field use, either by themselves or another member of the same firm, for at least one growing season before they would recommend the compound to their general clientele.

In the discrete or ordinal preference functions, some variability was observed in the difference in preference between levels. For efficacy, some respondents indicated they would

strongly prefer higher levels, whereas others indicated they would have only slight preference. To reflect this difference, the strong preference function was constructed so that for small differences in efficacy, twice the preference change was assigned than for the slight preference levels. A similar method was employed for pollinator and beneficial species toxicity responses. For pollinator toxicity, an additional response type was observed, whereas at low levels of toxicity, smaller differences in rating corresponded to a strong preference, but at low levels, the difference in preference was only slight.

The resulting preference ranks are shown in figure 5.3 for the years 2005 and 2011. These preferences were converted to the probabilities of selection shown in table 5.3, corresponding to the probability of selection for an ovicide or larvicide in the first or second generation, without consideration of sequential probabilities of selection.

5.4.2 *Result of application extraction*

By combining the repeat probabilities from WSU Data and the limitation that a pesticide cannot be used in the second generation if used in the first, and the existing options for each year, the number of permutations of pesticide selection order for the two years' models can be computed. 1,281 possible different selection patterns were computed for 2005, and 278,564 possible selections were found for 2011. The average probability of selection for each compound to use in each of six sprays was computed and the six selection probabilities summed to calculate the overall percent probability of selection of a compound for spraying during a season (table 5.4). The percentage of the worked acreage predicted for treatment for each compound is compared to NASS percentages in table 5.4.

5.4.3 *Doses and exceedance fractions*

The selected pesticide health impacts screened from the human health risk assessments are summarized in table 5.5. Health outcomes fell into categories of acute neurotoxicity; non-cancerous liver, kidney, and thyroid toxicity; hemotoxicity, development toxicity, reproductive toxicity, ocular irritation, dermal irritation, and skin sensitization. Acute outcomes include dermal irritation, ocular irritation, dermal sensitization, and acute neurotoxicity. Developmental outcomes are also included as acute impacts because of the potential importance of timing rather than duration in doses impacting these health outcomes. The duration of the toxicological studies varied from acute (single dose) to sub-chronic (20 weeks), to chronic (18 months). Studies of developmental and reproductive outcomes generally began dosing prior to mating and continued through gestation or weaning, and in one case (pyriproxyfen dose and kidney nephritis) through sacrifice of the F1 generation adults. Specifics of the models fit to each health impact are included in supplemental materials.

The probabilistic estimates of doses for pesticide handlers through the inhalation and dermal routes combined are shown in figure 5.4 along with the benchmark doses produced through modeling of dose-response curves. The fraction of the population of handlers for each pesticide exceeding each benchmark dose are shown in table 5.6, along with the fraction exceeding the lower 95% confidence limit of the benchmark dose as a measure of uncertainty.

5.4.4 *Health tradeoff models*

5.4.4.1 Unicriterion flows

The unicriterion flows can illustrate the health impact "strengths and weaknesses" for each compound, without making use of the relative values of health impacts, as shown in figure 5.5. If azinphos methyl is included as an alternative, acetamiprid, azinphos methyl, phosmet, and

thiacloprid are all low-ranked alternatives for prevention of neurotoxicity, though azinphos methyl has the greatest negative ranking. Azinphos methyl also has the strongest negative rank for developmental toxicity, followed distantly by thiacloprid. Dermal sensitization is also a strong differentiator, although azinphos methyl and spinetoram are the only two dermal sensitizers, because the criterion is binary with no evaluation of relative potency of sensitization. Ocular irritation shows the strongest scores for emamectin benzoate and phosmet, and only one alternative, thiacloprid, was reported as a dermal irritant (of low potency), causing it to be ranked negatively for that aspect. Reproductive toxicity ranked emamectin benzoate and phosmet low, whereas hepatotoxicity and thyroid toxicity had the lowest scores among spinetoram and thiacloprid. Hemotoxicity was scored low for spinetoram and novaluron. Removal of azinphos methyl from the model leaves acetamiprid, phosmet, and thiacloprid as the least-preferred in neurotoxicity prevention. Thiacloprid is also the most negatively ranked for developmental and hepatotoxicity. Phosmet is the only negatively-ranked alternative for reproductive toxicity, and as before, spinetoram and novaluron are ranked negatively for hemotoxicity. Only two alternatives, methoxyfenozide and chlorantraniliprole, had positive ranks for all health impact categories.

5.4.4.2 Trade-offs

In general, pesticides with more negative scores in neurotoxicity had higher scores for hemotoxicity, the converse being true as well, indicating that switching between compounds would substitute one type of risk for the other. With the exception of the neonicotinoids thiacloprid and acetamiprid, this finding is also true for tradeoffs between neurotoxicity and hepatotoxicity. Four of the ten compounds have more than one negative score associated with any health impact: azinphos methyl, phosmet, thiacloprid, and spinetoram. Of all three, only

spinetoram is not acutely neurotoxic. The health impacts associated with spinetoram are all results from sub-chronic exposure studies, except dermal sensitization. Compounds with developmental impacts probable enough to result in a reduction in score were also neurotoxic, indicating no trade-off between those health impacts in the evaluated set of alternatives. Acetamiprid, thiacloprid, and emamectin benzoate were associated with developmental impacts specific to neurodevelopment (table 5.5), which may partially explain the association between neurotoxicity and developmental toxicity.

5.4.4.3 Overall health impact rankings

The preference rankings from the models (with and without azinphos methyl as an option) using criteria weights for each health impact as reported from the crop consultants are shown in figure 5.6. When azinphos methyl is included, it dominates the less-preferred options, indicating the greatest potential for human toxicity among all ten compounds. The other compounds which received negative preference scores include phosmet, thiacloprid, spinetoram, and, to a lesser degree, emamectin benzoate. If azinphos methyl is removed from the model, the ranking order of health impact minimization does not change, but the difference between the remaining positive and negative scores becomes more pronounced. In the models where criteria weightings for non-acute health impacts are down-weighted by 50%, the compounds with the greatest potential for acute or developmental health impacts receive the most negative scores (figure 5.6). These compounds include azinphos methyl, phosmet, thiacloprid, and emamectin benzoate. As with the previous set of models, azinphos methyl dominates the negative ranking, and when removed as an option, the division between the three remaining negatively-scored compounds and those with overall positive preference ranks is clearer.

For the most part, all consultants ranked health impacts similarly, which is reflected in the similarity of the health impact tradeoffs from their perspective. One participant's preference ranks run counter to the majority, however; this consultant ranked all health outcomes as the highest priority except those of dermal or ocular irritation and dermal sensitization, which were assigned the lowest ranks. The participant explained that those outcomes did not seem to them to be health impacts in the same way or same severity as the other ranked outcomes.

5.4.4.4 Extrapolation of health impacts from spray frequency

The result of combining the probability of a spray and the probability of exceeding the benchmark dose with safety factor adjustments is shown in table 5.7. Both the model-predicted pesticide usage and the NASS data show that the likelihood of any specific pesticide health impact decreases between 2005 and 2011 for pesticides used in both years. For all pesticides combined, the probability of acute neurotoxicity, developmental toxicity, and reproductive toxicity decreased. There were some small increases in hepatotoxicity, hemotoxicity, and thyroid toxicity.

5.5 Discussion

The purpose of this analysis was to use PROMETHEE methods both to estimate pesticide selection probability and usage rates and to examine health trade-offs resulting from selection among a variety of chemical insecticides. The results of this analysis indicate that the PROMETHEE model is a viable framework for health trade-off examination, and may have some value in pesticide selection predictions.

The predicted pesticide usage rates for 2005 and 2011 are of variable accuracy when compared to the NASS dataset. The predicted percent selection for acetamiprid and phosmet were quite accurate, but the usage of azinphos methyl in both years was underestimated. Instead,

the model predicted that use of methoxyfenozide and pyriproxyfen would be higher in 2005, and usage of chlorantraniliprole, novaluron, and phosmet in 2011 would be higher. The model also underestimated 2011 use of thiacloprid, spinetoram, and emamectin benzoate. There may be a number of reasons for these differences, which do not indicate the prediction model is invalid. One reason, which is difficult to assess without extensive additional modeling of other pest systems or obtaining grower application records, could be that the NASS dataset is not subdivided by pest.[20] Many of these compounds have multiple pest indications. For example, thiacloprid may also be used for red apple aphid and leafhopper. Acetamiprid may be used for campylomma, and chlorantraniliprole may be used for leafroller, another prominent pest of apple orchards.

The underestimation of azinphos methyl use in particular may also be due to differences between the consultant's perceptions of efficacy and efficacy recorded in the WSU *Crop Protection Guide*. Consultants reported only occasional use of the efficacy values in the *Guide*, instead preferring to rely on personal experience, manufacturer data, and consultation with other consultants to evaluate compound efficacy against codling moth. Since efficacy is the main driver of selection, differences in consultant and literature evaluations of it could have significant impacts on the model results. These caveats do not rule out PROMETHEE as a useful framework for decision modeling in this case, but rather indicate that the NASS dataset may not be a proper comparison or represent revealed preferences. That the model can predict stated preferences indicates validity in the method for matching the needs of the included stakeholders.

This study further demonstrates that it is feasible to examine health impact tradeoffs in a quantitative manner through the use of preference ranking and valuation of health states. The health impact ranking used in this study were elicited from consultants with experience in

occupational exposures, knowledge of pesticide health impacts and pesticide usage, and relatively high levels of education overall. The benefit of PROMETHEE is that use of other health valuations, from expert opinion, or sources such as disability weightings provided by the general population could easily be substituted or added to the model if a different perspective is desirable.

Questions remain regarding the importance of including sub-chronic health impacts in this model. Occupational exposures tend to be through the inhalation and dermal route, sporadic, and spread out over many weeks, theoretically, which would support the inclusion only of acute and developmental health impacts. This model assumes that a one-day treatment would occur in chronological isolation; however, an employee of a large operation may conceivably carry out multiple days of pesticide application in a row. In such cases, the pharmacokinetics of these compounds become critical to understand, and sub-chronic health impacts may be critical to consider. The results of this study indicate improvements in acute and developmental toxicity risks, but slight increases in subchronic impacts to the liver, thyroid, kidneys, and blood. If sub-chronic exposures and health impacts occur, a subtle trade-off in the health impacts of pesticide handlers is present.

Cumulative exposures are likewise not considered in this model, and mixtures are not considered to be additive, but both of these assumptions should be further investigated. For newer compounds, precise application timing to match the lifestage of the pest can be critical, as mechanisms are increasingly specific to ovicidal, residual larvicidal, and larvicidal action. Changes in climate may also impact the number, frequency, and spacing of sprays as generational development of the pest is reliant on degree days. As more chemical classes are

adopted, the possibility of mixture exposures, especially for re-entry workers, is increasingly likely.

Although all of the currently available compounds have been evaluated separately and found to produce acceptable margins of exposure, this analysis shows that further minimization of health impacts is possible through differential selection of pesticide alternatives. Some compounds are "win-win," in that they are both efficacious and feasible insect controls and relatively low toxicity, such as chlorantraniliprole, methoxyfenozide, and novaluron. The requirements of resistance management, budget limitations, and other trade-offs drive diversification of selections beyond the most efficacious and safest compounds, however. Diversification of insecticides has lowered the use of any one compound, reducing the health impacts overall through introduction of safer alternatives. In this way, additional chemical class availability is both beneficial to human health and to codling moth control, as more options improves the ability of growers to rotate class and manage resistance. Further, resistance management permits lower rates of chemical usage with no loss of crop quality.[34]

Despite the limitations of this analysis, the use of preference-ranking through MCDA methods has been demonstrated in both exploring decision spaces for chemical alternatives and in weighing health-health trade-offs that result.

Chapter 6. DISCUSSION

The adoption of alternatives assessment as a mainstream method of risk assessment is an inevitability as risk management increasingly requires answers to more complex questions and the low-hanging fruits of health and safety are often already harvested. The greatest obstacles in completing a study of this kind are the lack of quantitative and robust yet flexible methods and the quantity of information required to address multiple dimensions of a problem or scenario. This study has demonstrated that the PROMETHEE method of MCDA can provide a useful framework for alternatives assessment. The method has a framework for preference elicitation and characterization as well as freely available software useful in implementation. Most importantly, PROMETHEE is extremely flexible in the types of information which may be used as alternative valuations, selectin criteria weighting, and preference characterization. Both qualitative and quantitative data can be easily and systematically combined, as was accomplished with data on efficacy, pollinator toxicity, costs, and other pesticide selection criteria.

This research has also demonstrated that the construction of probabilistic exposure and dose models can be completed using open-source software and currently available data. The widespread adoption of probabilistic methods in regulation will enhance knowledge and precision regarding the hazards of workers and other exposed populations. It will create the potential for selection of more protective or more sensitive regulatory limits. As data on individual sensitivities and vulnerabilities becomes more available for chemicals of interest, it can be incorporated into probabilistic analyses to explore the impact on the population as a whole as well as in subgroups, much like the EPA's comparative risk assessment guidance framework suggests in the case of water treatment methods.[121]

Existing toxicological data was used to demonstrate the feasibility of large scale creation of benchmark dose models from studies based on current OECD guidelines. It was found that despite variable data quality and relatively few dose groups, benchmark doses were able to be derived from data previously used in the generation of NOAELs for regulation. Although the use of benchmark doses in regulatory frameworks has been widely suggested and in some cases adopted, this work shows that currently available data may be of use in advancing towards that goal and that redesign of toxicological study guidelines, while likely beneficial in many ways, does not need to limit the use of these methods.

While all of these methods have been previously described and promoted, this study demonstrates the compatibility of new and more complex methods of risk assessment with currently available data. Adoption of MCDA alternatives assessment with incorporation of probabilistic methods will open up new possibilities for regulation and informed selection of policies and alternatives both on a governmental and consumer level.

6.1 LIMITATIONS

Despite the broad scope of this analysis, a complete comparative risk and alternatives assessment would require still more dimensions. This study does not examine risks to other agricultural workers, community or environmental exposures to humans, or environmental impacts. However, each of these dimensions has established procedures for assessment by the EPA, which could be similarly adapted to this framework as has been demonstrated with the case of pesticide handlers.

In the recruitment of consultant participants, very few employed by chemical manufacturers or distributers responded to any overtures from this researcher. Those who responded were hesitant to participate fully despite assurances of confidentiality. This difficulty

in recruitment has likely led to some bias in the results of this experiment. One participating consultant worked for a manufacturer, and admitted that although they maintain the interests of their client above all, they also take into account the interests of their employer while making recommendations, and tend to use their companies' products more often. This perspective is not well-characterized in this study.

In the development of the probabilistic dose models, the paradigm of dermal fractional absorbance was used rather than the preferred method of flux. The available dermal absorbance studies used finite doses in their assessment, which complicates the modeling of dermal flux based on such data. While the use of advanced modeling techniques may permit the use of such data to calculate a probabilistic assessment of flux, this work was beyond the scope of the research presented here.

The greatest limitation of the study is the lack of agreement between the predicted pesticide usage rates and the NASS values reported for the same years. Reasons for this are posited in chapter 5. While this result does not preclude the usefulness of the MCDA method in evaluating health tradeoffs, it may limit the value of the model in predicting the future popularity of pesticide classes as they emerge. In addition, the MCDA model is highly situational, since it relies on comparative preference. An unforeseen technological improvement or paradigm shift in control methods would not be foreseen by this model, nor would impacts on changing climate or macroeconomic impacts on the pome fruit market.

6.2 Conclusions

Despite the limitations of the study, it was demonstrated that the currently available and most frequently-used compounds are in general safer for pesticide applicators following label instructions than alternatives of 10 years ago, when organophosphate use was more prevalent.

However, some pesticide handlers exceed the level of concern set by a benchmark dose, or by a NOAEL in many cases. The field study supported the finding that workers can exceed the risk estimates completed based on deterministic calculations, even under normal work conditions. The potential health tradeoffs seen in this study, combined with the exceedance of acceptable risk limits according to exposure studies and probabilistic assessments, make the case for the inclusion of these kinds of assessments in routine pesticide human health risk assessments. The further minimization of risks and a more complete understanding of potential risk substitutions, as well as a balanced assessment of the motivations of pesticide selection, can promote the use of effective yet safer chemical alternatives, improving the overall health and safety of orchard workers.

PART 6. TABLES

Table 2.1: Health impact categories and associated descriptions and examples presented to crop consultant participants for ranking on a scale of 1-10, where 10 is critical to prevent, and 1 is not at all important.

Health Impact	Descriptions
Acute Neurotoxicity	Non-permanent effects such as tremors, difficulty walking or moving normally, excess perspiration and salivation. etc.
Liver impacts	For example, enlargement of your liver or liver cells, or a higher workload being placed on your liver.
Thyroid impacts	For example, enlargement of your liver or liver cells, or a higher workload being placed on your liver which may not have any symptoms
Blood diseases	For example, damage to cells that produce thyroid hormones which may not have any symptoms
Reproductive impacts	Lowered fertility
Developmental impacts	Birth defects or delays in fetal or childhood development
Eye Irritation	Temporary eye irritation which might be severe enough to require medical assistance
Skin Irritation	Temporary skin irritation which might be severe enough to require medical assistance
Skin Sensitization	An allergy to the pesticide after the first exposure which may result in skin irritation or rashes

Table 2.2: Pesticide selection criteria ranks (scale of 1-10) provided by the 16 participating crop consultants and adjustments made prior to use in the decision model. Reported pollinator toxicity ranks are the ranks provided by the consultants in the initial part of the interview. Adjusted pollinator toxicities are the ranks remaining when those of participants who reported not recommending sprays during pollinator activity were set to zero. The specific beneficial species toxicities are derived by dividing the rank among the specified organisms provided from each consultant. The starred organism rank is the primary species mentioned and the species used in the decision analysis model.

Efficacy	Resistance Management	Pre-harvest Interval	Duration on	Protective Equipment	Adjusted Pollinator Toxicity	Pollinator Toxicity (reported)	Cost	Re-entry Interval	Persistence	Human health toxicity	Leafroller Control	Beneficial Species Toxicity	Western Predatory Mites	Aphid Predators	Ladybugs	Mite predators	Lacewings	Parasitoid wasps	Predatory bugs
10	10		10	9		10	8			10		10	**5***			5			
10	10	10	10	8	10	10	5	8		8		9	1.5		1.5	1.5	1.5	**1.5***	1.5
10	6	10	10				8	10		10		8			**8***				
10	10		10		2	2						1			0.3		**0.3***		0.3
10	7		9			7						8.5	2.1			2.1	2.1		**2.1***
10	7.5	5.5	9			9.5				7.5	8	8	**4***			4			
10	8		8		9.5	9.5	5	8				4				**1.3***			
10	8	10			10	10	7	10		10	10	10	2.5	2.5		2.5		**2.5***	
10	8	6				7	5	8				7	1.8	**1.8***		1.8			1.8
10	10					10						10	1.7	1.7	1.7	**1.7***	1.7		1.7
10	9	6	10			10		10				8	1.6	1.6	1.6	**1.6***			1.6
10	10					5	5					8	**2***	2			2	2	
10	8	10				10						7	**2.3***		2.3		2.3		
10	8	3	4.5		6.5	6.5	5	2				6.5	2.2			**2.2***			2.2
10	10	7	10			7.5	7	8	10	8.1		7	**1.8***		1.8	1.8	1.8		
10	8	6	7			10						9	**4.5***	4.5					

Table 2.3: Health impact criteria ranks (scale of 1-10) provided by the 16 participating crop consultants.

ID	Acute Neurotoxicity	Cancer	Developmental Toxicity	Hemotoxicity	Kidney toxicity	Liver toxicity	Reproductive toxicity	Thyroid toxicity	Eye irritation	Skin irritation	Skin sensitization
1	10	10	10	10	10	10	8	10	3	3	6
2	10	10	10	10	10	10	10	10	5	5	5
3	10	10	10	10	10	10	10	10	8	5	10
4	10	10	10	10	10	10	10	10	10	10	10
5	10	10	9	9	9	9	10	10	5	5	5
6	9	9.5	7.5	7.5	7.5	7	7	9	10	10	10
7	8	10	8	8	8.5	9	9	10	1	1	1
8	10	10	10	10	10	10	10	10	7	6	7
9	8	10	7	7	7	10	10	10	8	6	6
10	10	10	10	10	10	10	10	10	5	5	3
11	10	8	10	10	8	8	8	10	6.5	5.5	6
12	3	10	9	9	9	6	8	10	9	9	9
13	10	8	7	7	10	5	10	10	5	5	8
14	5	8	5	5	5	4.5	3	10	8	8	8
15	10	10	10	10	10	10	10	10	10	8	8
16	8	10	8	8	9	8	10	10	7	7	8

Table 2.4: Components and cumulative variance explained resulting from principal component analysis of the pesticide selection criteria used in the decision model both unrotated and rotated

	Component					
	1		2		3	
Cumulative Variance	33%		55.7%		68.7%	
		Rotated		Rotated		Rotated
Resistance management	0.08	**0.58**	**0.77**	-0.51	-0.06	0.04
Duration on Market	0.28	0.27	0.18	0.17	**0.80**	**0.80**
Preharvest Interval	0.48	-0.10	**-0.68**	**0.80**	-0.12	-0.23
Protective Equipment	**0.64**	**0.85**	0.57	0.02	0.00	0.05
Pollinator toxicity	0.58	**0.76**	0.48	0.03	-0.09	-0.05
Beneficial Species toxicity	0.46	0.36	-0.04	0.25	**-0.72**	**-0.74**
Re-entry interval	0.55	0.02	**-0.55**	**0.81**	0.27	0.17
Cost	**0.75**	0.50	-0.08	0.57	0.05	0.01
Human toxicity	**0.91**	**0.64**	-0.05	0.65	0.04	0.00

Table 2.5: Components and cumulative variance explained resulting from principal component analysis of the health impact ranks model with and without the outliers, and both unrotated and rotated.

	Cumulative Variance	Acute neurotoxicity	Cancer	Kidney (non-cancer)	Liver (non-cancer)	Thyroid (non-cancer)	Hemotoxicity	Reproductive impacts	Developmental impact	Eye irritation	Skin irritation	Skin sensitization
Outliers included												
1	45.2%	**0.69**	0.56	**0.88**	**0.88**	**0.84**	**0.81**	**0.82**	0.32	0.55	0.57	0.50
2	64.7%	0.19	-0.38	-0.20	-0.20	-0.22	-0.26	-0.16	-0.38	**0.79**	**0.71**	**0.72**
3	80.3%	-0.23	-0.35	-0.14	-0.14	-0.08	-0.20	-0.05	**0.86**	0.18	0.19	0.22
Outliers removed												
Non-rotated												
1	42.2%	**0.62**	**0.20**	**0.78**	**0.78**	**0.66**	**0.66**	**0.53**	**0.48**	**0.66**	**0.69**	**0.84**
2	60.7%	-0.39	**0.76**	0.30	0.30	0.22	0.46	0.09	0.31	-0.69	-0.46	-0.29
3	73.4%	-0.03	0.01	-0.45	-0.45	0.12	-0.05	0.80	0.57	0.00	0.04	-0.06
4	84.2%	0.27	0.48	-0.28	-0.28	-0.45	0.51	0.11	-0.42	-0.03	0.09	0.27
Varimax rotation												
1	42.2%	0.77	-0.21	0.25	0.25	0.16	0.32	0.33	-0.02	0.89	0.81	0.85
2	60.7%	0.10	0.11	0.93	0.93	0.62	0.30	-0.16	0.29	0.16	0.17	0.28
3	73.4%	0.04	0.09	0.07	0.07	0.54	0.13	0.85	0.86	0.10	0.16	0.11
4	84.2%	0.12	0.88	0.21	0.21	-0.01	0.84	0.28	0.02	-0.28	-0.04	0.23

Table 3.1 Characteristics of the studies comprising the four pesticide handling scenarios of interest in the AHED and PHED datasets

Scenario	Formulation	Data Source	n observations	n studies	Inhalation exposure	Dermal Exposure				Body dosimeter locations
						Hands	Head	Face/neck	Body	
Mixing-Loading	Wettable Powder (pourable)	PHED	77	7	Respirator filter or powered active air	Hand rinse or cotton glove	Patch inside and outside of hat	Extrapolated from head	Mixture of patches, body area dosimeters, wipes	Inside and outside of clothes
	Wettable Powder (packaged)	PHED	15	4	Respirator filter or powered active air	Hand rinse	Patch inside and outside of hat	Extrapolated from head	Mixture of patches and body area (usually forearm) dosimeters	Inside and outside of clothes
	Dry Flowable	AHED	25	5	powered active air	Hand rinse	Extrapolated from face	Wipe	Cotton dosimeters	Inside clothes
Open Cab Application	All	AHED	28	4	powered active air	Hand rinse	Patch inside and outside of hat	Wipe	Cotton dosimeters	Inside clothes

Table 3.2: Distributions of assumptions used in probabilistic risk assessments

Assumptions	GM	Mean	GSD	SD	Distribution Type	(min, max)	Dimension
Mixing and Loading Inhalation Rate (m^3/hr)							
Exposure Factors (All outdoor workers "medium")[73]		0.84		0.47	Normal	(0, ∞)	Variability
Exposure Factors (Essential outdoor workers "medium")[73]		0.84		0.54	Normal	(0, ∞)	Variability
NAFTA Technical Working Group[68]		1	NA		NA	NA	
Application Inhalation Rate (m^3/hr)							
Exposure Factors (All outdoor workers "slow")[73]		0.71		0.4	Normal	(0, ∞)	Variability
Exposure Factors (Essential outdoor workers "slow")[73]		0.78		0.36	Normal	(0, ∞)	Variability
NAFTA Technical Working Group[68]		0.5	NA		NA	NA	
Respirator Protection Fraction (from Nicas et. al.)[70]							
Cohen	0.035		2.65		Lognormal	(0, 1)	Variability
Galvin	0.013		3.13		Lognormal	(0, 1)	Variability
Reed	0.058		2.87		Lognormal	(0, 1)	Variability
Myers	0.014		5.43		Lognormal	(0, 1)	Variability
Myers	0.004		3.24		Lognormal	(0, 1)	Variability
Zhuang	0.0002		4.07		Lognormal	(0, 1)	Variability
Weber	0.027		2.16		Lognormal	(0, 1)	Variability
OSHA		0.1			Scalar	NA	NA
Cloth Protection Fraction							
CDPR[76]		0.9			Scalar	NA	NA
EPA[67]		0.5			Scalar	NA	NA
Keeble[74]		0.975		0.06	Normal	(0.78, 1)	Variability

Driver[75]	0.915	0.10	Normal	(0,1)	Variability
Driver	0.885	0.13	Normal	(0,1)	Variability
Chemical Resistant Fabric Protection Fraction					
Keeble	0.9993	0.21	Normal	(0, 1)	Variability
Keeble	0.9983	0.24	Normal	(0, 1)	Variability
Application Rate (lbs per acre)					
azinphos-methyl[42]	mode = 1.5		Triangular	(1, 1.5)	Variability
acetamiprid[36]	mode =0.15		Triangular	(0.7, 0.15)	Variability
emamectin benzoate[122]	mode = 0.015		Triangular	(0.003, 0.015)	Variability
application error (proportion)[123]	-0.028	0.26	Normal	(-1, 1)	Uncertainty
Application Size (Acres)					
mode=40			Triangular	(0.25, 60)	Variability
Body weight (kilograms)					
Exposure Factors Handbook	85.47	19.03	Normal	(0, ∞)	Variability
AHETF Studies[80]	87.25	16.84	Normal	(0, ∞)	Variability
Skin surface area (cm^2)[73]					
Lower Leg	2680	340.5	Normal	(0, ∞)	Variability
Upper Leg	4120	674.9	Normal	(0, ∞)	Variability
Chest	3875	829.9	Normal	(0, ∞)	Variability
Back	3875	829.9	Normal	(0, ∞)	Variability
Upper Arm	1720	291.8	Normal	(0, ∞)	Variability
Lower Arm	1480	297.9	Normal	(0, ∞)	Variability
Head/Neck	1620	109.4	Normal	(0, ∞)	Variability
Face/Neck	583	36.5	Normal	(0, ∞)	Variability
Dermal Fractional Absorbance					
azinphos-methyl[84]	0.42	0.08	Normal	(0, 1)	Uncertainty
acetamiprid[82]	0.31	0.03	Normal	(0, 1)	Uncertainty
emamectin benzoate[83]	0.02	0.01	Normal	(0, 1)	Uncertainty

Table 3.3 Kolmogorov-Smirnov p-values generated by comparison of clustered and non-clustered distributions of exposure rate by body area and exposure scenario.

