Regulatory Toxicology and Pharmacology 56 (2010) 28–37

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Human health risk assessment of endosulfan. Part III: Occupational handler exposure and risk

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ARTICLE INFO

Article history:
Received 8 July 2009
Available online 23 October 2009

Keywords:
Endosulfan
Pesticide
Handler
Exposure assessment
Risk assessment

ABSTRACT

The United States Environmental Protection Agency (USEPA) and the California Department of Pesticide Regulation (CDPR) have authority to regulate pesticides, respectively, within the United States and within the state of California. Both agencies are obligated to protect human and environmental health within the geographical boundaries where they have authority. Risk assessment of pesticidal active ingredients is conducted by both USEPA and CDPR, yet the agencies have different legal mandates that influence how they conduct assessments. Exposure estimates are key inputs into the risk assessment. Both agencies released draft risk assessments for endosulfan in the same time frame, and while some exposure estimates were similar, many differed considerably. This paper focuses on the differences in exposure estimates for individuals involved in endosulfan applications (handler exposures). Although CDPR and USEPA relied on the same data sets for their exposure estimates for most handler scenarios, CDPR estimates were in some cases more than an order of magnitude higher than estimates from USEPA. Reasons underlying these disparities, and their effects on risk estimates and resulting regulatory decisions, are discussed in this paper. Additionally, because of differences in legal mandates, CDPR estimated exposures for scenarios lacking data, whereas USEPA did not.

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1. Background

Risk assessment of pesticidal active ingredients (AIs) is conducted by the United States Environmental Protection Agency (USEPA) and the California Department of Pesticide Regulation (CDPR). USEPA and CDPR have authority to regulate pesticides, respectively, within the U.S. and within the state of California. By law, CDPR is allowed to register only pesticides that are registered by USEPA, but can place additional restrictions on use beyond those required by USEPA. Such restrictions may be needed because of California's unique climatic and cultural conditions. Differences in legal mandates and scope of responsibility can cause USEPA and CDPR to approach risk assessment differently, resulting in exposure and risk estimates that vary between agencies for the same chemical compound.

Endosulfan is a cyclodiene chlorinated hydrocarbon that is used as a broad-spectrum foliar insecticide and miticide on more than 50 crops in California. In the U.S. outside California, use is allowed on additional crops such as potatoes, sweet potatoes, and tobacco. Formulations registered in California include an emulsifiable concentrate containing 34% AI and a wettable powder containing 50% AI; other emulsifiable concentrates containing 9–24% are registered in the U.S. but not in California. Exposure and risk assessments for endosulfan were released for public comment by USEPA in November 2007 (USEPA, 2007a) and by CDPR in January 2008 (Beauvais, 2008; Silva, 2008). A recently registered cattle ear tag consisting of impregnated material containing 30% endosulfan was not included in either risk assessment.

Several endosulfan product labels have California-specific application directions; in some cases, fewer applications or lower application rates are allowed in California than in other states. In part, this is because pesticide residues can take longer to dissipate under the arid conditions that commonly occur in California's growing season. For many crops, growing seasons are longer in California than in other parts of the U.S., leading in some cases to more occasions when pesticides may be used. These factors contribute to dissimilar handler exposures and risks being estimated by CDPR and USEPA.

With regard to legal mandates, USEPA performs risk assessments to meet requirements of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Under FIFRA, USEPA conducts reregistration of pesticides initially registered prior to November 1984, preparing quantitative risk assessments to determine which uses are eligible for reregistration under current scientific and regulatory standards. Uses are eligible for reregistration following one

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0273-2300/$ - see front matter Published by Elsevier Inc.
doi:10.1016/j.yrtph.2009.10.002

of two determinations by USEPA: (1) the use is associated with acceptable risks, or (2) uses may have unacceptable risks yet have favorable risk–benefit results that trigger USEPA to allow reregistration. For uses that do not meet these criteria, a registrant desiring to reregister a use may negotiate changes such as lower application rates, packaging changes, etc. USEPA will sometimes consider these changes in its exposure assessment; for this reason, some exposure calculations may not reflect current product labels. Exposure estimates prepared by USEPA for handlers consider a range of conditions, including what USEPA refers to as "baseline" (i.e., no personal protective equipment (PPE) or engineering controls are used) through the levels of engineering controls and PPE needed to get acceptable risk estimates.

CDPR conducts risk assessments on currently registered pesticides under multiple sections of the California Food and Agriculture Code, for the purpose of determining whether there are unacceptable risks requiring mitigation, based on current product labels. In CDPR's risk assessment, human health risks associated with exposures by all routes and all uses are assessed. When the risk assessment is completed, CDPR may address risks determined to need mitigation by requiring changes in how affected products are used, or CDPR may cancel certain uses. Unlike USEPA, CDPR has no reregistration authority; a product is registered in California indefinitely unless CDPR determines that its use results in unacceptable risks that cannot be mitigated by other means.

Differences between the agencies in toxicology data review, in hazard identification and in endpoint selection ("no-observed-effect-levels" or NOELs), are addressed by Silva and Beauvais (2009); comparison of dietary exposure assessments is covered by Silva and Carr (2009); and dissimilarities in estimating exposure to field workers and the public through non-dietary exposures are discussed by Beauvais et al. (2009). Key differences in handler exposure assessment, and their impact on handler risk estimates, are discussed in this paper.

2. Handler exposure scenarios

In quantitative risk assessments prepared by USEPA and CDPR, numerical risk estimates are calculated from toxicity endpoints and exposures estimated for individual exposure scenarios. An exposure scenario describes a situation where people may contact pesticides or pesticide residues, as defined by combinations of factors such as product formulation, equipment, and specific activities.

Persons mixing, loading and applying pesticides, flaggers (persons who mark the location for a pesticide application while the application is occurring), or anyone otherwise involved in a pesticide application (e.g., cleaning equipment following an application) are referred to collectively as "handlers." Handler exposure scenarios are described as combinations of task, type of pesticide formulation, and equipment used in handling activities. Only agricultural uses are allowed for endosulfan in California; federally, residential uses were canceled in 2000 at the request of the registrants (USEPA, 2002). Therefore, all exposure scenarios considered in the risk assessments involve agricultural applications.

Most AIs, including endosulfan, have a wide variety of handler exposure scenarios, or combinations of task, formulation type, and equipment. It would be desirable to have exposure estimates for each scenario. However, little information is available for many scenarios. Furthermore, some scenarios are likely to result in similar exposures, and can be combined into broad categories such as aerial applicators, which encompass exposures of individuals applying pesticides from any of several types of aircraft. For these reasons, both USEPA and CDPR estimate exposure and risk for a finite set of scenarios. Although handler scenarios considered by the two agencies have substantial overlap, there are differences as well.

3. Exposure durations

For each scenario in its endosulfan risk assessment, CDPR provided estimates for short-term (defined as acute and up to one week), seasonal (intermediate-term intervals, lasting from one week to one year), and annual exposures. Seasonal exposure is defined by CDPR as a period of frequent exposure lasting more than a week but substantially less than a year, whether the exposure is constant or intermittent during the period. Annual exposure integrates all exposure periods during the year (Beauvais, 2008).

Exposure durations considered by USEPA differed somewhat from those considered by CDPR. USEPA defines short-term durations as 1–30 days, and intermediate-term durations as 1–6 months. USEPA (2007a) estimated handler exposures for short-term durations only. No explanation was given by USEPA (2007a) for only considering short-term scenarios for handlers. In the absence of evidence that a handler might be exposed for intermediate- or long-term durations, USEPA only estimated short-term exposures. In contrast, CDPR includes estimates for intermediate- and long-term exposures for handler scenarios, because no information is available on exposure durations and it is possible that commercial applicators might be repeatedly exposed.

