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Comparative Probabilistic Assessment of Occupational Pesticide Exposures Based on Regulatory Assessments

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Abstract

Implementation of probabilistic analyses in exposure assessment can provide valuable insight into the risks of those at the extremes of population distributions, including more vulnerable or sensitive subgroups. Incorporation of these analyses into current regulatory methods for occupational pesticide exposure is enabled by the exposure data sets and associated data currently used in the risk assessment approach of the Environmental Protection Agency (EPA). Monte Carlo simulations were performed on exposure measurements from the Agricultural Handler Exposure Database and the Pesticide Handler Exposure Database along with data from the Exposure Factors Handbook and other sources to calculate exposure rates for three different neurotoxic compounds (azinphos methyl, acetamiprid, emamectin benzoate) across four pesticide-handling scenarios. Probabilistic estimates of doses were compared with the no observable effect levels used in the EPA occupational risk assessments. Some percentage of workers were predicted to exceed the level of concern for all three compounds: 54% for azinphos methyl, 5% for acetamiprid, and 20% for emamectin benzoate. This finding has implications for pesticide risk assessment and offers an alternative procedure that may be more protective of those at the extremes of exposure than the current approach.

Keywords

Occupational exposure; pesticides; probabilistic exposure assessment

1. INTRODUCTION

Probabilistic analyses of hazard and exposure are increasingly used in environmental health in general[(1–5)] and particularly in risk assessment of pesticides.[(6–10)] Probabilistic exposure assessment has several potential advantages over deterministic methods for risk assessors and managers. The use of distributions instead of summary statistics can be more

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informative of exposure extremes and therefore more protective of the population at risk due to higher exposure. 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 variability and 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 separate characterization of uncertainty and variability in exposure contributes to the accurate estimation of the joint uncertainty and variability of risk.[11]

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.[12] 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 the most 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.[13]

The regulation of pesticides is an example of a framework that has commonly used deterministic estimations of exposure and dose to assess human health risks (HHRs). Occupational exposures are assessed for regulatory purposes as a measure of central tendency (arithmetic or geometric mean, or median, depending on the distribution of the data). This measure is combined with other exposure factors, some of which are measures of central tendency (inhalation rate), and some of which are a maximized value. This calculation produces a measure that is deterministic, but less conservative than dietary estimates, which are based on the 99th percentile of exposure. To date, most probabilistic pesticide exposure studies have focused on dietary exposures; only a few have addressed occupational exposures. Lunchick described a case study of developing exposure distributions for occupational pesticide handlers treating cotton.[13] Phung *et al.* used Monte Carlo simulation methods to characterize exposure of rice farmers to chlorpyrifos, finding evidence of potential acute overexposure.[14] The Bystanders, Residents, Operators, and WorkerS Exposure (BROWSE) project carried out through the E.U. seventh framework developed probabilistic models of pesticide exposure in a variety of occupational scenarios, demonstrating the utility of probabilistic assessment for use in regulatory assessments.[15] The BROWSE project as well as the Monte Carlo risk assessment model have been applied for aggregate and cumulative probabilistic assessments, demonstrating that these methods can improve on the information provided by worst-case deterministic methods in complex exposure scenarios.[16,17]

The Agricultural Handler Exposure Task Force curates a set of exposure studies that are used to derive average exposure mass/mass active ingredient rates (mass of exposure in micrograms of active ingredient per pound of active ingredient handled) during specific work tasks.[18,19] This exposure rate, an estimate of the amount of active ingredient that deposits on or is inhaled by a person per unit of work accomplished, together with

information on specific product application rates and exposure factors from sources such as the Exposure Factors Handbook, are used to calculate the daily dose (the amount of the active ingredient absorbed into the human body per kilogram body weight) used in regulation of the pesticide's use.[20] The resulting exposure rates from the AHETF data sets are used for risk-assessment-based pesticide regulation by the U.S. Environmental Protection Agency (EPA), the California Department of Pesticide Regulation, and 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.[21] Azinphos methyl, an organothiophosphate pesticide, causes neurotoxicity through the inhibition of cholinesterase.[22] One prominent use of azinphos methyl was the control of codling moth in pome fruit orchards. There are a variety of alternative insecticides and noninsecticidal methods that have taken the place of azinphos methyl. Some of these alternatives, for example, the avermectin benzoate salt known as emamectin benzoate and the neonicotinoid acetamiprid, also have the potential to cause neurotoxicity to mammals.[23,24] 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 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.