	Mixing and Loading			
	Dry Flowable	Wettable Powder	Wettable Powder (Packaged)	Open Cab Application
Inhalation	0.055	0.288	<0.001	0.371
Dermal				
Lower legs	0.997	<0.001	0.371	<0.001
Upper legs	0.342	<0.001	0.002	<0.001
Forearms	0.062	<0.001	<0.001	0.010
Upper arms	0.001	<0.001	NA*	0.043
Chest	0.611	<0.001	0.537	0.004
Back	0.026	<0.001	0.010	0.002
Head	0.004	<0.001	<0.001	0.013

Table 3.4: Exceedance fractions of probabilistic estimates for EPA HHR deterministic values of dose, margin of exposure (MOE) and level of concern (LOC), and NOAELs identified from relevant studies of neurotoxicity.

	NOAEL (µg/kg/day)	Mean of dose distribution (µg/kg/day)	EPA HHR dose (µg/kg/day)	% above deterministic dose (below MOE)	EPA estimated HHR MOE	% of MOE distribution beyond LOC‡
AZM	150	18.3	8.33†	19	18	54
Dermal	560	17	--	--	--	53
Inhalation	200	1.3	3.42	19	43	9
ACP	10,000	2.8	35.43	14	282	5
Dermal	10,000	2.2	31.71	13	315	4
Inhalation	10,000	0.6	3.72	20	2688	12
EB	75	0.4	0.09	36	837	20
Dermal	75	0.3	0.04	39	1705	15
Inhalation	75	0.1	0.05	29	1645	12

†The estimated dose used in the most recent EPA human health risk assessment of open-cab pesticide handlers for azinphos methyl is based on biomonitoring and inhalation data collected from mixer/loader/applicators (MRID 46316406).[88]

‡ The limits of concern (LOC) for margins of exposure for azinphos methyl and dermal exposures to acetamiprid are 100, the typical value for occupational scenarios. Because of a lack of inhalation study for acetamiprid, the occupational inhalation LOC for acetamiprid is 1000.[65] The LOC for emamectin benzoate inhalation and dermal occupational exposures is 300 for short term and 1,000 for intermediate exposures. The percent exceedance in this table uses 300 as the LOC MOE. The additional uncertainty factor of 3 was applied in the EPA human health risk assessment due to the severity of the health impact at the LOAEL (neuropathology).[66]

Table 3.6: Comparison of substitutions for values below the limit of detection (LOD) or quantitation (LOQ) in the PHED datasets for wettable powder mixing and loading (WP) and soluble packed wettable powder mixing and loading (WPS)

	WP (n)	% <LOD	WPS (n)	% <LOD	Wettable powder µg/cm²				Wettable powder (soluble packaging) µg/cm²			
Observations (n)	78	-	15	-	Interpolation		1/2 LOQ Substitution		Interpolation		1/2 LOQ Substitution	
Participants (n)	26	-	6	-	GM	GSD	GM	GSD	GM	GSD	GM	GSD
Outer Upper Leg	38	26	15	27	0.05	1.66	0.05	1.50	0.01	2.48	0.01	2.32
Outer Lower Leg = Shin + Calf + Ankle	34	18	12	42	0.07	1.36	0.03	1.40	0.003	1.42	0.002	1.31
Outer Hands	27	15	5	0	209	2.01	194	2.13	86.94	1.31	86.94	1.31
Outer Lower Arm	48	6	15	47	0.20	1.75	0.10	1.70	0.01	1.81	0.01	1.71
Outer Upper Arm = Shoulder + Upper Arm	44	0	6	83	0.10	1.24	0.06	1.21	0.0018	0.61	0.0010	0.51
Outer Chest	46	11	15	67	0.05	1.51	0.06	1.36	0.0016	1.69	0.0027	1.54
Outer Back	45	16	15	67	0.04	1.95	0.05	1.40	0.0012	1.27	0.0015	1.44
Outer Head/Neck	16	19	15	67	0.02	5.4E-16	0.02	5.44E-16	0.0031	1.35	0.0020	1.47
Inhalation	64	20	15	40	7.59	2.51	9.56	2.08	0.3989	2.49	0.358	2.61

Table 3.6: Supplemental material for Chapter 3: Selected body section comparisons of data resulting from ½ LOQ substation vs interpolated values.

				1/2 LOQ method		Interpolation method		
		N	%ND	GM	GSD	GM	GSD	% Difference in GM
Lower Leg	Inner	46	39%	0.022	10.3	0.011	10.3	50%
	Outer	26	38%	0.155	73.4	0.080	72.2	49%
Upper Leg	Inner	53	47%	0.023	8.6	0.009	10.7	63%
	Outer	37	16%	0.599	40.7	0.281	45.1	53%
Chest	Inner	60	28%	0.021	9.7	0.019	11.5	12%
	Outer	54	19%	0.243	31.2	0.211	38.4	13%
Back	Inner	60	35%	0.020	10.1	0.015	11.7	25%
	Outer	54	24%	0.150	37.9	0.138	41.5	8%
Upper Arm	Inner	49	18%	0.071	6.2	0.034	6.8	52%
	Outer	42	14%	0.999	27.3	0.491	28.3	51%
Forearm	Inner	57	21%	0.113	8.8	0.053	8.8	53%
	Outer	56	16%	0.978	27.7	0.477	29.5	51%
Hands	Inner	36	42%	36.142	38.5	31.949	54.0	12%
	Outer	29	0%	-	-	-	-	-
Head & Neck	Inner	18	92%	0.004	6.2	-	-	-
	Outer	31	42%	0.027	17.6	0.027	17.0	0%

Table 3.7: Supplemental material for Chapter 3: Endpoint selection details for all pesticides and outcomes used in health impact trade-off analysis for Chapter 5.

Pesticide	Category	Endpoints available	Endpoint Used in BMD Model	Reason for selection
Acetamiprid	Neurodevelopmental	Changes in auditory startle (PND 20) Changes in auditory startle (PND 60) Decreased body weight Decreased body weight gain Decreased post-weaning survival	Changes in auditory startle (PND 20)	BMD for developmental study was much higher. Neuro outcomes other than tremors and startle were observed only in highest dose groups. Locomotor activity was continuous and selected, although tremors produced similar results
	Developmental	Decreased viability index Decreased survival post-weaning	Viability index	Weaning index dose response was not significant.
	Hepatotoxicity	Hepatocellular hypertrophy Increased liver/body weight ratios Increased serum total cholesterol	Hepatocellular hypertrophy	All models showed similar fit and passed variance and goodness of fit testing, but hypertrophy had the lowest AIC by a small margin.
	Neurotoxicity	Locomotor activity tremors Altered gait Hunched posture Increased urination Pupillary dilation	Locomotor activity	Locomotor activity was decreased at the lowest doses, and was a continuous outcome.
Azinphos methyl	Neurotoxicity	RBC cholinesterase activity Plasma cholinesterase activity Brain cholinesterase activity	RBC Cholinesterase	Red blood cell cholinesterase provided best model fits and lowest BMD of all cholinesterases
	Developmental toxicity	Preimplantation loss Extra lumbar/missing sacral vertebrae Viability index Weaning index	Preimplantation loss	Vertebral changes were within historic control range. Viability and weaning index were observed in a study without adequate investigation of cause of death of pups. Preimplantation loss was observed in a rabbit study, and was the only other alternative.
Chlorantraniliprole	Hepatotoxicity	Hepatocellular hypertrophy eosinophilic loci increased liver weight	Hepatocellular hypertrophy	Hypertrophy models were best fit at the lowest doses, in comparison with loci and weight
Emamectin benzoate	Neurotoxicity	Tremors Ptosis Gait Abnormalities Hunched posture Labored breathing Decreased activity Urine staining	Tremors	Tremors were observed at the lowest dose groups and emerged before other outcomes, therefore was a more sensitive indicator
	Reproductive toxicity	Fertility index (female)	Fertility index (female)	Only option
	Developmental toxicity	Motor activity PND 17 Growth alterations	Motor activity PND 17	Motor activity was observed at the lowest doses compared with other outcomes

		Supernumary ribs Delayed maturation landmarks (vaginal canalization and preputial separation) Decreased brain weights		
Methoxyfenozide	Hemotoxicity	RBC count nucleated red cell increase platelet cell count	RBC count	Platelet counts and nucleated red cells failed variance modeling tests, leaving RBC
	Neurotoxicity	Hindlimb grip	Hindlimb grip	Only option
	Hepatotoxicity	Hepatocellular hypertrophy Increased liver/body weight ratio Kupffer cell pigmentation	Hepatocellular hypertrophy	Hypertrophy and liver weight time-course of the dose was shorter and therefore more relevant to occupational scenarios. Hepatocellular hypertrophy and cell pigmentation were modeled using all dichotomous options. Hepatocellular hypertrophy was considered more indicative.
Novaluron	Hemotoxicity	RBC count hematocrit hemoglobin levels splenic hematopoiesis splenic enlargement	RBC count	Hematocrit and hemoglobin models failed to fit, RBC and splenic hematopoiesis/enlargement produced similar results, but dose response was more marked with RBC count
	Neurotoxicity	Respiration rate piloerection vocalization increases staining irritability	Respiration rate	Results for piloerection and respiration rate both showed significant dose response curves with similar results. Respiration showed slightly better fits from qualitative evaluation of curves.
	Reproductive toxicity	Epididymal sperm count (F1)	Epididymal sperm count (F1)	Only option
Phosmet	Neurotoxicity	RBC Cholinesterase Plasma cholinesterase activity Brain cholinesterase activity	RBC Cholinesterase	Red blood cell cholinesterase provided best model fits and lowest BMD of all cholinesterases
	Reproductive toxicity	Fertility index	Fertility index	Only option
Pyriproxyfen	Hepatotoxicity	Cholesterol reduced nucleus/cytoplasm ratio dimunation of sinusoidal spaces in liver cells Increased phospholipids Liver weight increases Focal clear cells Liver discoloration	Cholesterol level	Focal clear cell models fit poorly, phospholipid and cellular changes modeled variance poorly. Serum cholesterol produced lower BMD than discoloration.
	Hemotoxicity	red blood cell count hematocrit	Red Blood Cell count	Dose reponse of hematocrit was inconsistent and variance could not be modeled
	Renal toxicity	kidney nephritis	Kidney nephritis	Only option

	Developmental toxicity	pup weight gain pup body weight	Pup weight gain	Weight gain differential was a persistent effect
Spinetoram	Hemotoxicity	Bone marrow necrosis macrophage vacuolization hematocrit blood cell counts arteritis	Bone marrow necrosis	Arteritis of limited utility since no animals in the control and lowest dose groups showed any effect, and all in the two highest dose groups had arteritis. Bone marrow necrosis observations had a more gradual increase in frequency. Macrophage vacuolization uncertainty regarding the adverse nature of the effect led to selection of bone marrow necrosis instead.
	Thyroid toxicity	T-4 TSH	T-4	No significant dose response was observed in TSH
	Hepatotoxicity	AST elevation Kupffer cell hyperplasia and vacuolization liver hematopoiesis	AST elevation	AST models were better fit based on qualitative evaluation of curve. AST is also a continuous outcome.
Thiacloprid	Hepatotoxicity	hepatocellular hypertrophy ECOD GST UDP-GLU-T EH N-demethylase O-demethylase CYP450	Hepatocellular hypertrophy	Dose response models of the individual enzyme levels either poorly modeled variance or the dose-response was inconsistent at low levels
	Thyroid toxicity	Thyroid follicular cell hypertrophy	Thyroid follicular cell hypertrophy	Only option
	Developmental toxicity	Auditory startle reflex Pup viability Decreased weight passive avoidance alterations delayed sexual maturation	Startle reflex	Individual pup data was not available for delayed maturation, decreased body weight, passive avoidance. Pup viability decrease was not significant
	Neurotoxicity	Motor activity ptosis tremors ataxia mydriasis fur staining lowered body temperatures	Motor activity	Motor activity was found in both sexes at lower doses than any other endpoint

Table 3.8: Supplemental material for Chapter 3: Selected body section comparisons of data resulting from ½ LOQ substitution vs interpolated values.

				1/2 LOQ method		Interpolation method		
		N	%ND	GM	GSD	GM	GSD	% Difference in GM
Lower Leg	Inner	46	39%	0.022	10.3	0.011	10.3	50%
	Outer	26	38%	0.155	73.4	0.080	72.2	49%
Upper Leg	Inner	53	47%	0.023	8.6	0.009	10.7	63%
	Outer	37	16%	0.599	40.7	0.281	45.1	53%
Chest	Inner	60	28%	0.021	9.7	0.019	11.5	12%
	Outer	54	19%	0.243	31.2	0.211	38.4	13%
Back	Inner	60	35%	0.020	10.1	0.015	11.7	25%
	Outer	54	24%	0.150	37.9	0.138	41.5	8%
Upper Arm	Inner	49	18%	0.071	6.2	0.034	6.8	52%
	Outer	42	14%	0.999	27.3	0.491	28.3	51%
Forearm	Inner	57	21%	0.113	8.8	0.053	8.8	53%
	Outer	56	16%	0.978	27.7	0.477	29.5	51%
Hands	Inner	36	42%	36.142	38.5	31.949	54.0	12%
	Outer	29	0%	-	-	-	-	-
Head & Neck	Inner	18	92%	0.004	6.2	-	-	-
	Outer	31	42%	0.027	17.6	0.027	17.0	0%

Table 4.7: Study MRID and selected toxicological endpoints for each pesticide. RBC = red blood cell

Pesticide	Study MRID	Endpoint Used in BMD Model	Timing of Dose	Class of Outcome	Type
Acetamiprid	462556-19 [124]	Changes in auditory startle	Perinatal	Neurodevelopmental	Continuous
Azinphos methyl	100644 [125]	RBC Cholinesterase	Subchronic (90 day)	Neurotoxicity	Continuous
Emamectin benzoate	428515-04 [86]	Tremors	Acute	Neurotoxicity	Quantal
Methoxyfenozide	446177-28 [126]	RBC count	Subchronic (10 week)	Hemotoxicity	Continuous
Novaluron	456515-03 [127]	RBC count	Subchronic (13 week)	Hemotoxicity	Continuous
Phosmet	446733-01 [128]	RBC Cholinesterase	Acute	Neurotoxicity	Continuous
Phosmet (dermal)	447968-01[129]	RBC Cholinesterase	Acute	Neurotoxicity	Continuous
Spinetoram	465685-01 [130]	Bone marrow necrosis	Subchronic (90 day)	Hemotoxicity	Quantal
Thiacloprid	449277-15 [131]	Hepatocellular hypertrophy	Subchronic inhalation (90 day)	Hepatotoxicity	Quantal

Table 4.2: Selected critical effect size, NOAEL from the investigated study, and Benchmark Dose with 95% Confidence limit for the critical effect size and alternate effect sizes (1 standard deviation for all continuous outcomes, and 10% inhibition for cholinesterase inhibitors), all in mg/kg/day. The EPA-calculated dose for pesticide handlers using open cab airblast methods in pome fruit multiplied by two uncertainty factors of 10 in mg/kg/day is also compared.

Pesticide	Selected CES	NOAEL	10% BMD	10% BMDL	1 SD-based BMD	1 SD-based BMDL	20% BMD	20% BMDL	Dose x 100
Acetamiprid	10%	10	1.74	0.30	44.62	26.74	--	--	0.768
Azinphos methyl	20%	0.15	0.23	0.17	4.42	3.51	0.50	0.35	0.833
Emamectin benzoate	10%	0.075	0.91	0.19	--	--	--	--	0.009
Methoxyfenozide	10%	16.8	27.69	9.56	28.93	10.13	--	--	0.343
Novaluron	10%	4.38	2.00	0.90	7.66	2.92	--	--	0.804
Phosmet	20%	4.5	2.75	0.58	0.16	0.10	4.60	4.53	3.000
Spinetoram	10%	2.7	6.62	3.31	--	--	--	--	0.028
Thiacloprid	10%	1.2	1.40	0.64	--	--	--	--	0.382

Table 4.3: Mean and confidence intervals for parameters generated for the dose-response models selected for each pesticide (the oral dosing models are presented here for phosmet and azinphos methyl)

Pesticide	Model	Variable	Mean	95% CL	
Acetamiprid	Hill	intercept	214.1	163.8	264.4
		maximum change	-101.6	-168.9	-34.3
		power	1	--	--
		dose w/ half-max change	6.5	-8.2	21.2
Azinphos methyl	Exponential	background response	2.0	1.8	2.3
		slope	0.9	0.3	1.4
		asymptote parameter	0.1	-0.01	0.2
Emamectin benzoate	Quantal-linear	background	0	--	--
		slope	0.1	-0.2	0.4
Methoxyfenozide	Exponential	background response	6.5	6.3	6.8
		slope	0.02	-0.002	0.04
		asymptote parameter	0.8	0.8	0.9
Novaluron	Exponential	background response	7.5	7.3	7.7
		slope	0.1	-0.03	0.2
		asymptote parameter	0.9	0.8	1.0
Phosmet	Hill	intercept	3730.7	3624.0	3837.3
		maximum change	-2805.2	-2944.4	-2666.1
		power	18	--	--
		dose w/ half-max change	4.87	4.8	5.0
Spinetoram	Logistic	intercept	-2.72	-5.0	-0.4
		slope	0.16	0.01	0.3
Thiacloprid	Log-logistic	background	0	--	--
		intercept	-2.54	-3.5	-1.6
		slope	1	--	--

Table 4.8: Ratios of points of departure and EPA-derived deterministic doses used in the human health risk assessment for pesticide handlers. Two values are presented for phosmet: oral is calculated using the oral dosing study values compared with doses calculated using an adjustment factor for dermal absorption. The dermal study does not include adjustment for dermal absorption and uses the dermal toxicity testing data.

	$\frac{\text{BMD}}{\text{BMDL}}$	$\frac{\text{BMD}}{\text{NOAEL}}$	$\frac{\text{BMDL}}{\text{NOAEL}}$	$\frac{\text{BMD}}{\text{Dose}}$	$\frac{\text{BMDL}}{\text{Dose}}$	$\frac{\text{NOAEL}}{\text{Dose}}$
Acetamiprid	5.76	0.17	0.03	226	39	1302
Azinphos methyl	1.40	3.32	2.36	60	43	18
Emamectin benzoate	4.83	12.15	2.52	10171	2106	837
Methoxyfenozide	2.90	1.65	0.57	8073	2787	4898
Novaluron	2.22	0.46	0.21	249	112	545
Phosmet						
Oral	1.02	1.53	1.01	153	151	92
Dermal	3.86	0.90	0.23	175	45	270
Spinetoram	2.00	2.45	1.23	23629	11820	9643
Thiacloprid	2.20	1.17	0.53	368	167	314

Table 4.5: Exceedance fractions of probabilistically-estimated doses for each compound and the associated points of departure estimated from the dose-response studies, and the ratio of these exceedance fractions, demonstrating the difference in protective ability of each selected point of departure as a regulatory limit

	Exceedance fractions			Ratio of Exceedance Fractions	
	NOAEL	BMD	BMDL	BMDL/BMD	BMD/NOAEL
Acetamiprid	5.0	24.8	61.2	2.5	5.0
Azinphos methyl	72.2	55.7	63.5	1.1	0.8
Emamectin benzoate	19.6	2.0	9.7	4.8	0.1
Methoxyfenozide	0.005	0.002	0.015	8.4	0.4
Methoxyfenozide (dermal + inhalation routes)	2.7	1.5	4.7	3.1	0.6
Novaluron	5.09	9.3	15.7	1.7	1.8
Phosmet (oral)	8.94	13.5	36.9	2.7	1.5
Phosmet (dermal)	12.62	13.8	34.9	2.5	1.1
Spinetoram	0.6	0.2	0.4	2.7	0.3
Spinetoram (dermal + inhalation routes)	22.6	15.3	20.8	1.4	0.7
Thiacloprid	32.0	30.1	40.2	1.3	0.9

Table 4.6: Selected critical effect size, NOAEL from the investigated study, and Benchmark Dose with 95% Confidence limit for the critical effect size and alternate effect sizes (1 standard deviation for all continuous outcomes, and 10% inhibition for cholinesterase inhibitors), all in mg/kg/day. The EPA-calculated dose for pesticide handlers using open cab airblast methods in pome fruit multiplied by two uncertainty factors of 10 in mg/kg/day is also compared.