4. Factors affecting handler exposure and risk estimates

Both CDPR and USEPA calculate screening estimates in their risk assessments. Although individuals in each scenario might potentially be exposed to a range of endosulfan concentrations, for quantitative risk assessment purposes the highest realistic exposures, based on available data, are determined; if these estimates indicate acceptable risk, then lower exposures will as well. Screening estimates are calculated using the maximum application rates allowed for each use, along with any other conditions that would tend to increase exposure. Ideally, screening estimates provide the maximum realistic exposure. To achieve this purpose it is critical that estimates do not underestimate actual exposures.

Handler scenarios are associated with some of the highest exposures to endosulfan. Although CDPR and USEPA relied on the same data sets for their exposure estimates for most handler scenarios, short-term CDPR estimates were in some cases more than an order of magnitude higher than corresponding estimates from USEPA. Toxicity endpoints and NOELs used to estimate risk are discussed in detail by Silva and Beauvais (2009); only the acute oral NOELs (USEPA NOEL = 1.5 mg/kg/day; Bury, 1997 versus CDPR NOEL = 0.7 mg/kg/day; Nye, 1981) differed between the agencies. NOEL values for dermal and inhalation routes were based on distinct toxicity endpoints from different studies; however, numerically they were similar and thus did not differ for the purpose of risk assessment. Risk estimates are calculated by both CDPR and USEPA as Margin of Exposure (MOE) values. The MOE is calculated by dividing the NOEL by the exposure estimate, and quantitatively estimates how much below the NOEL exposure is anticipated to be. Higher exposures result in smaller MOEs, and reflect higher risks.

CDPR considered a total of 28 endosulfan handler scenarios, including seventeen mixer/loader, six applicator, four mixer/loader/applicator (MLA), and one flagger scenario. For each scenario, the highest application rate allowed for the type of application was assumed. USEPA calculated exposure and risk for handlers involved in applications to specific crops, often with a range of application rates, yielding a total of 321 scenarios. Of these, 146 were mixer/loader, 83 were applicator, 64 were MLA, and 28 were flagger scenarios. CDPR and USEPA considered 26 overlapping scenar-

ios; USEPA did not calculate exposures for two of the 28 scenarios identified by CDPR, applicators dipping nursery stock into endosulfan solutions or for MLA applying endosulfan with a backpack sprayer. Handler exposures are expected to occur predominantly by dermal and inhalation routes. Both USEPA and CDPR calculated separate dermal and inhalation exposures and risks for handler scenarios. For all 26 overlapping scenarios, the dermal MOEs calculated by USEPA were greater than those calculated by CDPR, with dermal MOE ratios (USEPA/CDPR) ranging 2.1–41.1 (median 3.7).

Fig. 1 summarizes ratios of dermal MOEs (USEPA/CDPR) for five example scenarios, selected to illustrate specific factors (e.g., applicators using groundboom sprayers), or because their MOE ratios were the highest. For simplicity, Fig. 1 and Tables 1–7, which break down the exposure differences summarized in Fig. 1, are focused on the dermal route. Similar figures and tables could be constructed for inhalation exposure or exposures from inhalation and dermal routes combined; the dermal route alone is presented to improve clarity and because it dominates total exposure and risk (as shown in Tables 9 and 10). Fig. 1 shows that MOE ratios for the example scenarios range from 5.7-fold for groundboom applicators to 41-fold for aerial applicators. The critical dermal NOEL selected by USEPA for short-term exposures is approximately twice that used by CDPR (Silva and Beauvais, 2009), and exposures estimated by CDPR for these five scenarios range from 3- to 24-fold greater than those estimated by USEPA (the range of CDPR/USEPA dermal exposure ratios for all 26 scenarios was 1.2–24, with a median of 2.2).

4.1. Relative contribution of factors to exposure estimates

Table 1 summarizes ratios of six factors contributing to disparities in exposure estimates: amount of endosulfan assumed to be handled during a workday, percent dermal absorption, default body weight, exposure statistic used, assumption of PPE (and engineering control for aerial applicators), and CDPR's upper-bound upper confidence limit (UCL) estimate for short-term exposures. The ratios of these six factors, when multiplied together, equal the ratios of the exposures estimated by CDPR and USEPA. Of the factor ratios, the PPE and body weight are less than one for all selected scenarios, indicating that CDPR's assumptions result in lower exposure estimates than USEPA's assumptions. Each of the factors is examined in greater detail below.

Exposures (in mg/kg/day) are calculated by multiplying exposure rates (in μg/lb AI handled) by the amount of AI handled in pounds, divided by the body weight; to get absorbed-dosage estimates, the amount of endosulfan estimated to penetrate the skin, based on a laboratory study with rats, is also incorporated into the calculation. Table 1 illustrates that for all factors except pounds endosulfan handled, USEPA and CDPR used different values (i.e., ratios were not equal to one). Even for pounds handled, in both handwand-MLA scenarios CDPR assumed a higher amount than USEPA, based on product labels that allow application of solutions containing 1 lb AI/100 gallons to macadamia nut trees and an assumption that 40 gallons of solution would be used in a workday, for an assumption of 10 lbs handled. USEPA did not specifically address this use; the highest amount considered by USEPA was based on application of solutions containing 0.0075 lbs AI/gallon to stone fruit trees as a postharvest bark treatment and an assumption that 1000 gallons of solution would be used in a workday, for an assumption of 7.5 lbs handled.

For dermal absorption, USEPA and CDPR used data from the same study, but arrived at different estimates, 45% and 47.3%, respectively. Both estimates were based on an unpublished study in which female CD rats were dosed dermally with ^{14}C-endosulfan at 0.1, 1.0 and 10 mg/kg. Applied to a 10.8-cm^2 area of shaved dorsal surface, these treatment levels provided doses of approximately 0.037, 0.37 and 3.7 mg/cm^2, respectively. Treated areas were washed after a 10-h exposure duration, and groups of animals were euthanized at 24, 48, 72 and 168 h post-treatment, then radioactivity levels were quantified in tissue samples (Craine, 1988).

USEPA used a default body weight of 60 kg, according to its guidance which recommends that exposure assessors "use 60 kg for females when the selected endpoint is from a reproductive or developmental study" (USEPA, 1997b). This is based on the mean body weight of females during their reproductive stage, between ages 13 and 54 years. In contrast, CDPR used 70 kg, a default rounded from the median body weight of adults aged 18–74, reported in a survey conducted in the United States between 1976 and 1980 (USEPA, 1997a). Although CDPR recognizes that the body weight data were collected approximately 30 years ago, and newer estimates of average weight are available which suggest higher values (e.g., Ogden et al., 2004), CDPR continues to rely on the default of 70 kg because it was taken from the same data set as the height and weight measurements used by USEPA to estimate body surface areas for the U.S. population (USEPA, 1997a). Body surface area is used to calculate dermal exposure estimates from the Pesticide Handlers Exposure Database (PHED, 1995).

4.2. Pesticide Handlers Exposure Database

This section explains values in the sixth and seventh columns of Table 1, "Statistics" and "UCL on UB," both of which involve using data from PHED to estimate handler exposure.

Rarely is there sufficient chemical-specific data available to estimate exposure for all exposure scenarios. Even when chemical- and task-specific worker exposure studies are available, they cannot cover all application rates, application methods and protective clothing/PPE combinations. Gaps often exist in data used to estimate handler exposure.