2. METHODS

Simulations of occupational handler 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[19,25] using the same assumptions where possible.

Exposure was first estimated for the three 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 data sets contain exposure rates that were calculated based on data collected using slightly different methods. AHED® is considered the more robust data set, but at the time of data analysis, the AHED® wettable powder mixing and loading scenarios were not available. The collection methods and sample sizes for the applicable pesticide handling scenarios are summarized in Table I. Both data sets contain the necessary variables such as collected sample mass, flow rate of air sampling devices, and

length of time performing tasks to calculate the exposure rates reported along with the raw data.

2.1. 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.[19,25] The mass-normalized inhalable mass was estimated according to the exposure algorithm described below.

For masses collected using powered active air sampling, that is, with an air pump or impinger (air technology "2" or "3" in the PHED data set, and all samples in the AHED® data sets), normalized inhaled exposure is calculated as:

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

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

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

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 this case, to set up the variable for combination with the inhalation rate distribution, the assumed mixing and loading breathing rate of 16.7 L/minute (1.0 m^3/hour) was substituted in for the sample flow rate in the above calculation according to the Standard Operating Manual for the PHED software.[23] The distributions fit to air samples from each scenario are summarized in Table II.

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 among 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 nonessential). The third estimate of breathing rate is a deterministic value from the NAFTA Technical Working Group on Pesticides

recommendation for application task breathing rates.[26] Breathing rates for mixing and loading activities were determined similarly, but using values for “medium” activity levels. The distributions are summarized in Table II.

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.[27] The 2010 review article by Nicas summarized estimated protection factors for half-face respirators from seven studies.[28] Lognormal distributions were established according to reported geometric means and standard deviations from each study; see Table II. These distributions and the deterministic value of 0.1[27,29] were sampled with equal probabilities to create a distribution of protection factors where the deterministic value is sampled with 1/8 probability.

In the EPA HHR computations, inhalation doses are estimated using the normalized inhalation mass exposure previously described, multiplied by the amount of active ingredient applied. The amount applied is equal to an assumed maximum area (40 acres for airblast applications) multiplied by the highest application rate per unit area for the pest control product under consideration (acetamiprid: 0.15 lb/acre, azinphos methyl: 1.5 lb/acre, and emamectin benzoate: 0.015 lb/acre). The exposure is adjusted down by fixed percentages for half- and full-face respirators (90% and 98% protection is assumed, respectively), and the dose is calculated by dividing that exposure by an assumed body weight of 70 kg (or 60 kg in some older assessments, such as for acetamiprid airblast application).

2.2. 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.

2.2.1. 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.

2.2.2. 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,[30] 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.

2.2.3. 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.[30] 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 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.

2.2.4. Chemical-Protective Clothing—For each body section, the label-prescribed clothing and protective equipment was used to apply protective factors. For those pesticides that 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.*,[32] two distributions from Driver *et al.* for airblast application and wettable powder mixing and loading,[33] and deterministic values of 0.1 from CDPR assumptions[33] and 0.5 from EPA assumptions.[35] The chemical-resistant factor was drawn from sampling equally between the CDPR assumption of 0.01[34] and distributions based on data for Tyvek and PVC-coated cloth from Keeble *et al.*[32]

In EPA HHR assessments for dermal exposure scenarios, the exposure rates for each body part as described above are multiplied by fixed fractions of the mass assumed to be removed by clothing and protective gear (50% for each layer of clothing on the body whether normal cloth or chemical protective), or are based on measured deposited mass with and without protective layers, gloves, or hat. The individual mass rates are summed to create a total body

exposure rate normalized to the mass amount of active ingredient applied for a variety of task and protective equipment scenarios. As with the inhalation exposure rates, this value is multiplied by the highest rate of application per land area and the maximum assumed application area per day. The fraction of compound absorbed through the skin (acetamiprid: 30%, and then 10%, azinphos methyl: 42%, and emamectin benzoate: 1.8%) and an assumed body weight of 70 (or 60 kg) are used to adjust the exposure to a dose per day.