Pesticide	Selected CES	NOAEL	10% BMD	10% BMDL	1 SD-based BMD	1 SD-based BMDL	20% BMD	20% BMDL	Dose x 100
Acetamiprid	10%	10	1.74	0.30	44.62	26.74	--	--	0.768
Azinphos methyl	20%	0.15	0.23	0.17	4.42	3.51	0.50	0.35	0.833
Emamectin benzoate	10%	0.075	0.91	0.19	--	--	--	--	0.009
Methoxyfenozide	10%	16.8	27.69	9.56	28.93	10.13	--	--	0.343
Novaluron	10%	4.38	2.00	0.90	7.66	2.92	--	--	0.804
Phosmet	20%	4.5	2.75	0.58	0.16	0.10	4.60	4.53	3.000
Spinetoram	10%	2.7	6.62	3.31	--	--	--	--	0.028
Thiacloprid	10%	1.2	1.40	0.64	--	--	--	--	0.382

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Table 4.7: Fit results and information for continuous endpoints

Compound	Model	Specified Effect	Risk Type	BMD	BMDL	p-value Test 1	p-value Test 2	p-value Test 3	p-value Test 4	AIC	Scaled residual for dose group nearest the BMD	Scaled residual for control group
Acetamiprid	Hill	0.1	Relative deviation	1.735	0.301	0.082	0.322	0.873	0.960	389.3	-0.129	0.008
	Exponential2			9.965	5.860	0.082	0.322	0.873	0.341	389.4	-0.724	0.786
	Exponential3			9.965	5.860	0.082	0.322	0.873	0.341	389.4	-0.724	0.786
	Exponential4			2.363	0.575	0.082	0.322	0.873	0.804	389.3	-0.260	0.102
	Exponential5			2.363	0.575	0.082	0.322	0.873	0.804	389.3	-0.260	0.102
	Linear			12.289	8.347	0.082	0.322	0.873	0.291	389.8	-0.786	0.871
	Polynomial			12.289	8.347	0.082	0.322	0.873	0.291	389.8	-0.786	0.871
	Power			12.289	8.347	0.082	0.322	0.873	0.291	389.8	-0.786	0.871
Azinphos methyl	Hill	0.2	Relative deviation	0.674537	0.273635	<.0001	0.4671	0.3746	NA	-53.6	-0.000423	1.17
	Exponential2			0.485982	0.38887	< 0.0001	0.4671	0.3746	0.8392	-60.4	-0.01687	0.3692
	Exponential3			59.2109		< 0.0001	0.4671	0.3746	< 0.0001	-11.1	-3.198	1.824
	Exponential4			0.468416	0.345456	< 0.0001	0.4671	0.3746	0.5882	-58.5	0.1456	0.2833
	Exponential5			0.468416	0.345456	< 0.0001	0.4671	0.3746	0.5882	-58.5	0.1456	0.2833
	Linear			0.926849	0.808682	<.0001	0.4671	0.3746	0.03643	-54.2	-1.74	1.4
	Polynomial			0.926849	0.808682	<.0001	0.4671	0.3746	0.03643	-54.2	-1.74	1.4
	Power			0.926849	0.808682	<.0001	0.4671	0.3746	0.03643	-54.2	-1.74	1.4
Methoxyfenozide	Hill	0.1	Relative deviation	87.819		0.001306	0.3105	0.1972	0.1378	-10.01	-0.0155	0.353
	Exponential2			796.353	442.99	0.001306	0.3105	0.1972	0.005095	-3.41	0.1533	1.024
	Exponential3			796.352	442.99	0.001306	0.3105	0.1972	0.005095	-3.41	0.1533	1.024
	Exponential4			28.9341	10.1306	0.001306	0.3105	0.1972	0.1649	-10.6	1.303	0.05501
	Exponential5			38.1091	10.1441	0.001306	0.3105	0.1972	0.1356	-9.98	0.7769	0.3532

	Linear			1005.03	658.856	0.001306	0.3105	0.1972	0.004971	-3.36	0.138	1.03
	Polynomial			1005.03	658.856	0.001306	0.3105	0.1972	0.004971	-3.36	0.138	1.03
	Power			1005.03	658.856	0.001306	0.3105	0.1972	0.004971	-3.36	0.138	1.03
Novaluron	Hill	0.1	Relative deviation	44.2534		0.001483	0.3181	0.2707	0.4768	-41.88	-0.201	-0.107
	Exponential2			36.6296	26.3435	0.001483	0.3181	0.2707	0.4619	-43.81	0.5171	0.7673
	Exponential3			36.6296	26.3435	0.001483	0.3181	0.2707	0.4619	-43.81	0.5171	0.7673
	Exponential4			44.9443	17.1943	0.001483	0.3181	0.2707	0.7553	-43.82	-0.1604	-0.1007
	Exponential5			44.9443	15.7542	0.001483	0.3181	0.2707	0.7553	-43.82	-0.1604	-0.1007
	Linear			36.8442	26.9298	0.001483	0.3181	0.2707	0.4315	-43.63	0.514	0.82
	Polynomial			36.8442	26.9298	0.001483	0.3181	0.2707	0.4315	-43.63	0.514	0.82
	Power			36.8442	26.9298	0.001483	0.3181	0.2707	0.4315	-43.63	0.514	0.82
Phosmet	Hill	0.2	Relative deviation	4.59891	4.52582	<.0001	<.0001	<.0001	0.5139	1544.7	-0.23	-0.451
	Exponential2			3.9221	3.58418	< 0.0001	< 0.0001	< 0.0001	< 0.0001	1599.0	0.6277	-3.787
	Exponential3			6.67631	5.60923	< 0.0001	< 0.0001	< 0.0001	< 0.0001	1569.7	-2.38	-1.046
	Exponential4			3.9221	3.58418	< 0.0001	< 0.0001	< 0.0001	< 0.0001	1599.0	0.6277	-3.787
	Exponential5			4.5755	4.51643	< 0.0001	< 0.0001	< 0.0001	N/A	1553.0	-0.0005	-0.6
	Linear			5.92562	5.77355	<.0001	<.0001	<.0001	<.0001	1561.5	-1.49	-1.98
	Polynomial			7.76135	5.86397	<.0001	<.0001	<.0001	<.0001	1561.2	-2.46	-0.86
	Power			7.60666	6.04661	<.0001	<.0001	<.0001	<.0001	1560.2	-2.48	-0.733
Phosmet (dermal)	Hill	0.2	Relative deviation	37.3124		0.1147	0.7014	0.7162	NA	-68.08	0.0294	-0.106
	Exponential2			57.1192	35.7982	0.1147	0.7014	0.7162	0.5937	-71.03	0.2606	0.3879
	Exponential3			57.1193	35.7982	0.1147	0.7014	0.7162	0.5937	-71.03	0.2606	0.3879
	Exponential4			45.5845	15.4466	0.1147	0.7014	0.7162	0.6557	-69.88	-0.04784	-0.1582
	Exponential5			32.769	16.0394	0.1147	0.7014	0.7162	N/A	-68.08	0.02941	-0.1061
	Linear			58.7912	39.1498	0.1147	0.7014	0.7162	0.5409	-70.8534	0.242	0.478
	Polynomial			58.7913	39.1498	0.1147	0.7014	0.7162	0.5409	-70.8534	0.242	0.478
	Power			58.7913	39.1498	0.1147	0.7014	0.7162	0.5409	-70.8534	0.242	0.478

Table 4.8: Fit results and information for quantal endpoints

Compound	Model	Specified Effect	Risk Type	Chi-square	DF	Specified Effect	Risk Type	BMD	BMDL	P-value	AIC	Scaled residual for dose group nearest the BMD	Scaled residual for control group
Emamectin benzoate	Gamma	0.1	Relative deviation	0.47	3	0.1	Extra risk	0.815361	0.185655	0.925	9.89146	-0.094	0
	Logistic			0.73	3	0.1	Extra risk	0.464364	0.236773	0.8653	10.0738	-0.077	-0.204
	LogLogistic			0.47	3	0.1	Extra risk	0.834977	0.184284	0.9255	9.89084	-0.093	0
	LogProbit			0.92	3	0.1	Extra risk	0.536346	0.179528	0.82	10.1647	-0.113	-0.238
	Probit			0.72	3	0.1	Extra risk	0.488477	0.225902	0.868	10.0581	-0.091	-0.193
	Weibull			0.47	3	0.1	Extra risk	0.818901	0.186618	0.9253	9.89166	-0.092	0
	Quantal-Linear			0.45	4	0.1	Extra risk	0.911319	0.188685	0.978	7.89297	-0.071	0
Spinetoram	Gamma	0.1	Relative deviation	6.91	3	0.1	Extra risk	2.99629	1.84813	0.0747	33.9807	-0.499	0
	Logistic			9.86	2	0.1	Extra risk	10.7616	6.68818	0.0072	41.164	2.564	-1.255
	LogLogistic			2.34	3	0.1	Extra risk	1.40433	0.638499	0.5048	30.8165	-0.744	0
	LogProbit			9.49	3	0.1	Extra risk	3.66405	2.2077	0.0235	34.9573	1.883	0
	Probit			9.83	2	0.1	Extra risk	10.1096	6.6502	0.0073	40.9651	2.588	-1.221

	Weibull			6.91	3	0.1	Extra risk	2.99629	1.84813	0.0747	33.9807	-0.499	0
	Quantal-Linear			6.91	3	0.1	Extra risk	2.99629	1.84813	0.0747	33.9807	-0.499	0
Thiacloprid	Gamma	0.1	Relative deviation	6.91	3	0.1	Extra risk	2.99629	1.84813	0.0747	33.9807	-0.499	0
	Logistic			9.86	2	0.1	Extra risk	10.7616	6.68818	0.0072	41.164	2.564	-1.255
	LogLogistic			2.34	3	0.1	Extra risk	1.40433	0.638499	0.5048	30.8165	-0.744	0
	LogProbit			9.49	3	0.1	Extra risk	3.66405	2.2077	0.0235	34.9573	1.883	0
	Probit			9.83	2	0.1	Extra risk	10.1096	6.6502	0.0073	40.9651	2.588	-1.221
	Weibull			6.91	3	0.1	Extra risk	2.99629	1.84813	0.0747	33.9807	-0.499	0
	Quantal-Linear			6.91	3	0.1	Extra risk	2.99629	1.84813	0.0747	33.9807	-0.499	0

Table 5.1: Health impact categories and descriptions derived from human health risk assessments completed by the EPA for the ten compounds of interest in this study, as presented and described to crop consultants for valuation on a scale of 1-10.

Health Impact	*Descriptions*
Acute Neurotoxicity	Non-permanent effects such as tremors, difficulty walking or moving normally, excess perspiration and salivation. etc.
Liver impacts	For example, enlargement of your liver or liver cells, or a higher workload being placed on your liver.
Thyroid impacts	For example, enlargement of your liver or liver cells, or a higher workload being placed on your liver which may not have any symptoms
Blood diseases	For example, damage to cells that produce thyroid hormones which may not have any symptoms
Reproductive impacts	Lowered fertility
Developmental impacts	Birth defects or delays in fetal or childhood development
Eye Irritation	Temporary eye irritation which might be severe enough to require medical assistance
Skin Irritation	Temporary skin irritation which might be severe enough to require medical assistance
Skin Sensitization	An allergy to the pesticide after the first exposure which may result in skin irritation or rashes

Table 5.2: Probability of using a pesticide each number of times, given that the pesticide was used in a given growing season, reported from the Grower Surveys performed by the WSU IPM Transition Project. These conditional probabilities were combined with probability of selecting a pesticide once to account for likelihood of re-use being higher than individual selection.

Pesticide	Year	1	2	3	4
Acetamiprid	2008	0.686	0.275	0.035	0.004
	2010	0.68	0.285	0.027	0
Azinphos methyl	2008	0.179	0.368	0.358	0.095
	2010	0.34	0.49	0.144	0.026
Chlorantraniliprole	2008	--	--	--	--
	2010	0.663	0.312	0.019	0
Emamectin benzoate	2008	--	--	--	--
	2010	0.827	0.135	0	0
Methoxyfenozide	2008	0.892	0.088	0.01	0.01
	2010	0.898	0.084	0.048	0
Novaluron	2008	--	--	--	--
	2010	0.831	0.143	0.013	0
Phosmet	2008	0.698	0.25	0.042	0.01
	2010	0.598	0.309	0.072	0
Pyriproxyfen	2008	0.827	0.135	0	0
	2010	0.831	0.143	0	0
Spinetoram	2008	--	--	--	--
	2010	0.71	0.254	0.033	0
Thiacloprid	2008	--	--	--	--
	2010	0.824	0.164	0.014	0

Table 5.3: Probability of selecting each pesticide for a first application for four scenarios – the ovicidal treatment and first larvicidal treatment of each generation, for the years 2005 and 2011.

	1st generation ovicide				1st generation larvicide				2nd generation ovicide				2nd generation larvicide			
	2005		2011		2005		2011		2005		2011		2005		2011	
	Mean %	(SD)	Mean %	(SD)	Mean %	(SD)	Mean %	(SD)	Mean %	(SD)	Mean %	(SD)	Mean %	(SD)	Mean %	(SD)
Acetamiprid	16.2	(7)	8.3	(4.7)	25.3	(9)	8.1	(2.8)	24.9	(9)	8.5	(3.0)	24.9	(9)	8.3	(2.9)
Azinphos methyl	6.0	(5)	7.3	(3.5)	11.2	(8)	8.2	(2.4)	10.4	(7)	7.7	(2.3)	10.4	(7)	7.6	(2.4)
Chlorantraniliprole	--	--	29.9	(10.1)	--	--	26.2	(10.0)	--	--	24.5	(9.8)	--	--	24.3	(10.4)
Emamectin benzoate	--	--	0.9	(0.4)	--	--	6.2	(3.3)	--	--	1.1	(0.7)	--	--	6.8	(3.5)
Methoxyfenozide	38.6	(11)	8.6	(2.5)	31.8	(9)	12.6	(3.0)	32.4	(9)	14.1	(3.6)	32.4	(9)	13.7	(3.1)
Novaluron	--	--	12.0	(3.1)	--	--	0.9	(0.2)	--	--	7.7	(2.0)	--	--	0.8	(0.3)
Phosmet	8.6	(6)	6.5	(4.0)	15.5	(5)	8.2	(3.5)	15.9	(6)	9.2	(4.5)	15.9	(6)	9.0	(4.4)
Pyriproxyfen	30.6	(6)	7.6	(2.3)	16.1	(4)	8.9	(3.7)	16.4	(4)	10.0	(4.5)	16.4	(4)	9.7	(4.1)
Spinetoram	--	--	12.8	(3.9)	--	--	11.3	(6.7)	--	--	10.7	(7.2)	--	--	10.3	(6.4)
Thiacloprid	--	--	6.1	(3.3)	--	--	9.3	(2.6)	--	--	6.5	(1.8)	--	--	9.5	(2.7)

*. *Incomplete values represent pesticides not used in that year based on registration dates of that year or later. These probabilities were derived by taking the anti-log of each divided by the sum anti-log of the preference ranks generated by the pesticide selection PROMETHEE models.*

Table 5.4: Summarized individual likelihood of selection for the six theoretical codling moth sprays per growing season, based on models for each participating consultant (n=6), and extrapolation to percent of acres in Washington each compound was applied to based on the acreage covered by the participants' recommendations.

	Summary of individual likelihood of selection				% Acres applied to			
	2005		2011		2005		2011	
	Mean %	(SD)	Mean %	(SD)	Predicted*	NASS**	Predicted*	NASS**
Acetamiprid	25.0%	(0)	12.7%	(4.9)	26.5	25.00	13.98	14.06
Azinphos methyl	10.1%	(0)	10.9%	(6.2)	7.9	78.00	11.63	22.23
Chlorantraniliprole	--	--	25.8%	(8.8)	--	--	22.89	12.95
Emamectin benzoate	--	--	1.9%	(0.8)	--	--	1.79	9.78
Methoxyfenozide	51.7%	(0)	8.5%	(2.5)	52.0	28.18	8.84	20.38
Novaluron	--	--	12.3%	(3.3)	--	--	11.38	2.28
Phosmet	12.5%	(0)	8.0%	(4.4)	11.6	15.00	10.17	2.20
Pyriproxyfen	35.6%	(0)	8.6%	(3.0)	36.7	4.00	8.64	6.47
Spinetoram	--	--	18.5%	(4.9)	--	--	16.31	25.41
Thiacloprid	--	--	8.8%	(4.4)	--	--	10.41	47.46

** Calculated as the percent likelihood of selection multiplied by the acres covered by the individuals' recommendations for conventional orchards as reported in interview.*

***These percentages of acres are calculated as the percentages of bearing non-organic orchards in Washington state*

Table 5.5: Pesticide health impacts identified through screening the EPA Health impact assessments, and description of health impact and dosing regimen for the relevant study, identified by MRID (Master Record Identification Number) assigned by the EPA.

Pesticide	Study MRID	Occupational NOAEL	Endpoint Used in BMD Model	Timing of Dose	Dose duration	Class of Outcome	Type
Acetamiprid	462556-19	Y	Changes in auditory startle (PND 20)	During gestation and through weaning	6 weeks (dam)	Neurodevelopmental	Continuous
	449884-30	N	Viability index	Perinatal/gestation	3 weeks (dam)	Developmental	Quantal
	446518-43	N	Hepatocellular hypertrophy	Subchronic	13 weeks	Hepatotoxicity	Quantal
	446518-42	N	Locomotor activity	Acute	single dose	Neurotoxicity	Continuous
Azinphos methyl	100644	Y	RBC Cholinesterase	Subchronic	13 weeks	Neurotoxicity	Continuous
	407139-01	N	Preimplantation loss	During gestation and through weaning	6 weeks (dam)	Developmental toxicity	Quantal
Chlorantraniliprole	489797-20	N	Hepatocellular hypertrophy	Chronic	18 months	Hepatotoxicity	Quantal
Emamectin benzoate	428515-04	Y	Tremors	Acute	14 days	Neurotoxicity	Quantal
	428515-11	N	Fertility index (female)	Perinatal/gestation	3 weeks	Reproductive toxicity	Continuous
	428515-08	N	Motor activity PND 17	During gestation and through weaning	6 weeks (dam)	Developmental toxicity	Continuous
Methoxyfenozide	446177-28	Y	RBC count	Subchronic	10 weeks	Hemotoxicity	Continuous
	446178-02	N	Hindlimb grip	Acute	single dose	Neurotoxicity	Continuous
	446177-27	N	Hepatocellular hypertrophy	Subchronic	16 weeks	Hepatotoxicity	Quantal
Novaluron	456515-03	Y	RBC count	Subchronic	13 weeks	Hemotoxicity	Continuous
	450826-01	N	Respiration rate	Acute	single dose	Neurotoxicity	Continuous
	456515-05	N	Epididymal sperm count (F1)	During gestation and through weaning	6 weeks (dam)	Reproductive toxicity	Continuous
Phosmet	446733-01	Y	RBC Cholinesterase	Acute	single dose	Neurotoxicity	Continuous

	415200-01	N	Fertility index	Perinatal/gestation	3 weeks	Reproductive toxicity	Quantal
Pyriproxyfen	432105-04	N	Cholesterol level	Subchronic	13 weeks	Hepatotoxicity	Continuous
	413217-16	N	Red Blood Cell count	Subchronic	14 weeks	Hemotoxicity	Continuous
	421783-13	N	Kidney nephritis	Pre-natal to adulthood	20 weeks	Renal toxicity	Quantal
	421783-13	N	Pup weight gain	During gestation and through weaning	6 weeks (dam)	Developmental toxicity	Continuous
Spinetoram	465685-01	Y	Bone marrow necrosis	Subchronic	13 weeks	Hemotoxicity	Quantal
	468875-01	N	T-4	Subchronic	16 weeks	Thyroid toxicity	Continuous
	465685-01	N	AST elevation	Subchronic	13 weeks	Hepatotoxicity	Continuous
Thiacloprid	449277-15	Y	Hepatocellular hypertrophy	Subchronic inhalation	13 weeks	Hepatotoxicity	Quantal
	449277-02	N	Thyroid follicular cell hypertrophy	Subchronic	16 weeks	Thyroid toxicity	Quantal
	455166-01	N	Startle reflex	During gestation and through weaning	6 weeks (dam)	Developmental toxicity	Continuous
	449277-03/4	N	Motor activity	Acute	single dose	Neurotoxicity	Continuous

Table 5.6: Exceedance fraction of the probabilistic dose estimate for safety factor (100) adjusted limits derived from the toxicological studies for each pesticide and health impact category. The BMD fraction was used in the health impact tradeoff models.

Pesticide	Category	Exceedance fractions		
		NOAEL	BMD	BMDL
Acetamiprid	Neurodevelopmental	5.0	24.8	61.2
	Developmental	2.48	0.6	0.9
	Hepatotoxicity	7.29	0.7	3.3
	Neurotoxicity	5.0	5.1	63.7
Azinphos methyl	Neurotoxicity	63.9	55.7	61.8
	Developmental toxicity	10.5	65.2	100.0
Chlorantraniliprole	Hepatotoxicity	4.01	6.08	8.6
Emamectin benzoate	Neurotoxicity	8.4	2.0	3.4
	Reproductive toxicity	0.87	0.1	0.5
	Developmental toxicity	6.47	2.2	5.8
Methoxyfenozide	Hemotoxicity	2.7	1.5	4.7
	Neurotoxicity	0.006	0.01	0.1
	Hepatotoxicity	0.105	0.1	0.2
Novaluron	Hemotoxicity	5.09	9.3	15.7
	Neurotoxicity	0.0149	0.0008	0.01
	Reproductive toxicity	0.0037	0.07	0.2
Phosmet	Neurotoxicity	8.94	13.5	36.9
	Reproductive toxicity	21.13	24.46	98.2
Pyriproxyfen	Hepatotoxicity	0.145	0.911	1.4
	Hemotoxicity	0.7	2.15	4.1
	Renal toxicity	0.17	0.072	0.4
	Developmental toxicity	0.145	0.02	0.04
Spinetoram	Hemotoxicity	22.6	15.3	20.8
	Thyroid toxicity	4	31.32	90.5
	Hepatotoxicity	12.6	25.56	40.9
Thiacloprid	Hepatotoxicity	32.0	30.1	40.2
	Thyroid toxicity	12.2	7.01	9.8
	Developmental toxicity	17.9	19.01	100.0
	Neurotoxicity	21.2	11.85	20.8

Table 5.7: Extrapolated probability of health impacts among pesticide handlers applying six sprays for codling moth control in a single growing season, based on model predicted uses and NASS reported uses for the years 2005 and 2011.

Pesticide	Category	Model Result		NASS data	
		2005	2011	2005	2011
Acetamiprid	Developmental	6.2%	3.1%	6.2%	3.5%
	Hepatotoxicity	0.2%	0.1%	0.2%	0.1%
	Neurotoxicity	1.3%	0.6%	1.3%	0.7%
Azinphos methyl	Neurotoxicity	5.6%	6.1%	43.4%	12.4%
	Developmental toxicity	6.6%	7.1%	50.9%	14.5%
Chlorantraniliprole	Hepatotoxicity	--	1.6%	--	0.8%
Emamectin benzoate	Neurotoxicity	--	0.0%	--	0.2%
	Reproductive toxicity	--	0.0%	--	0.0%
	Developmental toxicity	--	0.0%	--	0.2%
Methoxyfenozide	Hemotoxicity	0.8%	0.1%	0.4%	0.3%
	Neurotoxicity	0.0%	0.0%	0.0%	0.0%
	Hepatotoxicity	0.1%	0.0%	0.0%	0.0%
Novaluron	Hemotoxicity	--	0.0%	--	0.0%
	Neurotoxicity	--	0.0%	--	0.0%
	Reproductive toxicity	--	0.0%	--	0.0%
Phosmet	Neurotoxicity	5.6%	1.1%	43.4%	0.3%
	Reproductive toxicity	3.1%	2.0%	3.7%	0.5%
Pyriproxyfen	Hepatotoxicity	0.3%	0.8%	0.0%	0.1%
	Hemotoxicity	0.8%	0.0%	0.1%	0.0%
	Renal toxicity	0.0%	0.0%	0.0%	0.0%
	Developmental toxicity	0.0%	0.3%	0.0%	0.0%
Spinetoram	Hemotoxicity	--	2.8%	--	3.9%
	Thyroid toxicity	--	5.8%	--	8.0%
	Hepatotoxicity	--	4.7%	--	6.5%
Thiacloprid	Hepatotoxicity	--	2.6%	--	14.3%
	Thyroid toxicity	--	0.6%	--	3.3%
	Developmental toxicity	--	1.7%	--	9.0%
	Neurotoxicity	--	1.0%	--	5.6%
All*	Neurotoxicity	6.9%	2.8%	44.7%	6.8%
	Developmental	12.8%	12.3%	57.1%	27.3%
	Hepatotoxicity	0.6%	5.1%	0.2%	15.3%
	Hemotoxicity	1.5%	3.0%	0.5%	4.2%
	Thyroid toxicity	0.0%	0.6%	0.0%	3.3%
	Reproductive toxicity	3.1%	2.0%	3.7%	0.6%
	Renal toxicity	0.0%	0.0%	0.0%	0.0%

**Represents the sum of probabilities for each health impact; this result is less meaningful than a true cumulative risk assessment given the lack of similar mechanisms of action. The impacts may not be truly additive, but data on this question is lacking.*

PART 7. FIGURES

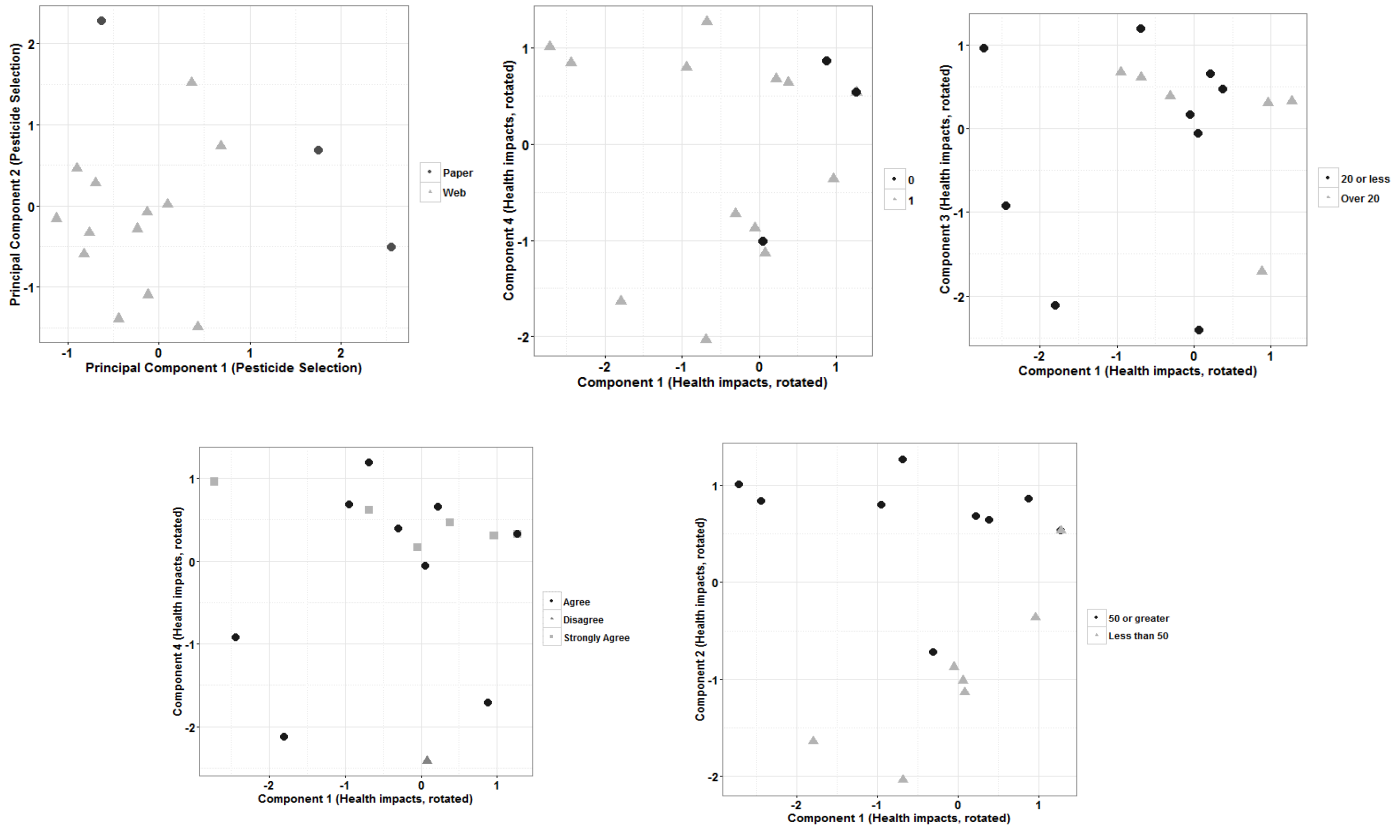

Figure 2.1: Clustering in participant scores for principal components: 1a) Components 1 and 2 derived from pesticide selection criteria ranks, shown with the mode of survey participation (online vs web) 2a) Rotated health impact components 1 and 4 with pesticide applicator occupational history 3a) Rotated health impact components 1 and 3 with years' experience as a crop consultant categorized as greater than 20 or less than/equal to 20 4a) Rotated health impact components 1 and 4 with agreement or disagreement with the statement: "It's important to avoid products that may cause chronic toxicity to orchard workers." 5a) Rotated health impact components 1 and 2 with ages dichotomized into 50 years or greater, or less than 50 years.