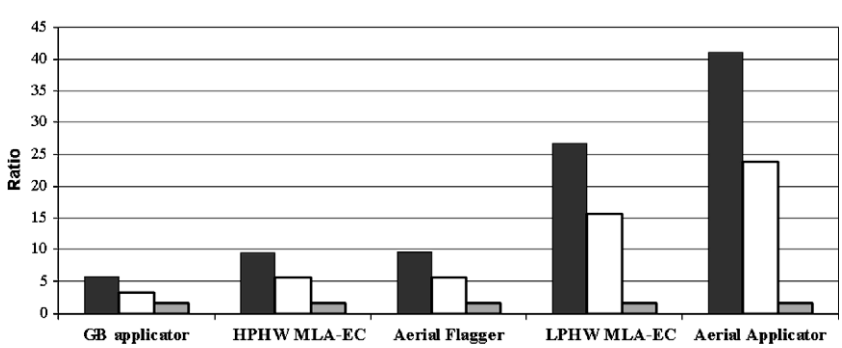

Fig. 1. Comparison of selected handler dermal risk estimates calculated by USEPA and CDPR. Black bars represent ratios of Margins of Exposure calculated by USEPA/CDPR. White bars represent ratios of dermal exposures calculated by CDPR/USEPA. Gray bars represent the ratio of the "no observed effect level" or NOEL (USEPA/CDPR). Abbreviations: GB, groundboom; HPHW, high-pressure handwand; MLA-EC, mixer/loader handling emulsifiable concentrate; LPHW, low-pressure handwand.

Table 1
Ratios of factors contributing to differences between short-term dermal exposures estimated by CDPR and USEPA for selected scenarios.

Scenario[a]	Exposure ratio[b]	Pounds handled	Dermal absorption	Body weight[c]	Statistic[d]	UCL on UB[e]	PPE[f]
GB applicator	3.3	1.0	1.05	0.86	1.82	4	0.51
HPHW MLA-EC	5.6	1.3	1.05	0.86	2.77	5	0.33
Aerial flagger	5.7	1.0	1.05	0.86	3.95	4	0.40
LPHW MLA-EC	13.9	1.3	1.05	0.86	3.67	6	0.52
Aerial applicator	24.0	1.0	1.05	0.86	12.4	6	0.36

[a] Abbreviations: GB, groundboom; HPHW, high-pressure handwand; MLA-EC, mixer/loader handling emulsifiable concentrate; LPHW, low-pressure handwand.
[b] Ratio of exposure estimated by CDPR to exposure estimated by USEPA.
[c] Ratio of default body weight assumed by USEPA to CDPR (ratio inverted because exposure calculation divides by body weight).
[d] Ratio of statistics used by CDPR and USEPA to summarize PHED results, whether arithmetic mean (CDPR) or median or geometric mean (USEPA).
[e] CDPR's approximation of upper confidence limit on an upper bound.
[f] CDPR assumed lower penetration than did USEPA through coveralls and chemical-resistant gloves that handlers are required to wear. Ratios in this column are of the decrease in dermal exposure calculated with protection factors.

Table 2
Pesticide Handlers Exposure Database central tendency estimates for dermal exposure rates in selected scenarios (μg/lb AI handled).[a]

Scenario[b]	Median	Geometric mean	Arithmetic mean	Ratio of AM to:	
				Median	GM
GB applicator	12.1	14.7	25.5	2.11	1.73
HPHW MLA-EC	2450	2730	7040	2.87	2.58
Aerial flagger	10.3	14.5	43.4	4.21	2.99
LPHW MLA-EC	402	533	1580	3.93	2.96
Aerial applicator-OC	31.2	30.0	148	4.78	4.97
Aerial applicator-CC	3.93	4.70	12.1	3.08	2.58

[a] Handlers wearing long-sleeved shirt, long pants, and chemical-resistant gloves. Foot exposure calculated as 0.52 times lower-leg exposure. Results rounded to three significant figures.
[b] Abbreviations as in Table 1, plus OC = open cockpit, CC = closed cockpit.

Table 3
Pesticide Handlers Exposure Database (PHED) exposure rates generally used by USEPA for short-term exposures in selected scenarios (μg/lb AI handled).[a]

Scenario	Frequency distributions of samples reported in PHED[b]	USEPA	GM
GB applicator	Lognormal (chest = normal, legs and thighs = other)	14	14.3
HPHW MLA-EC	Lognormal	2500	2530
Aerial flagger	Other (hands, head and neck = lognormal)	11	14.2
LPHW MLA-EC	Other (neck, upper arms, lower legs = lognormal)	430	518
Aerial applicator-CC	Lognormal	5.0	4.55

[a] Handlers wearing long-sleeved shirt, long pants, and chemical-resistant gloves. Foot exposure omitted. USEPA rounds PHED results to two significant figures.
[b] PHED classifies distributions as normal, lognormal, or "other" (i.e., neither normal nor lognormal).

Table 4
Pesticide Handlers Exposure Database (PHED) exposure rates generally used by CDPR for short-term exposures in selected scenarios (μg/lb AI handled).[a]

Scenario	Non-hand dermal mean	Non-hand dermal multiplier	Mean hand	Hand multiplier	Total dermal (non-hand + hand)
GB applicator	20.9	4	4.56	4	102
HPHW MLA-EC	6580	5	339	5	34,600
Aerial flagger	37.4	4	0.597	4	152
LPHW MLA-EC	1570	6	10.4	6	9480
Aerial applicator-OC	52.2	6	9.63	6	371
Aerial applicator-CC	2.56	5	0.957	4	16.6

[a] Handlers wearing long-sleeved shirt, long pants, and chemical-resistant gloves. CDPR rounds PHED results to three significant figures.

PHED is a computerized database containing monitoring data on inhalation and dermal exposures for pesticide handlers performing mixing, loading, application and flagging tasks, primarily in support of agricultural pesticide applications. PHED was developed by USEPA, Health Canada and the American Crop Protection Association to provide chemical-nonspecific pesticide handler exposure estimates for specific handler scenarios. It combines exposure data from multiple field monitoring studies of different AIs. The use of these chemical-nonspecific (or "generic") exposure estimates is based on two main assumptions, that exposure of handlers performing these tasks is primarily a function of the pesticide application method/equipment and formulation type rather than the physical–chemical properties of the specific AI, and that exposure is proportional to the amount of AI handled (Reinert et al., 1986; Versar, 1992). These assumptions are supported by comparisons of exposure across several studies with multiple AIs, formulations, and types of equipment (Rutz and Krieger, 1992; van Hemmen, 1992; USEPA, 1996). CDPR and USEPA use PHED to estimate handler exposure for scenarios that do not have adequate chemical-specific exposure data.

An exposure assessor using PHED selects a subset of the data having the same or a similar application method and formulation type as the target scenario. Selection of subsets involves making multiple choices, and subsets generated by different users may give different exposure estimates. Additionally, data contained in PHED come from diverse studies conducted under various conditions and employing different monitoring protocols. For example, some studies monitored exposure only to hands or to other parts of the body where investigators anticipated significant exposure. PHED reports three statistics (i.e., medians and geometric and arithmetic means) of inhalation exposure and dermal exposures to the following body regions: head, neck (front and back), chest, back, upper and lower arms, upper and lower legs, feet, and hands. PHED calculates total dermal exposure by summing average exposures over body regions. However, foot exposure rate estimates provided by PHED are not used by either CDPR or USEPA, due to an error in that PHED field (USEPA, 1998). USEPA omits feet from their dermal exposure estimates based on PHED, while CDPR substitutes a value for feet that is calculated as 0.52 times the lower-leg exposure, because the median surface area of the feet is 52% of the median surface area of the lower legs (USEPA, 1997a). This substitution involves a de facto assumption that shoes or boots worn by handlers provide similar protection from exposure as clothing worn on the lower legs; no data are available on the relative protection provided by various types of footwear against penetration of pesticide residues to skin.

USEPA uses central tendency estimates from PHED; different statistics are used for the central tendency of each body region depending on the distribution of data reported by PHED. To determine

Table 5
Example exposure rate calculations for groundboom applicator by USEPA and CDPR for short-term exposures (μg/lb AI handled).