2.3. Exposure Data Structure and Interpolation

A number of both the dermal and inhalation exposure measurements in PHED were below the limit of quantification (see Table III). The protocol for those values in the EPA exposure algorithm is to substitute ½ LOQ. 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.[36] For each sampled skin section and for the mass collected with air sampling, as listed in Table III, the missing values were therefore estimated via interpolation. The interpolation was accomplished by assignment of a distribution to the log-transformed values with the *fitdistr* function of the R package fitdistrplus. Randomly selected values from the distribution below the LOQ were back-transformed and substituted for missing data. The preinterpolation and postinterpolation distributions are compared in Table III. 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 data set from AHED® had very limited numbers of samples below the LOD (limit of detection) or LOQ(limit of quantitation) 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 data sets but also creates the possibility that the data sets 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, or 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 data set. 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.[19,37,38]

To check the effect of including the study as a clustering variable, distributions were fit to the body area sections using the unclustered 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.[39] 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.

2.4. Dose Calculations

Inhalation exposures were assumed to be completely absorbed and available to target systems, so no adjustments to the exposure amounts 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.[40–42] Assumption of fixed fractional dermal absorption is traditional in pesticide exposure assessment, but has significant limitations.[43] It is adopted here for simplicity and comparability with prior analyses.

To calculate the body weight, two distributions were sampled with equal probability: the body weights of participants in the AHETF studies and body weights of adult males from the Exposure Factors Handbook.[31] All variables were combined to calculate dose and margin of exposure (MOE) in a Monte Carlo simulation and distributions of 10,000 doses were simulated 1,000 times for each pesticide using the mc2d package. Variable distributions that represented uncertainty were sampled separately from those representative of variability, and combined as described in Pouillot and Delignette-Muller's 2010 article.[39] In the two-dimensional procedure, variability factors are estimated conditionally for each value of the uncertainty factors. Whether a variable was representative of uncertainty or variability is described in Table II. The *cornode* function of the mc2d package was used to set correlations between within-person exposure rates per body area, and between the body weight and surface areas. The surface area and body weight correlation was set as 0.986.[44] Correlations of exposure between body areas were derived from the AHED® data set. MOEs were calculated as the ratio of the no observable adverse effect level (NOAEL) from each neurotoxicity study to the calculated dose.[45–47] In the EPA HHR assessments, MOE is calculated by dividing the dose, separately for inhalation and dermal doses or as a total dose in some cases, by a reference dose from the selected toxicological study (often an NOAEL). In the case of the three compounds examined in this study, the NOAELs for occupational assessments were selected from studies of neurotoxicity. The short-term NOAEL for acetamiprid is 10 mg/kg, and for emamectin benzoate, 0.075 mg/kg. These values are applied to both separate inhalation and dermal assessments, and to total dose assessments for occupational handlers. In the case of azinphos methyl, a separate dermal and inhalation study produced the NOAELs used in the assessment of 1999[48] and an NOAEL from an oral study was used for comparison with biomonitoring data in the 2006 assessment.[49] The MOEs are considered acceptable if they are above the ratio established as the product of relevant safety factors. The levels of concern (LOCs) for azinphos methyl and dermal exposures to acetamiprid are 100, the typical value for occupational scenarios (the product of factors for human population variability and interspecies differences). Because of a lack

of an inhalation study for acetamiprid, the occupational inhalation LOC for acetamiprid is 1,000.[22] The LOC for emamectin benzoate inhalation and dermal occupational exposures is 300 for short-term and 1,000 for intermediate exposures. The additional uncertainty factor of 3 was applied for short-term exposures due to the severity of the health impact at the LOAEL (neuropathology).[23]

3. RESULTS

3.1. Exposure Rates

The probabilistic estimates of exposure rates in micrograms 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 Figs. 1 and 2. In the case of inhalation exposures, comparison with deterministic values showed exceedance in all cases: 16% for open-cab application, 25% for dry flowable mixing and loading, 43% for packaged wettable powders, and 23% for pourable wettable powders. Dermal exposure exceedances of the deterministic values were similar: 18% exceeded for open-cab application, 22% for dry flowable mixing and loading, 43% for packaged wettable powders, and 66% for the pourable unpackaged wettable powders.

3.2. 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 nonclustered distributions produced for each scenario and exposure rate are shown in Fig. 3. Kolmogorov–Smirnov *p*-values are shown in Table IV. In all scenarios, one or more body sections showed significant differences between the clustered and nonclustered 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 nonclustered 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 MOEs produced were not significantly different for these three pesticides whether clustered or nonclustered distributions were used in their construction.

3.3. Dose

The estimated dose distributions, repeated 1,000 times (1,000 iterations to estimate the uncertainty, 10,000 of variability), are summarized in Table V and illustrated in Fig. 4. Table V also summarizes the deterministic values used in the EPA HHR assessments for tree fruit applicators and mixer-loaders and provides the arithmetic means of distributions for comparison with the HHR values as the HHR values are based on arithmetic means of exposure. 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 from the simulation exceeded that value for each compound (Table V).