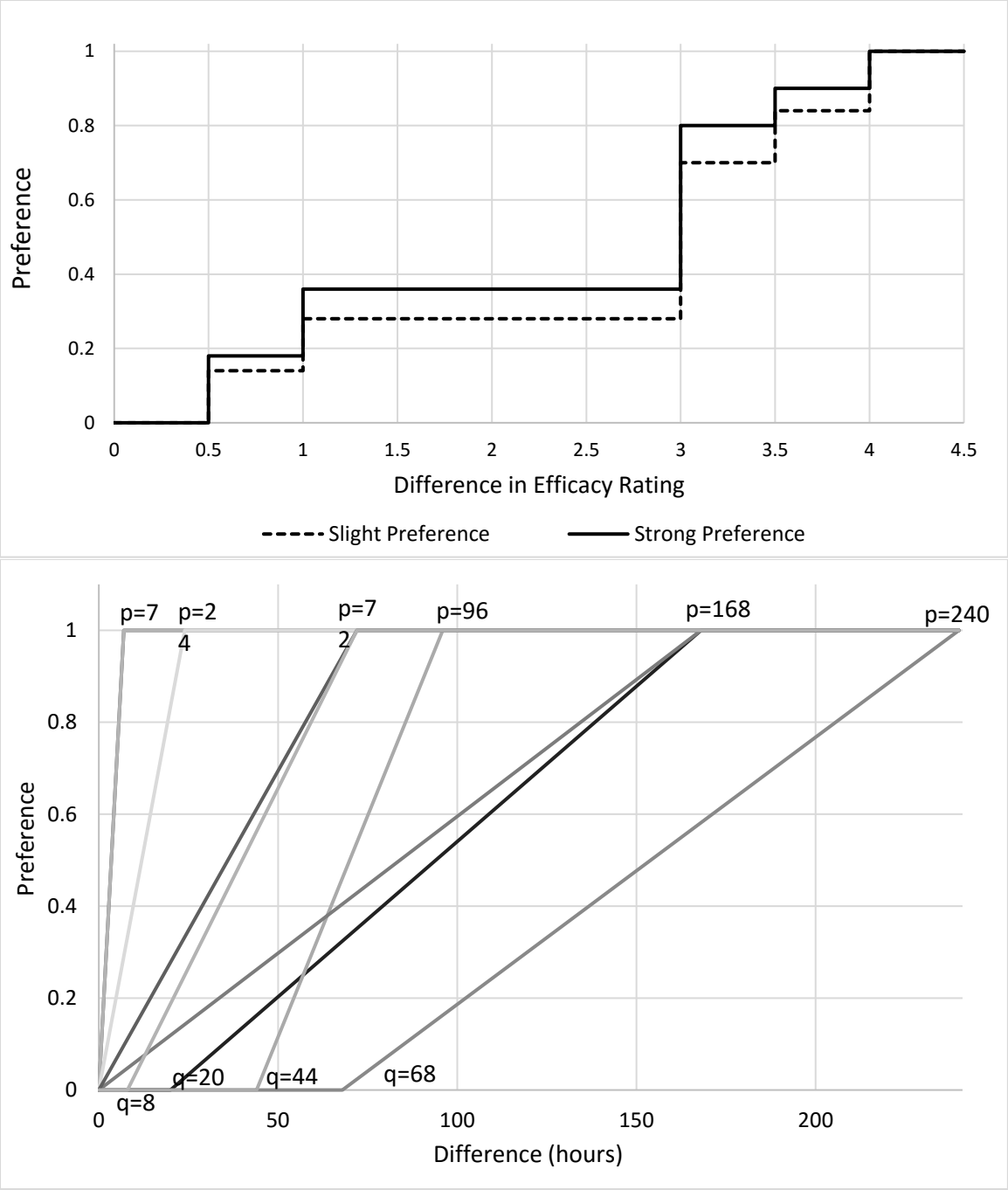

Figure 2.2: Example step and linear preference functions for pesticide selection criteria: 2a) Efficacy step function for participants reporting slight and strong preference for higher levels of efficacy as listed in the WSU Crop Protection Guide 3a) Linear preference functions for re-entry interval showing indifference thresholds (q) and preference thresholds (p) reported by participants.

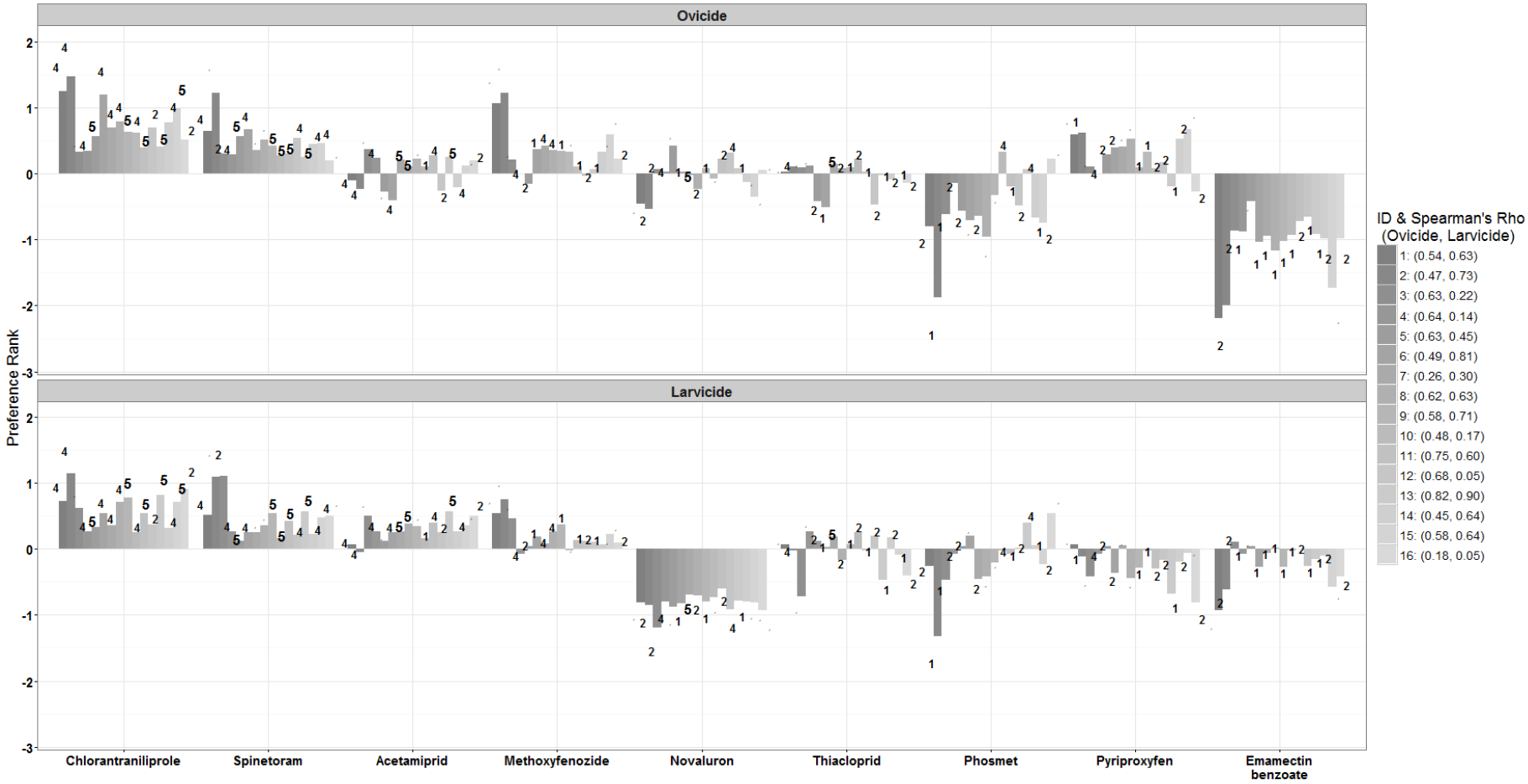

Figure 2.3: Preference Ranks output for each compound for a model constructed for each individual participant, and the Spearman's Rho showing correlation of the ranks of the preference model output with the ranks of the frequency of recommendation for each compound as reported in the web survey. Numbers with the bars indicate the frequency of recommendation in a growing season, where "5" = Almost Always, "4"=Usually, "2"=Rarely, and "1"=Never. Models were completed separately for ovicide and larvicide selection, assuming that ovicide application would occur during or immediately following bloom.

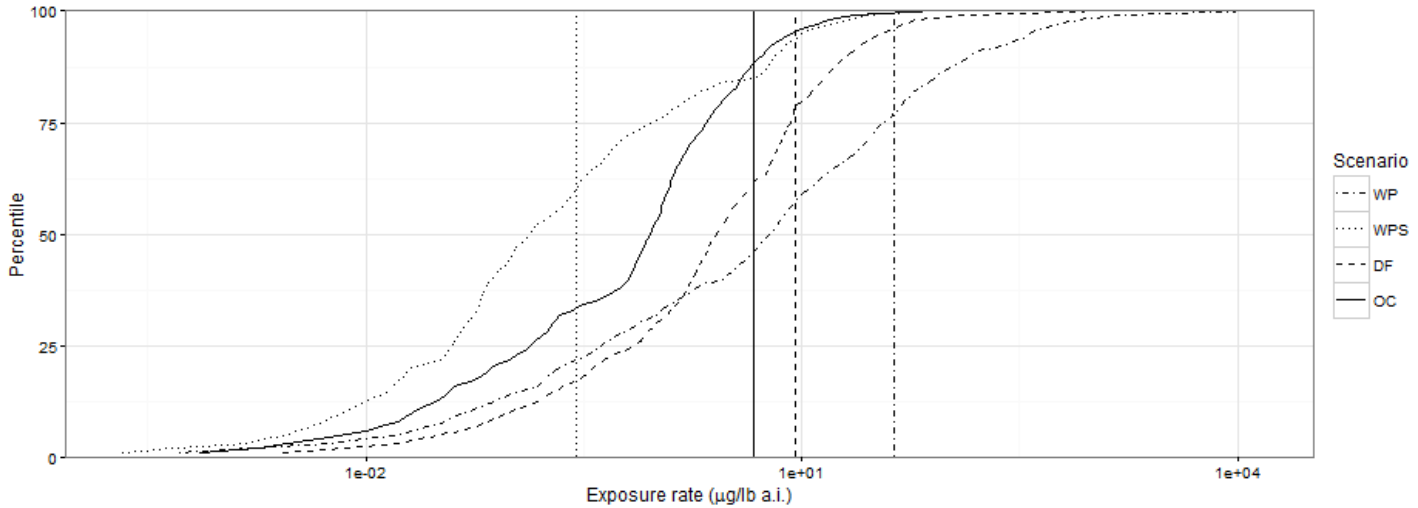

Figure 3.1: Inhalation exposure rate distributions for each pesticide handling scenario: wettable powder mixing and loading (WP), wettable powder with solupack mixing and loading (WPS), dry flowable mixing and loading (DF), and open cab application (OC). Vertical lines represent the deterministic exposure rate developed from the same data.

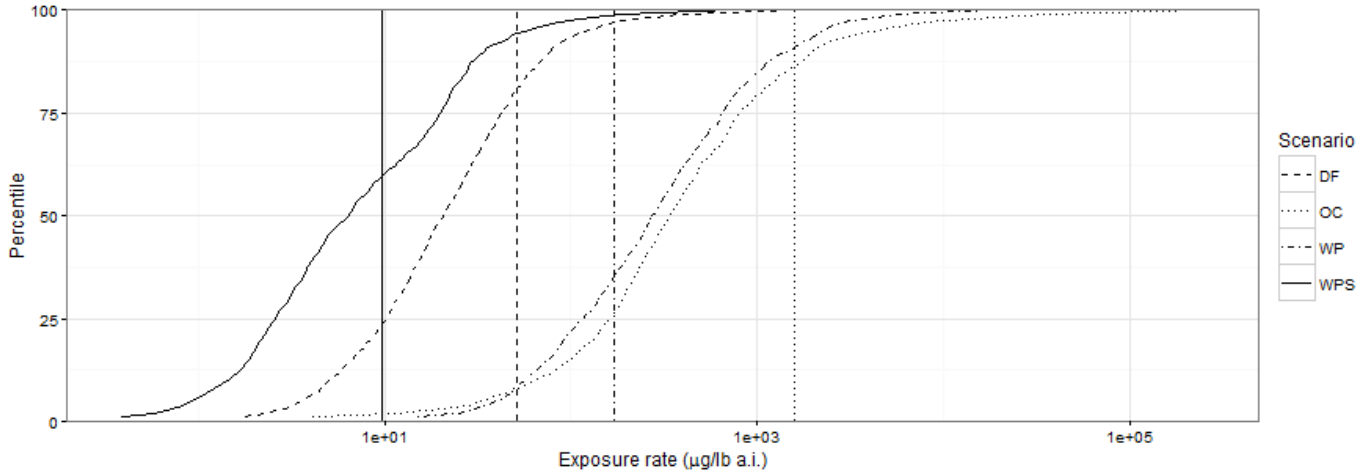

Figure 3.2: Dermal exposure rate distributions for each pesticide handling scenario: wettable powder mixing and loading (WP), wettable powder with solupack mixing and loading (WPS), dry flowable mixing and loading (DF), and open cab application (OC). Vertical lines represent the deterministic exposure rate developed from the same data.

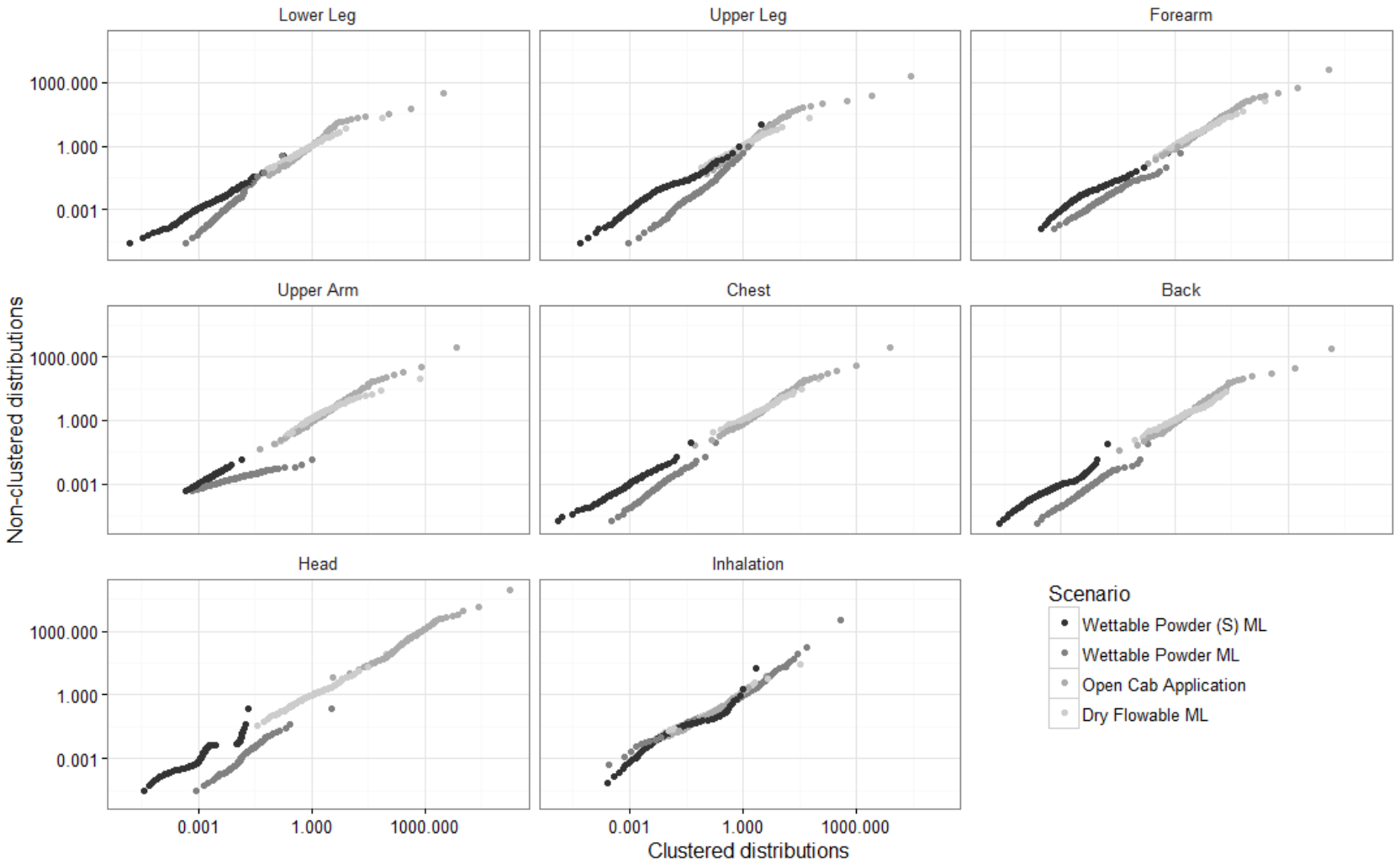

Figure 3.3: Quantile-quantile plots of exposure rate distributions by body area and exposure scenario illustrating the agreement between the clustered and non-clustered distributions.

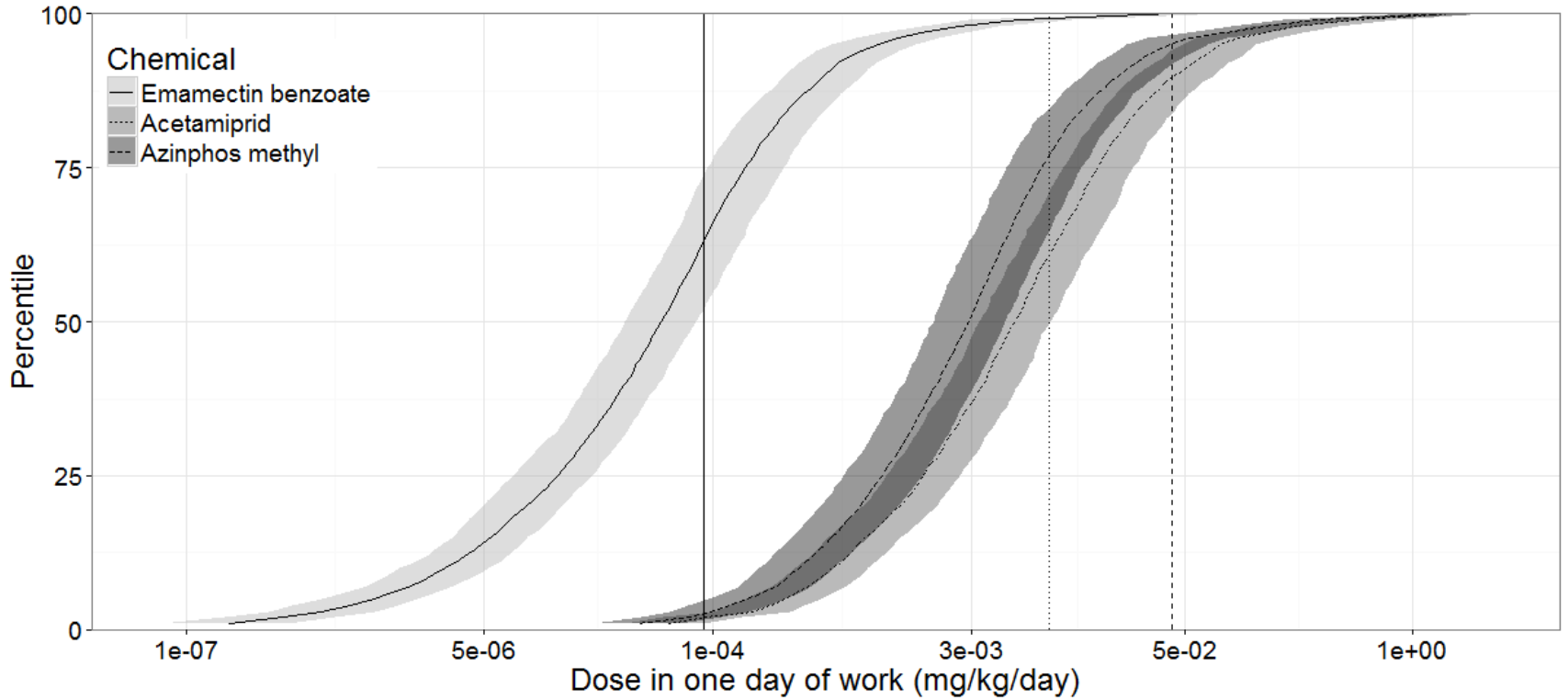

Figure 3.4: Probabilistic dose estimation for one day's dose following mixing and loading and application for each pesticide. The vertical lines represent the dose used in the human health risk assessment.

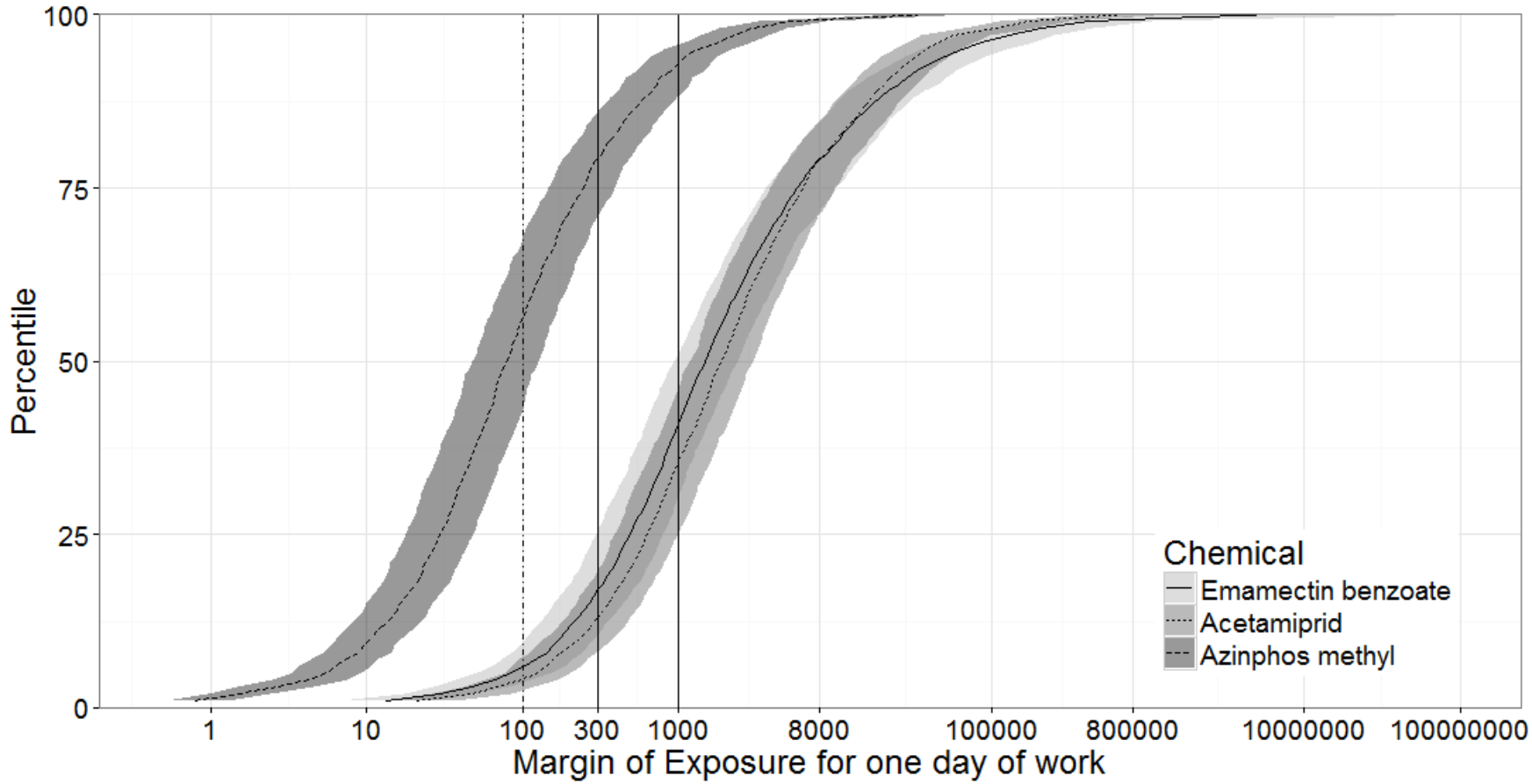

Figure 3.5 Probabilistic margin of exposure estimations for one day's dose following mixing and loading and application for each pesticide. The Vertical lines represent the level of concern used in the human health risk assessment: 100 for azinphos methyl and for Acetamiprid, and 300 for Emamectin benzoate short-term exposures, 1000 for intermediate exposures.