	CDPR	USEPA
Step 1. Adjust for coveralls		
Non-hand dermal from PHED	20.9	7.73
Neck, front	1.5763	0.3296
Neck, back	1.0063	0.2335
Upper arms	1.6914	1.1637
Chest	1.7581	1.7581
Back	3.0175	1.3959
Forearms	2.7301	0.564
Thighs	3.1255	0.764
Lower legs	2.1148	0.476
Total of covered area	17.02	6.685
Protection factor for coveralls (reduction of amount reaching skin)	90%	50%
Adjust covered area (apply protection factor)	1.70	3.34
Area not covered (non-hand dermal – covered area)	3.88	1.05
Non-hand dermal adjusted for coveralls	5.58	4.39
Step 2. Adjust for chemical-resistant gloves		
Hand without chemical-resistant gloves	45.6	6.50
Protection factor for gloves (reduction of penetration)	90%	NA[a]
Hand exposure with gloves (apply protection factor)	4.56	6.29
Total dermal adjusted for coveralls and chemical-resistant gloves	10.1	10.7
Step 3. Upper confidence level estimate (CDPR only)		
Non-hand dermal adjusted for coveralls	5.58	NA
Short-term multiplier for non-hand dermal	4	NA
UCL non-hand dermal adjusted for coveralls	22.3	NA
Hand exposure with chemical-resistant gloves	4.56	NA
Short-term multiplier for hand exposure	4	NA
UCL hand exposure with chemical-resistant gloves	18.24	NA
UCL dermal adjusted for coveralls and chemical-resistant gloves	40.6	NA

[a] NA: not applicable. USEPA did not apply protection factor to exposure data without chemical-resistant gloves; instead, USEPA relied on a smaller data set of exposure monitoring of gloved handlers.

Table 6
Exposure rates used by USEPA and CDPR for short-term exposures including protection factors (μg/lb AI handled).

Scenario	Additional protective measures[a]	USEPA	CDPR[b]
GB applicator	Chemical-resistant gloves and coveralls	11	40.6
HPHW MLA-EC	Coveralls	1600	7400
Aerial flagger	Chemical-resistant gloves and coveralls	10	62.8
LPHW MLA-EC	Coveralls	370	4270
Aerial applicator-CC	Coveralls	5.0	46.7
Aerial applicator-OC	Coveralls[c]	NA	133

[a] Protective clothing and personal protective equipment required by product labels but not worn in studies in the Pesticide Handlers Exposure Database that were used to estimate exposure.
[b] Exposure rates used by CDPR include a multiplier to approximate an upper confidence limit on an upper bound.
[c] Use of coveralls was assumed by CDPR, but not by USEPA.

Table 7
Dermal exposures estimated by CDPR and USEPA for short-term durations for selected scenarios.

Scenario	Application rate[a]	Amount treated[b]	Amount handled (pounds)	Exposure rate (μg/lb AI handled)	Exposure (mg/kg/day)[c]
CDPR					
GB applicator	2.0	80	160	40.6	0.0439
HPHW MLA-EC	0.01	1000	10	7400	0.500
Aerial flagger	2.5	350	875	62.8	0.371
LPHW MLA-EC	0.01	40	0.4	4270	0.0115
Aerial applicator	2.5	350	875	133	0.786
USEPA					
GB applicator	2.0	80	160	11	0.013
HPHW MLA-EC	0.0075	1000	7.5	1600	0.090
Aerial flagger	2.5	350	875	10	0.066
LPHW MLA-EC	0.0075	40	0.3	370	0.00083
Aerial applicator	2.5	350	875	5.0	0.033

[a] Application rates are in pounds active ingredient per acre, except for the two mixer/loader/applicator scenarios, where rates are expressed in pounds active ingredient per gallon of solution.
[b] Amounts treated are in acres treated per day, except for the two mixer/loader/applicator scenarios, where amounts are expressed in gallons of solution per day.
[c] Calculated with the following equation: Exposure = [(0.001 μg/mg) × (exposure rate) × (dermal absorption) × (acres treated/day) × (application rate)]/(body weight). USEPA assumed a dermal absorption of 45%, and CDPR assumed 47.3%. USEPA assumed a body weight of 60 kg, and CDPR assumed 70 kg.

distributions, PHED sequentially tests first for a lognormal distribution, by log-transforming the values within each subset (for dermal subsets, each body region is separately tested). If the log-transformed data fail the normal distribution test, then PHED tests the untransformed data for a normal distribution. Both tests are Kolomogrov–Smirnov tests (Versar, 1992). Data failing tests for both lognormal and normal distribution are classified by PHED as having a distribution of "other." For each body part, when PHED reports a normal distribution, USEPA uses the arithmetic mean. Similarly, USEPA uses the geometric mean for data classified as lognormal, and the median when PHED reports a distribution of "other."

USEPA relies on central tendency estimates from PHED regardless of exposure duration while CDPR, in contrast, uses different statistics to estimate handler exposures of different durations. For short-term exposures, CDPR estimates the highest exposure an individual may realistically experience during or following legal endosulfan uses. CDPR believes upper-bound estimates are appropriate for short-term exposures because high-end exposures are possible, and CDPR has an obligation to protect all individuals exposed to pesticides as a result of legal uses. Protecting at the level of average exposure would, by definition, suggest that some individuals (with above-average exposure) could acceptably be exposed to acutely toxic concentrations. CDPR generally uses the estimated population 95th percentile of daily exposure to estimate a realistic upper bound of daily exposure. To estimate seasonal and annual exposures, CDPR estimates the average daily exposure because, over these intervals, an individual is expected to encounter a range of daily exposures (i.e., CDPR assumes that with increased exposure duration, repeated daily exposure at the upper-bound level is unlikely). Although exposure monitoring data are likely to be lognormally distributed (Ott, 1990), and it can be argued that the geometric mean (GM) is closer to the center of a skewed distribution, it is not the center that is of interest in exposure assessment, but the magnitudes of the exposures. The GM is reflective of an exposure near the median; as such, it approximately represents exposure on the day that is higher than half the days and lower than half the days. When the total mass exposure is important, however, the magnitudes of all the daily exposures must be represented, as they are in the arithmetic mean (AM). While extremely high daily exposures are low-probability events, they do occur, and the AM appropriately gives them weight in proportion to their frequency of occurrence.

The decision to use the median, GM, or AM of PHED data in calculating handler exposure can substantially affect the result; the "Statistic" column in Table 1 shows that statistics used by CDPR (AM) ranged from 1.8- to 12-fold higher than those used by USEPA (median or GM). To isolate the effect of statistic selection on exposure, Table 2 summarizes central tendency estimates from PHED for dermal exposure rates of the five example scenarios. For this comparison, the same set of clothing was assumed for all scenarios and estimates include foot exposure estimated according to CDPR practice. For each of the scenarios, the AM is larger than the GM, with ratios between the two ranging 1.7–5.0. Ratios of AM to median for these scenarios range 2.1–4.8. Although it is not the case for scenarios shown in Table 2, with some scenarios in PHED the AM is as much as an order of magnitude greater than the GM and median.

For all but aerial applicators, the ratios in the "Statistics" column of Table 1 are intermediate between ratios of AM:median and AM:GM in Table 2. To help explain why, Table 3 summarizes exposure rates generally used by USEPA, comparing them with the GM. The frequency distribution reported by PHED is included in Table 3; for the two scenarios in which data for all body regions are lognormally distributed (MLA applying emulsifiable concentrates with a high-pressure handwand, and aerial applicator), the exposure rate used by USEPA is identical to the GM, except that USEPA rounded values to two significant figures. Values in Table 3 were calculated without foot exposure, as USEPA practice is to omit foot exposure from PHED-based exposure calculations. Comparison of GM values for MLA applying emulsifiable concentrates with a high-pressure handwand and aerial applicator between Tables 2 and 3 show that CDPR's practice of estimating foot exposure contributed 7% and 3%, respectively, to the GM exposures in Table 2. In general, foot exposures are anticipated to be higher for application methods such as handwands, in which the spray is pointed downward toward the feet (Abbott et al., 1987).