3.4. MOEs

Computed distributions of MOEs generated from comparison of the NOAEL and total dose distributions are shown in Fig. 5. MOEs were also calculated for separate inhalation and dermal doses as shown in Table V. The MOE for azinphos methyl ranged from 0.1 to 116,556, with a geometric mean of 83 (GSD = 6). One percent of the MOE 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 HHR assessments through both inhalation and dermal doses (see Table V) for some fraction of the pesticide handler population.

3.5. 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 data for coefficients). 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 that 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 MOEs do not change significantly depending on the assignment.

4. DISCUSSION

Exposure data sets 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 the EPA assessments were followed as a framework, with addition of variability and uncertainty where possible. The exposure distributions were translated to doses that 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 MOEs 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 estimates.

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 combined impacts of dermal and inhalation exposure must also be considered in cases where the separate pathways do not exceed levels of concern; however, the combined MOEs are not consistently evaluated in cases where the NOAELs come from toxicological studies based on different exposure routes or scenarios. 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[49] although the calculations in this analysis are based on PHED and AHED® data. For acetamiprid and emamectin benzoate, no biomonitoring data are available for comparison. Although the percent of the estimates that exceed the level of concern for those pesticides is lower than for azinphos methyl, they represent a potential for overexposure 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 data sets exist, opening up other options for calculation of regulatory limits such as a selected 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 uncharacterized differences in the degree of protection against chemical exposures, as seen in this analysis. For example, acetamiprid and emamectin benzoate are both permitted for use and therefore might be perceived as equally safe for workers. However, different percentages of the worker population using each pesticide are potentially exposed beyond levels of concern. It also obscures the true decision being made: What probability 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,[50] and yet among the occupationally exposed measures of central tendency are accepted. To incorporate probabilistic exposure assessment into the current regulatory framework, the concept of acceptable exposure and risk limits must be reevaluated in the context of variability and uncertainty. At minimum, a percentile exposure to be compared against toxicological measures such as the NOAEL or BMD must be established if the current risk assessment methods are to be used with the additional exposure information. The potential for compounded conservatism[51] 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, the 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 data sets curated by a task force supply a standard data set and the tasks are well defined. This analysis demonstrates calculations implemented using freely available open-source software. It may be that other occupational exposure data sets exist that could be used in a similar fashion to thoroughly examine the effects of a variety of regulatory limits on population exposures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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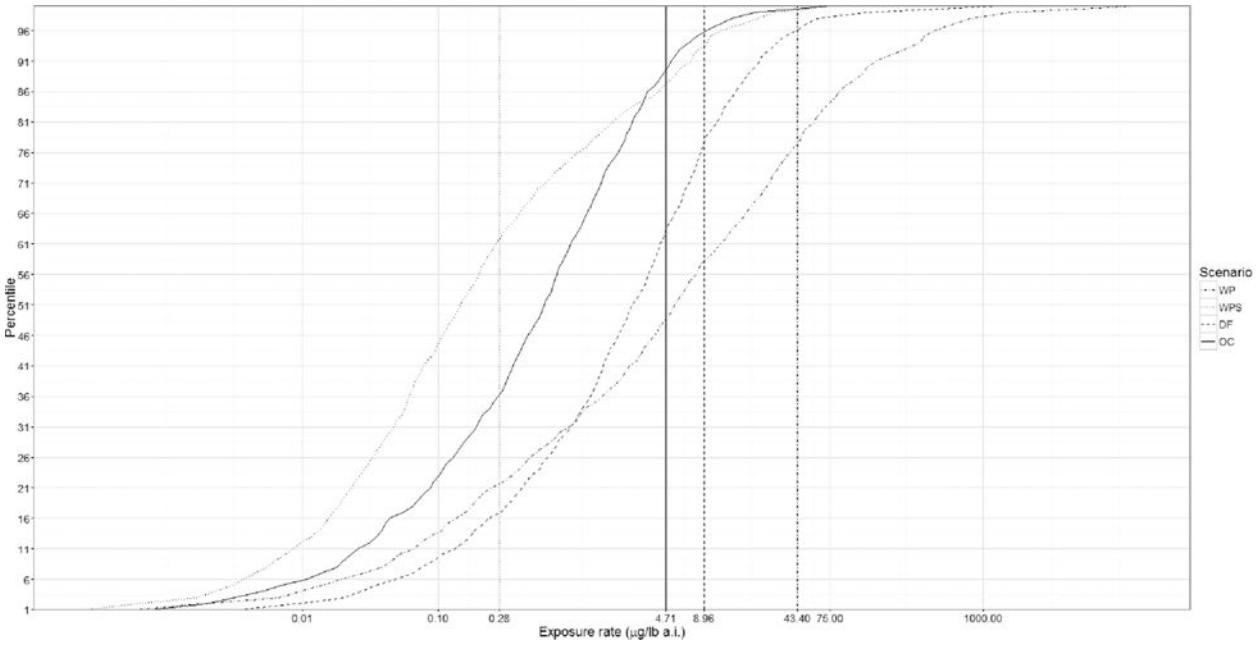

