Pesticide Risk Mitigation Engine

Cancer Risk Indices

White Paper—DRAFT

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DRAFT **Cancer Risk Index**

Introduction

The PRiME cancer risk index provides a quantitative estimate of the potential cancer risks associated with the consumption of foods treated with carcinogenic pesticides, as well as exposures that occur when workers reenter fields following pesticide application. Risk calculations are restricted to consumers and agricultural workers; risk for pesticide applicators is not considered as part of this index.

Risk is a function of hazard and exposure. Estimates of consumer exposure by the oral route are based on national consumption patterns for each crop and mean pesticide residues on foods. Worker dermal exposure is estimated based on skin surface area exposed, dislodgeable foliar residue as a function of application rate and foliar half-life, and the amount of pesticide absorbed through the skin into the body. The estimated absorbed dose of a given pesticide is evaluated in the context of its carcinogenic hazard potential—the cancer potency or slope factor (Q_1*). Lifetime cancer risk, often expressed as the excess number of cancers per million people, is the product of estimated absorbed dose and Q_1*. The PRiME cancer risk index is based on the magnitude of excess cancers per million associated with lifetime exposure to carcinogenic pesticides.

Data Sources for Consumer Cancer Risk Index

Cancer Slope Factors (Cancer Potency)

Carcinogenicity hazard endpoints, known as cancer slope factors, were obtained from US EPA reregistration eligibility decision documents and human health risk assessments for pesticides that produced statistically significant tumor incidence in laboratory studies. These documents are available at the US EPA Chemical Search web page.[1]

Exposure Data

Estimates of chemical exposure based on consumption of foods treated with pesticides are a product of the residue on the food item and the amount of food consumed. Described below are the independent data sources we used for development of the consumer cancer risk index. Both US EPA's Dietary Exposure Evaluation Model (DEEM) and point estimates were evaluated for potential incorporation into the consumer cancer index of the PRiME tool.

a) **Residue Data:** Mean pesticide residues were derived from U.S. Department of Agriculture (USDA) Pesticide Data Program (PDP) Summary Reports from 1992–2011.[2] Mean residue levels were calculated on the basis of samples testing positive for a given pesticide residue, and these values were used as a

comparison to the anticipated residues calculated as part of the cancer index algorithm.

b) **Consumption Data:** Quantitative data regarding consumption rates for foods analyzed in the cancer risk index were obtained from the Food and Commodity Intake Database – What We Eat in America (FCID/WWEIA).[3] The information contained within this database was derived from the National Health and Nutrition Examination Survey/"What We Eat in America" (NHANES/WWEIA).[4] Consumption data in grams per kg body weight for the risk index were obtained for the following age groups: 0–2 years, 2–16 years, and 16–70 years.

Application Rates

The application rates used to test the consumer cancer risk index algorithm were averages of the application rate for the particular active ingredient on a specific crop group (grapes, peaches, or strawberries) in California in 2011, as reported in the 2011 CA Pesticide Use Reporting (PUR) data.[5] In normal use of the PRiME tool, the application rate will be entered by the user.

Pre-harvest intervals

As a health protective measure, we used label pre-harvest intervals (PHIs) as estimates of the time between the last pesticide application and consumption of treated agricultural commodities. US EPA defines the pre-harvest interval (PHI) as the time between the last pesticide application and harvest of the treated crops.[6] PHIs are used as part of EPA's process for reviewing tolerance decisions:[7]

> *The most commonly used Magnitude of Residue data used in dietary risk assessments are data from crop field trial residue studies. The goal of field trial studies is to determine the maximum residue likely to result in or on food crops from legal use of the pesticide. Accordingly, crop field trial residue studies are conducted in several locations that are representative of the variety of growing conditions in areas where the crop is grown, and reflect maximum use rates, maximum number of applications, and minimum duration after application that the crop may be harvested (pre-harvest intervals (PHIs)), as defined by the pesticide registration and label.*

We found that US EPA does not always use label recommended PHIs in their determination of tolerance levels for pesticide-crop combinations (see discussion in Appendix 2). However, we used the PHI as an estimate of the time between the final pesticide application and crop harvest to test the consumer cancer risk algorithm. The user will enter PHIs in normal use of the PRiME tool.

Pesticide Tolerance Levels

US EPA is responsible for regulating the pesticides that growers use and for setting limits on the amount of pesticides that may remain in or on food marketed in the United States. The limits of pesticide residues left on foods are called "tolerances" in the U.S.[8] As discussed above, tolerances are generally determined based the results of crop residue studies. In developing the consumer cancer risk index, US EPA tolerances[9] were used as the maximum pesticide residue level anticipated following a one-time application at the maximum application rate and minimum time to harvest.

Foliar Half-Lives

The foliar half-lives (DT_{50}) are used to estimate degradation of pesticides on plant surfaces as a surrogate for the corresponding half-lives for pesticide degradation on the surface of various crop commodities. These values were calculated according to the algorithm in equation (3), derived by Mineau *et al.,* [10]

$$\text{Log}(DT_{50}) = 0.51 \times \log(\text{Soil } DT_{50}) + 0.11 \quad (R^2 = 0.4) \qquad (1)$$

where Soil DT_{50} is the "typical" soil half-life from the EU Footprint Database.[11]

Systemic pesticides that penetrate the surface of plant tissues and translocate throughout the entire plant will likely have different half-lives compared to conventional, non-systemic pesticides. However, data are sparse on the metabolism of systemic pesticides with known carcinogenic potential. The Cancer Index currently does not treat systemic pesticides differently than non-systemic pesticides.

Data Sources for Worker Cancer Risk Index

Cancer Slope Factor (Cancer Potency)

See "Data Sources for Consumer Cancer Risk Index" above for information regarding the use of slope factors (Q_1* values) in the PRiME cancer indices. In addition, Appendix 1 provides detailed information on dose-response modeling, and linear, low dose extrapolation methods used in the determination of Q_1*.

Foliar Half-Lives

See "Data Sources for Consumer Cancer Risk Index" above for information regarding the use and calculation of foliar half-lives in the PRiME cancer indices.

Surface Area Exposed

The US EPA Exposure Factors handbook[12] was used to obtain standard surface areas for the exposed parts of workers bodies (head, neck and hands were assumed to be exposed) when they are using label-recommended typical personal protective

equipment (PPE)—shoes, socks, and long sleeved shirts and pants. Exposure may be underestimated if the pesticide is transported through clothing, such as when leaves are wet or workers are sweating, which will make the clothing more permeable to dislodgeable foliar residues. Thus, the calculated exposure should be viewed as a minimum value, as this additional exposure is not currently accounted for by the PRiME cancer risk index.

The algorithm is constructed in such a way that the exposed surface area can be modified for different scenarios. For example, in developing countries, PPE is often not available, and workers in tropical climates tend to wear less clothing and may not even wear shoes. As a result, significantly more of the worker's skin may be exposed, which would increase the dermal dose received.

