Pesticide Risk Mitigation Engine

Inhalation Risk Index

White Paper

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Introduction

The inhalation risk index provides a quantitative estimate of the potential risk associated with bystander inhalation exposure that occurs when pesticides volatilize from a treated field after application. Spray drift is not considered as part of this index. Air concentration estimates are based on the vapor pressure of the applied active ingredient and the application rate. The estimated concentration is then compared to a level of concern—the non-cancer Reference Exposure Level (REL) for a one-year-old child, as defined and used by the California Office of Environmental Health Hazard Assessment (OEHHA). The probability that the estimated concentration will exceed the REL is then calculated, with risks in the red zone if the probability exceeds 50%, in the orange zone if the probability is between 10 and 50%, and in the yellow zone if the probability of exceeding the REL is less than 10%.

The VOC risk index uses California Department of Pesticide Regulation (CDPR) emission potential data to provide a risk score for the emission of pesticide Volatile Organic Compounds (VOCs) for farms in air basins that are out of compliance with the Clean Air Act. This score helps farmers meet basin-wide air quality goals, but is not directly related to bystander inhalation risks.

Data Sources for Inhalation Toxicity Reference Values

Reference Exposure Levels (RELs)

The short-term Reference Exposure Level (REL) used in the PRiME inhalation index is an air concentration of a single pesticide that is not anticipated to present a significant risk of an adverse non-cancer health effect for a one-year-old child for a few days of exposure, based on the known toxicity of the pesticide in question. California's Office of Health Hazard Assessment (OEHHA) uses RELs to determine potential risk from inhalation exposure.[1] The California Department of Pesticide Regulation (CDPR) utilizes a similar approach to estimate levels of potential concern for air monitoring projects,[2] calling the endpoints Screening Levels (SLs) prior to finalizing their risk assessments. OEHHA notes that:[1]

> *RELs are designed to protect the most sensitive individuals in the population including infants and children by the selection of appropriate toxicological endpoints and extrapolation models, and by the inclusion of margins of safety in the form of various uncertainty factors (UFs). Since uncertainty factors are incorporated to address data gaps and uncertainties, exposures that exceed the REL do not automatically indicate an adverse health impact.*

The REL is derived from the human-equivalent No Observed Adverse Effect Level (NOAEL) determined from an animal or human toxicity study and accounts for the breathing rate and body weight of the target population (1-year-old children), as well as any Uncertainty Factors

(UFs). The UFs include an intraspecies factor of 10 to account for differences in susceptibility between humans and laboratory animals. Another UF of 10 is generally used to account for intraspecies differences between different humans. When only a LOAEL is obtained from a study, an additional uncertainty factor of 3–10 is typically applied. Yet another uncertainty factor, the Food Quality Protection Act (FQPA) factor of 3–10, is also incorporated for pesticides that US EPA has determined to be more toxic to developing organisms than adults. Thus, the REL is calculated as follows:

$$\text{REL}\ (\mu g/m^3) = \frac{\text{NOAEL}\ (mg/kg\text{-}day) \times 10^3\ \mu g/mg}{1\text{-year-old BR}\ (0.59\ m^3/kg-day) \times \text{UF}_{\text{intra}} \times \text{UF}_{\text{inter}} \times \text{UF}_{\text{other}} \times \text{UF}_{\text{FQPA}}}$$

The NOAEL used in the above equation is either: 1) a human-equivalent inhalation NOAEL, already corrected to reflect continuous exposure duration, or 2) an oral NOAEL, if no inhalation toxicity study is available. When a route-to-route extrapolation like this is used, US EPA and CDPR typically assume that inhalation absorption is 100% of oral absorption (see the **Caveats** section below for additional commentary on this practice).

When an adult Human Equivalent Concentration (HEC) is used to determine the REL,[*] the equation is slightly different, as the value is adjusted by the ratio of the adult breathing rate (in m^3/kg-day) to the breathing rate of a 1-year-old.

$$\text{REL}\ (\mu g/m^3) = \frac{\text{Adult HEC}\ (\mu g/m^3) \times \text{Adult BR}\ (0.26\ m^3/kg-day)}{1\text{-year-old BR}\ (0.59\ m^3/kg-day) \times \text{UF}_{\text{intra}} \times \text{UF}_{\text{inter}} \times \text{UF}_{\text{other}} \times \text{UF}_{\text{FQPA}}}$$

US EPA typically provides HECs for adult males; CDPR typically provides HECs for a 1-year-old child.

Other Terms Used to Define Inhalation Toxicity

US EPA and CDPR have several similar reference metrics for inhalation exposure:

1) the Reference Concentration (RfC)—or more generally, a Reference Value— and

[*] The derivation of an HEC from an animal NOAEL accounts for the difference in exposure time between the animal inhalation study and the exposure time anticipated for humans, as well as differences in breathing rates, surface area of the respiratory tract, and deposition of the pesticide in both the gas phase and as an aerosol or particulate. The HEC is calculated differently depending on whether the pesticide has portal of entry effects only, systemic effects only, or a combination of both types of effects (see Reference 4). US EPA reduces the interspecies UF to three when using HECs. OEHHA's methods for determination of HECs are slightly different from US EPA's, as described in OEHHA's 2008 Technical Support Document for Non-Cancer RELs (see Reference 1 in Literature Cited). In particular, OEHHA is more health-protective, using an interspecies UF of six instead.

2) a Level of Concern (LOC) for short-term and intermediate-term exposure, based on the NOAEL or HEC divided by the target Margin of Exposure (MOE) that is the product of the Uncertainty Factors (UFs).

US EPA's methodology and terminology has been continuously changing over the last 15 years, leading to some differences in the risk assessments for different pesticides. Below are some common terms that are used in US EPA and CDPR risk assessments that may be helpful for understanding inhalation toxicology.

1) The Reference Concentration (RfC)

Prior to 2002, US EPA defined the RfC as follows: [3]

> *"**RfC:** An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effects during a lifetime."*

Historically, RfCs are based on the NOAELs from a chronic (lifetime) inhalation toxicity study, modified by the appropriate UFs. Currently, the term RfC is used for durations less than lifetime as well.

In 2002, a more general definition called the "Reference Value" (RV) was proposed by US EPA's Office of Research and Development (ORD), to replace the RfC and Reference Dose (RfD) (the term used for oral and dermal exposures) definitions and to reflect the fact that the order of magnitude in uncertainty is described by the uncertainty factors:[3]

> ***Reference Value**: An estimate of an exposure, designated by duration and route, to the human population (including susceptible subgroups) that is likely to be without an appreciable risk of adverse health effects over a lifetime. It is derived from a BMDL, a NOAEL, a LOAEL, or another suitable point of departure, with uncertainty/variability factors applied to reflect limitations of the data used.*

US EPA's Office of Pesticide Programs (OPP) has not adopted ORD's recommendations but has instead replaced the term "RfC" by "Level of Concern" (LOC), which to our knowledge has only been defined operationally as the human-equivalent NOAEL for an adult male divided by the various UFs. CDPR continues to use the term RfC, but applies it to different durations of exposure (acute, seasonal, and chronic), as recommended by ORD.

2) The Level of Concern (LOC)

The LOC is presented by US EPA as a human-equivalent NOAEL or HEC[4] divided by the appropriate Uncertainty Factors (UFs) that are expressed as a "target" Margin of Exposure (MOE) for an adult male.[†] For occupational inhalation exposures, short-term (one to thirty days) and intermediate-term (one to six months) LOCs are the most relevant to worker safety and are the most common values found in US EPA pesticide risk assessments. Short-term LOCs are also the most relevant for determining inhalation risks from pesticide volatilization to those who live or work near a pesticide application site. The body weight and breathing rate parameters used to determine EPA's LOCs are for adult males because these values are currently used by EPA in occupational risk assessments for adult male workers. Because the PRiME inhalation index is targeted at protecting vulnerable populations as well as adult males, exposure parameters (breathing rate and body weight) for the more sensitive one-year-old child and the FQPA safety factor are used in calculating RELs. The exposure parameters for an adult, a 7-year-old and a 1-year-old are summarized in Table 1.

Table 1: Exposure Parameters

	Body Weight (kg)	Breathing Rate (m^3/day)
Adult male	70	18
Seven-year old child	25	10
One-year old child	7.6	4.5

Data source: Reference 5.

Availability of RfCs/LOCs and Preferential Selection of Short-Term LOCs

As part of the registration process, US EPA requires the pesticide manufacturer to conduct a number of *in vivo* toxicity tests on laboratory animals to obtain LOCs for different durations of exposure (acute, short-term, intermediate-term and long-term). The exposure window we are trying to match is the day of the application and the few days following, when most of the volatilization occurs and the observed concentrations are highest. This exposure period would qualify as short-term exposure duration. Thus we selected the short-term LOC (one day to one week) when available, as the next most reasonable match for the available data (HECs are used over NOAELs, if they are available). If a short-term LOC is not available, the next preference is the intermediate-term LOC. We do not use the long-term LOC because the exposure duration is not sufficiently similar to the PRiME scenario to provide an accurate comparison (see the

[†] The target MOE is defined as the product of the UFs. For example, if a pesticide has an intraspecies UF of 10, an interspecies UF of 10 and another UF of 3 to account for the lack of a NOAEL, the target MOE is 10 x 10 x 3 = 300. Any exposure with an MOE less than the target MOE is higher than the level determined to be without adverse effects.

Caveats section below for additional commentary on issues related to matching exposure durations).

The LOCs used to calculate the RELs are typically available in EPA Registration documents or Reregistration Eligibility Decision Documents (REDs) and/or the supporting materials for the REDs, or in CDPR's Risk Characterization Documents (RCDs).[6] Where both US EPA and CDPR have determined a level of concern and these values are different, the PRiME index preferentially utilizes the LOC that has been scientifically peer reviewed, if possible. In practice, this means that CDPR's values are used preferentially over US EPA's for pesticides evaluated as California Toxic Air Contaminants (TACs) because a Scientific Review Panel has evaluated CDPR's TAC risk assesments.[7] Otherwise, we used US EPA's LOCs.