Fig. 1.

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.

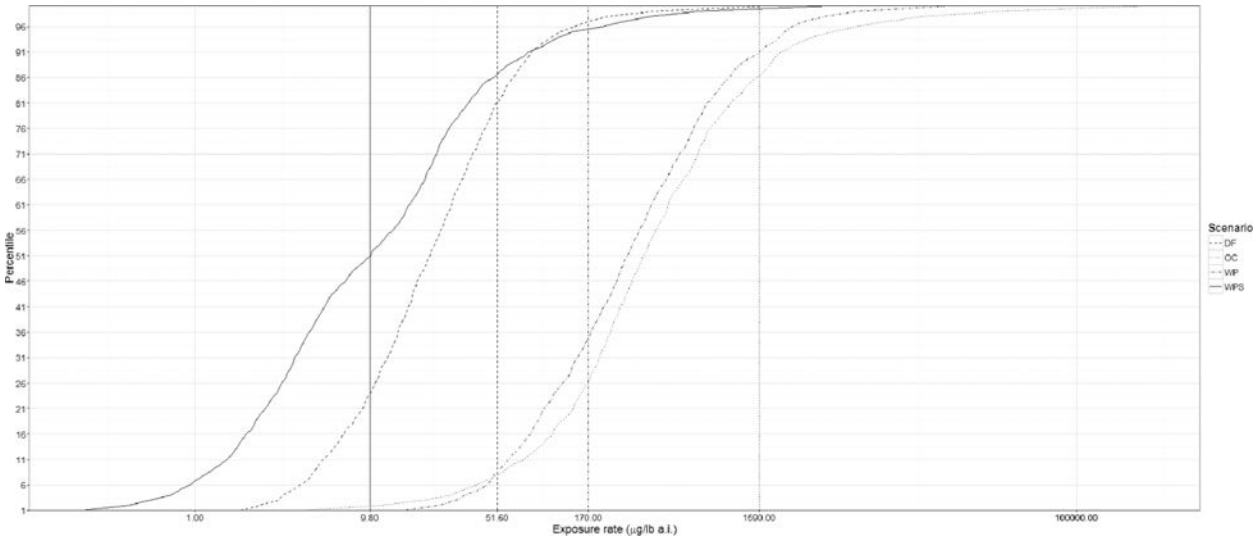

Fig. 2.

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.