Application Rates

See "Date Sources for Consumer Cancer Risk Index" above for information regarding the use of application rates in the PRiME cancer indices.

Restricted Entry Intervals (REI)

The restricted entry interval (REI) is the time interval after an application when reentry into a treated area is restricted to those with appropriate personal protective equipment. The REI values used to test the worker cancer risk index algorithm were taken from the CA product database published by the California Department of Pesticide Regulation.[13] In normal use of the PRiME tool, the user will be able to modify the time interval between pesticide application and field reentry. The average REI for products containing the specific active ingredient used on grapes, peaches and strawberries was used in the test data set.

PRiME Cancer Index Structure

Introduction

The PRiME cancer risk indices provide a quantitative estimate of the risk from oral (consumer) and dermal (worker) exposure, using readily available data. Consumer exposure is based on the amount of pesticide-treated foods consumed and predicted residues on these food items as a function of application rate, pre-harvest interval and foliar half-life. Worker exposure estimates are based on the pesticide application rate and foliar half-life, workplace parameters (hours in field, reentry interval), an estimate of the transfer rate of pesticide from foliage to the skin, and the amount of pesticide absorbed through the skin from measured absorption values. Risk estimates obtained with the index can be refined by the PRiME user to evaluate alternate application

scenarios, including modified application rates, surface area and field entry times. This approach permits extension of the indices to other workplace settings where PPE and other safety precautions are not necessarily utilized.

An estimate of cancer risk is calculated by multiplying the estimated dose by the cancer potency factor, Q_1*. Multiplying the risk by 1,000,000 provides an estimate of the number of excess cancers per million people. This structure allows comparison of different pesticides and application scenarios, facilitating the assessment of the relative consumer risks and worker reentry risks for different pesticides.

In developing the PRiME consumer cancer index, we evaluated US EPA and Cal EPA/ OEHHA cancer risk assessment methodologies. The method used for this risk index closely resembles both the US EPA and OEHHA guidelines. Modifications were incorporated to account for degradation of the applied pesticide over time and to calculate the residue levels on fruits and vegetables using tolerances, label and actual application rates, and post-harvest intervals. In most cases, the method provides an estimate of pesticide exposure to consumers without the need for post-application residue data, such as USDA Pesticide Data Program (PDP) data. The primary limitation for the consumer cancer index algorithm involves calculation of pesticide residue levels following post-harvest fungicide applications to stored agricultural commodities.

In developing the farmworker cancer index, we evaluated US EPA, [14, 15, 16, 17] USFS[18] and European Union[19] dermal risk assessment methodologies. The method used for the PRiME index most closely resembles that developed by the USFS, with modifications to account for degradation of the applied pesticide over time and using a dislodgeable fraction more representative of agricultural worker activities. In addition, measured dermal absorption factors from US EPA registration documents are used to estimate dermal absorption of the pesticide. The method provides an estimate of pesticide exposure without the need for post-application residue data, task-, crop- and chemical-specific transfer coefficients. The method for estimation of exposure from dermal contact with treated foliage is identical to that used for non-cancer effects described in the PRiME Dermal Index White Paper.

Overview for Cancer Indices

Cancer risk associated with exposure to a pesticide on raw agricultural produce is a function of three parameters:

1) **Cancer Potency**: Upper 95% confidence limit of the slope of the dose-response curve at low (environmentally relevant) exposure levels. This value is expressed as reciprocal dose, or $(mg/kg\ BW/day)^{-1}$.

2) **Age Sensitivity Factors:** Adjustment factors developed by US EPA and Cal EPA (OEHHA) to translate Q* values for adults to the corresponding values for individuals in sensitive life stages (postnatal and juvenile).

3) **Exposure:** The rate of chemical uptake (in mg/kg BW/day) due to consumption of pesticide-treated fruits and vegetables (consumer index) or dermal contact with treated vegetation (worker index).

Below, we provide information about how these parameters are used in the PRiME tool to estimate cancer risk.

Cancer Potency

The cancer potency factor—also called the slope factor (Q_1*)—is the upper 95th percent confidence limit of the slope of the extrapolated dose-response curve at low doses, and is commonly used in cancer risk assessments of chemicals suspected of inducing tumor development. We used US EPA-derived Q_1* values in the PRiME algorithm.

Q_1* is defined by US EPA as "an upper-bound estimate of risk per increment of dose that can be used to estimate risk probabilities for different exposure levels" and corresponds to a lifetime of exposure.[20] In carcinogenicity risk assessment, the Q_1* of a chemical is a measure of the increase in number of cancers over a lifetime per unit dose of the chemical. Cancer potency factors are expressed in terms of reciprocal dose, or (mg/kg-day)$^{-1}$; as such, larger Q_1* values translate to higher cancer potency.

US EPA applies an interspecies body weight scaling factor to extrapolate toxicologically equivalent doses of orally administered chemical agents from laboratory animal species to human equivalents**.** Body weight to the ¾ power (i.e., $BW^{3/4}$) is endorsed as the general default conversion factor. Cancer potency (Q_1*) values calculated by US EPA since 1994 were extrapolated from laboratory animals to humans using the current $BW^{3/4}$ scaling factor, as updated from the previous $BW^{2/3}$ scaling factor.[20] All Q_1* values used in the PRiME cancer indices were reported after 1994; therefore, all of the Q_1* values used in developing the PRiME cancer risk index utilize the $BW^{3/4}$ scaling factor.

$$\text{Human Equivalent Dose} = \text{Animal Dose (mg/kg } BW_{animal}^{3/4}\text{-day)}$$

Specific criteria must be met in order for US EPA to calculate the slope factor for a given carcinogen. Under current listing criteria (see Appendix 3), the chemical agent must be described as "carcinogenic to humans" or "likely to be carcinogenic to humans" based on evidence from human epidemiological studies and/or animal bioassays. Because slope factors are determined by linear extrapolation of tumor incidence data to low doses, these values are only calculated for carcinogens operating via linear modes of

action (MOAs), e.g., mutagenic, DNA-reactive chemicals. In addition, linear extrapolation is US EPA's default analytical method when a nonlinear MOA cannot be demonstrated based on the available toxicological information. An approach similar to that used for non-cancer effects—known as the margin of exposure (MOE) approach—is sometimes used for carcinogens operating via nonlinear MOAs.[20] See Appendix 1 for more information on the MOE approach to cancer risk estimation.

The procedure EPA uses for calculating slope factors involves two overall steps: (1) dose-response assessment, which characterizes the relationship between an applied dose of a carcinogen and tumor incidence in animals, and (2) linear extrapolation from experimental (high) doses to environmentally relevant (low) doses. General considerations and alternative approaches for both of these steps are further described in Appendix 1. In addition to EPA's default linear extrapolation, the linearized multistage model—US EPA's primary tool for performing dose-response analysis and linear, low dose extrapolation until 1996—is also discussed.