Caveats for Inhalation RELs

There are several factors that may contibute to inaccuracies in the inhalation RELs calculated using this methodology:

1) **The use of oral studies to determine an inhalation LOC has not been validated:** An inhalation toxicity study is most appropriate for determining an inhalation LOC, yet inhalation studies are not available for most pesticides. In the absence of inhalation data, both US EPA and CDPR use the NOAEL from an oral toxicity study and do a route-to-route extrapolation, assuming inhalation absorption is 100% of oral absorption. Significant questions were raised about the validity of this approach at a December 2009 US EPA Scientific Advisory Panel (SAP) meeting on volatilization drift. The digestive system degrades many pesticides, thereby reducing the amount absorbed compared to the inhalation exposure route.[8] Inhalation absorption is not 100% either, as some inhaled pesticide is exhaled before it is absorbed. Nevertheless, the SAP members indicated that it was likely that the absorbed dose will be higher by an inhalation route of exposure. In light of this conclusion, the SAP recommended that an additional uncertainty factor of 10 be included in the calculation of the LOC for cases in which a route-to-route extrapolation was used. The RELs used by PRiME to estimate inhalation risk do not incorporate this factor of 10 and therefore may be underprotective for pesticides for which an oral NOAEL serves as the basis for the REL.
2) **The exposure duration for humans does not match that of laboratory animals:** For a person living near a pesticide-treated field, inhalation exposure peaks approximately 4-20 hours after the application started, then decreases over the next several days. In contrast, laboratory animals are usually exposed for six hours per day, five days per week to a constant concentration over one week to three months. Although the conversion to human-equivalent NOAELs accounts for some of this difference, it does not correct for the fact that the animals do not experience the concentration spikes, nor

does it account for the fact that the animals have time to begin to recover from the toxic effects of the exposure during the off hours when they are not being exposed, and thus may exhibit fewer adverse effects than if they were subject to the same exposure pattern as a human. Conversely, for some pesticides, the short-term inhalation LOC is based on a 90-day exposure study for the laboratory animals, whereas bystanders are rarely exposed to a particular pesticide for longer than a week or two. Exceptions arise for the use of soil fumigants, where fumigation of subsequent "blocks" of a few acres could extend the fumigation season and its concomitant exposures to several months, rather than several weeks.

3) **Exposure to chemical mixtures is not accounted for:** The use of "tank mixes" or products that contain multiple active ingredients results in potential exposure to more than one chemical. Few multi-chemical risk assessments have been performed by US EPA or CDPR to date, but it is possible that additive or synergistic toxicities may result from exposures to multiple chemicals. It is unlikely that exposures to mixtures would result in fewer toxic effects. Therefore, the PRiME inhalation index may underpredict risk from exposures to mixtures.
4) **The variation in intra- and inter-species susceptibility is not well-known:** The uncertainty factors used to account for lack of information may be higher or lower than needed to protect children or other vulnerable populations. The UFs are only approximations.
5) **The exposure time period may not apply to everyone:** The inhalation risk index assumes that the exposed person remains in the vicinity of the treated field for 24 hours. This may be true for stay-at-home moms and young children, the elderly, people who work at home, and people who live in communities where multiple applications of the same pesticide (or multiple pesticides with the same mechanism of action) are being made in the same general time period. However, risks for people who spend some time away from the area will be lower. Nevertheless, a grower cannot normally predict the amount of time neighbors will be spending at home; to be protective, one must assume that a 24-hour exposure is possible.

Data Sources for Pesticide Volatilization

California Air Resources Board Air Monitoring Data

To create a measure of inhalation risk due to pesticide volatilization, available air monitoring data and vapor pressure data were used to develop an algorithm to predict the 4–12 hour maximum concentration of a pesticide in air based on its vapor pressure and application rate.[‡]

[‡] DPR and ARB conducted two types of air monitoring studies: "ambient" and "application" studies. "Ambient" studies are designed to monitor background air concentrations in areas of high use of the pesticide in

These predicted air concentrations were compared to the short-term REL for a one-year-old child. Air monitoring data were obtained from the California Air Resources Board (ARB) application site monitoring work under the Toxic Air Contaminant program for CDPR.[9]

The PRiME inhalation risk index reflects only exposures from volatilization drift and does not include exposures from spray drift, which may be problematic for some pesticides that may not drift via volatilization but are sufficiently toxic that even small amounts of spray drift can cause an inhalation hazard for workers in adjacent fields and/or bystanders near to application sites. These pesticides are flagged for the user with a comment, but not ranked.

Figure 1 shows a typical application site monitoring study conducted by DPR and ARB. Measurements were taken at four locations, with sampling periods ranging from 4 to 12 hours in the initial part of the sampling run. For semi-volatile pesticides, there is usually a prominent concentration peak that lags the start of the application by 5–15 hours. In Figure 1, the maximum concentration is measured west of the field, 12 hours after the start of the application. This concentration is referred to as the "4–12 hour maximum concentration" and is the air concentration used to generate the algorithm that correlates vapor pressure and application rate with maximum concentration (see **Index Structure**, below).

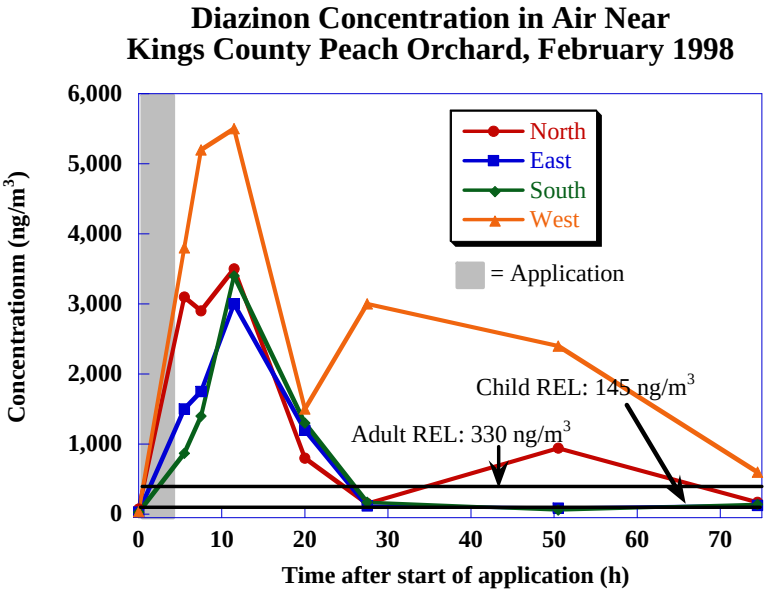

Figure 1. Diazinon concentrations as a function of time after application to a peach orchard.

question, but not directly adjacent to an application site. "Application" studies are designed to measure air concentrations before, during and after application of a specified amount of pesticide to a field of specified size. Application studies were used to create the air concentration algorithm.

One hundred fourteen (114) ARB and DPR application site monitoring studies were evaluated for inclusion in the index. Not all of these studies were appropriate to use for prediction of the maximum concentration, and criteria were developed for inclusion of studies. Only forty-three of the 114 studies—representing 30 chemicals—met the criteria for inclusion in the risk index. Studies were excluded for the following reasons:

- *Monitoring was conducted for less than 24 hours after the application.* Peak concentrations typically occur in the first 24 hours after the application and a comprehensive data set for this time period is required. Maximum concentrations observed *during* an application are likely due to spray drift (not volatilization) and were therefore excluded from the data set. In these situations, the next highest concentration was used in the regression.
- *Fewer than two air samplers were positioned around the application site.* For all but five of the 43 studies, there were at least four samplers placed on four different sides of the application site. For 14 studies, multiple samplers were arranged around the application site at varying distances.
- *No meteorological data were available.* Studies were included if they had at least a qualitative record of temperature, humidity, and prevailing wind (quantitative meteorological data were not presented in some studies). Studies in which rain fell during the application or during the sampling period when peak concentration occurred were omitted (three studies were omitted for this reason).
- *Application rate, field acreage, and detection limits were not reported.*
- *Applications were tarped.* Forty studies, 26 of which were methyl bromide studies, were omitted for this reason.
- *Sampling and analytical methodology was not properly documented and/or there were equipment malfunctions.* Thirteen studies failed to meet these criteria.
- *The pesticide was not applied to land.* Applications to water, a flooded landscape, or inside a building were excluded. Nine studies failed to meet this criterion.
- *The study was part of a county-wide pest eradication (Mexican fruitfly and medfly) program.* Three studies did not meet this criterion.
- *No detectable levels of a pesticide were measured.* When an experiment results in no detections, it is not clear whether there is a problem with the experiment or if the "non-detect" result is real. Three studies did not meet this criterion.

The data used to develop the algorithm are presented in Table A1 in Appendix 1.

Vapor Pressure Data

The primary source of vapor pressure data used in the regression analysis was the California Department of Pesticide Regulation's physical properties database.[10] For chemicals with more than one measurement, the geometric mean of the available values was used. Vapor pressure data for chemicals not found in CDPR's database were taken from the USDA Agricultural Research Services physical property data,[11] EPA Reregistration Documents for specific pesticides,[12] the European Union Footprint database,[13] and the WIN-PST physical properties database.[14] For pesticides for which vapor pressure data were not otherwise available, we utilized US EPA's Estimation Program Interface (EPI) Suite prediction routines.[15] There were some differences between the vapor pressure values in the different databases, some of them quite extreme. When the data from two databases disagreed by more than an order of magnitude, manual lookup of the data from multiple source documents was done to ensure the most accurate value was used in the inhalation risk index calculation.

In cases where a degradation product with a higher vapor pressure and toxicity is generated soon after the application, the vapor pressure of the degradation product was used in the calculation and compared to the REL for that degradation product. Representative examples of pesticides that fall in this category are: 1) metam sodium, which degrades immediately on contact with water and soil to the much more volatile compound methyl isothiocyanate. 2) Maneb, mancozeb, and metiram which degrade to form ethylene thiourea, a highly volatile and more toxic compound than the parent pesticides; 3) Sodium tetrathiocarbonate, which degrades to form the more volatile carbon disulfide; and 4) Salts of 2,4-D, MCPP, MCPA, and dicamba that react with moisture in the soil and air to form the parent acid.

Data Sources for Volatile Organic Compound (VOC) Emissions

Many pesticide active ingredients and other ingredients in pesticide products are Volatile Organic Compounds (VOCs) that contribute to smog formation via reaction with nitrogen oxides. Ground-level ozone is produced in this reaction, a criteria air pollutant regulated under the Clean Air Act. The VOC risk index provides an estimate of VOC emissions per acre treated for each pesticide under consideration for growers in areas that are out of attainment with the Clean Air Act. For growers not located in a non-attainment area, this information is provided but does not contribute to the overall risk index. Figure 2 shows a map of the US with non-attainment areas for the 8-hour ozone standard.