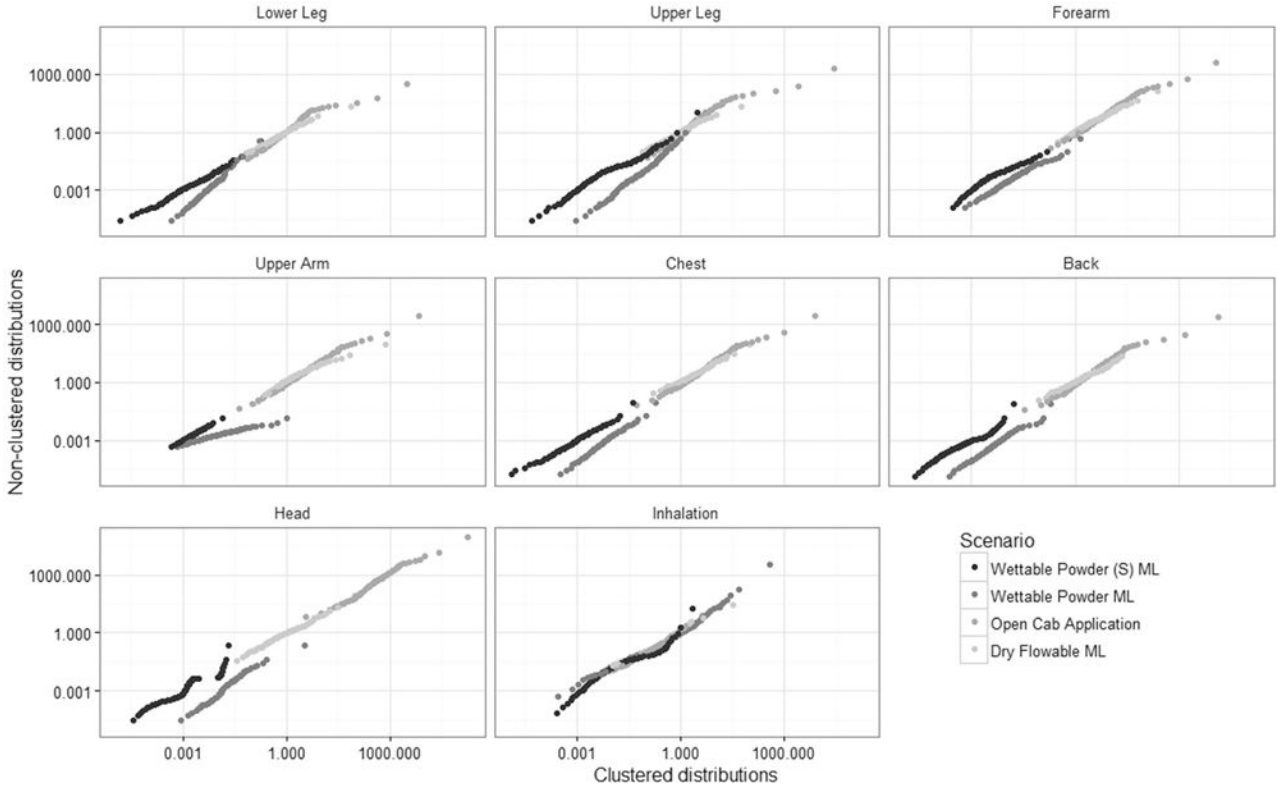

Fig. 3.

Quantile–quantile plots of exposure rate distributions by body area and exposure scenario illustrating the agreement between the clustered and nonclustered distributions.

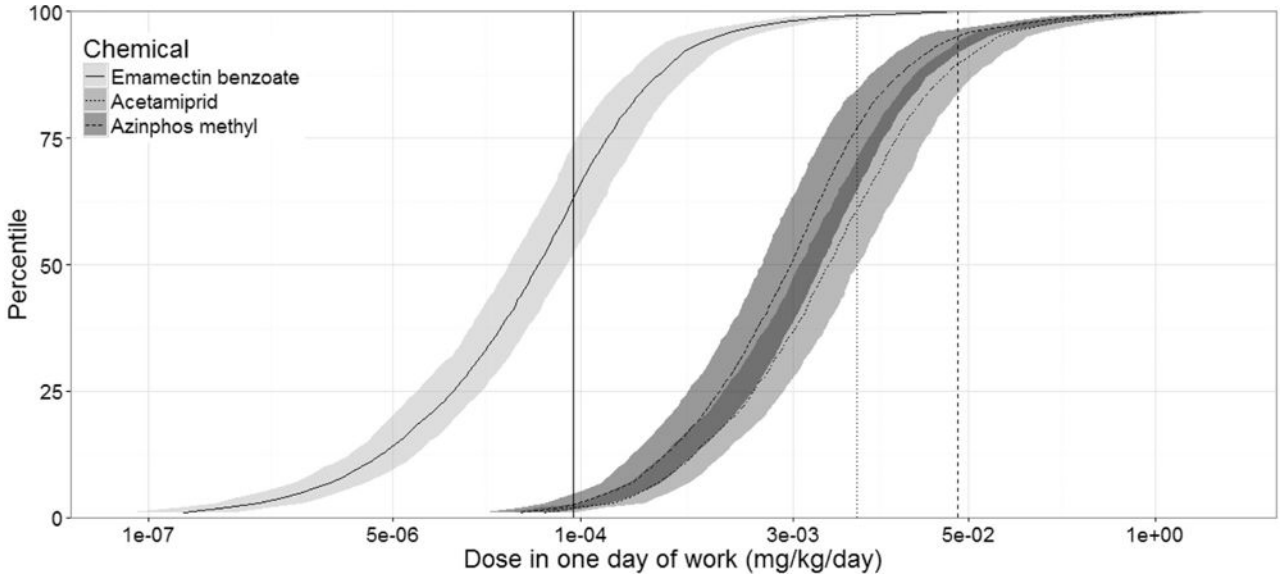

Fig. 4.