Age Sensitivity Factors

The current understanding of biological processes leads to the expectation that children are, in general, more susceptible to carcinogenic agents than adults. Extensive animal studies in the scientific literature have demonstrated that exposure to carcinogens early in life may result in enhanced susceptibility to the development of tumors, both malignant and benign.[21] US EPA and Cal EPA (OEHHA) conducted separate evaluations of the following types of dietary cancer toxicity studies: (1) those in which animals were dosed as juveniles compared to animals dosed as adults and (2) those in which animals were dosed through their entire lifetime compared to animals dosed only as adults. Subsequent modeling allowed for calculation of Q_1* values at two early human life stages (0–2 and 2–16 years) and at adulthood (16–70 years). The potential difference in susceptibility between early-life and adult exposure was calculated as the estimated ratio of cancer potency from early-life exposure over the cancer potency from adult exposure. These ratios provided a basis for adjusting the adult-based cancer potencies (Q_1*) when conducting carcinogenicity risk assessments. The following age-dependent adjustments to the adult-based cancer potency (Q_1*) were derived from an evaluation of the toxicology data:

- Postnatal (0–2 years) Q_1* = 10 × Adult Q_1*
- Juvenile (2–16 years) Q_1* = 3 × Adult Q_1*
- Adult (16–70 years) Q_1* = 1 × Adult Q_1*

US EPA suggests use of these early life adjustments only for agents operating through a mutagenic mode of action. However, there is an increasing body of evidence suggesting that exposure to non-mutagenic carcinogens early in life may also lead to biological transformations during key developmental periods that result in enhanced cancer risk. In contrast to the policy of US EPA, Cal EPA (OEHHA) applies the default Q_1* age adjustments to all carcinogens unless data are available to develop chemical-specific Q_1* age adjustments:[27]

> *OEHHA considers this* [US EPA's] *approach to be insufficiently health protective. There is no obvious reason to suppose that the toxicokinetics of non-mutagens would be systematically different from those of mutagens. It would also be inappropriate to assume by default that non-mutagenic carcinogens are assumed to need a toxicodynamic correction factor of 1. Most if not all of the factors that make individuals exposed to carcinogens during an early lifestage potentially more susceptible than those individuals exposed during adulthood also apply to non-mutagenic carcinogen exposures (e.g., rapid growth and development of target tissues, potentially greater sensitivity to hormonal carcinogens, differences in metabolism). It should also be noted that carcinogens that do not cause gene mutations may still be genotoxic by virtue of causing chromosomal damage. Additionally, many carcinogens do not have adequate data available for deciding on a specific mode of action, or do not necessarily have a single mode of action.*

In developing the PRiME cancer risk indices, we followed the health-protective guidance of OEHHA and applied ASFs to all carcinogenic pesticides for which cancer risk analysis using the Q_1* approach was recommended by US EPA.

Consumer Exposure Estimation

The algorithm for the PRiME consumer cancer risk index determines the risk of tumor development based on the following: (1) calculated pesticide residue level on raw agricultural commodities, (2) the 95th percentile consumption of raw agricultural commodities, and (3) the cancer slope factor (Q_1*) for a given pesticide. The first step of the algorithm calculates the pesticide residue on raw agricultural commodities immediately following application at the maximum application rate using the half-life equation for first-order degradation, equation 3:

$$R_t = R_0 \times (0.5^{t/DT50}) \quad (3)$$

Solving for R_0 (the residue level at time zero assuming the tolerance as the residue level at the minimum PHI for a given pesticide) provides the following rearranged first-order degradation equation:

$$R_0 = R_t / (0.5^{t/DT50}) \quad (4)$$

where:

R_t = Tolerance for a given pesticide residue on a raw agricultural commodity (mg/kg)

DT_{50} = foliar half-life of the chemical (days)

t = time to harvest used to establish tolerances, typically the label PHI specific to the pesticide active ingredient and crop (days)

For the consumer risk index, the value of R_0 calculated in the above equation reflects the maximum residue level left on raw agricultural commodities immediately following pesticide treatment at the maximum one-time application rate (AR_{MAX}) per label instruction. To correct for use of less than maximum application rates, the adjusted pesticide residue level at time 0 (R_{ADJ}) is estimated based on the ratio of the average and maximum application rates (AR_{AVG}/AR_{MAX}) multiplied by R_0 (eq. 5). The calculated R_{ADJ} is then substituted into the original first-order half-life expression (eq. 6) along with DT_{50} and the user-provided PHI to calculate the residue level at harvest (R_H), as shown in equation 6.

$$R_{ADJ} = (AR_{AVG}/AR_{MAX}) \times R_0 \quad (5)$$

$$R_H = R_{ADJ} \times (0.5^{PHI/DT50}) \quad (6)$$

Exposure depends on both the residue level of pesticides in raw agricultural commodities at the time of consumption, assumed to be residues at the time of harvest (R_H), as well as the quantity of the commodities consumed (C).

It should be noted that the first-order half-life equation breaks down for pesticides with extremely short or long foliar half-lives; however, other factors of the first-order half-life equation (i.e., degradation equation) correct for artificially high initial residue levels (R_0).

Consumer Cancer Risk Calculation

To determine the cancer risk for each age bin (0–2 yrs, 2–16 yrs, and 16–70 yrs of age), the amount of pesticide consumed per kg body weight per day is multiplied by the slope factor (Q_1*) and the corresponding age sensitivity factor (ASF). For example, the postnatal (0–2 years of age) cancer risk is determined using the following equation:

$$Risk_{0\text{-}2} = R_H \times C_{0\text{-}2} \times 0.001 \times (Q_1^*) \times ASF_{0\text{-}2} \times FL_{0\text{-}2} \quad (7)$$

where:

$C_{0\text{-}2}$ = 95th percentile NHANES consumption for individuals 0–2 years of age (in grams commodity per kg BW)

0.001 = Conversion factor for grams to kilograms in the consumption term

$ASF_{0\text{-}2}$ = Age sensitivity factor for individuals 0–2 years of age (10X)

$FL_{0\text{-}2}$ = Fraction of lifetime for individuals 0–2 years of age assuming a 70-year lifetime (2/70)

Lifetime cancer risk is calculated by summing the individual cancer risk terms for the three lifestages (0–2 years, 2–16 years, and 16–70 years). Factoring out common quantities from the separate age-specific terms results in the following equation for aggregate (lifetime) cancer risk:

$$Risk_{Lifetime} = R_H \times 0.001 \times (Q_1^*) \times [(C_{0\text{-}2} \times ASF_{0\text{-}2} \times FL_{0\text{-}2}) + (C_{2\text{-}16} \times ASF_{2\text{-}16} \times FL_{2\text{-}16}) + (C_{16\text{-}70} \times ASF_{16\text{-}70} \times FL_{16\text{-}70})]$$

$$Risk_{Lifetime} = Risk_{0\text{-}2} + Risk_{2\text{-}16} + Risk_{16\text{-}70} \quad (8)$$

Multiplying the lifetime cancer risk ($Risk_{Lifetime}$) by a factor of 1,000,000 provides an estimate of the number of excess cancers per million people.