For aerial applicators, Table 2 reports two sets of statistics, for applicators with open and closed cockpits, respectively. USEPA assumed a closed cockpit for aerial applicators. This assumption has some justification, as modern aircraft all have enclosed cockpits with a roof, doors, and windows, unlike the World War II vintage airplanes that were commonly used for aerial pesticides applications in past decades (NATA, 2007). However, there is no legal requirement for closed cockpits during applications, and modern aircraft with closed cockpits can be modified by opening windows or removing doors, which would allow the pilot contact with sprays. For example, CDPR enforcement staff has observed that during hot summer days doors are often removed from helicopters, resulting in open cockpits during application. Thus, in contrast to USEPA, CDPR assumes open-cockpit aerial applicator scenarios in its exposure assessment. In the aerial applicator ratios shown in Fig. 1, USEPA estimates were for applicators with closed cockpits and CDPR estimates were for applicators with open cockpits.

Following the "Statistics" column, the next column in Table 1 summarizes an adjustment used by CDPR to approximate an UCL on an upper bound. When using PHED data to estimate short-term exposure, CDPR estimates the 90% UCL on the 95th percentile; for seasonal or annual exposure, CDPR uses the 90% UCL on the arithmetic mean (Beauvais et al., 2007). The UCL is used to account for some of the uncertainty inherent in using surrogate data and to increase the confidence that the exposures are not underestimated. Estimating the UCL requires knowing the AM and standard deviation (SD) of total dermal exposure; as the SD for total body exposure is not available from PHED, each UCL is approximated by assuming that total exposure is lognormally distributed across persons and has a population coefficient of variation (CV) of 100%. The method of approximation is described in Powell (2007), and uses the fact that in any lognormal distribution with a given CV, the confidence limits are constant multiples of the AM for a given sample size.

Exposure rates generally used by CDPR for the selected handler scenarios are summarized in Table 4. In the risk assessment for endosulfan, CDPR used multipliers corresponding to the median sample size per body region. If the median sample size was between 20 and 119, a multiplier of 4 was used; if it was between 12 and 19, the multiplier was 5. For three of the five scenarios, groundboom applicator and MLA applying emulsifiable concentrates with a high-pressure handwand and low-pressure handwand, Table 1 shows that the upper-bound assumption made by CDPR is the factor with the largest contribution to the discrepancy between CDPR and USEPA. For aerial flaggers, both the upper-bound assumption and the use of the AM rather than the GM or median contributed about equally to the dissimilarity in estimates.

4.3. PPE and engineering controls

The last column in Table 1 summarizes the difference in exposure estimates contributed by assumptions about the effectiveness of PPE. USEPA's risk assessment included recommendations for measures to mitigate unacceptable risks, and a variety of exposure estimates were provided for each scenario, assuming different levels of clothing and PPE. In contrast, the risk assessment and risk mitigation processes occur in sequence at CDPR, and potential mitigation measures are not considered in the risk assessment. Instead, when CDPR estimates exposure for each scenario, only the

clothing, PPE, and engineering controls required by product labels and regulations are assumed. Any scenarios for which risks are considered unacceptable are subject to mitigation after the exposure and risk assessments are completed.

When available exposure data do not match conditions under which exposure is to be estimated, both USEPA and CDPR use generic protection factors as needed for protective clothing, PPE, and engineering controls. A protection factor is an estimated percentage by which the amount of AI reaching the skin is reduced. For example, a 90% protection factor for chemical-resistant gloves means that just 10% of the amount contacting the gloves will penetrate to the skin. These protection factors are based on data to the extent possible; however, because of limited data both agencies rely to some extent on professional judgment to determine protection factors. Recently, the agencies have begun discussions about reviewing protection factors and incorporating newer studies and current scientific understanding of pesticide penetration through various materials.

Table 5 summarizes calculations for one example scenario, the groundboom applicator. CDPR estimated exposure based on high-quality data in PHED for 29 handlers in which monitored subjects wore long-sleeved shirt and long pants, but not chemical-resistant gloves. Endosulfan product labels require handlers to wear chemical-resistant gloves and coveralls over long-sleeved shirt and long pants, and USEPA estimated exposure based on data in PHED for 21 handlers wearing chemical-resistant gloves; of these, eight were from a study with high quality-assurance results (i.e., recovery of laboratory spikes were in the range of 90–110% with a CV of <15%, and field spike recoveries were in the range of 70–120%) and 13 were from studies with lower quality assurance (i.e., recovery of laboratory spikes were in the range of 70–120% with a CV of <33%, and field spike recoveries were either missing or in the range of 30–120%). Rather than rely on studies with lower quality assurance, CDPR estimated exposure based on high-quality data handlers without chemical-resistant gloves and adjusted results with a 90% protection factor for chemical-resistant gloves. Both CDPR and USEPA applied protection factors for handlers wearing coveralls; however, whereas CDPR assumed a 90% protection factor for coveralls, USEPA assumed a 50% protection factor.

Table 6 summarizes the exposure rates used by USEPA and CDPR for each scenario, incorporating protection factors. Estimates used by CDPR also incorporate the multiplier used to approximate the UCL. Table 6 lists additional protective clothing and PPE that are required on current product labels but were not used in exposure monitoring studies in PHED for each example scenario. These include coveralls for all five scenarios (with one exception: USEPA did not estimate exposure for aerial applicators wearing coveralls), and chemical-resistant gloves for aerial flaggers and groundboom applicators. With the inclusion of the UCL multipliers, exposure rates used by CDPR were from 4.6- to 27-fold greater than the rates used by USEPA for the five scenarios. The 27-fold ratio is between exposure estimated by CDPR for open-cockpit aerial applicators and exposure estimated by USEPA for closed-cockpit aerial applicators; regulatory decisions by the two agencies for the aerial applicator scenario are based on different assumptions about equipment. CDPR's estimate for closed-cockpit aerial applicators would be just 9.3-fold greater than the aerial applicator estimated by USEPA. For aerial applicators, assumption of open cockpits by CDPR (i.e., removal of doors) and closed cockpits by USEPA contributed the most to the difference in exposure estimates.

4.4. Changes to handler exposure estimates since the 2007/2008 risk assessments

Since completing the endosulfan risk assessment, CDPR has modified its approach to PHED data (Powell, 2007). In response to external peer reviews, CDPR implemented two changes. First, a different statistical assumption is now used to derive the multipliers for the 90% UCLs on both the mean and the 95th percentile. This is that the population standard deviation is treated as known rather than as estimated from the data. Second, rather than the median sample size of the body regions, CDPR now estimates an effective sample size for each dermal subset as the harmonic mean sample size, weighted by the squared mean dermal exposure. The effect of these changes is generally to decrease short-term exposure estimates and either decrease or increase long-term estimates. Table 8 summarizes exposure rates for the five example scenarios according to the current CDPR policy.

Table 8
Pesticide Handlers Exposure Database (PHED) total dermal exposure rates formerly and currently used by CDPR for short-term and long-term dermal exposures in selected scenarios (μg/lb AI handled).[a]

Scenario	Short-term rate through 2007	Current short-term rate	Long-term rate through 2007	Current long-term rate
GB applicator	102	89.4	25.5	32.1
HPHW MLA-EC	34,600	27,000	13,800	9740
Aerial flagger	152	134	38.0	48.2
LPHW MLA-EC	9480	5360	3160	1930
Aerial applicator-OC	371	238	124	85.5
Aerial applicator-CC	16.6	12.5	12.1	4.49

[a] Handlers wearing long-sleeved shirt, long pants, and chemical-resistant gloves. CDPR rounds PHED results to three significant figures.