Supplemental material

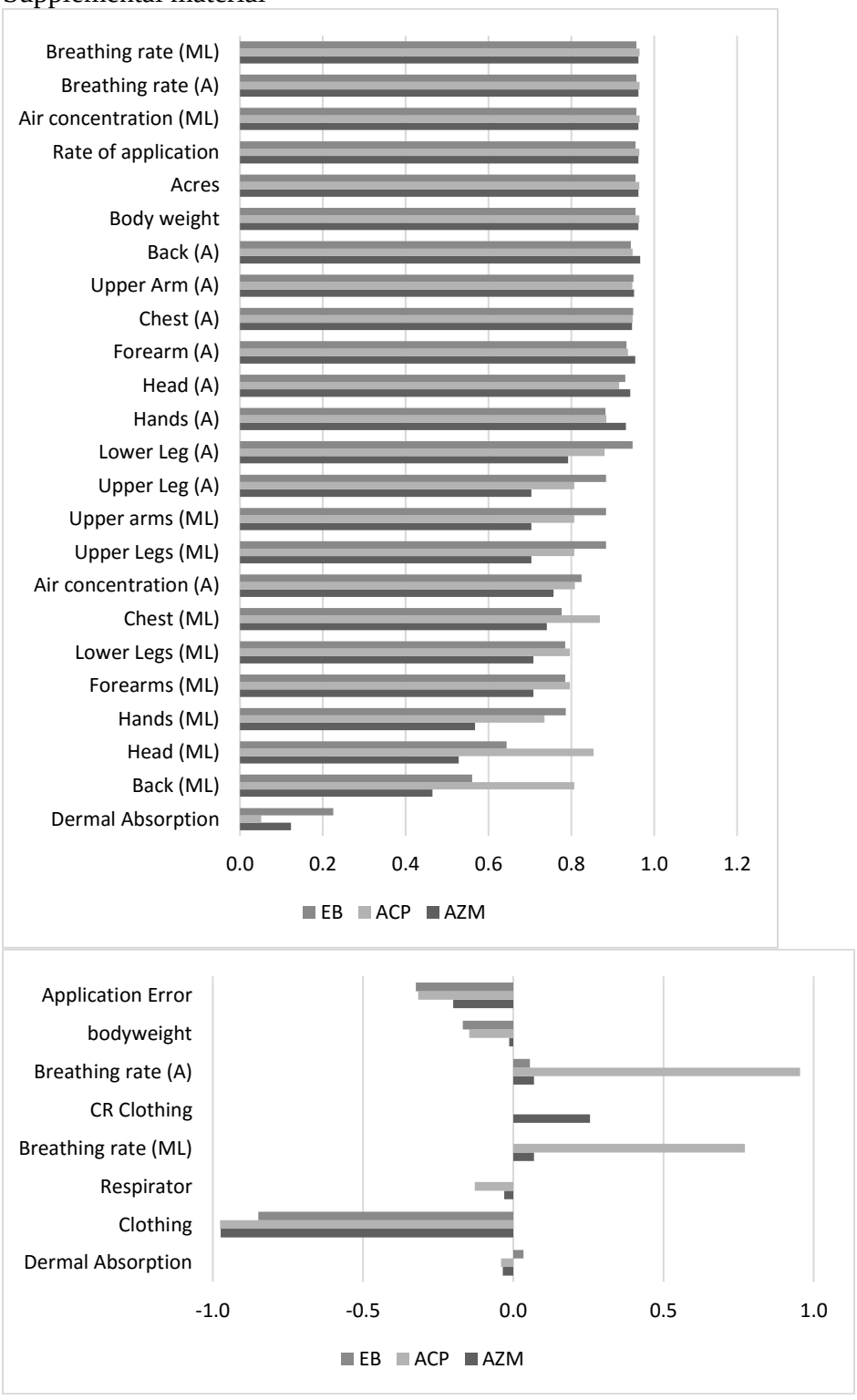

Figure 3.2: Spearman's Rho for variability and uncertainty with output of montecarlo simulation.

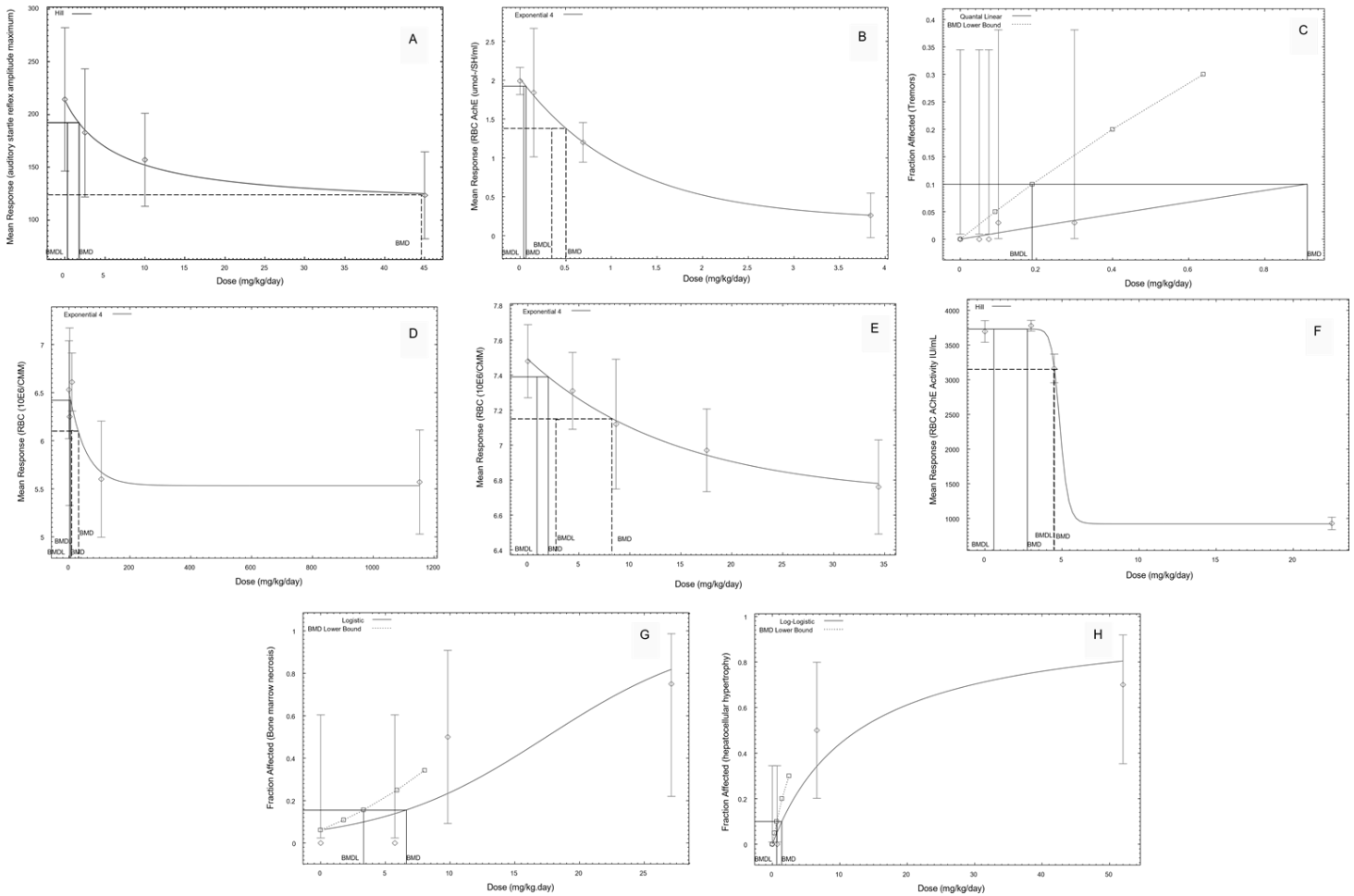

Figure 4.3: Graphs of dose-response models for the selected outcome for each pesticide. The dashed line represents the benchmark dose and confidence interval associated with an alternative critical effect size of 1 standard deviation from the control. The solid line benchmark dose is associated with the selected critical effect size listed in table 2 A) Hill model for acetamiprid-induced decreased maximum amplitude of auditory startle B) Exponential model of erythrocyte acetylcholinesterase activity and oral dose of azinphos methyl C) Quantal-linear model of emamectin benzoate-induced tremors D) Exponential model of decreased red blood cell count associated with methoxyfenozide dosing E)) Exponential model of decreased red blood cell count associated with Novaluron dosing F) Exponential model of erythrocyte acetylcholinesterase activity and oral dose of phosmet G) Logistic model of fraction of population with bone-marrow necrosis induced with spinetoram dosing H) Log-logistic model of hepatocellular hypertrophy associated with thiacloprid dosing

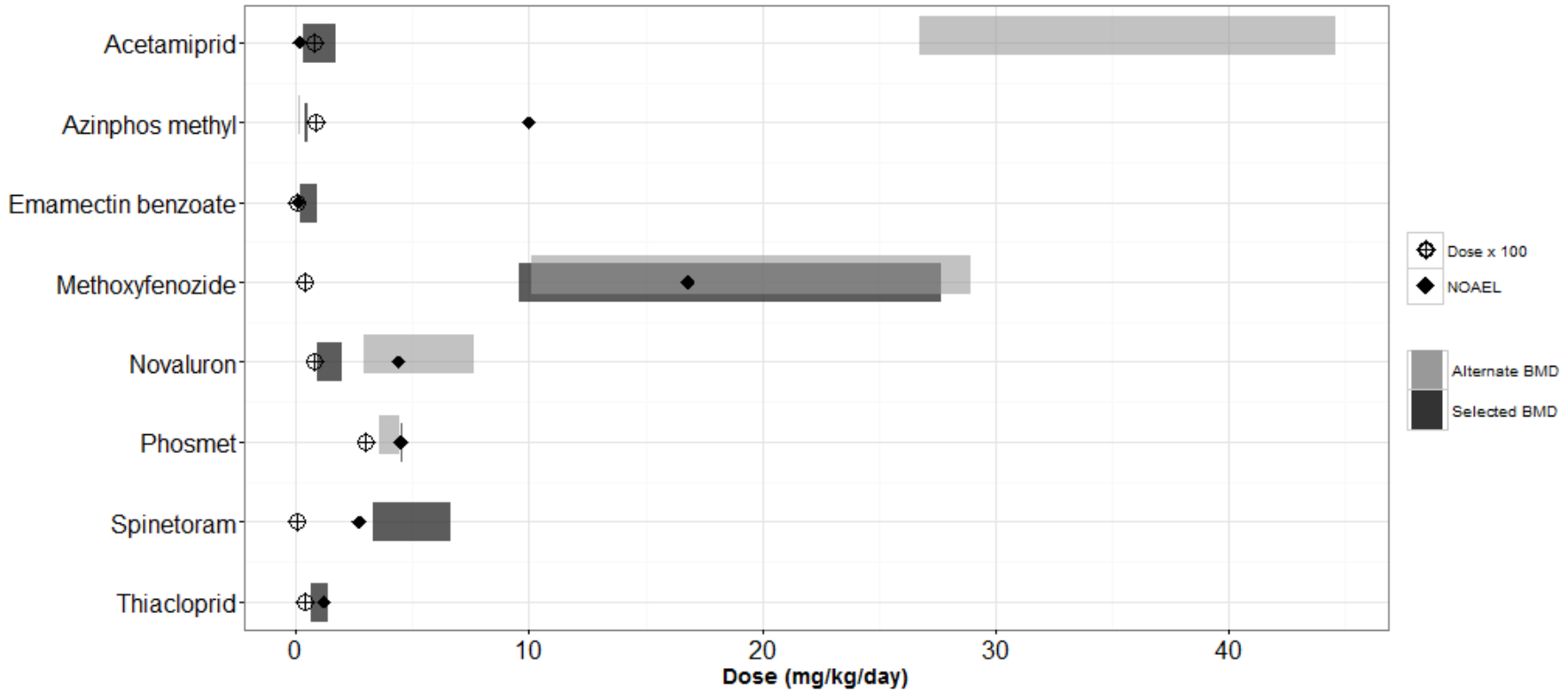

Figure 4.4: NOAEL, EPA-calculated daily dose of active ingredient to a mixer/loader/applicator in pome fruit using open cab application, and BMDL-BMD range for selected critical effect size, and alternative effect size for continuous endpoints. Selected effect size was 10% for all quantal impacts, 10% for all continuous except azinphos methyl and phosmet, and 20% for azinphos methyl and phosmet (cholinesterase inhibitors). The alternate effect size is 1 standard deviation from baseline.

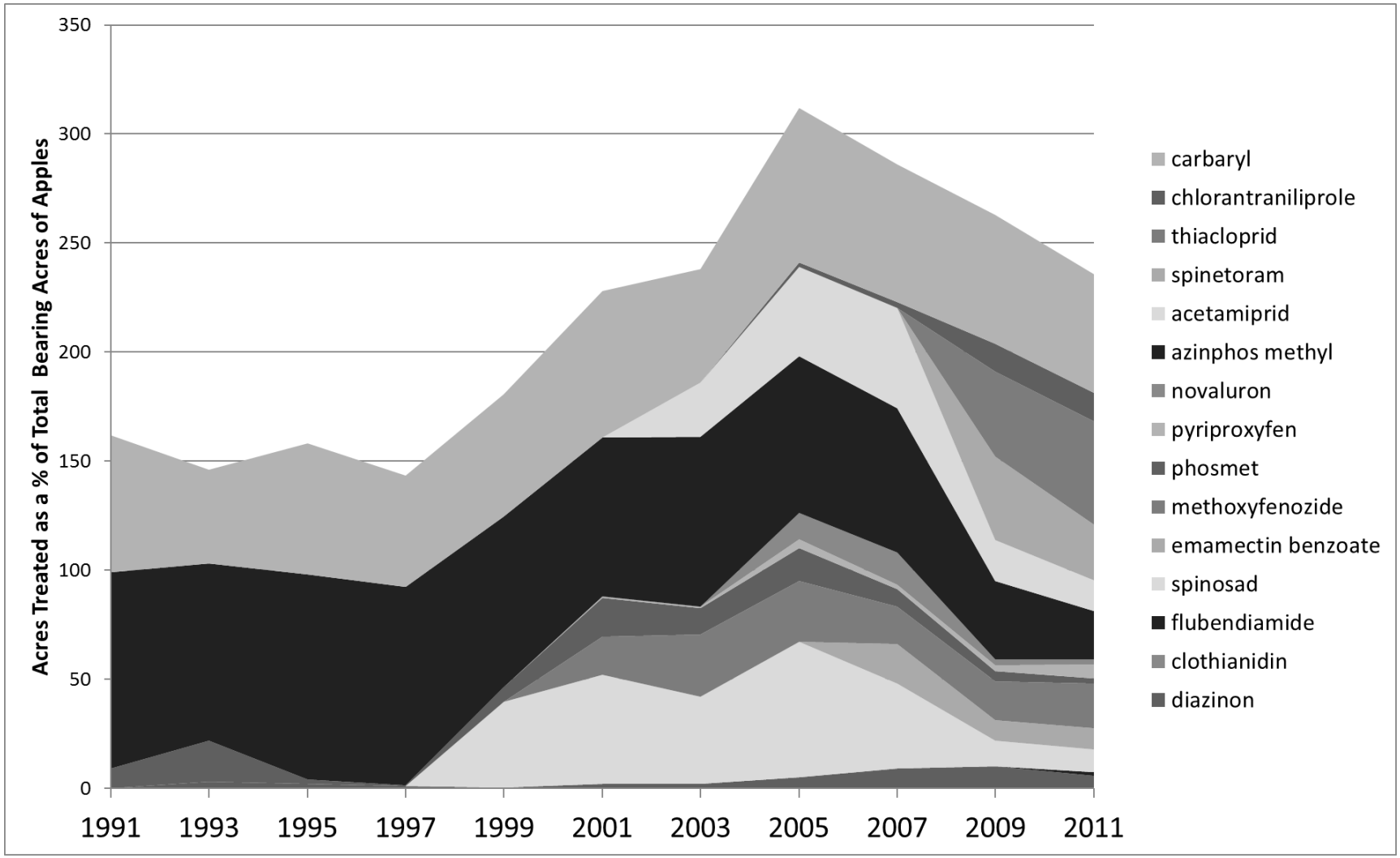

Figure 5.5: Use of pesticides registered for codling moth control as reported by the National Agricultural Statistics Service as percent of total bearing acres of apples treated with each compound. Note that the treatment reason is not specified. For instance, carbaryl may have been applied for the purposes of fruit thinning rather than pest control, or for a different pest species.

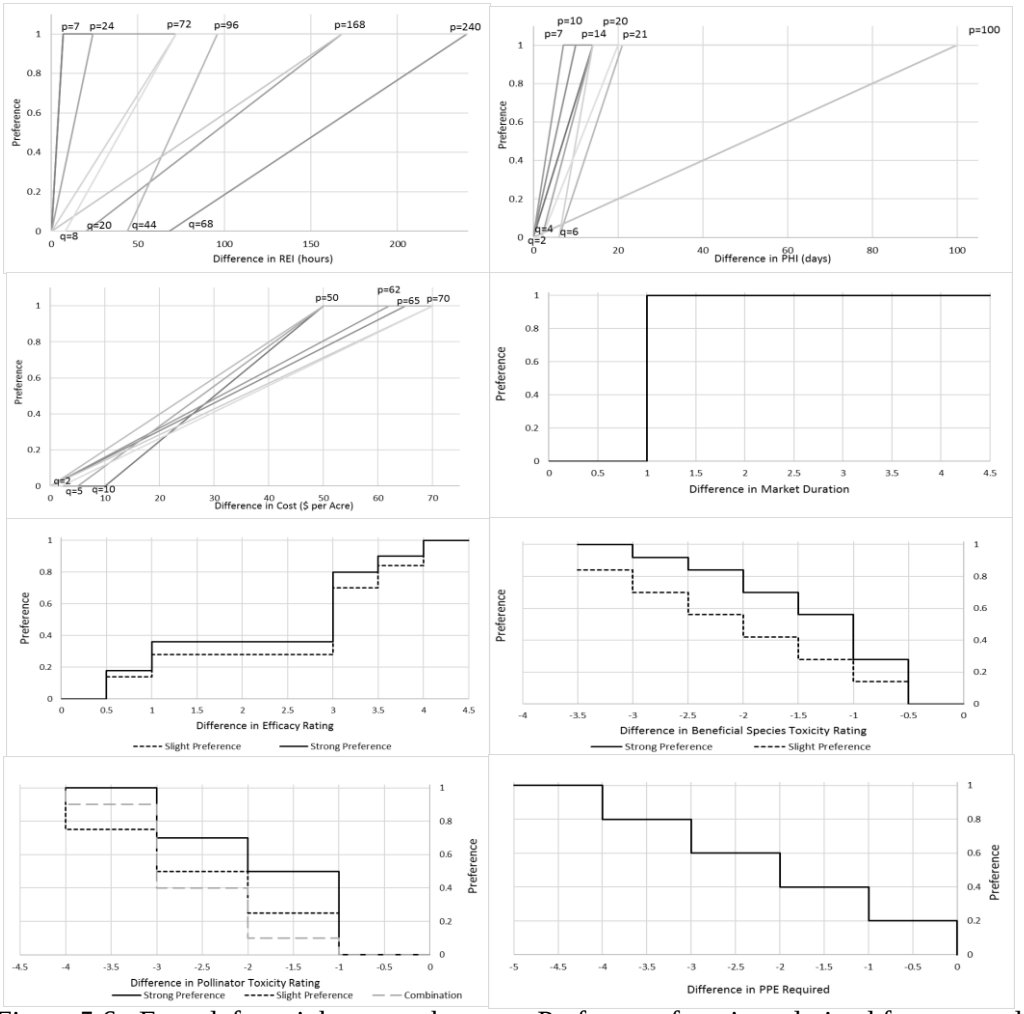

Figure 5.6: From left to right, top to bottom: Preference functions derived from consultant responses to questions on indifference and strict preference thresholds for the selection criteria of: From left to right, top to bottom: Difference in Re-entry interval, Difference in Pre-harvest interval, difference in cost per acre, difference in time available on the market, difference in efficacy rating for codling moth control as described by the WSU Crop Protection Guide, difference in beneficial species and pollinator toxicity as indicated in the Guide, and difference in label-prescribed protective equipment requirements, where levels 1-6 represent increasing requirements from normal work clothes, to work clothes and gloves, to full coverage in chemical resistant gear with respirator.

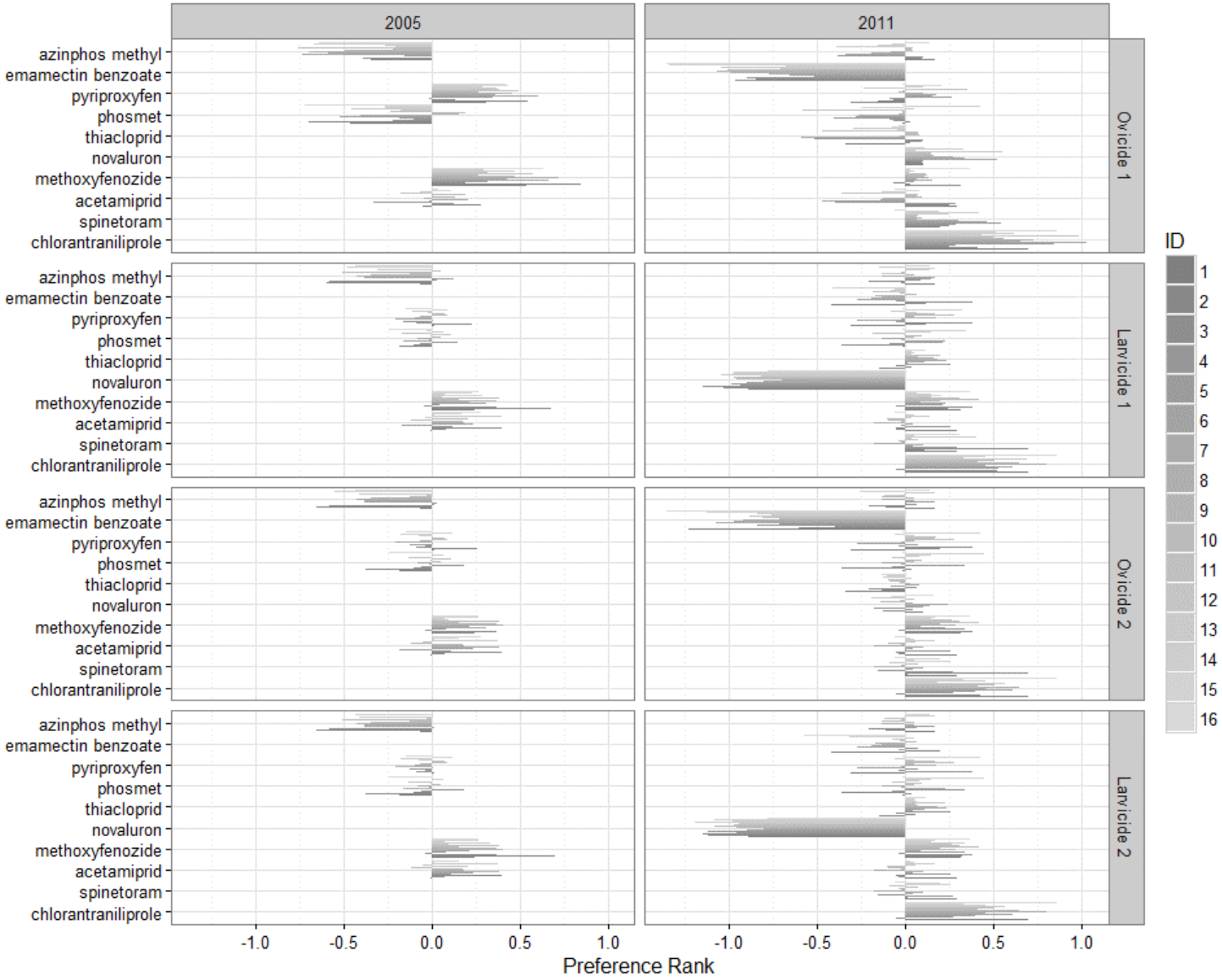

Figure 5.3: Preference rankings calculated based on all participants' interviews for each pesticide in a given year for one of four treatment types: 1st generation ovicide or larvicide, and second generation ovicide or larvicide. These ranks were used to derive probability of selection as reported in table 3.