Risk Index Values

The cancer risk indices are expressed as a hazard quotient—the ratio of the estimated cancer risk per million to the one in one million risk deemed to be acceptable by US EPA and CA OEHHA. Hazard quotients less than five represent low risk; between five and 50 are of concern and HQs greater than 50 represent exposures that may produce significant adverse effects. Risk scores are color-coded according to these values, as summarized in Table 1. Calculated hazard quotients for a subset of pesticides used on grapes are presented in Table 2.

Table 1: Cancer Score Bins for Consumer Cancer Index

Color	Hazard Quotient
Yellow	<5
Orange	5–50
Red	>50

Table 2: Consumer Cancer Risk for a Subset of Pesticides Used on Grapes

Chemical	Tolerance (ppm)	AR_{AVG} (lb/acre)[a]	PHI (days)	AR_{MAX} (lb/acre)[b]	R_{ADJ} (mg/kg)[c]	DT_{50} (days)[d]	R_H (mg/kg)[e]	Q* (mg/kg bw-day)$^{-1}$	Cancers per million (lifetime)	Cancers per million (0-2 yrs)
Clofentezine	1	0.204	21	0.25	1	12.13	0.2458	0.0376	95.334	34.331
Iprodione	10	0.663	45	1	10	8.45	0.1653	0.0439	74.859	26.958
Tetraconazole	0.2	0.045	14	0.04	0.32	20.35	0.2250	0.023	53.376	19.221
Spirodiclofen	2	0.286	14	0.31	2	2.81	0.0582	0.0149	8.947	3.222
Diuron	0.05	0.647	0	4	0.05	20.57	0.0081	0.0191	1.593	0.574
Pyraflufen-ethyl	0.01	0.00241	0	0.0053	0.01	2.14	0.0045	0.0332	1.557	0.561
Thiophanate-methyl	5	0.853	14	1.05	5	1.11	0.0006	0.0116	0.078	0.028
Maneb	7	0.998	66	3	7	2.38	1.07E-08	0.06	6.59E-06	2.37E-06
Oxyfluorfen	0.05	0.283	180	1.5	0.05	6.24	1.96E-11	0.0732	1.48E-08	5.32E-09
Mancozeb	7	1.43	66	3.2	7	1.53	3.50E-13	0.06	2.17E-10	7.80E-11
Hydrogen cyanamide	0	15.875	3	17.5	0	1.11	0	0.0664	0	0

AR_{AVG} = average application rate; PHI = pre-harvest interval; AR_{MAX} = maximum application rate; R_{ADJ} = maximum residue; DT_{50} = foliar half-life; R_H = calculated residue at harvest; Q* = cancer slope factor.

Table Notes:

[a] Application Rate (AR) based on 2011 California Pesticide Use Reporting data for grapes in California.

[b] Obtained from the labels of pesticide products used on grapes.

[c] Calculated using tolerance (R_t), PHI (t) in the pesticide half-life degradation equation (eq. 4).

[d] Calculated using equation 1.

[e] Calculated using R_{ADJ} as the residue at t=0 (actual application rate) and PHI as the time in the pesticide degradation half-life equation 6.

Table 3: Consumer Cancer Risk for a Subset of Pesticides Used on Peaches

Chemical	Tolerance (mg/kg)	AR_{AVG} (lb/acre)[a]	PHI (days)	AR_{MAX} (lb/acre)[b]	R_{ADJ} (mg/kg)[c]	DT_{50} (days)[d]	Calc Residue (mg/kg)[e]	Q* (mg/kg bw-day)$^{-1}$	Cancers per million (lifetime)	Cancers per million (0-2 yrs)
Iprodione (post-harvest)	20	0.666	45	1	20	8.45	1.7600	0.0439	395.6	161.2
Captan	15	3.5	0	4	15	1.00	13.1250	0.0024	161.3	65.7
Thiophanate-methyl	3	0.835	1	1.05	3	1.11	1.2777	0.0116	75.9	30.9
Clofentezine	1	0.207	21	0.25	1	12.13	0.2494	0.0376	48.0	19.6
Fenbuconazole	1	0.0936	0	0.094	1	8.18	0.9957	0.00359	18.3	7.5
Carbaryl	10	2.13	3	3	10	2.60	3.1946	0.00088	14.4	5.9
Spirodiclofen	1	0.275	7	0.28	1	2.81	0.1745	0.0149	13.3	5.4
Permethrin	1	0.248	14	0.25	1	5.78	0.1849	0.0096	9.1	3.7
Iprodione (pre-harvest)	0.05	0.666	45	1	2.01	8.45	0.0333	0.0439	7.5	3.0
Oryzalin	0.05	2.7	365	2	N/A	8.38	0.0675	0.00779	2.7	1.1
Pyraflufen-ethyl	0.01	0.00341	0	0.0053	0.01	2.14	0.0064	0.0332	1.1	0.4
Oxyfluorfen	0.05	0.303	14	1.5	0.05	6.24	0.0021	0.0732	0.8	0.3
Chlorothalonil	0.5	3.04	30	3.09	0.5	6.24	0.0176	0.00766	0.7	0.3
Mancozeb	7	0.75	45	1.5	7	1.53	5.17E-09	0.06	1.59E-06	6.47E-07
Propargite	7	1.92	365	6	7	6.67	7.63E-17	0.0033	1.29E-15	5.25E-16

AR_{AVG} = average application rate; PHI = pre-harvest interval; AR_{MAX} = maximum application rate; R_{ADJ} = maximum residue; DT_{50} = foliar half-life; R_H = calculated residue at harvest; Q* = cancer potency factor.

Table Notes:

[a] Based on 2011 California Pesticide Use Reporting data for peaches in California.
[b] Obtained from the labels of pesticide products used on peaches.
[c] Calculated using tolerance (R_t), PHI (t) in the pesticide half-life degradation equation (eq. 4).
[d] Calculated using equation 1.
[e] Calculated using R_{ADJ} as the residue at t=0 (actual application rate) and PHI as the time in the pesticide degradation half-life equation 6.