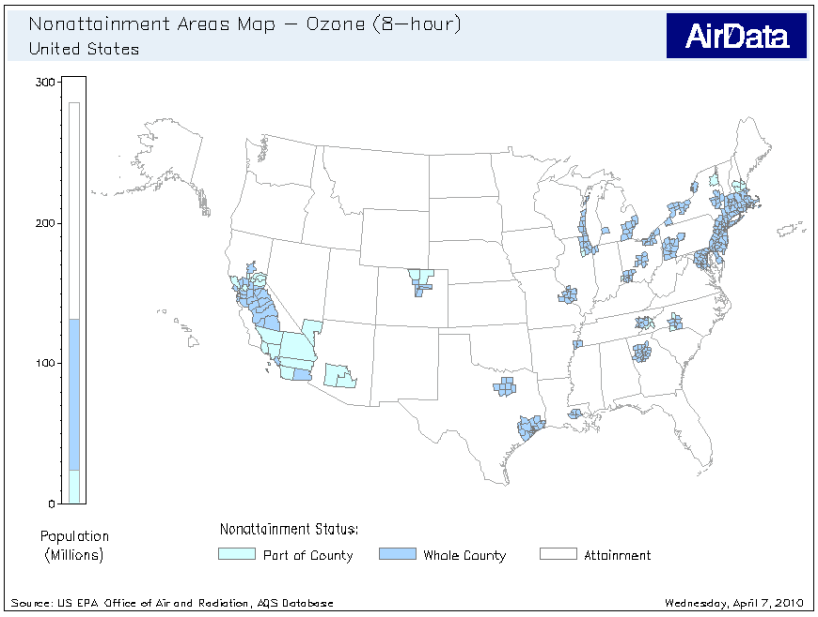

Figure 2. Areas in the U.S. that are out of attainment with the Clean Air Act 8-hour ozone standard. *Source:* Reference 16.

To estimate air pollution potential from pesticide VOCs, VOC emission potential data for pesticide products were obtained from California DPR.[17] Emission potentials are a measure of the VOC content of pesticide products and are multiplied by the application rate entered by the user to obtain a value for pounds of VOC emissions per acre.

Clean Air Act non-attainment areas were downloaded from the US EPA's Air Data web site[16] and categorized by zip code, which can be matched to the grower's zip code. The database of zip codes was purchased from Zip Codes To Go.[18]

Inhalation Risk Index Structure

The inhalation risk index provides a prediction of air concentration based on the vapor pressure of the pesticide and the application rate. Similar relationships have been evaluated by other researchers.[19] This exposure estimate is formulated as the probability of exceeding a concentration of concern (the REL) for human health effects for a 1-year-old child.

In theory, a number of parameters are likely to affect the observed maximum concentration of a pesticide after application. These parameters include the vapor pressure of the pesticide (*VP* in mm Hg), application rate (*AR* in pounds/acre), soil adsorption coefficient (K_{oc} in L/kg), water solubility (*sol* in moles/L), Henry's law constant (K_H in mm Hg m^3/mole), temperature (*T* in

degrees Celsius), and the distance (*d* in feet) between the edge of the treated field and the sampler.[§]

Maximum pesticide concentration in air, $C = f(VP, AR, sol, K_{oc}, K_H, T, d)$

Evaluation of the relevant equilibria can simplify the number of variables to some extent. The processes described in Appendix 3 occur following the application of the pesticide to leaf and soil surfaces. Therefore, in an equilibrium situation, the vapor pressure parameter accounts for both the Henry's Law constant and the water solubility. The number of potential variables thus decreases to:

Maximum pesticide concentration in air, $C = f(VP, AR, K_{oc}, T, d)$

Fitting the Data to a Mathematical Model

Various functional forms of the variables were considered in the analysis (see Table 2). Ultimately, the best fit was obtained from a regression of log*C* against log (*VP* x *AR*). The equation of the line is shown below.

Air Concentration Prediction Algorithm:

$$\log(C) = 0.740 + 0.326 \log(VP \times AR) \qquad R^2 = 0.88,\ n = 43$$
$$(0.096)\ \ (0.018)$$

where concentration (C) is the maximum concentration of volatilized pesticide measured in ppb, application rate (AR) is in pounds/acre and vapor pressure (VP) is in mm Hg. The numbers in parentheses directly under the regression coefficients in the equation are the associated estimated standard errors of the two coefficients. If the ratio of a regression coefficient to its standard error is greater than two, the variable is considered to be statistically significant at $P < 0.05$. Figure 3 shows the data (gray dots) and concentration predictions (black line). The colored lines are the confidence bounds at varying levels of confidence, discussed in detail below.

[§] Plant surface area (SA) will also likely affect the extent and rate of post-application volatilization that occurs. It is not clear how this will affect the observed maximum concentration, since there are two competing processes: 1) absorption of the pesticide by the plant leaves into plant tissue, a process that would reduce the total amount of pesticide available for volatilization; and 2) evaporation from leaf surfaces, with the high surface area of the leaves resulting in an increase in the rate of volatilization.

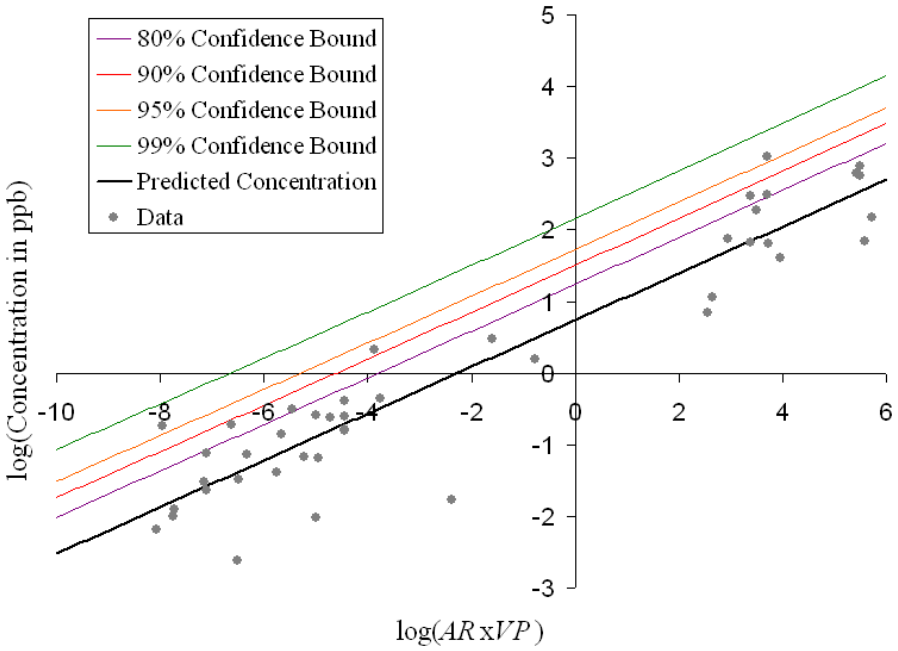

Figure 3. The gray dots are the concentrations observed for the *n* = 43 ARB and DPR data points. The black line is the regression prediction line. The colored lines are confidence bounds for the varying confidence probabilities.

There are two clusters of points in Figure 3: a cluster in the upper right of the figure at values of log(*AR* x *VP*) greater than 2 and a cluster of points in the lower left at values of log(*AR* x *VP*) less than -3. The two clusters are considered to be part of the same regression line because either of the clusters plotted alone has nearly identical slope and intercept parameters:

Upper Right Cluster: $\log(C) = 0.792 + 0.324 \log(VP \times AR)$ $R^2 = 0.27$, $n = 15$
(0.548) (0.130)

Lower Left Cluster: $\log(C) = 0.807 + 0.330 \log(VP \times AR)$ $R^2 = 0.40$, $n = 25$
(0.481) (0.080)

The regression line shown in Figure 3 is used to predict air concentrations corresponding to different values of log(*VP*x*AR*) for comparison with RELs. The colored lines are the upper confidence bound for the predictions with varying degrees of confidence. For example, the green line indicates that there is a 0.99 probability that the true concentration value at a given log(*VP*x*AR*) value is below the green line.[**] The confidence bound is similar to an ordinary

[**] It is assumed that standard regression model criteria are met: linearity, constant variance, independence and normality.

confidence interval except that it is "one-sided." No lower bounds are included because only concentrations above the line would put bystanders at risk.

Table 2: Regressions Tested for Predicting Exposure from Concentration Data[a]

Trial	Correlation Considered	R^2	Y-intercept and standard error	Slope coefficient #1 and standard error	Slope coefficient #2 and standard error
Single-Variable Expressions					
1	log C vs log VP	0.860	1.231, 0.120	0.396, 0.025	---
2	log C vs log Vp – $[\log Vp]^2$	0.861	1.116, 0.158	0.443, 0.049	0.011, 0.010
3	log C vs log AR	0.802	-1.268, 0.153	1.518, 0.116	---
4	log C vs log AR – $[\log AR]^2$	0.797	-1.231, 0.151	1.011, 0.309	-0.235, 0.133
5	log C vs log K_{oc}	0.436	2.241, 0.423	0.941, 0.163	---
6	log C vs log K_{oc} + $[\log K_{oc}]^2$	0.513	4.232, 0.824	-2.750, 0.675	0.325, 0.118
7	log C vs T	0.033	1.152, 0.881	-0.060, 0.042	---
8	log C vs log T	0.033	98.519, 69.51	-39.954, 28.182	---
9	log C vs d	0.030	0.798, 0.542	-0.015, 0.010	---
Multi-Variable Expressions					
10	log C vs log VP + log AR	0.886	0.312, 0.307	0.262, 0.047	0.599, 0.187
11	log C vs log VP – log K_{oc}	0.861	1.460, 0.221	0.369, 0.033	-0.133, 0.108
12	log C vs log (VP x AR)	0.882	0.740, 0.096	0.326, 0.018	---
13	log C vs log (VP x AR) + $[\log (VP \times AR)]^2$	0.881	0.623, 0.178	0.337, 0.023	0.0051, 0.0642

C = air concentration of pesticide in ppb; VP = vapor pressure in mm Hg; AR = application rate in lbs/acre; K_{oc} = soil adsorption coefficient in L/kg; T = temperature in degrees Celsius; d = distance of sampler to nearest field boundary, in feet. N = 43, except for correlations with temperature, where N = 31.

[a] The general linear regression model is: $\log(C) = b + m_1 \log(x_1) + m_2 \log(x_2) + \ldots + m_k \log(x_k)$, where concentration (in ppb) is the dependent variable we wish to predict, *b* is the y-intercept of the line, x_i is the *i*th independent variable (*e.g.* application rate or vapor pressure), and m_i is the slope associated with the *i*th dependent variable.