The studies in PHED were conducted between 1977 and 1994. It has been recognized for quite some time that newer data are needed, generated using currently accepted methods (FIFRA SAP, 2007). In 2001, a consortium called the Agricultural Handler Exposure Task Force, LLC (AHETF) was formed to address insufficiencies in PHED (USEPA, 2007b). AHETF data will supplement and in many cases replace PHED data, for both USEPA and CDPR. Both agencies review submitted exposure monitoring studies to determine that they were well-conducted, including how well study conditions match real-world conditions and that quality assurance is acceptable.

In some cases, new studies submitted by the AHETF and others address data gaps and are not a direct replacement for PHED because they provide data for a scenario not contained in PHED. An example of such a study is one conducted by the AHETF in which exposure of 25 handlers was monitored during airblast applications to mature, commercial orchard crops in Florida, Idaho, and Georgia (Smith, 2005). These applicators drove open-cab tractors and wore chemical-resistant headgear; PHED lacks data for this scenario. Both USEPA and CDPR used this study in their endosulfan assessments to estimate exposure of airblast applicators, according to their respective policies. USEPA used a central tendency statistic and CDPR used an upper-bound estimate (CDPR did not calculate an UCL on these data because this was a well-conducted, well-described study). CDPR and USEPA jointly reviewed the study, and agreed that the appropriate central tendency statistic for dermal exposure was the arithmetic mean, 70 μg/lb AI handled (USEPA, 2007a). CDPR used this exposure rate when calculating seasonal and annual exposures for this scenario; for short-term exposure, CDPR used the 95th percentile calculated assuming a lognormal distribution, 276 μg/lb AI handled (Beauvais, 2008).

4.5. Risk estimates: Margin of Exposure

Table 9 summarizes dermal and inhalation exposures estimated by CDPR and USEPA; USEPA estimated only short-term exposures for handler scenarios. Inhalation exposures estimated by both CDPR and USEPA for all five example scenarios are lower than dermal exposures, by 30- to 200-fold. As was true for dermal expo-

Table 9
Dermal, inhalation, and aggregate exposure estimates by CDPR and USEPA for selected scenarios (mg/kg/day).[a]

Scenario	Short-term[b]			Seasonal[c]			Annual[d]		
	Dermal	Inhalation	Aggregate (% diet)[e]	Dermal	Inhalation	Aggregate (% diet)[e]	Dermal	Inhalation	Aggregate (% diet)[e]
CDPR									
GB applicator	0.0439	0.001	0.047 (4%)	0.047	0.0005	0.048 (<1%)	0.008	0.00008	0.008 (2%)
HPHW MLA-EC	0.501	0.010	0.513 (<1%)	0.15	0.003	0.153 (<1%)	0.025	0.001	0.026 (<1%)
Aerial flagger	0.371	0.002	0.375 (<1%)	0.057	0.0002	0.057 (<1%)	0.019	0.00005	0.019 (<1%)
LPHW MLA-EC	0.013	0.0001	0.015 (13%)	0.003	0.00002	0.003 (5%)	0.0005	0.000003	0.0005 (25%)
Aerial applicator	0.786	0.004	0.792 (<1%)	0.157	0.001	0.158 (<1%)	0.053	0.0003	0.053 (<1%)
USEPA									
GB applicator	0.013	0.00034	0.017 (21%)	Not estimated			Not estimated		
HPHW MLA-EC	0.090	0.0026	0.096 (4%)						
Aerial flagger	0.066	0.00088	0.070 (5%)						
LPHW MLA-EC	0.00083	0.000026	0.0044 (81%)						
Aerial applicator	0.033	0.00085	0.037 (9%)						

[a] CDPR estimated handler exposures for short-term (defined as acute and up to one week), seasonal (intermediate-term intervals, lasting from one week to one year), and annual durations. USEPA defines short-term durations as 1–30 days; thus, short-term exposure estimates by USEPA overlap CDPR's short-term and seasonal estimates. Exposures are rounded to three significant figures by CDPR and two by USEPA.

[b] Calculated with the following equation: Exposure = [(0.001 μg/mg) × (exposure rate) × (absorption) × (acres treated/day) × (application rate)]/(body weight). USEPA assumed a dermal absorption of 45%, and CDPR assumed 47.3%; for inhalation exposure, both assumed 100% absorption. For dermal exposure, USEPA assumed a body weight of 60 kg, and CDPR assumed 70 kg; for inhalation exposure, both assumed a body weight of 70 kg.

[c] CDPR calculated seasonal exposure using the same equation as short-term exposure and different exposure rates (average rather than upper bound).

[d] CDPR calculated annual exposure with the following equation: Exposure = (seasonal exposure) × (high use months per year)/(12 months per year).

[e] Aggregate = [Total worker (occupational exposure: Dermal + inhalation)] + dietary exposure. %Diet = [Dietary exposure ÷ Aggregate exposure] × 100. CDPR calculated short-term dietary exposure = 0.00206 mg/kg/day based on the 95th percentile of user-day exposure for females (13 + years), nursing; CDPR calculated seasonal and annual dietary exposure = 0.00017 mg/kg/day (%CT; mean annual consumption for females (13 + years)). USEPA calculated short-term dietary exposure = 0.003546 mg/kg/day based on the 99.9th percentile of adults ages 20–49 years.

sures, inhalation exposures estimated by USEPA are lower than those estimated by CDPR.

In addition to dermal and inhalation exposures, Table 9 summarizes aggregate exposure estimates, which also include dietary exposures reported by Silva and Carr (2009) combined with dermal and inhalation exposures. USEPA (2007a) did not estimate aggregate exposures for endosulfan; instead, USEPA considered dietary exposures separately (USEPA, 2007c). The short-term dietary exposure, based on the 99.9th percentile of adults ages 20–49 years, was estimated by USEPA (2007c) at 0.003546 mg/kg/day; this value was added to dermal and inhalation exposures to provide aggregate exposure estimates in Table 9. In comparison, CDPR estimated dietary exposure, based on the 95th percentile of user-day exposure for nursing females 13 years old and above, at 0.00206 mg/kg/day (Silva and Carr, 2009). As shown in Table 9, both dermal and inhalation exposures estimated by CDPR were higher than those estimated by USEPA; total exposures (combined dermal and inhalation) estimated by CDPR ranged 0.012–0.756 mg/kg/day higher, for MLA applying emulsifiable concentrates with low-pressure handwand and for aerial applicator, respectively. CDPR estimated dietary exposure at 0.0015 mg/kg/day less than USEPA. In aggregate exposure estimates, the dietary

Table 10
Dermal, inhalation, total (dermal + inhalation), and aggregate (total + dietary) Margins of Exposure (MOE) used by CDPR and USEPA for selected scenarios.

Scenario	Short-term MOE[a]				Seasonal MOE[a]				Annual MOE[a]			
	Dermal	Inhalation	Total	Aggregate[b]	Dermal	Inhalation	Total	Aggregate[b]	Dermal	Inhalation	Total	Aggregate[b]
CDPR												
GB applicator	**16**	194	**16**	**14**	**25**	388	**25**	180	**71**	243	**71**	112
HPHW MLA-EC	**1**	**20**	**1**	**1**	**8**	**65**	**8**	**7**	**23**	**19**	**22**	**10**
Aerial flagger	**2**	**97**	**2**	**2**	**21**	970	**21**	**20**	**30**	388	**30**	**28**
LPHW MLA-EC	**54**	1940	**54**	**45**	393	9700	393	341	1140	6467	1140	757
Aerial applicator	**1**	**49**	**<1**	**1**	**8**	194	**8**	**7**	**11**	**65**	**11**	**9**
USEPA												
GB applicator	**280**	590	**82**	**68**	Not estimated				Not estimated			
HPHW MLA-EC	**41**	**78**	**12**	**11**								
Aerial flagger	**56**	230	**17**	**17**								
LPHW MLA-EC	4400	7800	1245	316								
Aerial applicator	**110**	240	**32**	**30**								