Table 4: Consumer Cancer Risk for a Subset of Pesticides Used on Strawberries

Chemical	Tolerance (mg/kg)	AR_{AVG} (lb/acre)[a]	PHI (days)	AR_{MAX} (lb/acre)[b]	R_{ADJ} (mg/kg)[c]	DT_{50} (days)[d]	Calc Residue (mg/kg)[e]	Q* (mg/kg bw-day)$^{-1}$	Cancers per million (lifetime)	Cancers per million (0-2 yrs)
Thiophanate-methyl	7	0.639	1	0.7	7	1.11	3.422	0.0116	199.2	59.0
Captan	20	1.7	0	3	20	1.00	11.333	0.0024	136.5	40.4
Iprodione	15	0.86	45	1	15	8.45	0.322	0.0439	70.9	21.0
Carbaryl	4	1.75	7	2.13	4	2.60	0.510	0.000875	2.2	0.7
DCPA	2	3.69	45	9	2	8.11	0.018	0.00149	0.1	0.04
Oxyfluorfen	0	0.328	60	0.5	0	6.24	0	0.0732	0	0
Chlorothalonil	0	1.18	365	1.16	0	6.24	0	0.00766	0	0

AR_{AVG} = average application rate; PHI – pre-harvest interval; AR_{MAX} = maximum application rate; R_{ADJ} = maximum residue; DT_{50} = foliar half-life; R_H = calculated residue at harvest; Q* = cancer slope factor.

Table Notes:

[a] Based on 2011 California Pesticide Use Reporting data for strawberries in California.

[b] Obtained from the labels of pesticide products used on strawberries.

[c] Calculated using tolerance (R_t), PHI (t) in the pesticide half-life degradation equation (eq. 4).

[d] Calculated using equation 1.

[e] Calculated using R_{ADJ} as the residue at t=0 (actual application rate) and PHI as the time in the pesticide degradation half-life equation 6.

Overview for Cancer-Farmworker Index

The PRiME farmworker cancer risk index is based solely on dermal exposure during post-application worker activities. It is assumed that growers will adhere to the label restricted entry interval (REI) as a minimum precaution to safeguard worker health and safety. Because of this provision, average air concentrations of the volatile and semi-volatile pesticides considered in this cancer risk index are expected to be minimal during the worker exposure period.

Monitoring data and available models do not support the development of an inhalation-based cancer risk index for post-application worker activities. Air monitoring studies conducted by the California Department of Pesticide Regulation (DPR) indicate that maximum air concentrations typically occur within twelve hours of application, with variable concentrations recorded several days after application. US EPA has also pointed out that empirical models are only applicable to the first day post-application.[22] Lastly, revised REI guidelines for fumigants, such as Chlorpicrin and Telone, further minimize the likelihood of post-application inhalation worker exposure to the most problematic volatile pesticides.

According to the methods described in the PRiME *Dermal Index*, estimation of the dose of a pesticide received from fieldworker activities can be conceptualized as two distinct processes:

1) **Transfer:** Transfer of the chemical from the crop to the skin when a person works in a treated area.
2) **Absorption:** Absorption of the chemical on the skin into the body.

The risk (or excess cancers per million) associated with working in a field treated with carcinogenic pesticides is determined through comparison of the exposure level (dose) with the cancer slope factor (Q*).

Dermal Exposure

See the PRiME Dermal White Paper for details regarding determination of the potential dose (D_{pot}), dislodgeable foliar residue (DFR), transfer rate (TR), internal dose (D_{int}) and other dermal exposure parameters.

Lifetime Exposure

Determination of the cancer risk associated with seasonal farmworker exposure to carcinogenic pesticides requires an understanding of the daily dose over the course of a lifetime. For the PRiME cancer worker index, we assumed that farmworkers would be exposed to a specific carcinogenic pesticide over a consecutive five-day period once per

year and that this exposure scenario would be repeated annually. We calculated an average annual dose based on the cumulative dose accrued during the five-day period. The dislodgeable foliar residue changes over time due to pesticide degradation; therefore, we calculated an average DFR, TR, and D_{pot} for each workday during the five-day period and summed the five individual D_{pot} values to obtain $D_{pot, 5d}$. Equations 9–12 were used to calculate lifetime exposure levels:

$$D_{int} = (D_{pot, 5d}\ (\mu g) \times AF \times 0.001\ mg/\mu g)/64\ kg/365\ days \quad (9)$$

where:

The factor of 365 days in equation (18) corrects the five-day cumulative dose to an average dose per day. See PRiME Dermal White Paper for more detailed explanations of dermal exposure equations.

$$D_{pot, 5d} = SA \times WT \times (TR_1 + TR_2 + TR_3 + TR_4 + TR_5) \quad (10)$$

$$TR_X = (DFR_X)^{1.09} \times 1.12 \quad (11)$$

$$DFR_X = DFR_0 \times (0.5^{(REI+Y)/DT50}) \quad (12)$$

where:

X = 1, 2, 3, 4, 5 (day of exposure)

Y = 0.2 (day 1), 1.2 (day 2), 2.2 (day 3), 3.2 (day 4), 4.2 (day 5). Refers to the time (in days) from end of the REI to midpoint of the given 8-hour workday.

Risk Index Values

The cancer risk index is expressed as the number of excess cancers per million. This value is based on the three-fold product of exposure (mg/kg-day), cancer slope factor (Q^*; $(mg/kg\text{-}day)^{-1}$, and a factor of 1,000,000. Q^* values for all carcinogenic pesticides in the cancer risk index are based on oral studies; therefore, the comparison is between D_{int} and Q^*_{oral}. The interested reader is referred to the "caveats for dermal exposure" section below for additional information regarding the potential correlation between Q^*_{dermal} and Q^*_{oral} for pesticides covered under this risk index. Excess cancers less than one represent low risk; between one and 10 are of concern and cancers greater than 10 represent exposures that may produce significant carcinogenic effects due to prolonged exposure. Risk scores are color coded according to these values, as summarized in Table 5. Calculated excess cancers for a subset of pesticides on grapes, peaches, and strawberries are presented in Tables 6–8.

The “hazard quotient” provided in table 1 below can be conceptualized as the ratio of the excess cancer per million calculated for the pesticide exposure level divided by the acceptable number of cancers per million (i.e., one per million).