Determining the Probability of Exceeding a Reference Exposure Level

Sampling air at a number of monitoring sites involves uncertainty. Repeating the sampling experiment would yield new and different data. To assess how "safe" a new application would be, it is important to determine the probability that the new application would yield a concentration greater than the reference exposure level, or

$$\Pr[\log C(x_0) > \log REL]$$

In the equation above, Pr[ ] means the probability of the quantity within the brackets, x_0

denotes the true value of $x = \log(VP \times AR)$ for the new application, $C(x_0)$ denotes the actual concentration for that application, and the *REL* is the reference exposure level.

A standard probability proposition[20] about prediction from a regression of the form $\log C(x) = a + bx$, at a particular value $x = x_0$, is that the expression

$$\frac{\log C(x_0) - \log \hat{C}(x_0)}{s_F}$$

can be characterized by a Student's *t* distribution with $n-2$ degrees of freedom, where $\hat{C}(x_0)$ denotes the regression prediction and s_F denotes the prediction standard deviation, as defined below.

$$s_F = \sqrt{\frac{SSE}{n-2}\left(1 + \frac{1}{n} + \frac{(x_0 - \bar{x})^2}{\sum(x - \bar{x})^2}\right)}$$

In this equation, *SSE* is the sum of squares of the regression residuals, $\bar{x}$ is the mean over the observed values of *x* used in the regression, and the sum $\sum(x - \bar{x})^2$ is the summation over the observed values of *x*. Rearranging the original probability expression above yields:

$$\Pr[\log C(x_0) > \log REL] = \Pr\left[\frac{\log C(x_0) - \log \hat{C}(x_0)}{s_F} > \frac{\log REL - \log \hat{C}(x_0)}{s_F}\right]$$

$$= \Pr\left[t_{n-2} > \frac{\log REL - \log \hat{C}(x_0)}{s_F}\right]$$

Rephrasing this equation in words, to be more intuitive:

$$\begin{pmatrix}\text{Probability that the actual}\\ \text{concentration } C(x_0) \text{ exceeds the}\\ \text{reference concentration } REL\end{pmatrix} = \begin{pmatrix}\text{Probability that a Student's } t\\ \text{variable with } n-2 \text{ degrees of freedom}\\ \text{exceeds the critical value}\end{pmatrix}$$

$$\text{critical value} = \frac{\log REL - \text{regression prediction of } \log C(x_0)}{\text{prediction standard deviation}}$$

Thus, when the difference between the REL and the predicted concentration is small or negative, the critical value is small and there is a high probability that the actual concentration will be greater than the REL. When the difference is large and positive, there is a small probability that the REL will be exceeded.

An upper bound can be computed using closely related information based on the Student's *t*

proposition, such that the actual log-concentration at a given value of *x* has probability 1–α of being smaller than that bound. Figure 3 illustrates the confidence bounds for various values of *x* and α. The black line is the estimated regression line. The green upper-bound line corresponds to α = 0.01. At a given value of *x* = log(*VP* x *AR*) on the *x*-axis, a vertical line perpendicular to the *x*-axis can be drawn. The predicted concentration is at the intersection of the black regression line with this vertical line. The intersection of the same vertical line with the green line gives a concentration bound such that the actual concentration would be smaller 99% of the time. If the *REL* is greater than or equal to the intersection with the green confidence bound, then the actual concentration will be less than the *REL* at least 99% of the time.

Although the confidence bounds on Figure 3 appear to be straight lines, they are in fact nonlinear. If the graph covered a wide enough range of horizontal axis values, concavity in the lines would become apparent.

Inhalation Risk Index Values

Determining the probability of exceeding the REL provides a quantitative risk estimate; however, this assessment is incomplete without a comparison among different chemicals and the development of bins for quantitative risk categorizations. As an example, risk index scores (probability of exceeding the REL) for a subset of pesticides used on apple crops are presented in Appendix 2. The average application rate used on apples, obtained from the 2007 California Pesticide Use Reporting (PUR) data, is used as the application rate for calculating the risk scores in this example. When the PUR application rates were not available, application rates from the National Agricultural Statistics Service (NASS) data were used.

Risk scores are color-coded yellow for chemicals with a probability of less than 10% of exceeding the REL based on volatilization alone; orange for probabilities between 10 and 50%; and pink for probabilities exceeding 50%. These values are summarized in Table 3 below.

Table 3: Risk Score Bins for Volatilization Inhalation Index

Color	Probability of Exceeding REL
Yellow	<10%
Orange	>10–50%
Pink	>50%

Pesticides that are carcinogenic, but have low acute or subchronic toxicity, will not have a high risk score using this method of assessing inhalation risk. Inhalation cancer risks are therefore not currently accounted for by the PRiME inhalation index.

Caveats for Concentration Estimates

Natural systems are complex and difficult to parameterize. Some sources of complexity include:

- Nature is rarely at equilibrium; nevertheless, these equilibrium constants have predictive value for determining the direction in which a reaction will proceed.

- There are a number of processes competing with volatilization from soils or plant surfaces that will change the equilibrium concentration of the pesticide in the gas phase and/or change the rate at which the volatilized pesticide is released to the environment, thus affecting the maximum concentration observed. These competing reactions are described in Figure 3 and explained in more detail below.

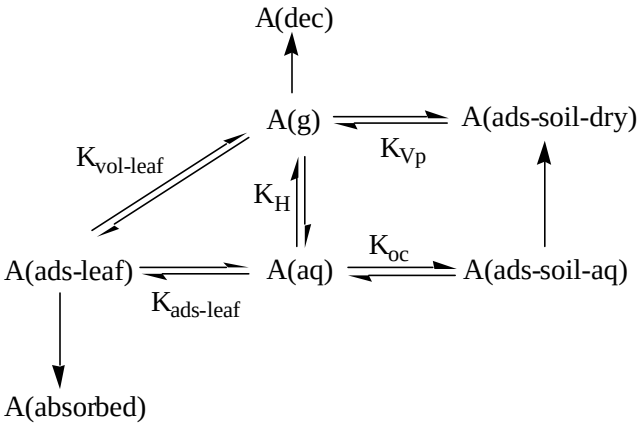

Figure 3. The maximum measured concentration of a pesticide in air is a function of vapor pressure and application rate; however a number of different processes compete for capture or degradation of the pesticide.

1) Dissolution of the gas-phase pesticide in soil water (the reverse of the Henry's Law process).

$$A\ (g) \rightleftharpoons A\ (aq) \qquad 1/K_H = \frac{A\ (aq)\ (mol/L)}{P_A\ (mm\ Hg)}$$

2) Adsorption of the pesticide contained in the water to the soil (the K_{oc} process). For pesticides with high K_{oc} values, this process may be significant.[21]

$$A\ (aq) \rightleftharpoons A\ (ads\text{-}soil\text{-}aq) \qquad K_{oc} = \frac{A\ (ads\text{-}soil\text{-}aq)\ (mg/kg)}{A\ (aq)\ (mg/L)} = L/kg$$

3) Adsorption of the pesticide to the leaf surfaces of plants. The constant K_{leaf} was not explored as a variable because there are no available data for this constant, and in any case, it is likely to vary depending on the crop.

$$A\ (aq) \rightleftharpoons A\ (ads\text{-}soil\text{-}leaf) \qquad K_{leaf} = \frac{A\ (ads\text{-}soil\text{-}leaf)\ (mg/kg)}{A\ (aq)\ (mg/L)} = L/kg$$

4) Systemic absorption of the pesticide into the plant tissue (A_{abs} in Figure 3). Many pesticides are taken up into plant tissue through absorption through the leaf surfaces. This process reduces the availability of pesticides for volatilization.

5) Decomposition of the pesticide (A_{dec} in Figure 3). Pesticides decompose by photolysis in air and water, hydrolysis, and microbial degradation.

- A number of other variables may affect the position of these equilibria, including concentrations of other ions in soils or solution, pH of soils or solutions, type of organic matter in the soil or dissolved in water, the minerals contained in the soil, the polarity of leaf surfaces of different plants, and the presence of surfactants that may be applied with the pesticide.
- The maximum measured concentration of pesticide in air is affected by the relative rates of the forward and reverse reactions for the different processes. In general, an equilibrium constant (K) is related to the rate of the forward reaction (k_f) and the rate of the reverse reaction (k_r) as follows:

$$K = \frac{k_f}{k_r}$$

Under non-equilibrium conditions, the relative rates of the different competing reactions may have a significant effect on observed maximum concentrations of pesticides in air.

- The maximum measured concentration of pesticide in air is also affected by application parameters such as distance of the sampler from the field, temperature, humidity, crop treated, number of acres treated, and application method. These parameters are quite variable in the ARB data set; nevertheless, the correlation is highly significant, which suggests that vapor pressure and application rate are the predominant terms in the equation.

VOC Risk Index Structure

The VOC index is intended to help farmers in Clean Air Act non-attainment areas reduce their VOC contributions to the air basin. The "risk" in this case is basin-wide and not specific to neighbors and workers in adjacent fields. The index was developed by determining the range of VOC emissions for pesticide products per acre treated and classifying pesticide products according to VOC contributions in pounds of product per acre. To determine the range, we calculated an average product application rate in pounds of product applied per acre from the California PUR data for every pesticide product applied to acres, averaged over all crops. These data points were multiplied by DPR's product VOC emission potentials (EPs) to provide an

estimate of VOCs produced per acre treated for each product for the average application rate for that product. A statistical plot of these data is shown in Figure 2 (left). We also plotted the distribution of EPs for all products for comparison, as shown in Figure 2 (right). For both plots, the fumigant pesticides dominate the high end of the scale. Emulsifiable concentrates containing pesticides that are themselves VOCs dissolved in solvents that are VOCs also contribute substantially, but their actual contributions to VOC emissions are dependent on the application rate. Thus, VOC emissions in pounds of product per acre is the best measure on which to base a risk score.