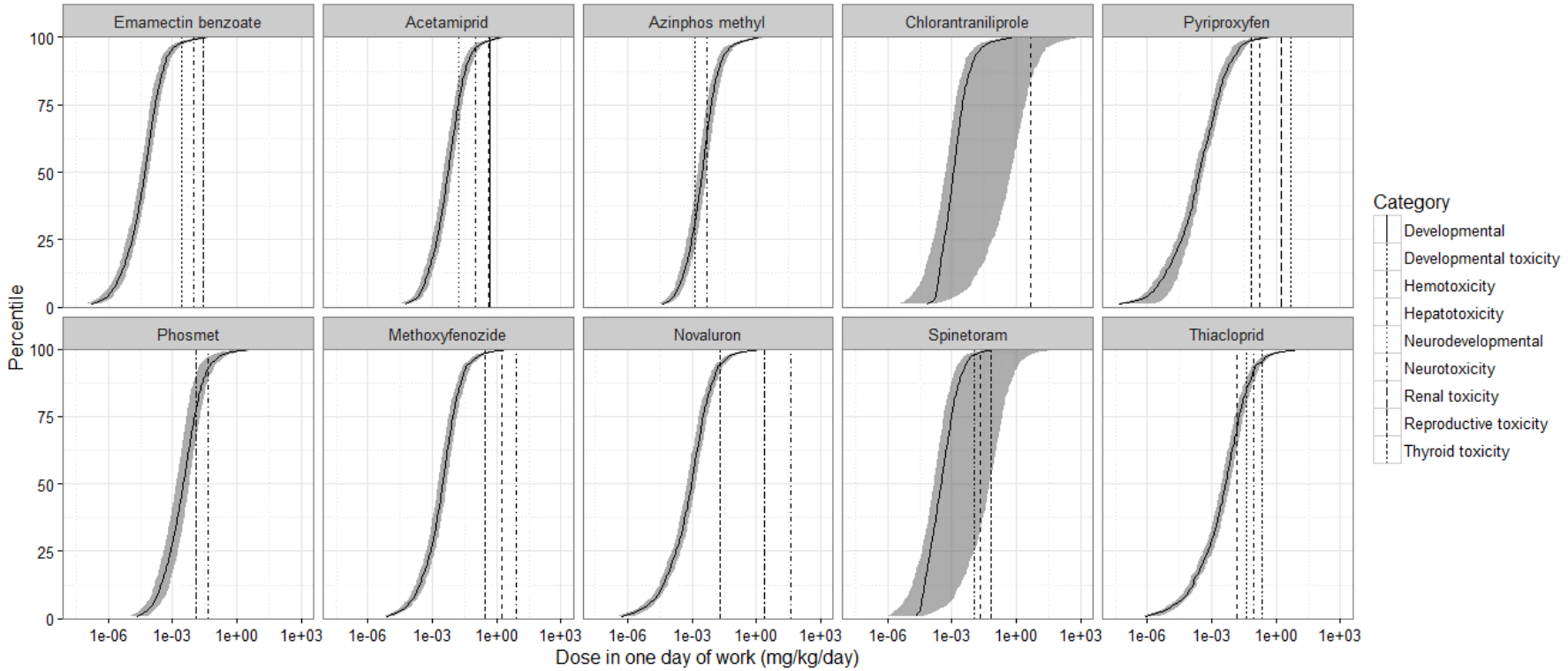

Figure 5.4: Cumulative distributions of pesticide doses calculated as previously described with associated (100x) safety factor adjusted benchmark doses used to calculate exceedance fractions for pesticide handlers working with each compound, for all associated health impact categories.

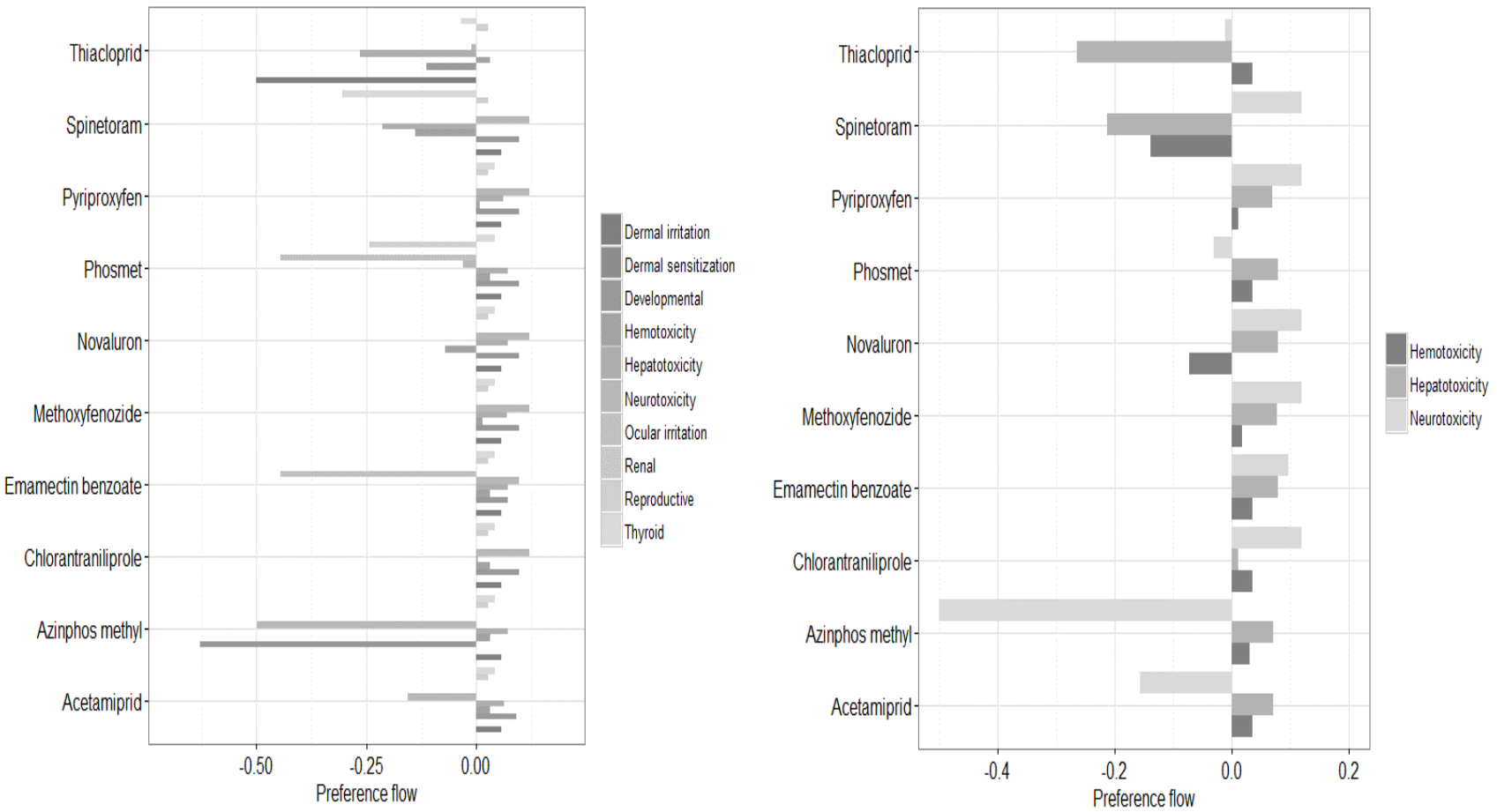

Figure 5.5: Left: Health impact tradeoffs represented by preference flows for each health impact category associated with a given pesticide. Right: Preference flows specifically for hepatotoxicity and hemotoxicity vs neurotoxicity: note the opposing values for many of the evaluated compounds for these impacts, illustrating a potential tradeoff between the health impacts.

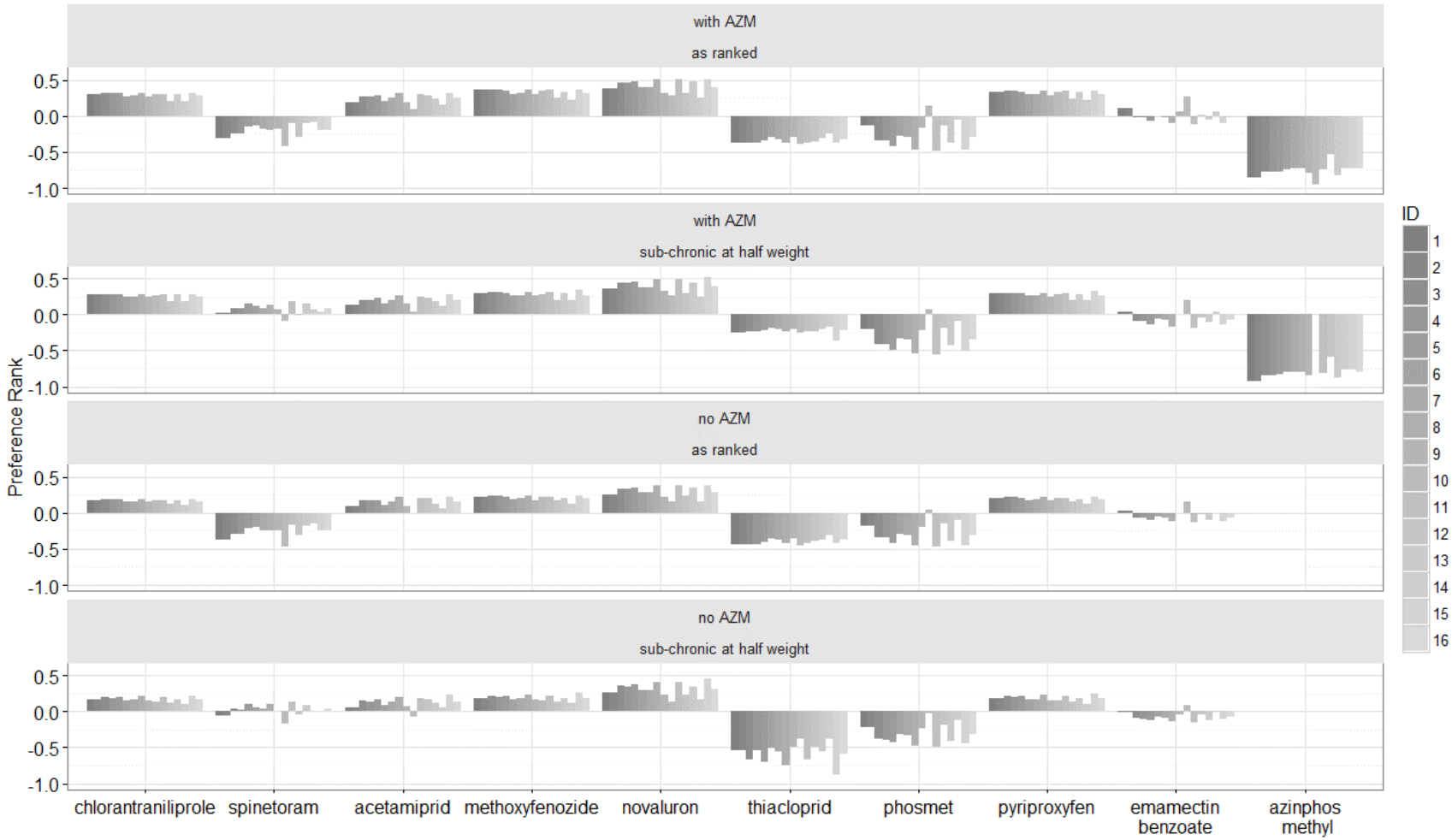

Figure 5.6: Preference ranking scores for each consultant for each pesticide, with and without azinphos methyl, and with subchronic health impacts as rated by consultants and with ratings adjusted to 50% compared with acute outcomes.

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APPENDIX A

A comparative exposure and risk assessment of the organophosphate azinphos-methyl and the reduced-toxicity alternative acetamiprid for pesticide handling activities in tree fruit orchards in Washington state.

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1. Introduction

Exposure and risk assessments of chemical pesticides are typically performed in isolation, and rarely examined in a comparative framework. However, alternatives within a pest treatment program are frequently substituted for a number of reasons, and may lead to differences in exposure and risk among applicators and workers in contact with pesticide residue. The EPA's expedited review program for "OP alternatives" and "Reduced-risk" chemicals reflects the value of identifying comparatively safer pesticide alternatives. The gradual phase-out of azinphos-methyl products provided a unique opportunity to directly measure exposure to both azinphos-methyl and one alternative, acetamiprid, being used for the same purpose and using the same sampling techniques.

Azinphos-methyl was at one time a heavily used in pome fruit orchards, primarily for the control of *Cydia pomonella*, or codling moth. At the height of its use, some growers applied Azinphos-methyl 4-6 times per year.[132] Azinphos-methyl is an organophosphorous pesticide for which mechanism of toxicity is the irreversible inhibition of Acetylcholinesterase.[133] Environmental impacts and occupational exposures prompted the gradual withdrawal of azinphos-methyl products starting in 2006 and ending in 2013.[21, 63] The availability of viable alternatives to azinphos-methyl for codling moth control as of 2005 was found to be sufficient to prevent significant economic impacts to the industry by the EPA.[134] It was believed, however, that the available alternatives would require more frequent applications to maintain fruit quality, and were more likely to permit secondary pest problems due to impacts on beneficial insect species that prey on other orchard pests.[19] Although these alternatives are considered relatively safer for exposed workers and consumers compared to azinphos-methyl, health risks may still be possible at higher doses.

Several studies on occupational exposures to azinphos methyl have been completed over the decades of its use, using external exposure dosimeters such as patches and various residue removal techniques as well as biomonitoring techniques. Estimates of dermal exposure of pesticide handlers to azinphos methyl have been highly variable, including estimates between 9.0-43.1 µg/kg active ingredient[135] and 2,991 ± 1,540 µg/kg active ingredient[136], and 1,117 µg/kg active ingredient.[137] Inhalation exposures have been estimated at an average of 8.8 µg/kg active ingredient[88] and at 459 µg/kg active ingredient.[137] Biomonitoring studies generally agree with these estimates, estimating exposures of 1,120 µg/kg active ingredient[136] and an average of 2,093.7 µg/kg active ingredient.[88]

This study focuses on comparison of the occupational risks associated with azinphos-methyl to those associated with one alternative pesticide for codling moth control, acetamiprid. Acetamiprid is a neonicotinoid pesticide, which works as an agonist for the nicotinic

acetylcholine receptor (nAChR). The greater affinity for insect subtypes of the nAChR compared with mammal subtypes results in a lower mammalian toxicity.[138] Despite this favorable toxicological profile, human poisonings resulting from neonicotinoid exposures have been reported.[139-141]

In contrast to azinphos methyl, few studies of occupational exposures to acetamiprid have been completed. One study of dermal and inhalation exposures was completed with greenhouse applicators[142]. Another study was performed in South Korea with four applicators using airblast spraying in apple orchards. The study measured exposures to the hands during mixing and loading activities, and whole body dermal and inhalation exposure during application. It was estimated that, without gloves and with one layer of clothing, average dermal exposure was 788 µg/day and average inhalation exposure was 0.03 µg/day. Using an acceptable operator exposure level of 0.124 mg/kg/day, all applicators in the study had an acceptable margin of safety.[143] Estimates of dermal exposure during airblast mixing and loading and application made based on the PHED data for registration are 8.16 mg/kg active ingredient and 794 µg/kg active ingredient, respectively, with normal work clothing. Inhalation exposures were estimated as 94.8 µg/kg active ingredient and 9.9 µg/kg active ingredient.[144]

In this study, dermal and inhalation exposures were assessed for pesticide handlers applying either azinphos methyl or acetamiprid for the purpose of codling moth control in pome fruit orchards in Washington State. Dermal exposures were measured by collection of residues from the hands and face and through the use of patch dosimeters for all clothed areas of the body, and air concentrations in the handlers' breathing zones were estimated using active air sampling. Clothing and protective equipment used by the handlers and managers was observed and applied in calculating dose and risk estimations for both compounds. The purpose of this study was to observe and measure exposures to both compounds in a real workplace setting to allow comparisons between their use and the resulting exposures and estimated risks to pesticide handlers.

2. Materials and Methods

Dermal and inhalation exposures were measured for pesticide handlers working with azinphos methyl (Guthion 50W Soluble) and acetamiprid (Assail 70WP). Twenty-five pesticide handlers participated in the study, 15 working with azinphos-methyl, and 10 working with acetamiprid. Azinphos-methyl handlers were recruited from 4 different orchards over 5 days, and Acetamiprid handlers from three different orchards over four days. Some azinphos-methyl handlers and acetamiprid handlers worked at the same orchard, although the data was collected in different years. The handlers performed mixing and loading of the pesticide followed by air blast spraying in orchards using open-cab tractors. Participants were asked to dress and work as normal for handling these pesticides. All handlers were observed to follow label instructions when mixing, loading, and applying pesticides, except one azinphos methyl handler who cut open the soluble packaging and emptied the powder into the tank. All sample types were stored on dry ice immediately after collection and transferred to a -20° C freezer as soon as possible.

Three of the acetamiprid handlers were performing more targeted sprays, treating individual trees or short sections rather than entire orchard blocks. A smoking status question was added in the second season of the study; 30% of all acetamiprid handlers were current smokers and of the 20% of azinphos-methyl handlers asked, all were current smokers. None of the participants was observed taking a smoking break during pesticide handling activities.

Information on protective equipment, clothing, and various demographic data were collected. A variety of protective equipment was used by the handlers in both groups, summarized in table 1. All azinphos methyl handlers wore a half-face respirator with oil/vapor cartridges and R95 particle filters except one who used a full-face respirator with the same cartridges. Three of the acetamiprid handlers wore half-face respirators with oil/vapor cartridges and R95 particle filters, and seven wore N95 filtering facemasks. All azinphos methyl handlers and two of the acetamiprid handlers wore PVC-coated two-piece rain suits. Eight of the acetamiprid handlers wore Tyvek® Coveralls. All handlers wore at least one layer of long pants and long sleeves underneath the rain suit, except one azinphos-methyl handler who wore short sleeves under his rain suit. A variety of face protection was used, ranging from prescription eyeglasses to splash-protective goggles worn underneath face shields. All handlers wore chemical-resistant boots and gloves. Many of the handlers wore cloth or disposable gloves beneath the chemical-resistant nitrile gauntlets as well as a knit hat or baseball cap beneath the hood of their PPE. One azinphos methyl handler used only the cloth hood and left the PPE hood off while working.

2.1 Inhalation exposure

For each participant, an SKC personal sampling pump (SKC Universal Pump Model PCXR8) was calibrated to 1.5 L/min using a Bios DryCal Defender (Mesa Labs, Butler, NJ) primary calibrator on the day of use. Before use in the field, the DryCal was calibrated against a bubble-buret system. The personal sampling pump was connected with tygon tubing to a plastic PUF tube holder fitted over a glass PUF tube (SKC Inc, Eighty Four, PA). Each glass tube contained front and back sections of PUF separated by a glass fiber filter and a PTFE separator ring. The back section was 30 mm in length and the front section was 30 mm in length during the first two seasons of sampling and 60 mm in length for the last sampling season. The PUF tube was when a new tank of pesticide solution was mixed by the participant where possible; otherwise, it was changed at approximately 3-4 hour intervals. The front and back sections of the PUF were analyzed separately to check for breakthrough, and the glass fiber filter included with the back section.

2.2 Dermal exposure

2.2.1 Dosimeter patches

All participants wore 11 external dermal dosimeter patches for the duration of their pesticide handling shift. The dermal patches were constructed from 0.35 mm thick cellulose chromatography paper (Fisher Scientific, Pittsburgh, PA). The paper was cut into 100 cm^2 squares. A square of aluminum foil of the same size was cut and taped to one side of the paper to form a backing. Patches made for the participants' legs had two layers of chromatography paper since a single layer patch on the legs became saturated in initial sampling trials. Eleven patches were attached to the handler's outermost layer of PPE with surgical tape on the lower legs, thighs, forearms, upper arms, chest, head, and back. After sampling, the patches were collected and placed in a foil envelope. Prior to analysis, the central 25 cm^2 square of the patch was cut out with a clean paper cutter (rinsed with ethanol between samples). The two inner layers of aluminum foil (those in direct contact with the paper) were included for extraction with the patch.

2.2.2 Hand Rinsing

The solution used for hand rinse samples was prepared from solid sodium dioctyl sulfosuccinate (Cytec, Woodland Park, NJ). A 0.15% (v/v) solution was prepared in deionized water from an

initial stock solution in 200-proof ethanol. One liter of solution was used for each rinsing of both hands. The liter was divided into four aliquots of 250 ml and poured gently into Ziploc bags just before use. The participant's hands were inserted into the bag and a researcher held the bag tightly at their wrist. The researcher then agitated the hand in the bag by shaking up and down at a rate of 60 shakes per 30 seconds and allowed the hand to drip dry into the bag. Each hand was rinsed twice, and all four rinses were combined into one sample. This procedure was followed when worker took a break and at the end of the pesticide application, following removal of the outermost protective garments.

2.2.3 Face and Neck Wipes

Sterile gauze wipes (North Safety Products, Smithfield, RI) were pre-cleaned by ultrasonication in acetone (Analytical grade, EMD Millipore, Billeria, MA) prior to use. The gauze pads were allowed to dry for at least 10 hours in a fume hood. At the end of the application shift, the participant's face and neck were wiped with sterile cotton gauze dampened with four sprays of the hand rinse solution. The order, direction, and number of wipes were standardized and each participant's face was wiped with four pads, two for each side of the face and front half of the neck.

2.3 Field Sample Quality Assurance

Positive and negative controls were prepared in the field for all sampling media on each day of sample collection at the sampling location. Positive controls of two mass amounts of either azinphos-methyl (1.0 mg/mL stock solution, Accu-Standard, Inc., New Haven, CT) or acetamiprid (99.9% purity solid, Sigma Aldrich, Inc, St. Louis, MO) were prepared, along with duplicate negative controls. The quality assurance samples were handled, stored, and analyzed in the same way as the exposure samples.

2.4 Sample Analysis

The samples for all but three of the azinphos-methyl handlers were analyzed for both azinphos-methyl and azinphos-methyl oxon, using isotopic internal standards for quantification (AZ-MD_6, 100 ng/µl, EQ Laboratories GmBH, Augsburg, Germany, and AZ-OD_6 Bayer K-176, 99.3% purity solid, Bayer Crop Science, Research Triangle Park, NC). Three of the azinphos methyl handler samples were not analyzed for the oxon due to labeled standard availability. All acetamiprid handler samples were analyzed for acetamiprid, using an isotopic internal standard acetamiprid-d_3 (≥98.0% purity solid, Sigma Aldrich, St. Louis, MO).

All sampling media except for the hand rinse solutions were extracted via submersion and ultra-sonication in an acetonitrile solution (HPLC grade, EMD Millipore, Billeria, MA) containing the internal standards for each appropriate compound. Hand rinse samples were injected directly after addition of internal standard. Samples were analyzed using HPLC-MS-MS (Aglient 1200 Quartenary HPLC; Aglient 6410 and 6460 MS-MS, Agilent Technologies, Santa Clara, CA).

2.5 Data Analysis

An exposure value for each handler was calculated based on the masses deposited on all sampling devices. Masses were not corrected for recovery of field controls. To calculate dermal exposure, masses collected from the hands and face were added to the mass exposure for the body as calculated based on extrapolation of the patch deposition values to the appropriate body surface area. Surface area for each body part was calculated by applying the individual handlers' weight and height to formulae generated from body surface area measurement studies[107]. Based on these surface area estimations, the patch deposition masses were extrapolated to full body depositions. An assumed protection factor for personal protective equipment and the work clothing worn underneath was applied to each individual handler to estimate the mass which

reached the skin. The values used for personal protective equipment (99.48% for a PVC coated rain-suit and 99.08% for Tyvek coveralls) were the minimum protection factors reported in a study of Azinphos methyl penetration through PPE[74]. A protective factor of 50% was applied for a single layer of ordinary work clothing, as assumed by the Environmental Protection Agency in pesticide risk assessments[67].

Inhalation exposures were calculated by converting the mass deposited on front and back sections of the PUF to an air concentration via sampling rate and time. An assumed breathing rate used in EPA risk assessments[73] for mixing and loading (16.7 L/min) and ap**Error! Not a valid filename.**plication activities (8.3 L/min) and the observed time spent in these activities was applied to the air concentrations. For half of the participants, exact time spent mixing and loading was not recorded, and was estimated based on the number of tanks mixed in a sampling period and the time it was observed to take to mix one tank among the other handlers. This calculated exposure was modified based on the OSHA assigned protection factor (APF) for the respirator worn by the applicator (10 in all cases but one, where a full-face respirator with an APF of 50 was used).[69]

Since the acetamiprid handlers all wore more PPE than was required by the label, the measured depositions were also used to calculate a hypothetical exposure the handlers would have received if they followed the label recommendations. The requirements for mixing and loading and applications in tree fruit are normal work clothes (long sleeves, pants, socks and shoes) and chemical-resistant gloves. Depositions were extrapolated to exposure and dose based on the assumption that the applicator would wear one layer of long sleeves and pants and shoes and socks, providing 50% reduction of mass, and chemical-resistant gloves. Masses collected from the face were adjusted using the assumption that the mask or respirator prevented approximately 30% of potential facial deposition (based on a 135 cm^2 surface area as a percent of the surface area of the applicators' faces).[72] Hand exposure needed no adjustment, since all handlers wore the label-required gloves. The reduction of inhalation exposure for respirator protection was not used in the calculation of hypothetical exposure.