Table 1: Cancer Score Bins for Farmworker Cancer Index

Color	Hazard Quotient
Yellow	<0.5
Orange	0.5–1
Red	>1

Table 5: Farmworker Cancer Risk for a Subset of Pesticides Used on Grapes

Chemical	AR (lb/acre)[a]	DT_{50} (days)[b]	REI (days)[c]	Q* [(mg/kg b.w.-day)$^{-1}$][d]	$D_{pot, 5d}$ (μg)	AF[d]	$D_{int, 5d}$ (mg/kg b.w.)	$D_{daily, 5d}$ (mg/kg-day)	Lifetime Cancer Risk	Cancers per Million
Hydrogen cyanamide	15.875	1.11	3	0.0664	168903	0.11	0.29030	8.0E-04	5.28E-05	52.81
Oxyfluorfen	0.283	6.24	1	0.0732	32544	0.18	0.09153	2.5E-04	1.84E-05	18.36
Iprodione	0.663	8.45	2	0.0439	82748	0.05	0.06465	1.8E-04	7.78E-06	7.78
Maneb	0.998	2.38	1	0.06	74648	0.02	0.02333	6.4E-05	3.83E-06	3.83
Diuron	0.647	20.57	0.5	0.0191	105523	0.04	0.06595	1.8E-04	3.45E-06	3.45
Mancozeb	1.43	1.53	1	0.06	71959	0.01	0.01124	3.1E-05	1.85E-06	1.85
Tetraconazole	0.045	20.35	7	0.023	4531	0.12	0.00850	2.3E-05	5.35E-07	0.54
Thiophanate-methyl*	0.853	1.11	2	0.0116	13778	0.07	0.01507	4.1E-05	4.79E-07	0.48
Clofentezine	0.204	12.13	0.5	0.0376	28060	0.01	0.00438	1.2E-05	4.52E-07	0.45
Spirodiclofen	0.286	2.81	0.5	0.0149	24821	0.02	0.00776	2.1E-05	3.17E-07	0.32
Pyraflufen-ethyl	0.00241	2.14	0.5	0.0332	114	0.4	0.00071	2.0E-06	6.48E-08	0.06

AR = application rate; DT_{50} = foliar half-life; REI = restricted entry interval; Oral Q* = cancer slope factor; D_{pot} = maximum potential dose; AF = absorption fraction; D_{int} = internal dose; D_{Daily} = adjusted daily dose.

Table Notes:

[a] Application Rate (AR) based on 2011 California Pesticide Use Reporting data for grapes in California.

[b] Calculated using equation 1.

[c] Obtained from the labels of pesticide products used on grapes.

[d] Obtained from EPA Reregistration Eligibility Decision (RED) documents, human health risk assessment, and other publicly-available EPA literature.

Table 6. Farmworker Cancer Risk for a Subset of Pesticides Used on Peaches

Chemical	AR (lb/acre)[a]	DT_{50} (days)[b]	REI (days)[c]	Q* [(mg/kg b.w.-day)$^{-1}$][d]	$D_{pot, 5d}$ (µg)	AF[d]	$D_{int, 5d}$ (mg/kg b.w.)	$D_{daily, 5d}$ (mg/kg-day)	Lifetime Cancer Risk	Cancers per Million
Oxyfluorfen	0.303	6.24	1	0.0732	35058.64391	0.18	0.09860	2.70E-04	1.98E-05	19.77
Iprodione	0.666	8.45	2	0.0439	83156.51288	0.05	0.06497	1.78E-04	7.81E-06	7.81
Propargite	1.92	6.67	2	0.0033	239742.6285	0.14	0.52444	1.44E-03	4.74E-06	4.74
Oryzalin	2.7	8.38	1	0.00779	417248.3121	0.023	0.14995	4.11E-04	3.20E-06	3.20
Carbaryl	2.13	2.60	0.5	0.00088	211614.1321	0.13	0.42984	1.18E-03	1.04E-06	1.04
Mancozeb	0.75	1.53	1	0.06	35611.07446	0.01	0.00556	1.52E-05	9.15E-07	0.91
Permethrin	0.248	5.78	0.5	0.0096	29236.8527	0.057	0.02604	7.13E-05	6.85E-07	0.68
Thiophanate-methyl*	0.835	1.11	2	0.0116	13461.84603	0.07	0.01472	4.03E-05	4.68E-07	0.47
Clofentezine	0.207	12.13	0.5	0.0376	28510.53519	0.01	0.00445	1.22E-05	4.59E-07	0.46
Spirodiclofen	0.275	2.81	0.5	0.0149	23781.91593	0.02	0.00743	2.04E-05	3.03E-07	0.30
Chlorothalonil	3.04	6.24	0.5	0.00766	459881.4487	0.002	0.01437	3.94E-05	3.02E-07	0.30
Pyraflufen-ethyl	0.00341	2.14	0.5	0.0332	166.3762012	0.4	0.00104	2.85E-06	9.46E-08	0.09
Fenbuconazole	0.0936	8.18	0.5	0.00359	11117.81656	0.043	0.00747	2.05E-05	7.35E-08	0.07
Captan	3.5	1.00	1	0.0024	109472.0517	0.004	0.00684	1.87E-05	4.50E-08	0.04

AR = application rate; DT_{50} = foliar half-life; REI = restricted entry interval; Oral Q* = cancer slope factor; D_{pot} = maximum potential dose; AF = absorption fraction; D_{int} = internal dose; D_{Daily} = adjusted daily dose.

Table Notes:

[a] Application Rate (AR) based on 2011 California Pesticide Use Reporting data for peaches grown in California.

[b] Calculated using equation 1.

[c] Obtained from the labels of pesticide products used on peaches.

[d] Obtained from EPA Reregistration Eligibility Decision (RED) documents, human health risk assessments, and other publicly-available scientific literature.

Table 7: Farmworker Cancer Risk for a Subset of Pesticides Used on Strawberries

Chemical	AR (lb/acre)	DT_{50} (days)	REI (days)	Q* [(mg/kg b.w.-day)$^{-1}$]	$D_{pot, 5d}$ (μg)	AF	$D_{int, 5d}$ (mg/kg b.w.)	$D_{daily, 5d}$ (mg/kg-day)	Lifetime Cancer Risk	Cancers per Million
Oxyfluorfen	0.328	6.24	1	0.0732	38223.03233	0.18	0.1075	2.95E-04	2.16E-05	21.56
Iprodione	0.86	8.45	2	0.0439	109878.4871	0.05	0.0858	2.35E-04	1.03E-05	10.32
DCPA	3.69	8.11	0.5	0.00149	608878.728	0.22	2.0930	5.73E-03	8.54E-06	8.54
Thiophanate-methyl	0.639	1.11	1	0.0116	19864.07416	0.07	0.0217	5.95E-05	6.90E-07	0.69
Carbaryl	1.75	2.60	4	0.000875	61866.99315	0.13	0.1257	3.44E-04	3.01E-07	0.30
Chlorothalonil	1.18	6.24	0.5	0.00766	163932.504	0.002	0.0051	1.40E-05	1.08E-07	0.11
Captan	1.7	1.00	1	0.0024	49826.27421	0.004	0.0031	8.53E-06	2.05E-08	0.02

AR = application rate; DT_{50} = foliar half-life; REI = restricted entry interval; Oral Q* = cancer slope factor; D_{pot} = maximum potential dose; AF = absorption fraction; D_{int} = internal dose; D_{Daily} = adjusted daily dose.

Table Notes:

[a] Application Rate (AR) based on 2011 California Pesticide Use Reporting data for strawberries grown in California.