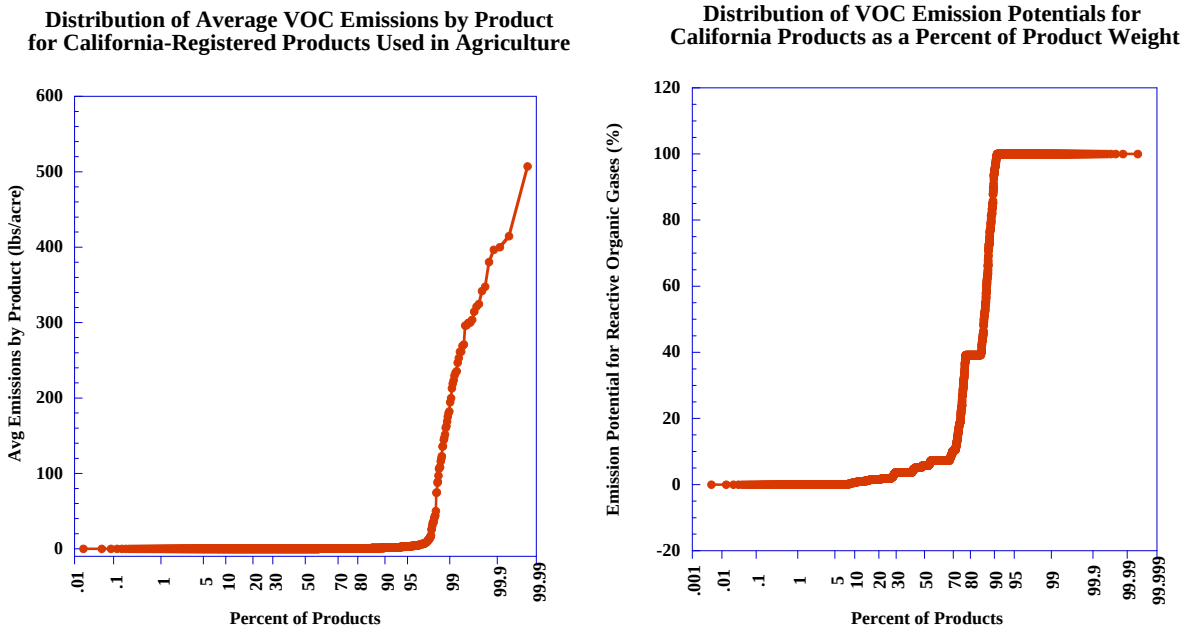

Figure 2. Percentile plots showing the range of VOC emissions from pesticide products. Left: average pounds of VOCs per acre for pesticide products used in agricultural settings, based on an average use rate for all crops. Right: VOC emission potentials (EPs) as a percent of product weight for all CA products.

To set the breakpoints for the VOC index for red, orange and yellow (high, medium and low contributors to VOC emissions), we evaluated CDPR's reformulation requests for emulsifiable concentrates to determine which pesticide products CDPR deems to be most problematic (after fumigants). In a February 2010 notice to registrants,[22] CDPR singled out products containing seven active ingredients: abamectin, chlorpyrifos, dimethoate, gibberellins, oxyfluorfen, permethrin, trifluralin. We used the average product application rate and the average emission potential for each product containing these active ingredients to obtain the average VOC emissions in lbs/acre (see Table 4). We also evaluated glyphosate- and chlorothalonil-containing pesticides for comparison. The data indicate that all of CDPR's choice of products for reformulation contributed more than 0.21 lbs VOCs/acre; therefore, we set the bottom of the orange zone to be 0.2 lbs VOCs/acre. Approximately 60% of the registered products in California have VOC contributions below this value; these would be in the yellow (low risk)

range. The top of the orange range was set at 2 lbs VOCs/acre, with approximately 90% of products having VOC contributions below this value. Any product with VOC emissions above 2 lbs/acre is in the red range (see Table 5).

Table 4: Emission Data for Pesticides Targeted by CDPR for Reformulation

Pesticide	Avg. EP (%) for Products Containing These AIs	Avg. Product Application Rate over All Crops (lbs Product/acre)	Avg. Emissions over All Crops (lbs VOCs/acre)	Acres Treated in 2007 in CA	Total VOC Emissions (thousands of lbs)
Abamectin	32.8	0.64	0.21	1,254,000	263
Chlorpyrifos	25.8	3.85	0.99	1,153,000	1,145
Dimethoate	29.0	1.38	0.40	608,000	243
Gibberellins	33.2	1.15	0.38	447,000	171
Oxyfluorfen	31.4	4.83	1.52	1,599,000	2,425
Permethrin	38.6	0.70	0.27	721,000	195
Trifluralin	20.6	19.52	4.02	771,000	3,100
Glyphosate[a]	7.6	3.15	0.24	3,580,000	855
Chlorothalonil[a]	5.6	2.72	0.15	389,000	59

Source: Reference 22.

[a] Not part of CDPR's list, but added for comparison.

Table 5: Risk Score Bins for VOC Index

Color	VOC Emissions (Lb/acre)	Percent of Products
Yellow	0–0.2	0–60%
Orange	>0.2–2	>60–90%
Red	>2	>90%

UPAFs for Inhalation Risk Index

There are currently no Use Pattern Adjustment Factors (UPAFs) for the Inhalation Risk Index. When more data are available, we plan to incorporate UPAFs for distances between pesticide application sites and residences or workplaces (including farm workers in adjacent fields). In most of the applications monitored by ARB, the sampling stations were placed within 30 to 75 feet of the field, but within the data set, no correlation of concentration was observed with distance, probably because of variations in wind patterns and also because the range of distances was too small to enable prediction of variation in concentration with distance. This concentration estimate is complicated by the fact that growers of a given crop tend to apply the same pesticide at the same time of year, so exposures from multiple applications occurring in the geographic area are also possible, making it even more difficult to predict concentration as a function of distance.

Other Considerations: Spray Drift of Highly Toxic, Low-Volatility Pesticides

The inhalation risk index is designed to evaluate exposure risks from pesticide volatilization; however, spray drift will occur with any application. If the application is conducted to minimize off-site spray drift, the primary exposure for volatile and semi-volatile pesticides will be from volatilization. For low volatility pesticides with high acute toxicity or for highly corrosive pesticides, even a small amount of spray drift can be problematic for bystanders or workers in adjacent fields. Pesticides that fall in this category include paraquat, emamectin benzoate, and some of the pyrethroids, among others. To inform farmers of this scenario, an alert flag will warn the user about spray drift risks for these pesticides.

Appendix 1: Air Monitoring Data from ARB Studies

Table A1: Application Parameters and Concentration Data from DPR and ARB studies.

Chemical Name	Max Post-Application Conc. (ppb)	log (Max Conc.)	Vapor Pressure (mm Hg at 20–25°C)	Log (Vapor Pressure)	Appli-cation rate (lb/acre)	Total acres treated	Omit Study	Comments
Studies included in the analysis:								
1,3-Dichloropropene	186	2.27	29	1.46	320.00	3	No	
Atrazine	0.29	-0.54	1.68×10^{-7}	-6.77	1.89	121	No	
Benomyl	0.151	-0.82	3.73×10^{-8}	-7.43	0.50	81	No	
Bifenthrin	0.17	-0.77	1.81×10^{-7}	-6.74	0.10	300	No	
Bromoxynil Octanoate	2.34	0.37	1.4×10^{-6}	-5.86	1.56		No	
Captan	0.03	-1.52	8.0×10^{-8}	-7.10	3.89	18	No	
Carbofuran	0.66	-0.18	8.7×10^{-7}	-6.06	0.55	70	No	
Carbon disulfide	200	2.30	300	2.48	18.00	39	No	
Chlorothalonil	0.74	-0.13	0.000002	-5.70	3.00	35	No	
Chlorpyrifos	30.95	1.49	0.0000221	-4.66	6.00	60	No	
Cycloate	0.15	-0.82	0.0016	-2.80	2.58	67	No	
DEF	0.45	-0.35	0.0000065	-5.19	1.40		No	
Diazinon	5.5	0.74	0.0000898	-4.05	2.00	40	No	
Endosulfan	4	0.60	0.000013	-4.89	1.50	6	No	
EPTC	12	1.08	0.0289	-1.54	5.74	35	No	
Fenamiphos	0.12	-0.92	0.0000017	-5.77	6.00	4	No	
Linuron	0.42	-0.38	0.0000014	-5.85	1.25	100	No	
Metalaxyl	0.74	-0.13	0.0000056	-5.25	2.00	80	No	
Methamidophos	0.89	-0.05	0.0000353	-4.45	1.00	35	No	
Methidathion	3.16	0.50	0.0000034	-5.47	3.00	15	No	
Methomyl	1.64	0.21	0.000049	-4.31	0.73	80	No	
Methyl Bromide	3000	3.48	1,800	3.26	176.00	15	No	
Methyl Bromide	586	2.77	1,800	3.26	298.50	5	No	
Methyl Bromide	2420	3.38	1,800	3.26	149.00	8	No	
Methyl Bromide	268	2.43	1,800	3.26	210.00	10	No	
Methyl Bromide	2186	3.34	1,800	3.26	174.00	31	No	
Methyl Bromide	4.38	0.64	0.000018	-4.74	2.00	100	No	Do not omit, but note: 24-hour average sampling

Chemical Name	Max Post-Application Conc. (ppb)	log (Max Conc.)	Vapor Pressure (mm Hg at 20–25°C)	Log (Vapor Pressure)	Appli-cation rate (lb/acre)	Total acres treated	Omit Study	Comments
Methyl Bromide	1.75	0.24	0.000018	-4.74	2.00	38	No	Do not omit, but note: 24-hour average sampling
MITC	880	2.94	16	1.20	155.00	85	No	
MITC	200	2.30	16	1.20	155.00	80	No	
MITC	224	2.35	16	1.20	56.00	95	No	
MITC	3139	3.50	16	1.20	318.00	20	No	
MITC	920	2.96	16	1.20	310.00	3	No	
MITC	560	2.75	16	1.20	198.00	1	No	Do not omit, but note: spill of dazomet adjacent to monitoring site.
MITC	20.8	1.32	16	1.20	22.10	2	No	
MITC	34.4	1.54	16	1.20	27.40	2	No	
Molinate	22.61	1.35	0.005	-2.30	5.00	99	No	
Naled	2.981	0.47	2.63×10^{-7}	-6.58	0.89	20	No	
Permethrin	0.106	-0.97	2.15×10^{-8}	-7.67	0.39	10	No	
Propargite	1.1	0.04	4.0×10^{-8}	-7.40	1.92	12	No	
Propargite	0.435	-0.36	4.0×10^{-8}	-7.40	1.80	20	No	
Simazine	0.19	-0.72	2.21×10^{-8}	-7.66	3.60	20	No	
Ziram	2.26	0.35	2.43×10^{-9}	-8.61	4.56	54	No	
Studies that were not included:								
1,3-Dichloropropene	75.86	1.88	29	1.46			Yes	Tarped.
1,3-Dichloropropene	62	1.79	29	1.46	110.18	11	Yes	Tarped.
Acrolein			210	2.32			Yes	This study was omitted because acrolein was applied to water.
Acrolein			210	2.32			Yes	This study was omitted because acrolein was

Chemical Name	Max Post-Application Conc. (ppb)	log (Max Conc.)	Vapor Pressure (mm Hg at 20–25°C)	Log (Vapor Pressure)	Appli-cation rate (lb/acre)	Total acres treated	Omit Study	Comments
								applied to water.
Acrolein			210	2.32			Yes	This study was omitted because acrolein was applied to water.
Aldicarb	0.0209	-1.68	0.000029	-4.54	0.90	137	Yes	Equipment malfunctions; ARB re-did the study.
Aldicarb	0.0044	-2.36	0.000029	-4.54	2.10	35	Yes	Results were below the quantitation limit.
Amitraz	0.001125	-2.95	0.0000026	-5.59	0.38	56	Yes	Equipment malfunctions.
Azinphos-methyl			0.0000016	-5.80	2.00	118	Yes	Results were below the quantitation limit.
Benomyl			3.73×10^{-8}	-7.43	1.33	40	Yes	Methodology incompletely described; concentration data were omitted.
Bromoxynil Octanoate			0.0000014	-5.86	0.36	28	Yes	Results were below the quantitation limit.
Carbaryl			0.0000012	-5.93	0.90	14	Yes	Methodology incompletely described; post-application concentration data were omitted.