[a] Bold indicates that MOE is below target MOE (USEPA target is 300 for dermal MOE; all other target MOEs are 100). MOE = Oral NOEL ÷ Exposure Dosage. CDPR used the following NOELs: *For dermal MOE:* Acute (short-term) oral NOEL = 0.7 mg/kg, based on salivation, convulsions/thrashing, noisy/rapid breathing, hyperactivity salivation and nasal discharge in a rabbit developmental study. Subchronic (seasonal) oral NOEL was 1.18 mg/kg/day, based on increased relative liver and kidney weights, decreased food consumption and decreased body weights in a rat reproduction study. Chronic (annual) oral NOEL = 0.57 mg/kg/day, based on premature deaths and neurotoxicity in a 1-year dog study. *For inhalation MOE:* Acute and subchronic NOEL was 0.194 mg/kg/day, based on increased clinical signs in a rat subchronic inhalation study; the estimated chronic NOEL was taken from the same study, and calculated as follows: subchronic NOEL ÷ 10 = 0.0194 mg/kg/day. USEPA used the following NOELs: *For dermal MOE:* Acute (short-term) oral NOEL = 3.7 mg/kg/day, based on decreased pup weight in rat developmental neurotoxity study. *For inhalation MOE:* Acute and subchronic NOEL was 0.2 mg/kg/day, based on decreased body weight gain in a 21-day rat inhalation toxicity study. Exposure doses from Table 9. MOE values were rounded to whole integers.

[b] Aggregate MOE calculation for CDPR: Dietary MOE contribution to aggregate estimations: Acute = 340, 95th percentile for females (13 + years), nursing; Chronic (used also for subchronic) = 3448, females (13 + years), nursing. Aggregate MOE calculation:Aggregate Total MOE (MOE_T) = $\frac{1}{\frac{1}{MOE\ dermal}+\frac{1}{MOE\ inhal}+\frac{1}{MOE\ diet}}$.Aggregate MOE calculation for USEPA (calculated for this paper, not included in USEPA risk assessment): Dietary MOE contribution to aggregate estimations: Acute = 422, 99.9th percentile of adults ages 20–49 years. Aggregate MOE calculation:Aggregate Total MOE (MOE_T) = $\frac{1}{\frac{1}{MOE\ dermal}+\frac{1}{MOE\ inhal}+\frac{1}{MOE\ diet}}$.

contribution estimated by CDPR ranged from less than 1% to 13%, while the corresponding contribution calculated from USEPA estimates ranged 4–81%. CDPR estimated lower percent dietary contributions to aggregate exposures than USEPA mainly because dermal contributions were 4–67% higher.

Table 10 summarizes total and aggregate risks estimated by CDPR and USEPA for the five example scenarios. CDPR determined that all five scenarios were associated with unacceptable risk, while USEPA found that one scenario, MLA applying emulsifiable concentrates with a low-pressure handwand, had MOEs above the target MOE. The practical consequence of this discrepancy is that USEPA would be likely to reregister the use, but CDPR would require additional mitigation.

4.6. Nursery stock root dipping

A consequence of the legal mandate under which CDPR conducts risk assessments is the need to estimate risk for all possible exposure scenarios. Because USEPA's risk assessment determines uses that are eligible for reregistration, USEPA can and does address data gaps by noting that in the absence of required data, specific uses are not eligible for reregistration. Current endosulfan product labels provide directions for preparation of a dipping solution into which nursery stock roots can be dipped. Roots of cherry, peach and plum seedlings used as nursery stock may be dipped in solutions of 1.25 lb endosulfan in 40 gallons of water to prevent peach tree borer damage. This scenario was considered only in CDPR's risk assessment.

Dipping can be accomplished by spraying as well as immersion of the material to be dipped. Exposures from spraying are covered by other scenarios, including high-pressure handwand-MLA and low-pressure handwand-MLA. For this scenario, CDPR assumed that applicators immerse seedling roots into a container such as a bucket or vat while grasping the seedlings just above the roots, and that hands were immersed in the pesticide solution or slurry (Beauvais, 2008). PHED lacks data for this or any similar activity, and in its assessment CDPR estimated dermal and inhalation exposure separately using models available from USEPA's website. Applicator dermal exposure was estimated from equations on dermal absorption of chemicals from water in the Risk Assessment Guidance for Superfund, Part E (RAGS-E; USEPA, 2004). Applicator inhalation exposure was estimated from equations in SWIMODEL (USEPA, 2003). Calculation details are provided as supplementary material as indicated in Appendix A. The total absorbed dose for individuals dipping nursery stock in an endosulfan solution is 41.4 mg/kg/day; this is the highest endosulfan exposure for any scenario estimated by CDPR (Beauvais, 2008), and higher than any exposures estimated by USEPA (2007a). The dermal MOE is <1, and the inhalation MOE is 39; total MOE is <1 (Silva, 2008).

5. Conclusions

Approaches to pesticide exposure assessment differ between regulatory agencies. Differences are due in part to legal mandates under which the agencies conduct risk assessment. In many cases, different approaches can result in substantially different estimates. Because quantitative risk assessment involves comparing exposure estimates to toxicity endpoints when estimating risk, differences in exposure estimates can lead to substantially different estimates of risk as well.

Risk assessments for endosulfan that were recently released by CDPR and USEPA provide concrete examples. Five handler scenarios for which CDPR estimated substantially higher exposures than did USEPA were discussed, and a total of six factors contributing to the differences were identified, including the statistic used (either the AM, GM, or median); assumptions about PPE and engineering controls; CDPR's practice of calculating an upper-bound UCL estimate for short-term exposures based on data from PHED; the amount of endosulfan assumed to be handled during a workday; the percent dermal absorption; and the default body weight. With the exception of body weight, these factors potentially have effects that vary from one risk assessment to the next. For example, CDPR assumed a dermal absorption of 50% for carbofuran (Beauvais and Johnson, 2006), in contrast to the 6% assumed by USEPA (2007d). And for some scenarios, such as dermal exposure of right-of-way applicators or open-pour mixing and loading of liquid formulations, the data are highly skewed and the AM is more than an order of magnitude greater than the GM (USEPA, 1998; Beauvais et al., 2007).

Because USEPA reregisters pesticides, when insufficient data are available to calculate risk estimates for certain pesticidal uses USEPA deems those uses ineligible for reregistration. In contrast, with regard to uses that are registered in California, CDPR does not have a reregistration process, but has authority only to mitigate (including suspending or canceling if necessary) uses it has determined to be associated with unacceptable risks. For endosulfan, CDPR estimated quantitative risks for one handler scenario that USEPA did not, nursery stock root dipping. This scenario had the highest exposure estimate in CDPR's assessment for endosulfan; the estimate was also greater than exposures estimated by USEPA for any scenario.

CDPR and USEPA have separate risk mitigation processes through which unacceptable risks are addressed. USEPA proposed several mitigation measures in its 2002 Reregistration Eligibility Decision; changed risk calculations in its 2007 risk assessment may result in USEPA requiring still other measures in the future. Scenarios in which CDPR has higher exposure estimates than USEPA might prompt CDPR to require additional measures beyond any proposed by USEPA, if proposed measures do not fully address risks identified by CDPR.

Acknowledgments

Policies and practices described in this paper have developed over many years with the input of numerous individuals. Discussions with and writings from scientists at multiple agencies were drawn upon for CDPR's exposure assessment and this paper: from CDPR, we thank Joseph Frank, Susan Edmiston, and our colleagues in the Worker Health and Safety Branch; from USEPA, we thank Jeff Dawson, Jeff Evans, Matt Crowley, and other staff; and from Canada's Pest Management Regulatory Agency we thank Cathy Campbell and others, past and present. We also thank an anonymous reviewer for many helpful suggestions to improve the manuscript.

The authors declare that there are no conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.yrtph.2009.10.002.