[b] Calculated using equation 1.

[c] Obtained from the labels of pesticide products used on strawberries.

[d] Obtained from EPA Reregistration Eligibility Decision (RED) documents, human health risk assessments, and other publicly-available scientific literature.

Caveats for Dermal Exposure

There are several factors that may contibute to inaccuracies in the use of Q_1* values obtained from animal studies using oral dosing to estimate cancer risk from dermal exposure:

1) **Oral dosing and dermal dosing are not equivalent.** The digestive system degrades many pesticides, thereby reducing the amount absorbed compared to the administered dose. Exposure via dermal contact often results in localized skin cancer responses, e.g., for polycyclic aromatic hydrocarbons (PAHs), as well as systemic oncogenicity.[23]
2) **The use of oral studies to determine cancer risks from dermal exposure has not been validated:** A dermal toxicity study is most appropriate for determining the internal dose through dermal absorption, yet dermal carcinogenicity studies are not available for most pesticides. In the absence of dermal cancer data, US EPA recommends adjusting the oral Q* by the fraction of chemical absorbed through the gastrointestinal (GI) tract as the default approach for estimating dermal Q* values. [24, 25] This route-to-route extrapolation is represented mathematically below (equation 13) as an absorption efficiency adjustment of the oral Q*. Organic chemicals are generally well absorbed (≥50%) across the GI tract, and therefore US EPA assumes a 100% ABS_{GI} value for these types of compounds. This assumption is also applied to the PRiME Farmworker Cancer Risk Index.

$$Q^*_{Dermal} = Q^*_{Oral} / ABS_{GI} \quad (13)$$

where:

Q^*_{Dermal} = Dermal cancer slope factor

Q^*_{Oral} = Oral cancer slope factor

ABS_{GI} = Fraction of chemical absorbed in gastrointestinal tract (dimensionless) in the critical toxicity study.

UPAFs for Consumer Cancer Risk Index

Significantly lower exposure levels are anticipated for pesticides applied to dormant crops (i.e., dormant sprays), granular treatments, and applications made prior to bloom. A UPAF of 0.1 will be applied for pesticide application patterns unlikely to result in significant pesticide residues in the resulting agricultural commodity.

Variable Parameters of Dermal Risk for Re-entering Workers

Reduction in exposure (and therefore risk) can be achieved by reducing the amount of time workers are in contact with treated vegetation, reducing the surface area of exposed skin or using less permeable clothing, and/or increasing the amount of time between pesticide application and field reentry. Providing wash stations with soap and water for workers will reduce dermal exposure to some extent, but this is not readily quantifiable, as each pesticide is absorbed at different rates into the upper layer of skin where it cannot be washed off. Some crops and pesticide formulations also have an inherently low exposure potential, so adjustment factors have been developed for these scenarios. The original hazard quotient is multiplied by this adjustment factor to provide a more accurate estimate of risk.

Work Time

Work time (WT) enters directly into the exposure calculation, with a default value of eight hours. Users can enter a different value if appropriate to their particular situation. A reduction in the time spent by workers in a treated field below eight hours will reduce the dermal risk hazard quotient.

Surface Area Exposed

Surface area (SA) enters directly into the exposure calculation, with a default value of 1,730 cm^2 for hands, face and neck. Having workers use gloves in the field will reduce the calculated exposure by 45%. Working in short sleeves will approximately double the exposure.

Field Entry Interval

PRiME uses a Field Entry Interval (FEI), which is the time interval between a pesticide application and worker reentry into the treated area. The FEI enters directly into the exposure calculation. In PRiME, the user will have an opportunity to adjust the FEI to reflect the actual time after the application that workers enter the field. Default FEIs are based on a typical restricted entry interval for a given chemical. The degree to which increasing the FEI will decrease the hazard quotient will vary by pesticide, according to the foliar half-life of each pesticide.

Crop

Different crops and the tasks required for each crop have vastly different exposure potential for re-entering workers, based on the potential for contact with leaf surfaces treated with a pesticide. We used the EU's guidelines[Error! Bookmark not defined.] for transfer coefficients to assign an adjustment factor based on crop, with the baseline (no adjustment) assigned to vegetables and ornamentals (see Table 3). High-contact crops

such as caneberries, tree fruits, and grapes have a transfer coefficient that is four times greater than that for vegetables because there is more leaf surface area and the foliage can readily contact a larger fraction of the body; thus, an adjustment factor of 4 is assigned for these crops. For strawberries, a low-growing crop, an adjustment factor of 0.6 was assigned. For field crops where much of the worker activity involves little contact with the crop, an adjustment factor of 0.1 is used. The original hazard quotient is multiplied by this adjustment factor to provide a more accurate estimate of risk.

Table 3: Adjustment Factors by Crop

Crop Type	Transfer Coefficient (cm^2/person/hr)[a]	UPAF
Vegetables	5,800	1
Ornamentals	5,000	1
Fruit, high-growing crops (e.g., tree and vine crops)	20,000	4
Strawberries	3,000	0.6
Field crops	1,000	0.1

[a] From EU guidelines, Reference **Error! Bookmark not defined.**.

Product Formulation and Use Pattern

Product formulation can significantly affect dermal exposure potential for re-entering workers and Use Pattern Adjustment Factors (UPAF) are used in the PRiME tool to account for this fact (see Table 4). In general, pesticides that are applied as sprays or dusts have the highest dermal exposure potential, since the pesticide is applied in such a way to maximize leaf surface coverage. Granular pesticides are typically applied to soils and pose less dermal risk. Gaseous pesticides such as fumigants do not pose a risk of dermal exposure for re-entering workers because the pesticide does not remain as a residue on surfaces contacted by workers. Impregnated materials pose less risk because they are not broadcast onto plant surfaces. The original hazard quotient is multiplied by this UPAF to provide a more accurate estimate of risk.

Table 4: Use Pattern Adjustment Factors by Formulation

Formulation/Application Type	UPAF
Liquid spray or dust to foliage	1
Granular application to soil	0.1
Liquid spray or dust to soil	0.1
Gaseous	0

Uncertainties in the PRiME Cancer-Farmworker Index

There remains uncertainty in the estimated value of dermal exposure, thus it is necessary to consider the uncertainty of the components of the dermal index and the

potential for these uncertainties to interact and overly influence estimates obtained with the index. These uncertainties can be classified into three broad categories: parameter, model, and scenario uncertainty.[17]

Parameter Uncertainty

Parameter uncertainty pertains to the accuracy of the vapor pressure values used to estimate the foliar half-life. Vapor pressure varies depending on temperature and the polarity of the surface from which the pesticide is volatilizing.