Chemical Name	Max Post-Application Conc. (ppb)	log (Max Conc.)	Vapor Pressure (mm Hg at 20–25°C)	Log (Vapor Pressure)	Appli-cation rate (lb/acre)	Total acres treated	Omit Study	Comments
Carbaryl			0.0000012	-5.93		20	Yes	Methodology incompletely described; post-application concentration data were omitted.
Chlordimeform			0.00035	-3.46	0.25	186	Yes	Methodology incompletely described; post-application concentration data were omitted.
Chloropicrin	150	2.18	23.8	1.38	150.00	5	Yes	Tarped.
Chloropicrin	100	2.00	23.8	1.38	200.00	8	Yes	Tarped.
Chloropicrin	39	1.59	23.8	1.38	125.00	22	Yes	Tarped.
Chlorothalonil			0.000002	-5.70	1.20	7	Yes	Methodology incompletely described; post-application concentration data were omitted.
Dacthal	1	0.00	0.0000025	-5.60	7.50	2	Yes	This study employed very different methodology.
DEF	4.02	0.60	0.0000065	-5.19			Yes	Methodology incompletely described; application rate omitted.
Ethoprop	0.21	-0.68	0.00038	-3.42	10.00	80	Yes	Rain directly before application. Application

Chemical Name	Max Post-Application Conc. (ppb)	log (Max Conc.)	Vapor Pressure (mm Hg at 20–25°C)	Log (Vapor Pressure)	Appli-cation rate (lb/acre)	Total acres treated	Omit Study	Comments
								sperad over many days.
Malathion	2.4	0.38	0.000023	-4.64	1.50	50	Yes	Adjacent fields were being treated at the same time.
Malathion	0.106	-0.97	0.000023	-4.64	0.09	10,541	Yes	This monitoring was for the medfly program.
Malathion	0.5163	-0.29	0.000023	-4.64	0.21	10,240	Yes	This monitoring was for the Mexican fruit fly program.
Malathion	0.39	-0.41	0.000023	-4.64	0.21	371,640	Yes	This monitoring was for the Mexican fruit fly program.
Mancozeb			1.32×10^{-10}	-9.88	1.60	40	Yes	Methodology incompletely described; post-application concentration data were omitted.
MCPA			8.2×10^{-7}	-6.09	2.10	74	Yes	Methodology incompletely described; post-application concentration data were omitted.
Methyl Bromide	466	2.67	1,800	3.26	200.00	10	Yes	Tarped.

Chemical Name	Max Post-Application Conc. (ppb)	log (Max Conc.)	Vapor Pressure (mm Hg at 20–25°C)	Log (Vapor Pressure)	Appli-cation rate (lb/acre)	Total acres treated	Omit Study	Comments
Methyl Bromide	2000	3.30	1,800	3.26	234.00	10	Yes	Tarped.
Methyl Bromide	210	2.32	1,800	3.26	213.00	11	Yes	Tarped.
Methyl Bromide	1070	3.03	1,800	3.26	236.50	11	Yes	Tarped.
Methyl Bromide	365	2.56	1,800	3.26	231.00	1	Yes	Tarped.
Methyl Bromide	431	2.63	1,800	3.26	234.00	1	Yes	Tarped.
Methyl Bromide	295	2.47	1,800	3.26	236.00	1	Yes	Tarped.
Methyl Bromide	551	2.74	1,800	3.26	233.00	1	Yes	Tarped.
Methyl Bromide	318	2.50	1,800	3.26	231.00	1	Yes	Tarped.
Methyl Bromide	497	2.70	1,800	3.26	220.00	1	Yes	Tarped.
Methyl Bromide	303	2.48	1,800	3.26	226.00	1	Yes	Tarped.
Methyl Bromide	272	2.43	1,800	3.26	238.00	1	Yes	Tarped.
Methyl Bromide	509	2.71	1,800	3.26	277.00	1	Yes	Tarped.
Methyl Bromide	1254	3.10	1,800	3.26	284.00	1	Yes	Tarped.
Methyl Bromide	210	2.32	1,800	3.26	277.00	1	Yes	Tarped.
Methyl Bromide	1204	3.08	1,800	3.26	386.00	1	Yes	Tarped.
Methyl Bromide	753	2.88	1,800	3.26	280.00	1	Yes	Tarped.
Methyl Bromide	889	2.95	1,800	3.26	286.00	1	Yes	Tarped.
Methyl Bromide	621	2.79	1,800	3.26	214.00	2	Yes	Tarped.
Methyl Bromide	1942	3.29	1,800	3.26	206.00	5	Yes	Tarped.
Methyl Bromide	326	2.51	1,800	3.26	426.00	0	Yes	Tarped.
Methyl Bromide	1231	3.09	1,800	3.26	205.00	12	Yes	Tarped.
Methyl Bromide	738	2.87	1,800	3.26	163.00	5	Yes	Tarped.
Methyl Bromide	1278	3.11	1,800	3.26	343.00	0	Yes	Tarped.
Methyl Bromide	214	2.33	1,800	3.26	180.00	9	Yes	Only 24-hour average concentration was given. Application type is not listed.
Methyl Bromide	3751	3.57	1,800	3.26	196.00	16	Yes	Tarped.
Methyl Bromide	1091	3.04	1,800	3.26	250.00	12	Yes	Tarped.
Methyl Bromide	3223	3.51	1,800	3.26	433.00	1	Yes	Tarped.
Methyl Bromide	3266	3.51	1,800	3.26	234.00	10	Yes	Tarped.
Methyl Bromide	7766	3.89	1,800	3.26	215.60	25	Yes	Tarped.

Chemical Name	Max Post-Application Conc. (ppb)	log (Max Conc.)	Vapor Pressure (mm Hg at 20–25°C)	Log (Vapor Pressure)	Appli-cation rate (lb/acre)	Total acres treated	Omit Study	Comments
Methyl Bromide	3883	3.59	1,800	3.26	191.10	19	Yes	Tarped.
Methyl Bromide	1980	3.30	1,800	3.26	215.60	14	Yes	Tarped.
Methyl Bromide	7378	3.87	1,800	3.26	196.00	14	Yes	Tarped.
Methyl Bromide	5436	3.74	1,800	3.26	343.00	19	Yes	Tarped.
Methyl Bromide	3493	3.54	1,800	3.26	194.00	25	Yes	Tarped.
Methyl Parathion	1.16	0.06	0.000018	-4.74		24	Yes	Rice fields were flooded.
Methyl Parathion	0.35	-0.46	0.000018	-4.74		80	Yes	Rice fields were flooded.
MITC	35	1.54	16	1.20	135.00	9	Yes	Tarped.
MITC	35	1.54	16	1.20	330.00	13	Yes	Tarped.
Molinate	7.82	0.89	0.005	-2.30	40.00	24	Yes	Rice fields were flooded.
Oxydemeton-methyl	0.049	-1.31	0.0000383	-4.42	0.50	14	Yes	Samples were below the quantitation limit.
Phorate	0.08	-1.10	0.000644	-3.19	7.00	6	Yes	Rain during application.
Sulfuryl Fluoride	29000	4.46	12,750	4.11			Yes	Structural fumigation study.
Sulfuryl Fluoride	100000	5.00	12,750	4.11			Yes	Structural fumigation study.

Appendix 2: Inhalation Risk for a Subset of Pesticides Used on Apples

Chemical	Average 2007 Application Rate (lbs/acre)	Log VP	1-year-old REL (ppb)	Risk Score (probability of exceeding REL)
Chloropicrin	8.27	1.37	0.317	0.9992
Chlorpyrifos	1.64	-4.69	0.012	0.9775
Paraquat dichloride	1.06	-7.00	0.004	0.9215
Endosulfan	1.46	-5.29	0.020	0.8992
Methyl bromide	155.07	3.26	60.800	0.8865
Mancozeb[a]	3.68	-1.15	2.021	0.6611
Metiram[a]	2.59	-1.15	2.021	0.6296
Maneb[a]	2.39	-1.15	2.021	0.6226
Ethion	0.22	-5.62	0.054	0.4744
Hydrogen cyanamide	12.27	1.15	49.114	0.3540
Pyridaben	0.25	-4.09	0.291	0.3330
Oxamyl	1.99	-4.23	0.533	0.3231
Dimethoate	1.13	-5.73	0.176	0.2725
Emamectin, benzoate	0.01	-7.52	0.012	0.2630
Methidathion	1.32	-5.47	0.273	0.2272
Metaldehyde	1.40	-1.48	7.031	0.1788
Formetanate hydrochloride	0.76	-7.92	0.053	0.1545
Azinphos-methyl	1.19	-5.80	0.402	0.1104
Flumioxazin	0.23	-5.62	0.350	0.0793
Glufosinate-ammonium	0.77	-6.12	0.396	0.0683
Cyfluthrin	0.04	-7.56	0.067	0.0515
Diazinon	1.41	-3.97	3.024	0.0493
Triadimefon	0.13	-6.35	0.478	0.0168
Malathion	2.08	-5.05	3.214	0.0151
Cyhalothrin, lambda	0.04	-8.81	0.073	0.0096
Phosmet	2.94	-6.31	1.952	0.0086
Carbaryl	1.74	-5.93	2.257	0.0081
Pendimethalin	1.34	-5.03	4.893	0.0057
Fluazifop-P-butyl	0.13	-5.18	2.154	0.0054
Chlorothalonil	1.30	-5.70	3.106	0.0052
Pyraflufen-ethyl	0.01	-1.49	19.989	0.0022
Avermectin	0.01	-8.82	0.118	0.0021
Fenpropathrin	0.39	-5.67	3.546	0.0020
Diuron	0.95	-7.16	1.772	0.0015
Ziram	5.22	-7.11	3.376	0.0014
Pyraclostrobin	0.12	-9.19	0.245	0.0012
Dicofol	1.50	-6.40	4.458	0.0010
Terbacil	0.83	-6.51	3.811	0.000775
Norflurazon	1.68	-7.70	2.148	0.000668
Thiophanate-methyl	2.06	-7.15	4.020	0.000474
Indoxacarb, S-isomer	0.09	-7.35	1.565	0.000317
Tebufenozide	0.08	-7.00	2.343	0.000216
Fenpyroximate	0.05	-7.19	1.959	0.000171
Simazine	1.69	-7.66	4.266	0.000161
Triflumizole	0.22	-5.84	10.153	0.000105
Fenarimol	0.07	-6.66	4.849	0.000063