References

Abbott, I.M., Bonsall, J.L., Chester, G., Hart, T.B., Turnbull, G.J., 1987. Worker exposure to a herbicide applied with ground sprayers in the United Kingdom. Am. Ind. Hyg. Assoc. J. 48, 167–175.

Beauvais, S., Johnson, J., 2006. Estimation of Exposure of Persons in California to Pesticide Products that Contain Carbofuran. Report No. HS-1803. Worker Health and Safety Branch, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA. Available from: <http://www.cdpr.ca.gov/docs/whs/pdf/hs1803.pdf>.

Beauvais, S., 2008. Estimation of Exposure of Persons in California to Pesticide Products that Contain Endosulfan. CDPR Report No. HS-1647. Final Draft dated January 2008. Worker Health and Safety Branch, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA.

Beauvais, S., Powell, S., Zhao, W., 2007. Surrogate Handler Exposure Estimates for Use in Assessments by the California Department of Pesticide Regulation. CDPR Report No. HS-1826. Worker Health and Safety Branch, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA.

Beauvais, S., Silva, M.H., Powell, S., 2009. Human health risk assessment of endosulfan. IV. Occupational reentry and public non-dietary exposure and risk. Regul. Toxicol. Pharmacol. 56, 38–50.

Bury, D., 1997. Neurotoxicological Screening in the Male and Female Wistar Rat; Acute Oral Toxicity. Unpublished study conducted by Hoechst Marion Roussel, Preclinical Development Germany, Drug Safety, FRG.

Craine, E.M., 1988. A Dermal Absorption Study in Rats with ^{14}C-Endosulfan with Extended Test Duration. Unpublished study submitted by Hoechst Celanese Corporation, Lab Project No. WIL 39029.

FIFRA SAP, 2007. A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding: Review of Worker Exposure Assessment Methods. SAP Minutes No. 2007-03. Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel. Available from: <http://www.epa.gov/scipoly/sap/meetings/2007/january/january2007finalmeetingminutes.pdf>.

NATA, 2007. General Aviation in the United States. National Air Transportation Association, Alexandria, VA. Available from: <http://www.nata.aero/data/files/NATA%20publications/NATA_factbook.pdf>.

Nye, D., 1981. Teratology Study with FMC 5462 in Rabbits. Unpublished study submitted by FMC Corporation.

Ogden, C.L., Fryar, C.D., Carroll, M.D., Flegal, K.M., 2004. Mean Body Weight, Height, and Body Mass Index, United States 1960–2002. Advance Data from Vital and Health Statistics, Report No. 347. National Center for Health Statistics, Centers for Disease Control and Prevention, Hyattsville, MD. Available from: <http://www.cdc.gov/nchs/data/ad/ad347.pdf>.

Ott, W.R., 1990. A physical explanation of the lognormality of pollutant concentrations. J. Air Waste Manage. Assoc. 40, 1378–1383.

PHED, 1995. The Pesticide Handlers Exposure Database, Version 1.1. Prepared for the PHED Task Force representing Health and Welfare Canada, U.S. Environmental Protection Agency, and the National Agricultural Chemicals Association; prepared by Versar Inc., 6850 Versar Center, Springfield, VA 22151.

Powell, S., 2007. Recommended Method for Approximating Confidence Limits for Upper Bound and Mean Exposure Estimates from the Pesticide Handlers Exposure Database (PHED) to Replace the Method of HSM-02037. Memo No. HSM-07004. Worker Health and Safety Branch, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA.

Reinert, J.C., Nielsen, A.P., Lunchick, C., Hernandez, O., Mazzetta, D.M., 1986. The United States Environmental Protection Agency's guidelines for applicator exposure monitoring. Toxicol. Lett. 33, 183–191.

Rutz, R., Krieger, R.I., 1992. Exposure to pesticide mixer/loaders and applicators in California. Rev. Environ. Contam. Toxicol. 129, 121–139.

Silva, M.H., 2008. Endosulfan Risk Characterization Document, Volume I. Final Draft dated January 2008. Medical Toxicology Branch, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA.

Silva, M.H., Beauvais, S.L., 2009. Human health risk assessment of endosulfan. I. Toxicology and hazard identification. Regul. Toxicol. Pharmacol. 56, 4–17.

Silva, M.H., Carr, W.C., 2009. Human health risk assessment of endosulfan. II. Dietary exposure and risk. Regul. Toxicol. Pharmacol. 56, 18–27.

Smith, L.D., 2005. Amended Report: Determination of Dermal and Inhalation Exposure to Workers During Application of a Liquid Pesticide Product by Open Cab Airblast Application to Orchard Crops. Study Number AHE07, dated August 23. Unpublished study submitted by Agricultural Handlers Exposure Task Force.

USEPA, 1996. Occupational and Residential Exposure Test Guidelines. OPPTS 875.1000: Background for Application Exposure Monitoring Test Guidelines. EPA 712-C-96-261. Office of Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency, Washington, DC.

USEPA, 1997a. Exposure Factors Handbook. EPA/600/P-95/002Fa. U.S. Environmental Protection Agency, Washington, DC. Available from: <http://www.epa.gov/ncea/pdfs/efh/front.pdf>.

USEPA, 1997b. Standard Operating Procedures (SOPs) for Residential Exposure Assessments. Draft dated 12/17/97. Work Assignment No. 338102. Residential Exposure Assessment Work Group, including Office of Pesticide Programs, Health Effects Division, U.S. Environmental Protection Agency and Versar Inc.

USEPA, 1998. PHED Surrogate Exposure Guide. Estimates of Worker Exposure from the Pesticide Handler Exposure Database, Version 1.1. Washington, DC: Office of Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency.

USEPA, 2002. Reregistration Eligibility Decision for Endosulfan. Case 0014. Office of Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency, Washington, DC. Available from: <http://www.epa.gov/oppsrrd1/REDs/endosulfan_red.pdf>.

USEPA, 2003. User's Manual: Swimmer Exposure Assessment Model (SWIMODEL) Version 3.0. Office of Pesticide Programs, Antimicrobials Division, U.S. Environmental Protection Agency, Washington, DC. Available from: <http://www.epa.gov/oppad001/swimodelusersguide.pdf>.

USEPA, 2004. Risk Assessment Guidance for Superfund (RAGS), Volume 1: Human Health Evaluation Manual (Part E, Supplemental Guidance for Dermal Risk Assessment). July 2004. Available from: <http://www.epa.gov/oswer/riskassessment/ragse/pdf/chapter3.pdf>.

USEPA, 2007a. Revision of Occupational and Residential Exposure/Risk Assessment for the Endosulfan Reregistration Eligibility Decision Document (RED)(Revised). DB Barcode D339509, dated May 3. Office of Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency, Washington, DC.

USEPA, 2007b. Pesticide Registration (PR) Notice 2007-3: The Agricultural Handlers Exposure Task Force, L.L.C. Notice dated September 20, 2007. Available from: <http://www.epa.gov/PR_Notices/pr2007-3.htm>.

USEPA, 2007c. Endosulfan. Acute and Chronic (Food and Drinking Water) Dietary Exposure Assessment to Update the 2002 Reregistration Eligibility Decision. DB Barcode D336646, dated March 14. Office of Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency, Washington, DC.

USEPA, 2007d. Reregistration Eligibility Decision for Carbofuran. Case 0101. Office of Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency, Washington, DC. Available from: <http://www.epa.gov/pesticides/reregistration/REDs/carbofuran_red.pdf>.

van Hemmen, J.J., 1992. Agricultural pesticide exposure data bases for risk assessment. Rev. Environ. Contam. Toxicol. 126, 1–85.

Versar, 1992. PHED: The Pesticide Handlers Exposure Database Reference Manual. Prepared for the PHED Task Force: Health and Welfare Canada, U.S. Environmental Protection Agency, National Agricultural Chemicals Association. Versar Inc., Springfield, VA.