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. The shaded portions represent the 95th percentile of the uncertainty simulations surrounding the median estimate of dose.

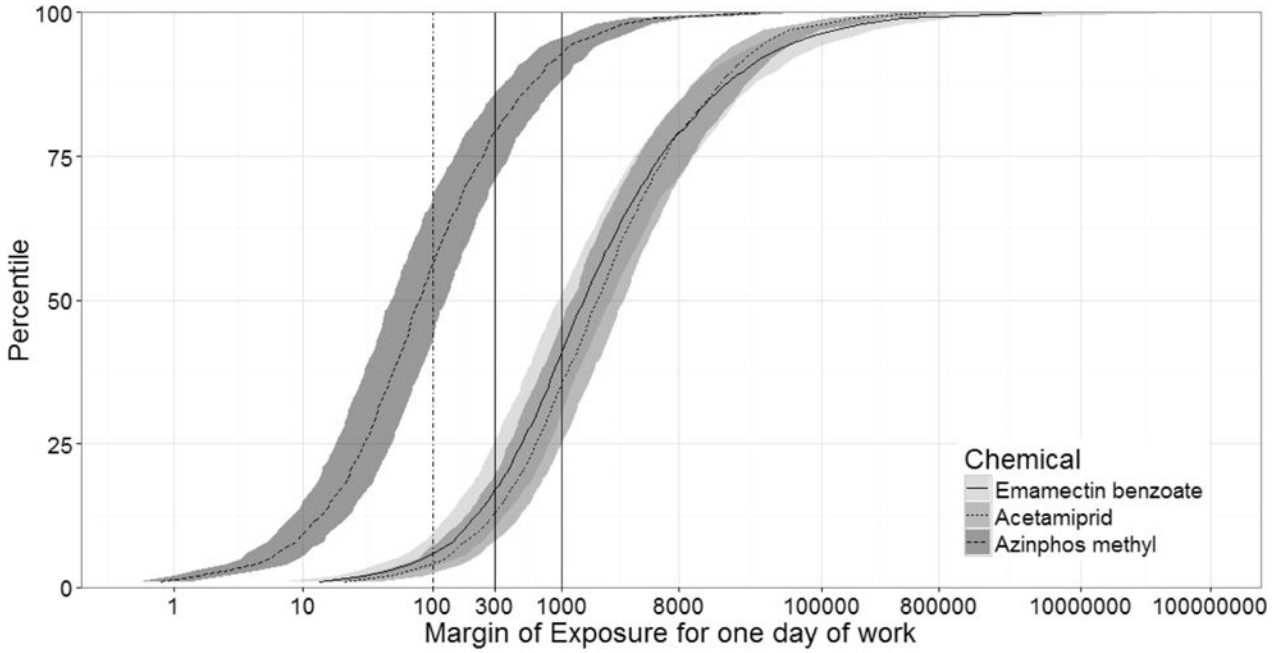

Fig. 5.

Probabilistic margin of exposure (MOE) 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 exposures, and 300 for emamectin benzoate short-term exposures, 1,000 for intermediate exposures to emamectin benzoate. The shaded portions represent the 95th percentile of the uncertainty simulations surrounding the median estimate of MOE.

Table I

Characteristics of the Studies Comprising the Four Pesticide Handling Scenarios of Interest in the AHED® and PHED Data Sets

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 II

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/hour)							
Exposure factors (all outdoor workers "medium")[31]		0.84		0.47	Normal	(0, ∞)	Variability
Exposure factors (essential outdoor workers "medium")[31]		0.84		0.54	Normal	(0, ∞)	Variability
NAFTA Technical Working Group[26]		1	NA		NA	NA	
Application inhalation rate (m^3/hour)							
Exposure factors (all outdoor workers "slow")[31]		0.71		0.4	Normal	(0, ∞)	Variability
Exposure factors (essential outdoor workers "slow")[31]		0.78		0.36	Normal	(0, ∞)	Variability
NAFTA Technical Working Group[26]		0.5	NA		NA	NA	
Respirator protection fraction (from Nicas *et al.*)[27]							
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[34]		0.9			Scalar	NA	NA
EPA[25]		0.5			Scalar	NA	NA
Keeble[32]		0.975		0.06	Normal	(0.78, 1)	Variability
Driver[33]		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[52]		Mode = 1.5			Triangular	(1, 1.5)	Variability