Chemical	Average 2007 Application Rate (lbs/acre)	Log VP	1-year-old REL (ppb)	Risk Score (probability of exceeding REL)
Fenbuconazole	0.06	-7.00	3.678	0.000062
Myclobutanil	0.14	-5.63	14.300	0.000048
Thiacloprid	0.18	-11.22	0.295	0.000046
Propargite	1.91	-7.38	9.393	0.000046
2,4-D	0.45	-4.55	46.705	0.000046
Spirodiclofen	0.27	-8.28	2.811	0.000041
Esfenvalerate	0.10	-8.38	1.967	0.000038
Etoxazole	0.13	-7.14	5.308	0.000036
Fenbutatin-oxide	0.39	-10.74	0.667	0.000027
Methomyl	0.90	-4.31	89.689	0.000025
Trifloxystrobin	0.07	-7.59	3.843	0.000024
Pyrimethanil	0.24	-4.78	47.875	0.000018
Bifenazate	0.46	-6.96	13.749	0.000013
Pyrethrins	0.02	-6.29	9.644	0.000011
Ethephon	0.32	-7.00	17.147	5.62E-06
Oxyfluorfen	0.73	-6.70	34.251	3.34E-06
Thiamethoxam	0.12	-10.30	1.699	2.73E-06
Imidacloprid	0.09	-7.00	16.150	2.46E-06
Napropamide	1.36	-6.77	45.663	2.34E-06
Acetamiprid	0.20	-8.00	11.065	2.03E-06
Spinosad (mixture of Factors A and D)	0.12	-9.82	2.764	1.90E-06
Captan	2.35	-7.59	35.915	1.52E-06
Novaluron	0.19	-10.01	3.671	9.90E-07
Oryzalin	2.31	-8.00	33.383	8.79E-07
Cyprodinil	0.21	-5.44	113.644	6.21E-07
Dodine	0.80	-9.10	14.366	4.74E-07
Boscalid	0.24	-7.82	26.230	3.91E-07
Flonicamid	0.09	-7.72	21.624	3.52E-07
Pyriproxyfen	0.09	-7.00	45.102	2.09E-07
Clethodim	0.98	-7.00	114.737	1.26E-07
Prohexadione calcium	0.17	-6.89	76.320	1.12E-07
Sethoxydim	0.28	-6.80	102.134	9.43E-08
Benzoic acid	0.20	-3.16	1534.805	5.78E-08
Glyphosate, isopropylamine salt	1.12	-7.12	167.531	4.43E-08
Glyphosate, potassium salt	1.47	-7.12	184.503	4.31E-08
Permethrin	0.001	-7.91	11.398	3.88E-08
Fosetyl-Al	3.14	-7.00	349.858	1.97E-08
Glyphosate	0.71	-7.12	226.063	1.51E-08
1-Naphthaleneacetamide (NAD)	0.06	-7.12	111.475	1.28E-08
Hexythiazox	0.15	-8.00	280.838	6.45E-10
Carfentrazone-ethyl	0.02	-6.92	500.908	2.15E-10

[a] The REL and VP for ethylene thiourea, the degradation product of maneb, mancozeb, and metiram were used to calculate probabilities for this chemical.

Appendix 3: Equilibria Involved in Volatilization of Pesticides from Leaf and Soil Surfaces

In theory, a number of parameters are likely to affect the observed maximum concentration of a pesticide after application. These parameters include the vapor pressure of the pesticide (*VP* in mm Hg), application rate (*AR* in pounds/acre), soil adsorption coefficient (K_{oc} in L/kg), water solubility (*sol* in moles/L), Henry's law constant (K_H in mm Hg m^3/mole), temperature (*T* in degrees Celsius), and the distance (*d* in feet) between the edge of the treated field and the sampler.[6]

Maximum pesticide concentration in air, $C = f(VP, AR, sol, K_{oc}, K_H, T, d)$

Evaluation of the relevant equilibria can simplify the number of variables to some extent. The processes described below occur following the application of the pesticide to leaf and soil surfaces.

Equilibrium constants are associated with the following processes:

K_{sol}	Dissolution of the pesticide in its native state in water (water solubility)
K_H	Transfer of a dissolved pesticide from water to a gaseous state above the solution (Henry's Law constant)
K_{Vp}	Volatilization of a pesticide on a glass surface from its native state to a gaseous state (vapor pressure)
$K_{vol\text{-}soil}$	Volatilization of a pesticide on a soil surface from its native state to a gaseous state
$K_{vol\text{-}leaf}$	Volatilization of a pesticide on a leaf surface from its native state to a gaseous state
K_{oc}	Adsorption of a pesticide to soil in aqueous solution, accounting for the fraction of organic matter in the soil (soil adsorption coefficient)

[6] Plant surface area (SA) will also likely affect the extent and rate of post-application volatilization that occurs. It is not clear how this will affect the observed maximum concentration, since there are two competing processes:
1) absorption of the pesticide by the plant leaves into plant tissue, a process that would reduce the total amount of pesticide available for volatilization; and 2) evaporation from leaf surfaces, with the high surface area of the leaves resulting in an increase in the rate of volatilization.

We define the following terms:

A = pesticide

P_A = the pressure of the pesticide in the gas phase

A (aq) = pesticide dissolved in water (many pesticides are applied to crops in aqueous solution)

A (n) = pesticide in its native physical state at 20°C—solid or liquid

A (g) = pesticide in the gaseous state

A (ads-soil-aq) = pesticide adsorbed to soil in aqueous solution

A (ads-leaf) = pesticide in native physical state adsorbed to leaves

A (dec) = decomposed pesticide

Vapor pressure, water solubility and the Henry's Law constant are all related, as shown below:

$$\text{A (n)} \rightleftharpoons \text{A (aq)} \qquad K_{sol} = \text{A (aq) (mol/L)}$$

$$\text{A (aq)} \rightleftharpoons \text{A (g)} \qquad K_H = \frac{P_A \text{ (mm Hg)}}{\text{A (aq) (mol/L)}}$$

$$\text{A (n)} \rightleftharpoons \text{A (g)} \qquad K_{Vp} = P_A \text{ (mm Hg)} = K_{sol} * K_H$$

Therefore, in an equilibrium situation, the vapor pressure parameter accounts for both the Henry's Law constant and the water solubility. The number of potential variables thus decreases to:

Maximum pesticide concentration in air, $C = f(VP, AR, K_{oc}, T, d)$

Appendix 4: Peer Review Comments

This white paper was reviewed by the following independent experts. Below are their comments, listed anonymously, along with the author's responses.

- **Nu-may Ruby Reed**, Ph.D., D.A.B.T., staff toxicologist, California DPR
- **Daniel L. Sudakin**, MD, MPH, FACMT, FACOEM, associate professor, Oregon State University

Comment 1: One overarching comment pertains to the transparency of documentation. When the pre-loaded database consists of values from multiple sources (e.g., NASS application rate versus DPR PUR use data; or the RfC from USEPA versus REL from DPR versus value calculated from RfD using Page 4 equation), the risk analysis presentation can be enhanced by providing the source of information in the output, and the hierarchy of data selection preference.

> **Response:** *We have added this information for the choice of the Level of Concern (LOC) for the REL. We select the LOC in the following order of priority, in order to use the best data that most closely matches the exposure time period: short-term HEC (peer-reviewed—most of these are from CDPR) > short-term HEC (not peer reviewed) > short-term LOC > intermediate-term LOC. This LOC selection process is scripted into the data set.*

Comment 2: Page 3: Including the mention of Human Equivalent Concentration (HEC) together with Reference concentration (RfC) and Reference Exposure Level (REL) is confusing especially when the discussion continues onto the application of uncertainty factors (UFs). This is because the HEC does not have the equal meaning to the RfC or REL. While only a 3-fold UF is applied to the No Observed Adverse Effect Level (NOAEL) to deriving the HEC, another 3-fold interspecies UF is applied conventionally when the HEC is used for determining the level of acceptable risk. Thus, it is misleading to describe the 10-fold versus 3-fold interspecies UFs without mentioning this second 3-fold UF.

> **Response:** *Agreed. The section on what the REL/RfC/LOC are and how they are calculated from NOAELs and UFs has been greatly expanded and rewritten and more fully cited back to OEHHA and US EPA documents.*

Comment 3: A related question is, are HECs included in the pre-loaded database in PRiME, and how often the HEC is expected for use in IRI calculation. If HECs are one of the options within PRiME, it would be desirable to convert it to a value equivalent to the RfC or REL term by incorporate a total UF of 30. This should be explicitly stated both in the white paper and in the PRiME tool output for transparency sake.

> **Response:** *Yes, HECs are included if they are available (see Response 1). They are converted to RELs for a one-year old, if necessary, using the appropriate ratio of breathing weights and body weights, as well as the UFs.*

Comment 4: Another related question is the use of the FQPA factor. The factor is mentioned but not clearly whether it is incorporated into the RfC, REL or used in the IRI calculation. The use of the FQPA factor, if only used for estimating the dietary risk and reflected in the populated adjusted aRfD, should be clarified.