The dermal exposures calculated by this method were extrapolated to doses using the dermal absorbance percentages reported in the EPA human health risk assessments for azinphos methyl and acetamiprid, that is, 42% and 10%, respectively[21, 144] and the body weight of the handler. Inhaled exposures are assumed to translate completely to an internal dose. A dermal and inhalation margin of exposure (MOE) for each handler was calculated following the methods applied in the EPA's risk assessments for these compounds, where the No Observed Adverse Effect Level (NOAEL) is divided by the dose. For azinphos methyl, the NOAEL for dermal estimates is 0.2 mg/kg/day, and the NOAEL for inhalation is 0.56 mg/kg/day. For acetamiprid, the NOAEL is 10 mg/kg/day for both inhalation and dermal scenarios. In calculating the dermal MOE for azinphos methyl, the dermal absorption fraction is not used since the NOAEL is generated through a dermal toxicity study. The dose used in the acetamiprid MOE calculation is adjusted for dermal absorption since the NOAEL comes from a study where the dose was administered orally.

The extrapolated dermal deposition, the dermal and inhalation doses, and the corresponding MOEs were evaluated using the R function "manova" to perform multivariate analysis of variance (MANOVA) and determine whether these outcomes were significantly different between azinphos methyl and acetamiprid handlers while including the amount of active ingredient handled by the participants as a separate predictor.

3. Results

Descriptive statistics for participant demographics and observed tasks are summarized in table 1. All participants were male and 93% identified as Hispanic or Latino. Ages ranged from 21 to 57, and years of experience handling pesticides ranged from 1 to 32. Heights and weights were similar among acetamiprid and azinphos methyl handlers. The amount of time spent in pesticide handling tasks varied from 2.5 to 9.1 hours. Seventy percent of acetamiprid handlers and 46% of azinphos-methyl handlers stopped for a lunch break. Azinphos methyl handlers all took their breaks after finishing a tank spray, whereas acetamiprid handlers more often took their break after mixing a tank or in the middle of spraying a tank.

The masses recovered from hand, face, and patch samples are summarized in table 2. Deposition mass was slightly higher among azinphos methyl handlers compared with acetamiprid handlers, but the normalized rate of deposition was similar for both pesticides on most body areas, excepting the lower arms and upper legs. Calculated body surface areas (cm^2) used to extrapolate masses recovered from the patches are summarized in table 3. Body weights and heights were not highly variable among the handlers, resulting in relatively similar estimated surface areas. Extrapolated masses deposited on the body areas represented by the patches, and on the face, hands, and air samples are summarized in table 4 along with the calculated exposures as translated from the depositions. Estimated dermal depositions were significantly higher for azinphos methyl handlers (geometric means of 255,784 vs 18,595 µg). Dermal exposures normalized to the amount of active ingredient handled were higher on average for some body areas among acetamiprid handlers, in particular the lower arms and upper legs. Whole-body dermal exposures with observed protective equipment were similar between the two compounds (117 µg vs 863 µg). Using the label assumptions to extrapolate deposition, it was found that acetamiprid exposures would have hypothetically been substantially higher than azinphos methyl exposures (9.9 mg vs 862 µg) if the extra PPE was not used (table 5). Inhalation exposures with respirator protection were similar among azinphos methyl and acetamiprid handlers (2.7 µg and 4.4 µg), but normalized inhalation exposures were slightly higher among acetamiprid handlers (table 6). Hypothetical exposures to acetamiprid without a respirator would have significantly exceeded those observed in azinphos methyl handlers. Observed breathing zone concentrations were similar between the two groups, though slightly higher on average for azinphos methyl handlers.

These exposures (the mass assumed to penetrate clothing and PPE) were translated into the doses and MOEs summarized in table 7. As with the exposures, the dermal doses of azinphos methyl handlers were on average slightly higher than acetamiprid doses, but the difference was non-significant. Inhalation doses were significantly different between chemicals, both with and without assumed respirator protection for acetamiprid handlers. For the acetamiprid handlers, the lowest combined MOE was 5,189. The lowest azinphos methyl handler MOE was calculated to be 3. 86% of azinphos methyl handlers' dermal and combined MOEs were calculated as below 100, the designated level of concern for these exposure scenarios. None of the inhalation MOEs alone were found to be below 100 with the assumed protective capabilities of the respirators worn by the workers in this study. The hypothetical MOEs calculated based on label assumptions for acetamiprid were significantly different for inhalation doses, but not for dermal doses, in comparison with azinphos methyl exposures. One acetamiprid handler's MOE using label-prescribed levels of protection would have fallen below 100 using only label-prescribed PPE.

The results of the MANOVA tests (table 8) of external deposition, dose, and MOE indicate that when the amount of active ingredient is included in a model along with type of chemical (acetamiprid or azinphos methyl), it has significant effects on the amount of deposition, the dermal dose through the observed PPE, the dermal margin of exposure, and the inhalation margin of exposure. Type of chemical had significant effects on the dermal margin of exposure and the inhalation dose of workers with observed PPE protections, beyond the effects of mass of active ingredient handled. Under the assigned protection granted by label requirements, amount of active ingredient had significant effects on dermal and inhalation margins of exposure, and type of chemical had additional significant effect only on inhalation dose. Dermal doses did not significantly differ between chemical types under assumed hypothetical protection provided by label requirements.

4. Discussion

This study examined occupational exposures and associated risks of two alternative chemicals for control of codling moth in tree fruit orchards. The registration of azinphos methyl was cancelled in part due to occupational risks to pesticide handlers, which the findings of this study support based on the estimated margins of exposure found below 100 despite appropriate handling procedures applied in the majority of observations. Overall mass deposited on pesticide handlers' outer garments was significantly higher for azinphos methyl users, a difference which seems to be mostly driven by the higher application rate requiring more mass to be handled per day of application. When considering the protective factors based on what the handlers were observed to be wearing, this depositional difference translates into a difference in dermal and inhalation doses and for this reason as well as the difference in toxicity, very different margins of exposure were estimated for the two compounds. However, the overall difference in risk relies in part on the protective equipment worn voluntarily by the acetamiprid handlers, which is not required by the label.

When the deposited masses for acetamiprid handlers are extrapolated based on the label requirements instead of observed gear, the difference in dermal dose becomes non-significant. Although the margins of exposure for inhalation and dermal routes are still both significantly different between azinphos methyl and hypothetical acetamiprid scenarios, the range of dermal margins of exposure for acetamiprid does fall below 100 in one case. This finding indicates that despite the lower mass depositions and mammalian toxicity, based on current assumptions of PPE protectiveness, dermal absorption, and toxicity, handlers of acetamiprid in tree fruit who follow proper label instructions may still be at risk of neurotoxic impacts through the route of dermal exposure.

The amount of assigned protection provided by work clothes and protective equipment have a key role in estimating the margins of exposure associated with application activities. If work clothing provided even 30% higher protection than is assumed here, the MOE range for acetamiprid exposures would not reach 100. This protection goal could be achieved with a second layer of clothing under the current EPA assumptions. The default CDPR assumption for normal work clothes is 90% protection,[76] and Driver et al estimated a grand mean of 88.1% protection based on patch dosimeter data from the Pesticide Handler Exposure Database.[75] The variety of clothing permeation estimates could provide conflicting calculation of the risks undertaken with current label requirements for acetamiprid.

Comparison of these results with the datasets used by the EPA for occupational risk assessments related to pesticide exposure shows many consistencies and a few key differences. Data from

PHED on mixer/loader/applicators (MLAP) using wettable powder was used to compare depositions on the outer patch samples (see table 4). In general, higher normalized depositions were seen in this study than in the PHED dataset, for both Azinphos methyl and Acetamiprid, even though the PHED data is all from handlers using open-pour wettable powder formulations. Some patterns of deposition are similar; in the PHED dataset, the highest areas of deposition were the legs, in particular the upper legs, and the lowest area was the head. The depositions on acetamiprid handlers, who also used an open-pour wettable powder, follow the same pattern. The Kim et al study also found that the upper legs were the area of highest dermal deposition, although the masses deposited on dermal samplers in that study were higher, as were depositions normalized to the mass of active ingredient used. In that study, the clothing protection factor was assumed to be 90%, and dermal absorption 10%. If those numbers were adjusted to 50% and 30% as in the EPA's first pome fruit risk assessment, three of the four handlers would have had a margin of safety of less than one.

Two sets of generalized exposure factors are available for comparison to these results. The earlier data is based on the PHED dataset for mixing/loading and open cab application, and the later updated with results from the AHETF dataset for the open cab application scenario. The risk assessments for both acetamiprid and azinphos methyl were both performed based on PHED, and an additional biomonitoring study performed for azinphos methyl. In all cases with equivalent PPE, higher dermal depositions and exposures were observed in this study than in the PHED and AHETF-based surrogate exposure measures. Lower exposures were estimated in this study for azinphos methyl handlers than were calculated based on PHED; however, handlers in this study wore full-body chemical-resistant garments and the PHED estimations assumed a single layer of clothing and chemical-resistant gloves. Inhalation exposures estimated in this study were lower than the relevant surrogate scenario estimates in general.

For the purposes of risk assessment, the surrogate exposures are paired with maximum application rate and area estimates to generate a conservative estimate of exposure, dose, and margin of exposure. For azinphos methyl, the biomonitoring data suggested an average dose of 8.14 µg/kg/day for handlers wearing two layers of clothes, respirators, and chemical-resistant hats, gloves, and boots.[88] This value falls within the range of doses observed in this study, despite the difference in protective equipment. In contrast, there is not agreement between estimates of inhalation dose. The biomonitoring study estimated an inhalation exposure of 167 µg without a respirator, which is within the range of potential inhalation exposures (0.91-311 µg) observed among applicators without respiratory protection, although higher than the average. The minimum total MOE estimated from the biomonitoring study was 18, which falls within the range of azinphos methyl combined MOEs estimated in this study (4-212).[88]

The human health risk assessment for acetamiprid estimates handlers' dermal exposure to be 22 mg (assuming 40 acres of application at the maximum rate), slightly lower than the arithmetic mean of hypothetical exposures in this study which was 28 mg. The maximum far exceeds this estimation at 93 mg. Fractional dermal absorbance for acetamiprid was estimated at 30% at the time of the pome fruit risk assessment, and has since been lowered to 10%, the value used in this study. The dermal dose estimate for the risk assessment therefore translates to 110 µg/kg/day[144], which is close to the maximum hypothetical dose calculated for this study (112 µg/kg/day). Inhalation exposures and doses based on PHED and AHETF data were higher than those observed in this study. The NOAEL used for short-term inhalation and dermal exposures has been revised from 17.9 mg/kg/day to 10 mg/kg/day[65], which contributes to the lower MOEs calculated for acetamiprid in this study compared to the EPA assessment. The minimum

combined MOE in this study was 88, compared with 262 as calculated in the dermal handler assessment. If the NOAEL of 10 mg/kg/day were used in the original assessment and dermal availability had not also changed, the MOE would have been calculated as 91, below the level of concern.

Several uncertainties are highlighted by these comparisons. The assumed clothing and protective equipment used in the risk assessment may not match what is selected and worn by applicators. The protective abilities of work clothes and PPE are not clearly and consistently established and may produce conflicting estimates of risk for a single scenario. Mass depositions which translate to dermal exposures were higher in this dataset than the surrogate exposure values used for risk assessments, and lead to MOEs beyond the level of concern. Finally, changes in assumed dermal availability and toxicity endpoints may have significant impacts on estimated risks as assessments are updated and should require reassessment of many use scenarios.

Conclusion

An exposure assessment of pesticide handlers working with two different neurotoxic pesticide alternatives supports the cancellation of azinphos methyl in favor of alternative pest control methods, since worker exposures were above the level of concern for acute neurotoxicity. However, acetamiprid handlers who follow label instructions on use of protective equipment may also be exposed at levels beyond the level of concern, despite the comparatively low toxicity of the compound. All of the acetamiprid handlers in this study exceeded the label requirements for protective gear, and exposures calculated on the observed PPE in use were well below the level of concern. The difference in risk between acetamiprid and azinphos methyl is significant, and contributed to by differences in mass of potential exposure, required PPE, formulation, dermal availability, and toxicity for each compound. However, acetamiprid is also a neurotoxic compound, and current label requirements may not provide adequate protection in all occupational contact scenarios, given the variability of exposures and the comparatively high mass depositions observed in this study.

Table 9: Protective equipment and clothing used by pesticide handlers as a percent of the total (n=15 azinphos methyl, n=10 acetamiprid) and task and handler characteristics

	Acetamiprid		Azinphos-methyl	
	Mean	(SD)	Mean	(SD)
Active ingredient mixed, loaded, and applied (kg)	0.58	(0.5)	6.42	(1.9)
A.I. mixed/loaded before break (kg)	0.33	(0.3)	5.13	(1.4)
A.I. mixed/loaded after break (kg)	0.25	(0.3)	1.29	(1.6)
A.I. sprayed before break (kg)	0.25	(0.2)	5.13	(1.4)
A.I. sprayed after break (kg)	0.33	(0.3)	1.29	(1.6)
Acres sprayed	8.50	(6.6)	14.26	(4.5)
Tanks mixed	2.68	(1.9)	3.18	(1.0)
Length of shift (hours)	6.29	(2.7)	5.34	(1.3)
Body weight (kg)	79.52	(9.7)	82.25	(12.3)
Height (m)	1.71	(0.1)	1.68	(0.1)
Age (years)	37.50	(12.7)	33.67	(10.6)
Pesticide application experience (seasons)	8.30	(9.0)	5.27	(3.7)
Protective Equipment	%		%	
Chemical-resistant boots	100		100	
Chemical-resistant gauntlets (nitrile)	100		100	
Cloth gloves under nitrile gauntlets	10		53	
Disposable nitrile under nitrile gauntlets	10		20	
Long pants/long sleeve shirt	100		93	
Chemical-resistant hooded rain suit	20		100	
Hooded Tyvek Coverall	80		0	
Hat or cap beneath CR Hood	80		60	
Half-face respirator w/ oil/vapor cartridge + R95 filter	30		93	
N95 Respirator	70		0	
Full-face respirator w/ oil/vapor cartridge + R95 filter	0		7	
Splash-protective chemical-resistant goggles	10		13	
Face Shield + goggles	0		26	
Safety glasses	80		53	
Prescription Eyeglasses	10		0	

Table 10: Masses deposited on patch samples and masses normalized to surface area and mass of active ingredient handled

	Deposition (µg)				Normalized Dep Rate (µg/cm² *g a.i.)			
	Acetamiprid		Azinphos-methyl		Acetamiprid		Azinphos-methyl	
	GM	(GSD)	GM	(GSD)	GM	(GSD)	GM	(GSD)
Head (Excludes Face and Front of Neck)	4	(12)	331.12	(18)	0.0018	(7)	0.0022	(5)
Back	14	(8)	245.19	(3)	0.0014	(5)	0.0016	(3)
Chest	9	(8)	220.3	(3)	0.0009	(3)	0.0014	(3)
Upper Arms	43	(6)	734.34	(2)	0.0022	(3)	0.0024	(2)
Lower Arms	88	(10)	768.8	(2)	0.0045	(4)	0.0025	(2)
Upper Legs	76	(8)	561.33	(2)	0.0039	(4)	0.0018	(2)
Lower Legs	53	(11)	520.89	(2)	0.0027	(5)	0.0017	(2)

Table 11: Body segment surface areas in cm^2 as calculated based on height and weight of participants and regressions reported in EPA 1985.

	Acetamiprid		Azinphos-methyl	
	Mean	(SD)	Mean	(SD)
Head (Excluding Face and Front of Neck)	1011	(49)	1022	(58)
Back	3721	(371)	3804	(461)
Chest	3721	(371)	3804	(461)
Upper Arms	1672	(252)	1742	(203)
Lower Arms	1400	(191)	1453	(185)
Upper Legs	3870	(279)	3907	(379)
Lower Legs	2539	(178)	2516	(193)

Table 12: Depositions estimated by extrapolation of patch loading to body surface areas summarized in table 2, normalized to mass of active ingredient handled, and estimated exposures based on PPE and cloth protective factors, also normalized to mass a.i.

	Deposition (µg)		Normalized Deposition (µg/g a.i.)		
	Acetamiprid	Azinphos-methyl	Acetamiprid	Azinphos-methyl	PHED wettable powder MLAP
	GM (GSD)	GM (GSD)	GM (GSD)	GM (GSD)	GM (GSD)
Head (Excludes Face & Front of Neck)	710 (12)	13522 (4)	1.8 (7)	2.2 (5)	0.19 (10)
Back	2014 (8)	37050 (3)	5.2 (5)	6.0 (3)	1.37 (4)
Chest	1358 (8)	33290 (3)	3.5 (4)	5.4 (3)	1.70 (4)
Upper Arms	1434 (6)	25530 (3)	3.7 (3)	4.2 (3)	0.89 (3)
Lower Arms	2433 (10)	22276 (2)	6.3 (4)	3.6 (2)	1.61 (9)
Upper Legs	5880 (8)	43829 (2)	15.1 (4)	7.2 (2)	13.02 (5)
Lower Legs	2698 (11)	26471 (2)	6.9 (5)	4.3 (2)	2.40 (4)
Total Dermal	18595 (8)	255784 (2)	48 (4)	42 (2)	24 (4)

Table 13: Extrapolated exposures and exposures normalized to grams of active ingredient handled to acetamiprid and azinphos methyl handlers assuming protective factors based on their observed protective equipment and clothing, and hypothetical exposure based on label requirements for acetamiprid applications to tree fruit.

	Exposure (µg)			Normalized Exposure (µg/g a.i.)		
	Acetamiprid	Acetamiprid (label)	Azinphos-methyl	Acetamiprid	Acetamiprid (label)	Azinphos-methyl
	GM (GSD)	GM (GSD)	GM (GSD)	GM (GSD)	GM (GSD)	GM (GSD)
Hands	11.8 (4)	11.8 (4)	34.4 (8)	0.030 (2)	0.030 (2)	0.006 (7)
Face	6.0 (6)	7.7 (7)	5.0 (4)	0.015 (3)	0.023 (3)	0.001 (5)
Head (Excludes Face & Front of Neck)	3.3 (15)	666.2 (12)	54.8 (8)	0.009 (8)	1.712 (7)	0.009 (9)
Back	7.8 (10)	944.8 (8)	80.1 (3)	0.020 (5)	2.428 (5)	0.013 (3)
Chest	5.6 (9)	636.9 (8)	71.9 (3)	0.014 (4)	1.637 (4)	0.012 (3)
Upper Arms	5.9 (7)	672.7 (6)	55.2 (3)	0.015 (3)	1.729 (3)	0.009 (3)
Lower Arms	10.0 (12)	1141.0 (10)	57.9 (2)	0.026 (5)	2.932 (4)	0.009 (2)
Upper Legs	24.1 (9)	2757.8 (10)	114.0 (2)	0.062 (4)	7.087 (4)	0.019 (2)
Lower Legs	11.1 (13)	1265.5 (11)	68.8 (2)	0.028 (6)	3.252 (5)	0.011 (2)
Total Dermal	117.4 (7)	9943.1 (8)	862.6 (3)	0.302 (3)	25.558 (4)	0.141 (2)
Inhaled	2.7 (9)	27.2 (9)	4.4 (4)	0.007 (4)	0.070 (4)	0.001 (3)

Table 14: Masses collected on PUF active air samplers and extrapolated breathing zone concentrations and inhalation exposures based on sampling time and activity level.

	Acetamiprid				Azinphos methyl			
	GM	GSD	min	max	GM	GSD	min	max
Mass Collected (µg)	27.02	(9)	0.13	28.82	49.27	(3)	0.47	26.90
% Breakthrough	9%	(2)	1%	63%	7%	(2)	1%	33%
Air Concentration (ng/L)	11.6	(5)	0.53	136.01	18.22	(1)	3.20	164.40
Within Worker Concentration Variance	0.001	(0.002)	0	0.005	0.001	(0.002)	0	0.006
Inhalation Exposure (µg)	2.72	(4)	0.09	22.75	4.43	(9)	0.09	31.06
Normalized Inhalation Exposure (µg/g a.i.)	0.01	(4)	0.00	0.05	0.001	(3)	0.000	0.003
Inhalation Exposure (no respirator)	44.30	(4)	0.94	227.48	28.50	(9)	0.91	310.59

Table 15: Estimated dermal and inhalation doses (µg/kg/day) for azinphos methyl and acetamiprid handlers, and associated Margins of Exposure

	Acetamiprid				Acetamiprid (label)				Azinphos methyl			
	GM	(GSD)	min	max	GM	(GSD)	min	max	GM	(GSD)	min	max
Dermal	0.15	(7)	0.01	1.14	12.59	(8)	0.34	111.57	4.45	(3)	1.10	60.42
Inhalation	0.03	(9)	0.0013	0.35	0.34	(9)	0.0130	3.47	0.05	(4)	0.0012	0.45
Dermal MOE	67298	(7)	8755	1512013	794	(8)	90	2879	53	(3)	4	214
Inhalation MOE	290226	(9)	28794	7717867	29023	(9)	2879	34780	3679	(4)	445	170676
Combined MOE	52391	(7)	7200	1264319	766	(8)	88	1107	52	(3)	4	212

Table 16: F statistics and p values from MANOVA analysis of significant differences in deposition, dose and MOE based on use of acetamiprid or azinphos methyl while controlling for amount of active ingredient handled.

	Observed		Hypothetical	
	F(1,22)	p value	F(1,22)	p value
Dermal deposition				
Amount handled	18.40	<0.001*	18.40	0.0003*
Pesticide	2.36	0.138	2.36	0.138
Dermal Dose				
Amount handled	38.84	<0.001*	0.70	0.412
Pesticide	2.65	0.118	3.67	0.069
Inhalation Dose				
Amount handled	3.54	0.073	1.81	0.192
Pesticide	4.45	0.047*	14.10	0.001*
Dermal MOE				
Amount handled	148.64	<0.001*	22.79	<0.001*
Pesticide	21.79	<0.001*	0.90	0.354
Inhalation MOE				
Amount handled	54.21	<0.001*	17.11	<0.001*
Pesticide	0.473	0.499	0.92	0.348

References
Appendix B: Target Journals
CHAPTER 2: Integrated Environmental Assessment and Management

CHAPTER 3: Risk Analysis

CHAPTER 4: Regulatory Toxicology and Pharmacology

CHAPTER 5: Risk Analysis or Journal of Multi-criteria Decision Analysis

APPENDIX C:
SURVEY AND INTERVIEW INSTRUMENTS

C.1 Web survey

2 How long have you been a professional consultant?

3 Are you a Certified Crop Adviser?
- ❍ Yes (1)
- ❍ No (2)
- ❍ No response (3)

4 What kind of firm or company do you work for?
- ❑ Independent firm (1)
- ❑ Local division of a national independent firm (2)
- ❑ Employed by one grower or grower co-op (3)
- ❑ Manufacturer-affiliated firm (4)
- ❑ Self-employed (5)
- ❑ Other (6) _____

6 What is your age?

7 What is your gender?
- ❍ Male (1)
- ❍ Female (2)
- ❍ No response (3)

8 What is your highest level of education?

- ❍ Some high school (1)
- ❍ High school graduate (2)
- ❍ Some College (3)
- ❍ College Graduate (Associate' Degree) (4)
- ❍ College Graduate (Bachelor' Degree) (5)
- ❍ Some Graduate School (6)
- ❍ Master' Degree (7)
- ❍ Doctoral Degree (8)
- ❍ No Response (9)

9 Have you ever personally applied pesticides on the job?

- ❍ Yes (1)
- ❍ No (2)
- ❍ No response (3)

10 Do you own or operate a farm, or did your parents farm during any part of your childhood (age 0-18 years)?

- ❍ Yes (1)
- ❍ No (2)

11 How often are you the sole or main decision-maker in selecting a pest control program for your clientele?

- ❍ Never (1)
- ❍ Rarely (2)
- ❍ Sometimes (3)
- ❍ Usually (4)
- ❍ Always (5)

12 How many total pome fruit orchard acres did you make recommendations for in 2014?

13 Of the total pome fruit orchard acres you made recommendations for in 2014, how many acres were managed as organic (with or without certification) or transitioning to organic?

14 In what regions are the orchards for which you make recommendations located?

- ❑ Columbia Basin (1)
- ❑ Wenatchee (2)
- ❑ Okanogan (3)
- ❑ Lower Yakima Valley (Union Gap to Benton City) (4)
- ❑ Chelan/Manson (5)
- ❑ Upper Yakima Valley (6)
- ❑ Tri-Cities (7)
- ❑ Columbia Gorge (8)
- ❑ Ellensburg (9)
- ❑ Other (10) _____

Q36 Over the past year, how important were each of the following as sources of information in helping you provide pest control recommendations?

	Not at all Important (1)	Not very Important (2)	Somewhat Important (3)	Important (4)	Very Important (5)
Agricultural chemical distributors (1)	❍	❍	❍	❍	❍
Internet resources (2)	❍	❍	❍	❍	❍
Formal education or continuing education classes (3)	❍	❍	❍	❍	❍
Field days or farm tours (4)	❍	❍	❍	❍	❍
Commodity or grower associations (5)	❍	❍	❍	❍	❍
WSU Decision Aid System (web-based IPM models and management) (6)	❍	❍	❍	❍	❍
WSU researchers or extension educators (7)	❍	❍	❍	❍	❍
WSU Crop Protection Guide (8)	❍	❍	❍	❍	❍

Q37 Over the past year, how important were each of the following as sources of information in helping you provide pest control recommendations?