Assumptions	GM	Mean	GSD	*SD*	Distribution Type	(Min, Max)	Dimension
Acetamiprid[53]		Mode = 0.15			Triangular	(0.7, 0.15)	Variability
Emamectin benzoate[54]		Mode = 0.015			Triangular	(0.003, 0.015)	Variability
Application error (proportion)[55]		−0.028		0.26	Normal	(−1, 1)	Uncertainty
Application size (acres)							
mode = 40					Triangular	(0.25, 60)	Variability
Body weight (kg)							
Exposure Factors Handbook		85.47		19.03	Normal	(0, ∞)	Variability
AHETF studies[38]		87.25		16.84	Normal	(0, ∞)	Variability
Skin surface area (cm^2)[31]							
Lower leg		2,680		340.5	Normal	(0, ∞)	Variability
Upper leg		4,120		674.9	Normal	(0, ∞)	Variability
Chest		3,875		829.9	Normal	(0, ∞)	Variability
Back		3,875		829.9	Normal	(0, ∞)	Variability
Upper arm		1,720		291.8	Normal	(0, ∞)	Variability
Lower arm		1,480		297.9	Normal	(0, ∞)	Variability
Head/neck		1,620		109.4	Normal	(0, ∞)	Variability
Face/neck		583		36.5	Normal	(0, ∞)	Variability
Dermal fractional absorbance							
Azinphos methyl[42]		0.42		0.08	Normal	(0, 1)	Uncertainty
Acetamiprid[40]		0.31		0.03	Normal	(0, 1)	Uncertainty
Emamectin benzoate[41]		0.02		0.01	Normal	(0, 1)	Uncertainty

Table III

Comparison of Substitutions for Values Below the Limit of Reporting (LOR, i.e., the Limit of Detection or Reporting) in the PHED Data Sets for Wettable Powder Mixing and Loading (WP) and Soluble Packed Wettable Powder Mixing and Loading (WPS)

	WP (n)	% <LOR	WPS (n)	% <LOR	Wettable Powder $\mu g/cm^2$				Wettable Powder (Soluble Packaging) $\mu g/cm^2$			
Observations (*n*)	78	–	15	–	Interpolation		1/2 LOR substitution		Interpolation		1/2 LOR 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 IV

Kolmogorov–Smirnov *p*-Values Generated by Comparison of Clustered and Nonclustered 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

*A single study provided these values and therefore clustered and nonclustered are the same.

Table V

Exceedance Fractions, Expressed as Population Percentages, of Probabilistic Estimates and Summary Statistics for EPA Human Health Risk (HHR) Deterministic Values of Dose and Margin of Exposure (MOE) and Level of Concern (LOC), and NOAELs Identified from Relevant Studies of Neurotoxicity

	NOAEL (μg/kg/day)	EPA HHR Deterministic Dose (μg/kg/day)	EPA HHR Estimated MOE	EPA Levels of Concern (LOCs) Used to Evaluate MOE	Mean of Probabilistic Dose Distribution (μg/kg/day)	% (95% CI) of Probabilistic Dose Distribution Greater than HHR Deterministic Dose	% (95% CI) of Probabilistic MOE Distribution Beyond (Less Than) LOC
AZM	150	8.33[a]	18	100	18.3	27 (19,38)	54 (42,64)
Dermal	560	–	–	100	17	–	53 (43,64)
Inhalation	200	3.42	58		1.3	19 (6,43)	9 (3,15)
ACP	10,000	35.43	282	100	2.8	14 (4,21)	5 (3,8)
Dermal	10,000	31.71	315	100	2.2	13 (8,18)	4 (3,8)
Inhalation	10,000	3.72	2,688	1000	0.6	20 (12,28)	12 (6,18)
EB	75	0.09	837	300	0.4	36 (28,47)	20 (14,26)
Dermal	75	0.04	17,05	300	0.3	39 (5,59)	15 (10,26)
Inhalation	75	0.05	1,645	300	0.1	14 (5,29)	12 (4,20)

[a]The estimated dose used in the most recent EPA human health risk (HHR) assessment of open-cab pesticide handlers for azinphos methyl is based on biomonitoring and inhalation data collected from mixer/loader/applicators (MRID 46316406).(47)

[≠]The levels 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 1,000.(22) 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 HHR assessment due to the severity of the health impact at the LOAEL (neuropathology).(23)