> **Response:** *The FQPA factor is utilized to calculate the inhalation REL. If children are more sensitive than adults to oral exposure, there is no reason to believe that they would not also be more sensitive via inhalation exposure. This is noted in the text.*

Comment 5: The equation for deriving the REL needs to be modified to indicate that the 100% factor, as can be indicated from item #2 to represent the inhalation absorption factor (AF), should be in the denominator and not the numerator. On the other hand, if this "100%" denotes the oral route AF, it can stay in the numerator, however, the "RfD" should be verified as an external exposure dose, and that a clear distinction be made regarding what the default inhalation AF is.

> **Response:** *The re-working of the section on the REL and in the **Caveats** section resulted in a change in the equation, so the 100% is no longer needed.*

Comment 6: Thus, a related comment is the need to clarify the description of oral versus inhalation AF in item #2. The route-specific contrast as presented would indicate a general trend that the oral AF is usually lower than the inhalation AF. This is not necessarily the case. First of all, the RfD can be expressed as the absorbed dose, not the exposure dose (See comments above). Thus, it is important to verify that each RfD used in the PRiME are comparably termed. Secondly, it is misleading to state that "An inhaled pesticide can pass directly into the blood stream from the lung" without mentioning that not all the chemical containing in the inhaled air may be retained in the respiratory system such that each volume of the exhale air is 100% chemical free. Many factors are involved in this exposure pathway. Suffice it to say that an assumption of a 100% inhalation AF can be made but caution should be given for the assumption, at least at a similar level of discussion as for the oral AF.

> **Response:** *The re-working of the section on the REL and in the **Caveats** section accommodates this suggestion. We also noted the recommendation of the EPA Scientific Advisory Panel (from the Dec. 2, 2009 meeting) to add another uncertainty factor of 10 when an oral study is used to estimate inhalation toxicity.*

Comment 7: Another related issue on the equation is the description in item #3. The 24-h assumption is not only for protecting small children who may spend most of their time at home, but also to account for their time spent in similar environment, e.g., those living in agricultural communities where the same or similar chemicals are used.

> **Response:** *Included in the **Caveats**.*

Comment 8: Regarding multiple sources or chemicals exposure, does the PRiME estimate the IRI for multiple pesticides of common mode of action within a tank mix for during the same period of time?

Response: *Not at this time.*

Comment 9: Page 5. It is not clear if the 4-12 hour maximum concentration is amortized over a 24-h or is assumed to be the level for a 24-h period in the IRI calculation. When data are available for a time point near hour 24 (as demonstrated in Figure 1) or can be modeled as described later in the white paper, it would be more realistic to use a 24-h level for the IRI calculation especially when the RfCs or RELs are for a 24-h period. If data are not available or cannot be modeled, a caution should be given in the PRiME output.

Response: *This is a problem with the existing data and the current paradigm used for inhalation toxicity studies. The solution we have developed utilizes existing data and accounts for observed adverse effects. It is not a perfect solution, but the data do not yet permit a perfect solution. Here's why:*

The maximum concentrations observed in the ARB studies and used in the regression analysis are time-weighted averages from sampling periods that last for 4–12 hours, depending on the data available in each study. These maximum concentrations are compared to a short-term REL because that is what is available from US EPA documents (except for fumigants, where an acute REL is sometimes available). While one might argue that the comparison should be based on a 24-hour time-weighted-average observed concentration, an averaging of the concentration does not adequately account for the adverse effects caused by the high concentration spikes. For example, symptoms of cholinesterase inhibition in adult males at a TWA concentration of chlorpyrifos that never exceeded more than 50% of the short-term adult REL have been observed in PANNA's Drift Catcher studies. This issue is complicated by the fact that the dosing of the laboratory animals in inhalation studies does not match the dose received by a person. The animals are dosed at a constant level for 6 hours per day, 5 days per week. No concentration spikes are experienced by the laboratory animals, unlike humans. Further complicating the comparison is that the animal studies last for 7 days, 30 days or 90 days. Few of these time periods are comparable to actual human exposure scenarios. Until additional data are available, our approach uses existing data and accounts in some way for concentration spikes by using the maximum 4-12-hr concentration to compare to the short-term REL.

Comment 10: Page 7. The use of transformation (or environmental breakdown or degradation) products in calculating the IRI may be misleading if without regard for their toxicological significance as compared to the parent chemical. The breakdown product(s) can be more (as mentioned in page 7) or less toxic. When they are more toxic, appropriate RfC or REL should be used to address their risk in addition to the risk from the remaining level of parent chemical, some procedure similar to the Toxicity Equivalence Factor (TEF) approach. When the breakdown product(s) are much less toxic, the IRI would be overestimated if they are

treated as having the same toxicity as the parent chemical and added to the parent chemical concentration for IRI calculation. This information should also be included in the PRiME for transparency sake. Based on Appendix 2, it would appear that the IRI for breakdown products is only accounted for manab, mancozeb, and metiram with a common degradation product of ethylene thiourea (ETU).

> **Response:** *The breakdown products and their RELs have now been incorporated into the index for all pesticides for which rapid degradation to a more volatile and/or toxic chemical occurs.*

Comment 11: Aside from the difficulty in assessing exposure to spray drift, it is difficult to understand the rationale behind not including this potentially important exposure factor as part of the inhalation risk index (particularly given that the intended purpose of the index is to stratify risk among workers/bystanders). It is commendable that there are plans for "flagging pesticides" that fit criteria for the possibility of problematic spray drift, but it is not clear how this will be integrated into the final version of the program. It is also not clear why certain pesticides (emamectin benzoate? Pyrethroids?) were identified as pesticides for which even a small amount of spray drift may be problematic. If there were specific criteria through which these assessments were made, it would be important to describe them. Also, if it would be possible to incorporate elements of other existing risk estimate methods (like AgDrift) into the Inhalation Risk Index, that would be a significant enhancement.

> **Response:** *Spray drift is being handled by a different part of the PRiME tool (and a different member of the PRiME team). Since spray drift is somewhat controllable by choice of application equipment, droplet size, etc., these factors are accounted for when the user selects his/her application method. The reason certain pesticides were mentioned as problematic in this regard is because they are high toxicity (low REL), but low volatility, so you wouldn't expect much volatilization drift, but because of the high toxicity, even small amounts of spray drift can be very problematic. Worker poisonings documented in California point to pyrethroids as a particular problem in this regard.*

Comment 12: The use of the "VOC Index," based upon estimates for VOC emission potential from California DPR, is problematic. While the intended purpose of its use in the Inhalation Risk Index is to be inclusive of potential risks from inhalation exposure to VOC's (including other ingredients) in pesticide formulations, the Cal-DPR emission inventory has many inherent limitations (as has been acknowledged by Cal-DPR). The purpose of the DPR VOC emission potential data is focused on long-term environmental monitoring, and to potentially reduce some of the "downstream" effects of VOC's, including their contribution to the production of ozone and smog. It is questionable in my mind as to whether these Cal-DPR emission inventory estimates have a valid role in assessing short-term inhalation risks associated with the diversity of VOC's that may be present in pesticide formulations. If US EPA were to actually move forward with their plans for more complete disclosure of other ingredients in pesticide formulations, that would present an obvious opportunity for significant enhancement of this element of the Risk Index, although at the current time I do not have any other suggestions.

Response: *Yes, you are correct. The VOC index is not an immediate "health-risk" index, but provides guidance to farmers interested in reducing basin-wide VOC loading. I have clarified this in the introduction and in the VOC Index development section. The index development section has been greatly expanded and the rationale for selecting the breakpoints has been more clearly explained.*

Comment 13: Page 8. What is the rationale for averaging the application rate for every pesticide active ingredient and over all crops for the VOC Index?

Response: *We changed this approach to use the average PRODUCT application rate times the emission potentials to get the percentile plot that shows the distribution of products containing varying levels of VOCs. We then evaluated the most recent DPR notice to registrants for the second tier pesticides of concern for VOCs, the emulsifiable concentrates (fumigants are first tier) and determined the breakpoints using this information. See the text for the details. The calculation done for the risk score on the web site uses the product application rate entered by the user times the emission potential for that product.*

Comment 14: In predicting pesticide air concentrations, the proposed model does not appear to take the soil water partitioning coefficient and temperature into account. The proposed model takes vapor pressure and application rate into account, but not the soil water partitioning coefficient. Without these parameters, the estimated concentrations of pesticides in air might be overestimated. It would be helpful to see if the model-predicted air concentrations change significantly when these parameters are included.

Response: *We did test the sensitivity of the regression to temperature and did not find much significance associated with temperature. See the new Table 2, in which we provide the results of various tests of the importance of different parameters. As far as the dependence on soil-water partition coefficient, we describe that in a new Appendix 3.*

Comment 15: Page 15. It is confusing that a 1 pound/acre rate is assumed when data for application rate is not available from the NASS and CA PUR database, especially that the PRiME tool as shown in page 35 indicates the option for entering a "new rate".

Response: *Agreed. In our updated apple pesticide example, we used the PUR 2007 application rates for apples if available, followed by the NASS rates. We excluded from the example any pesticides without an application rate. When using the tool, the application rates are entered by the user and these values are used in the calculation.*

Comment 16: I found the data in Table 4 to be quite interesting, but I am also perplexed at some of the active ingredients that were assessed to be higher risk (pink category), including pyrethrins, an active ingredient that is not considered (in my experience) to be a very high risk pesticide via inhalation exposure. It would have been helpful for the White Paper to include some discussion of these findings, and the extent to which they are consistent with "real-world" experience.

Response: *Good catch. There was a data entry error in the data table that led to pyrethrins being in the pink category. This has been fixed and another review of all data has been done. Table 4 is now Appendix 2.*

Comment 17: Appendix 2. For the "missing Data or Pass code" column, how is "H" code in the "FH" (False, do not calculate, low hazard) or "FEH" (False, do not calculate, low inhalation exposure potential and low hazard) designations determined for chemicals without RfCs or RELs?

Response: *For low-toxicity chemicals, US EPA normally waives many of the requirements for toxicity testing and states that they anticipate no adverse effects from use of these chemicals. This is true for many of the biopesticides and low-toxicity inorganics, as well as the Section 25(b) chemicals exempt from many FIFRA registration requirements. If this is the case, the chemical receives an FH pass code. If the vapor pressure of the chemical is very low, the chemical receives an FE pass code, because exposure due to volatilization will be negligible. If both conditions apply, the chemical receives an FEH pass code. This explanation has been added as a footnote to the table. Also, we changed the codes to the more intuitive LH, LE, and LEH for Low Hazard, Low Exposure and Low Exposure and Hazard.*

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