	Not at all Important (1)	Not very Important (2)	Somewhat Important (3)	Important (4)	Very Important (5)
Growers (1)	❍	❍	❍	❍	❍
Other professional consultants (2)	❍	❍	❍	❍	❍
Newsletters or magazines (3)	❍	❍	❍	❍	❍
Tree Fruit Magazines and Publications (such as Good Fruit Grower or Fruit Grower News) (4)	❍	❍	❍	❍	❍
Pest Control Magazines and Publications (such as International Pest Control and Pest Management Professional) (5)	❍	❍	❍	❍	❍
Marketing organizations and materials (6)	❍	❍	❍	❍	❍
Other (7)	❍	❍	❍	❍	❍

16 How often do you use the following kinds of media in general?

	Never (1)	Rarely (2)	Sometimes (3)	Often (4)	All of the Time (5)
Magazines (1)	❍	❍	❍	❍	❍
Newspaper (local) (2)	❍	❍	❍	❍	❍
Newspaper (regional/national) (3)	❍	❍	❍	❍	❍
Internet (4)	❍	❍	❍	❍	❍
Radio (local) (5)	❍	❍	❍	❍	❍
Radio (national) (6)	❍	❍	❍	❍	❍
Television (7)	❍	❍	❍	❍	❍

17 Which of these insecticides do you consider when providing recommendations for codling moth control, and how often do you estimate you use them?

	Never (96)	Rarely (97)	Sometimes (98)	Often (99)	Almost Always (100)
Altacor (Chlorantraniliprole/Rynaxypyr) (1)	❍	❍	❍	❍	❍
Calypso (Thiacloprid) (2)	❍	❍	❍	❍	❍
Delegate (Spinetoram) (3)	❍	❍	❍	❍	❍
Assail (Acetamiprid) (4)	❍	❍	❍	❍	❍
Exirel (Cyantraniliprole/Cynazypyr) (5)	❍	❍	❍	❍	❍
Rimon (Novaluron) (6)	❍	❍	❍	❍	❍
Esteem (Pyriproxyfen) (7)	❍	❍	❍	❍	❍
Imidan (Phosmet) (8)	❍	❍	❍	❍	❍
Intrepid (Methoxyfenozide) (9)	❍	❍	❍	❍	❍
Proclaim (Emamectin benzoate) (10)	❍	❍	❍	❍	❍
Success (Spinosad) (11)	❍	❍	❍	❍	❍
Belt (Flubendiamide) (12)	❍	❍	❍	❍	❍
Clutch (Clothianidin) (13)	❍	❍	❍	❍	❍
Diazinon (Diazinon) (14)	❍	❍	❍	❍	❍
Sevin (Carbaryl) (15)	❍	❍	❍	❍	❍
Warrior (lambda-cyhalothrin) (16)	❍	❍	❍	❍	❍
Danitol (fenpropathrin) (17)	❍	❍	❍	❍	❍
Other: (18)	❍	❍	❍	❍	❍
Other: (19)	❍	❍	❍	❍	❍
Other: (20)	❍	❍	❍	❍	❍
Entrust (Spinosad) (21)	❍	❍	❍	❍	❍
Provado (imidacloprid) (22)	❍	❍	❍	❍	❍
Apollo (clofentezine) (23)	❍	❍	❍	❍	❍

Q38 Before it was phased out in 2013, about how often did you recommend at least one Guthion spray per growing season to a typical client?

- ❍ Never (1)
- ❍ Rarely (2)
- ❍ Sometimes (3)
- ❍ Often (4)
- ❍ Almost Always (5)

18 Which of these methods do you consider when providing recommendations for codling moth control, and how often do you estimate you use them?

	Never (1)	Rarely (2)	Sometimes (3)	Often (4)	Almost Always (5)
Pheromone traps (1)	❍	❍	❍	❍	❍
”Attract and Kill” pheromone+pesticide traps (2)	❍	❍	❍	❍	❍
Mating disruption (3)	❍	❍	❍	❍	❍
petroleum oil alone (4)	❍	❍	❍	❍	❍
petroleum oil in combination with a chemical pesticide (5)	❍	❍	❍	❍	❍
Cydia pomonella granulosis virus, or CpCV (Cyd-X, Carpovirusine, Madex) (6)	❍	❍	❍	❍	❍
Trunk banding (7)	❍	❍	❍	❍	❍
Bin distribution and management (8)	❍	❍	❍	❍	❍
Kaolin clay (9)	❍	❍	❍	❍	❍
Releasing biological controls (10)	❍	❍	❍	❍	❍
Maintaining endemic biological controls (11)	❍	❍	❍	❍	❍
Other (12)	❍	❍	❍	❍	❍
Other (13)	❍	❍	❍	❍	❍
Other (14)	❍	❍	❍	❍	❍

19 In general, chemical pesticides are an inexpensive way to control codling moth.
- ❍ Strongly Disagree (1)
- ❍ Disagree (2)
- ❍ Neither Agree nor Disagree (3)
- ❍ Agree (4)
- ❍ Strongly Agree (5)

20 Chemical pesticides are the most effective way to control codling moth in apple orchards.
- ❍ Strongly Disagree (1)
- ❍ Disagree (2)
- ❍ Neither Agree nor Disagree (3)
- ❍ Agree (4)
- ❍ Strongly Agree (5)

21 Chemical pesticides are safe for people applying them when used according to the label.
- ❍ Strongly Disagree (1)
- ❍ Disagree (2)
- ❍ Neither Agree nor Disagree (3)
- ❍ Agree (4)
- ❍ Strongly Agree (5)

22 It's important to avoid products that may cause acute toxicity to orchard workers.
- ❍ Strongly Disagree (1)
- ❍ Disagree (2)
- ❍ Neither Agree nor Disagree (3)
- ❍ Agree (4)
- ❍ Strongly Agree (5)

Q46 It's important to avoid products that may cause chronic toxicity to orchard workers.
- ❍ Strongly Disagree (1)
- ❍ Disagree (2)
- ❍ Neither Agree nor Disagree (3)
- ❍ Agree (4)
- ❍ Strongly Agree (5)

23 Codling moth cannot be controlled effectively without some use of chemical pesticides.
- ❍ Strongly Disagree (1)
- ❍ Disagree (2)
- ❍ Neither Agree nor Disagree (3)
- ❍ Agree (4)
- ❍ Strongly Agree (5)

24 Integrated pest management practices improve codling moth control compared with conventional methods.
- ❍ Strongly Disagree (1)
- ❍ Disagree (2)
- ❍ Neither Agree nor Disagree (3)
- ❍ Agree (4)
- ❍ Strongly Agree (5)

26 In general, most newer pesticides are safer for humans and the environment than the older alternatives.
- ❍ Strongly Disagree (1)
- ❍ Disagree (2)
- ❍ Neither Agree nor Disagree (3)
- ❍ Agree (4)
- ❍ Strongly Agree (5)

27 In general, most newer pesticides are too expensive compared with the older alternatives.
- ❍ Strongly Disagree (1)
- ❍ Disagree (2)
- ❍ Neither Agree nor Disagree (3)
- ❍ Agree (4)
- ❍ Strongly Agree (5)

28 In general, new chemical pesticides are becoming more difficult to use and to teach growers to use effectively.
- ❍ Strongly Disagree (1)
- ❍ Disagree (2)
- ❍ Neither Agree nor Disagree (3)
- ❍ Agree (4)
- ❍ Strongly Agree (5)

Q49 Please provide any additional comments about codling moth controls you may have:

Q31 We will be conducting follow-up phone interviews about factors that are important in choosing codling moth controls. Please provide an email and/or phone number to hear more

about this project. If you do not wish to be contacted at your place of employment, you may provide other contact information.

- ❑ Phone number (1) _____
- ❑ Email address (2) _____

C.2 Phone interview base questions:

Web Survey ID: _____

Part I:

1)How many of your pest control recommendations do you estimate are for pome fruit?

2)How many of your pome fruit recommendations do you estimate are for codling moth?

3)What factors do you consider when you make a recommendation for codling moth control?

4)Do you ever consider any of the following factors?
Interviewer should mark yes for any factors already mentioned in question 3

___How well the method or chemical works to control CM
___Whether the method or chemical has been used in the same orchard before in the same generation (resistance management)
___Past good or bad experiences with the method or chemical in previous years
___Pre-harvest interval
___How much PPE the label says is needed during application of a chemical or other method
___How safe the method or chemical is for bees and other pollinators
___How safe the method or chemical is for beneficial orchard species (like parasitoids)
___Cost of the method per acre
___Length of re-entry interval
___How toxic the method or chemical is to people working with it on the job
___Other:___X

5)Would environmental or seasonal situations have an impact on the factors you consider important? (For example, is the importance of price the same no matter what season?)

___Yes
___No

5a) Explain how these situational factors impact your choices. For example, do you tend to prioritize REI and PHI at different times of the year?

6) In general, which factor is the most important to you when you are deciding on a codling moth control? (x)

7) Compared to (x), how important is each of the below to your codling moth recommendation on a scale of one to ten, where ten means they are the same importance?
Interviewer should fill out the chart below using the factors described as important in questions 3 and 4. Omit those not identified in 3 & 4. For the factor identified as most important, give a score of 10. For the each other factor ask the question:

___How well the method or chemical works to control CM
___Whether the method or chemical has been used in the same orchard before in the same year
___Past good or bad experiences with the method or chemical in previous years
___Pre-harvest interval
___How much PPE the label says is needed during application of a chemical or other method
___How safe the method or chemical is for bees and other pollinators
___How safe the method or chemical is for beneficial orchard species (like parasitoids)
___Cost of the method per acre
___Length of re-entry interval
___How toxic the method or chemical is to people working with it on the job
___Other:___X

Part II:

Next, I'd like to ask few questions about potential worker health impacts of some pesticides. These impacts are evaluated by the EPA during pesticide registration.

8) How would you rate the importance of preventing acute effects of pesticide exposure to workers and preventing chronic effects of pesticide exposure to workers?

__Acute effects are a much higher priority
__Acute effects are a somewhat higher priority
__Acute and Chronic effects have equal priority
__Chronic effects are a somewhat higher priority
__Chronic effects are a much higher priority

9) I'm going to list some of the health impacts evaluated by the EPA during pesticide registration. Please tell me what you would consider in general and hypothetically the relative importance of preventing each in orchard workers (in general and hypothetically) on scale of 1-10, where 1 is not important at all, and 10 is critical:

10) What is the highest chance of an acute health impact like the ones we just talked about that you would consider acceptable for on-the-job contact with pesticides (for instance, 5%, 10%, 50% chance)?

11) What is the highest chance of a chronic health impact like the ones we just talked about that you would consider acceptable for on-the-job contact with pesticides (for instance, 5%, 10%, 50% chance)?

Part III:

Let's move on to a new set of questions. I'd like to ask you about a few more details about the pest control decision factors we were talking about in the first part of our interview. (Note to interviewer, the appearance of these questions are based on their earlier responses)

a. Pesticide Efficacy

12) How do you get information on pest control strategies' efficacy?

13) How do you compare pest control method's efficacy?

14) Are you familiar with the WSU Crop Protection Guide's efficacy classification system (using categories of suppression activity vs acceptable control vs excellent control)?

___Yes
___No

15) If a pesticide provided suppression activity only for codling moth, would you ever choose it for codling moth control?

___Yes
___No

16a) If yes, under what conditions?

16) Imagine you are choosing between two hypothetical methods that are entirely equivalent except for efficacy. One is rated as having "excellent" control (such as Altacor, Calypso, or Assail) and one has "acceptable" control (such as Imidan, Intrepid, or Proclaim) How much preference would you have for the "Excellent" control?

___I wouldn't have any preference
___I would slightly prefer the excellent control
___I would strongly prefer the excellent control
___I would only use those rated as excellent control

b. *<u>Resistance Management (Repeating Classes)</u>*

17) How often do you recommend the same pesticide twice in the same generation for the same orchard?

___Never
___Rarely
___Sometimes
___Often
___All of the Time

18) How often do you recommend the same pesticide for two different generations for the same orchard?

___Never
___Rarely
___Sometimes
___Often
___All of the Time

19) How often do you recommend the same pesticide three or more times in the same generation for the same orchard?

___Never
___Rarely
___Sometimes
___Often
___All of the Time

20) How often do you recommend pesticides from the same chemical class in the generation for the same orchard?

___Never
___Rarely
___Sometimes
___Often
___All of the Time

21) How often do you recommend pesticides from the same chemical class three or more times in the same generation for the same orchard?

___Never
___Rarely
___Sometimes
___Often
___All of the Time

c. *Previous Experience*

22) I prefer to recommend methods I know have worked for me in previous years:

___Strongly Disagree
___Disagree
___Neither Agree nor Disagree
___Agree
___Strongly Disagree

23) If a new chemical class of pesticide is developed for codling moths, I would recommend it more readily than classes that have been around for longer:

___Strongly Disagree
___Disagree
___Neither Agree nor Disagree
___Agree
___Strongly Disagree

d. Post-Harvest Interval

24) What is the longest pre-harvest interval that you would accept in a codling moth pesticide?

25) If two pesticides are otherwise identical, and pesticide A has a pre-harvest interval of 1 day, what is the longest PHI pesticide B could have that would not affect your choice between them (3 days? 5 days?).

e. Protective Equipment

26) Why is Protective Equipment an important factor?

27) Pesticide A requires only long sleeves and pants, and shoes and socks, whereas pesticide B also requires chemically resistant gloves. They are otherwise equal. Which do you prefer?

__A is strongly preferred
__A is slightly preferred
__No difference
__ B slightly preferred

__B strongly preferred

28) Pesticide A requires long pants and sleeves, chemical resistant gloves, and socks and shoes, whereas pesticide B requires all of these an additional coverall. They are otherwise equal. Which do you prefer?

__A is strongly preferred
__A is slightly preferred
__No difference
__ B slightly preferred
__B strongly preferred

29) Pesticide A requires long pants and sleeves, chemical resistant gloves, socks and shoes, and a coverall, whereas Pesticide B requires a layer of chemical resistant clothing and a respirator. They are otherwise equal. Which do you prefer?

__A is strongly preferred
__A is slightly preferred
__No difference
__ B slightly preferred
__B strongly preferred

f) Pollinator Impacts

30) Pesticide A is not recommended for application to blooming trees at any time for protection of pollinators, whereas Pesticide B may be applied to blooming trees, but only when bees are not actively foraging. They are otherwise equal. Which do you prefer?

__A is strongly preferred
__A is slightly preferred
__No difference
__ B slightly preferred
__B strongly preferred

31) Pesticide A is recommended for application only when bees are not actively foraging, whereas Pesticide B can be applied to blooming trees any time day or night. If they are otherwise equal, what is your preference?

__A is strongly preferred
__A is slightly preferred
__No difference
__ B slightly preferred
__B strongly preferred

32) Do you avoid specific methods, pesticides or classes of pesticides because of their toxicity to pollinating insects?

___Yes
___No

33b) Which chemicals or methods do you avoid to protect pollinators?

g) Beneficial Impacts

33) Are there specific beneficial orchard insects that you consider most important to safeguard?

___Yes
___No

34b) Which species of beneficial orchard insects are most important to preserve?

34) Pesticide A has a high impact on an important beneficial, whereas Pesticide B has a medium impact. If they are otherwise equal, which do you choose?

__A is strongly preferred
__A is slightly preferred
__No difference
__ B slightly preferred
__B strongly preferred

35) Pesticide A has a medium impact on an important beneficial, whereas Pesticide B has a low impact. If they are otherwise equal, what is your preference?

__A is strongly preferred
__A is slightly preferred
__No difference
__ B slightly preferred
__B strongly preferred

h) Price

37) What is the most you would recommend a grower pay per acre for mating disruption?

38) What is the most you would recommend a grower pay per acre for a codling moth control pesticide?

39) What is the most you would recommend a grower pay per acre for a non-pesticide, non-mating disruption control method (like CM granulosis)?

40) Hypothetically, everything else about them is equal. What is the smallest difference in price that would matter in selecting a pesticide ($0.50? $1.00?)?

i) Re-entry Interval

41) What is the maximum re-entry interval you would consider acceptable for a codling moth pesticide?

42) If everything else about them is equal, but Pesticide A has an REI of 4 hours, what is the longest REI pesticide B could have that wouldn't make a difference in your decision (12 hours, 1 day, etc)?

j) Other Criterion (x) – text may be adjusted slightly to fit the criteria named by the participant

43) Is there a minimum acceptable value of (x)

44) Is there a maximum acceptable value of (x)

45) What's the smallest difference in (x) between two alternatives that would change your decision?

46) Do you have any other general comments or follow-up thoughts?

47) Thank you very much for your time and help with this project. Would you prefer your gift card emailed or physically mailed to you?

Survey end time:

APPENDIX D

BENCHMARK DOSE MODELING DATA FOR ALL ANCILLARY HEALTH IMPACTS (THOSE NOT INCLUDED IN CHAPTER 3)

Pesticide	Outcome	Model	Variable	Mean	SE	95% CL	
Acetamiprid	Changes in auditory startle (PND 20)	Hill	intercept	214.087	25.657	163.799	264.374
			maximum change	-101.587	34.322	-168.857	-34.318
			power	1.000	--	--	--
			dose with half maximal change	6.499	7.491	-8.182	21.181
	Viability index	Weibull	background	0.070	--	--	--
			slope	0.000	--	--	--
			power	14.296	--	--	--
	Hepatocellular hypertrophy	Log-logistic	background	0.000	NA	--	--
			intercept	-70.377	1.061	-72.456	-68.298
			slope	18.000	NA	--	--
	Locomotor activity	Hill	intercept	254.694	86.471	85.214	424.173
			maximum change	299.632	119.535	65.348	533.915
			power	3.196	4.583	-5.787	12.180
			dose with half maximal change	20.758	14.019	-6.718	48.235
Azinphos methyl	RBC Cholinesterase	Exponential	background response	2.022	0.123	1.780	2.264
			slope	0.859	0.263	0.343	1.376
			asymptote parameter	0.096	0.055	-0.012	0.204
	Preimplantation loss	Exponential	background response	1.500	0.894	-0.251	3.251
			slope	2.609	2.03E+10	-3.98E+10	3.98E+10
			asymptote parameter	14.622	8.908	-2.837	32.081
			power	4.821	4.53E+10	-8.88E+10	8.88E+10
Chlorantraniliprole	Hepatocellular hypertrophy	Log-probit	background	0.000	NA	--	--
			intercept	-3.096	0.447	-3.971	-2.220
			slope	0.298	0.079	0.144	0.453
	Tremors	Quantal-linear	background	0.000	--	--	--

			slope	0.116	0.149	-0.177	0.408
Emamectin benzoate	Fertility index (female)	Quantal-linear	background	0.201	0.045	0.114	0.289
			slope	0.042	0.038	-0.033	0.116
	Motor activity PND 17	Exponential	background response	1139.330	69.300	1003.503	1275.157
			slope	0.863	0.785	-0.676	2.401
			asymptote parameter	0.534	0.139	0.261	0.807
Methoxyfenozide	RBC count	Exponential	background response	6.519	0.131	6.262	6.776
			slope	0.018	0.010	-0.002	0.039
			asymptote parameter	0.849	0.026	0.797	0.901
	Hindlimb grip	Exponential	background response	435.295	21.574	393.010	477.580
			slope	0.00014	0.000038	0.00006	0.00021
			asymptote parameter	0.000	NA	--	--
	Hepatocellular hypertrophy	Log-probit	background	0.000	NA	--	--
			intercept	-16.555	1014.720	-2005.380	1972.270
			slope	2.976	195.258	-379.723	385.675
Novaluron	RBC count	Exponential	background response	7.490	0.095	7.304	7.677
			slope	0.068	0.050	-0.030	0.167
			asymptote parameter	0.895	0.032	0.832	0.958
	Respiration rate	Quantal-linear	background	0.001	0.024	-0.046	0.047
			slope	0.000	0.000	0.000	0.000
	Epidydimal sperm count (F1)	Exponential	background response	2110.010	94.200	1925.379	2294.641
			slope	0.003	0.002	-0.0003	0.006
			asymptote parameter	0.785	0.049	0.690	0.880
Phosmet	RBC Cholinesterase	Hill	intercept	3730.660	54.412	3624.010	3837.300
			maximum change	-2805.240	70.994	-2944.380	-2666.090
			power	18.000	--	--	--
			dose with half maximal change	4.866	0.052	4.764	4.967
	Fertility index	Log-probit	background	0.038	0.037	-0.035	0.111
			intercept	-1.339	0.415	-2.151	-0.526
			slope	0.344	0.164	0.021	0.666
Pyriproxyfen	Cholesterol level	Exponential	background response	62.529	2.246	58.126	66.932
			slope	0.005	0.002	0.002	0.009
			asymptote parameter	2.088	0.193	1.709	2.466
	Red Blood Cell count	Exponential	background response	9.589	0.099	9.396	9.782
			slope	0.019	0.008	0.003	0.036
			asymptote parameter	0.916	0.013	0.891	0.940
	Kidney nephritis	Log-probit	background	0.196	0.055	0.088	0.303
			intercept	-5.419	2.725	-10.759	-0.079
			slope	0.797	0.412	-0.010	1.604
	Pup weight gain	Power	background	52.481	0.721	51.068	53.894
			slope	0.000	0.000	0.000	0.000

			power	18.000	NA	--	--
Spinetoram	Bone marrow necrosis	Logistic	intercept	-2.724	1.168	-5.013	-0.436
			slope	0.156	0.073	0.014	0.298
	T-4	Exponential	background response	4.091	0.129	3.838	4.344
			slope	0.546	0.401	-0.240	1.333
			asymptote parameter	0.783	0.050	0.686	0.880
	AST elevation	Exponential	background response	28.787	1.401	26.041	31.534
			slope	0.131	0.087	-0.040	0.302
			asymptote parameter	1.440	0.240	0.968	1.911
Thiacloprid	Hepatocellular hypertrophy	Log-logistic	background	0.000	--	--	--
			intercept	-2.537	0.481	-3.479	-1.594
			slope	1.000	--	--	--
	Thyroid follicular cell hypertrophy	Log-probit	background	0.000	NA	--	--
			intercept	-2.537	0.481	-3.479	-1.594
			slope	1.000	NA	--	--
	Startle reflex	Hill	intercept	27.759	3.280	21.331	34.187
			maximum change	8.525	5.238	-1.742	18.792
			power	9.723	1542.440	-3013.410	3032.850
			dose with half maximal change	4.196	31.614	-57.767	66.159
	Motor activity	Hill	intercept	469.069	35.428	399.632	538.506
			maximum change	-661.112	460.951	-1564.560	242.335
			power	1.000	NA	--	--
			dose with half maximal change	122.203	163.392	-198.040	442.446

Table 17: Endpoints used in exceedance fraction calculations for health-health tradeoffs

Pesticide	Endpoint Used in BMD Model	Selected CES	Dose x 100	NOAEL	10% BMD	10% BMDL	20% BMD	20% BMDL
Acetamiprid	Changes in auditory startle (PND 20)	10%	0.768	10	1.74	0.30	--	--
	Viability index	10%		17.9	50.83	37.28	--	--
	Hepatocellular hypertrophy	10%		7.1	44.16	14.32	--	--
	Locomotor activity	10%		10	9.87	0.27	--	--
Azinphos methyl	RBC Cholinesterase	20%	0.833	0.15	0.23	0.17	0.50	0.35
	Preimplantation loss	10%		2.5	0.14	1.24E-05	--	--
Chlorantraniliprole	Hepatocellular hypertrophy	10%	23.900	935	437.45	219.07	--	--
Emamectin benzoate	Tremors	10%	0.009	0.075	0.91	0.19	--	--
	Fertility index (female)	10%		0.6	2.54	0.94	--	--
	Motor activity PND 17	10%		0.1	0.28	0.11	--	--
Methoxyfenozide	RBC count	10%	0.343	16.8	27.69	9.56	--	--
	Hindlimb grip	10%		1000	772.91	296.79	--	--
	Hepatocellular hypertrophy	10%		197.5	169.42	114.27	--	--
Novaluron	RBC count	10%	0.804	4.38	2.00	0.90	--	--
	Respiration rate	10%		650	3788.99	898.38	--	--
	Epididymal sperm count (F1)	10%		1551.9	233.28	96.86	--	--
Phosmet	RBC Cholinesterase	20%	3.000	4.5	2.75	0.58	4.60	4.53
	Fertility index	10%		1.5	1.18	0.00	--	--
Pyriproxyfen	Cholesterol level	10%	20.800	100	17.73	11.47	--	--
	Red Blood Cell count	10%		23.9	6.87	3.13	--	--
	Kidney nephritis	10%		87	180.14	40.80	--	--
	Pup weight gain	10%		100	484.27	302.37	--	--
Spinetoram	Bone marrow necrosis	10%	0.028	2.7	6.62	3.31	--	--
	T-4	10%		74.87	1.13	0.003	--	--
	AST elevation	10%		10	1.97	0.48	--	--
Thiacloprid	Hepatocellular hypertrophy	10%	0.382	1.2	1.40	0.64	--	--
	Thyroid follicular cell hypertrophy	10%		8.9	21.60	12.89	--	--
	Startle reflex	10%		4.4	3.89	4.08E-14	--	--
	Motor activity	10%		3.1	9.33	3.24	--	--

VITA

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