Scenario Uncertainty

Scenario uncertainty in the dermal index is associated with the occupational variables that define potential worker exposure. Worker contact with a pesticide-treated crop is determined by the duration of the field task performed and the length of time pesticide residue stays on the skin after the worker leaves the field. The duration of work time, WT, is fairly well established, but the exposure time, ET, for post-field skin residue is more difficult to determine and may introduce significant uncertainty. The ET for lipophilic compounds may be higher, as these substances rapidly pass into the outer layer of skin and cannot be washed off afterwards. The amount of pesticide absorbed through the clothing is another occupational variable that introduces uncertainty into the exposure scenario.

The sensitivity analysis in Appendix 2 provides an estimate of the relative magnitude of the effects of changing the factors that contribute to dermal exposure. In general, changes in the dislodgeable fraction (DF) and skin surface area exposed (SA) will have significant impacts on calculated doses; thus, any uncertainty in these parameters will have a large effect on absorbed dose.

Appendix 1: Methods for Determining Carcinogenic Potency

Cancer Slope Factors (Q_1*)

Linearized Multistage (LMS) Modeling. For over 15 years, the linearized multistage (LMS) model was the default linear, low-dose model of the US EPA, among other state and federal agencies, for calculating quantitative estimates of low dose risks from exposures to carcinogenic agents.[26]

The LMS model is a flexible statistical model that can be used to describe both linear and nonlinear dose-response relationships.[27, 28] In most cases, however, the LMS model predicts a polynomial form for the data at higher doses and linearity in the low dose regime. The probability of developing a tumor (P) induced through exposure to an average daily dose (d) is expressed mathematically in equation 14. While q_0 represents the background lifetime incidence of a tumor, the upper confidence limit of the slope factor q_1 (q_1*) is an estimate of the cancer potency factor used in carcinogenicity risk assessment.

$$P(d) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + \ldots + q_j d^j] \quad (14)$$

with constrainsts: $q_i \geq 0$ for all i

Toxicodynamic ("Biologically-Based") Modeling. This method is preferable if sufficient data is available to ascertain the mode of action and quantitatively derive model parameters (i.e., rates and other measures) associated with key precursor events of the specific MOA.[20] For carcinogenicity risk assessment, toxicodynamic modeling is the most comprehensive way of accounting for biological processes involved in tumor development. This approach may require either development of a new model for a specific agent or selection of a standard model already existing for the agent's MOA. Low dose extrapolation (see below) may be performed once a toxicodynamic model is developed or fit to the dose-response relationship.

Empirical Modeling ("Curve-Fitting"). In general, EPA recommends that empirical modeling should only be used in the range of observed data when a toxicodynamic model is not available.[20] In this type of analysis, a mathematical function can be fitted to the toxicology data on either tumor incidence or key tumor precursor events. A wide variety of empirical models are available for performing dose-response analysis in the range of observation. Following the curve-fitting procedure, a point of departure (POD) is selected and linear extrapolation to lower doses is performed for carcinogens having linear MOAs as well as those lacking definitive MOAs. Empirical modeling is the method most commonly used by US EPA in calculating cancer slope factors.

The California Office of Environmental Health Hazard Assessment (OEHHA) technical support document for cancer potency factors provides additional insight into the empirical modeling process, also referred to as benchmark dose methodologies.[27] As described above, the basic approach to this method is to fit an arbitrary function to the observed tumor incidence data and then select a POD or "benchmark dose" within the range of observation. The lower 95% confidence bound of the effective dose producing 10% tumor incidence is generally chosen when using animal data. Following empirical modeling and POD selection, linear extrapolation to low doses is conducted in order to calculate the cancer slope factor.

Low-Dose, Linear Extrapolation. In the 2005 cancer risk assessment guidelines, US EPA suggests use of the linear extrapolation method when mode of action (MOA) data indicate that the dose-response relationship is expected to behave linearly at low doses. Specifically, mutagenic and DNA-reactive chemical agents are generally considered to be linear in this region. It is also recommended that linear extrapolation be applied as a default method when the weight of evidence evaluation for all available data is insufficient to establish the MOA.[20]

When tumor data are used, a point of departure (POD) is obtained from modeled tumor incidences rather than the actual data points. For linear extrapolation, a line is drawn from the POD to the origin; the upper 95% limit of the slope of this line is defined as Q_1*. Models commonly used for carcinogenic dose-response assessment yield estimates of the POD at response levels of 1–10%, and the 95% lower confidence limit of the selected estimate (BMD lower bound, or BMDL) is used as the POD for extrapolating to low doses and calculating Q_1*.[20] As described above, the lowest calculated dose of the chemical agent that is expected to increase the cancer rate by 10 percent (LED_{10}) is commonly used to determine the POD for linear, low dose extrapolation. The slope factor may therefore be expressed as $0.1/LED_{10}$.[27]

Margin or Exposure (MOE)

The margin of exposure (MOE) is an expression of how many fold lower the average human exposure to a chemical agent is compared to the dose that causes cancer in rodents.[29] Specifically, the MOE for a chemical exposure is represented by the following ratio of concentrations:

$$\text{MOE} = \frac{\text{Calculated dose leading to cancer in 10\% of test rodents (mg/kg/day)}}{\text{Average Human Exposure (mg/kg/day)}}$$

An MOE result of 1 would indicate that the human exposure level is the same as the dose that resulted in tumor development in rodent bioassays. Alternatively, if the

calculated dose leading to cancer in 10% of test rodents (LED_{10}) is 1 mg and the anticipated environmental exposure is 0.01 mg, the MOE would be 100. The risk manager must determine an acceptable MOE, which typically incorporates 10-fold intra- and interspecies uncertainty factors (100 total). Some chemicals are assigned additional uncertainty factors for data gaps or extrapolation from a LOAEL to a NOAEL.

Known and likely human carcinogens that operate via a non-linear MOA and certain EPA group C chemicals (possible human carcinogens) are generally evaluated using the threshold MOE approach. However, we do not believe that the MOE approach is sufficiently robust for the evaluation of lifetime cancer risk associated with exposure to possible human carcinogens. In developing the current algorithm, we focused our efforts toward the development of cancer risk indices for human carcinogens with EPA-supported Q_1* values using linear methods. Future versions of the cancer index may include a non-linear analysis for group C chemicals and carcinogens with non-linear MOAs as additional literature becomes available.

TD_{50}

In addition to the cancer slope factor, TD_{50} is another numerical description of carcinogenic potency.[30] TD_{50} can be defined as the dose rate (in mg/kg BW/day) that is estimated to reduce by 50% the proportion of tumor-free animals at the end of a standard lifespan. Stated another way, the TD_{50} is the chronic dose rate that would induce tumor is half of animals at the end of the standard lifespan for the test species. Although TD_{50} does not involve extrapolation to low dose, TD_{50} is inversely related to the slope and a comparison with Q_1*can be made using the following relationship: $Q_1^* = \ln(2)/TD_{50}$.[31] The PRiME cancer risk indices rely on linear, low dose extrapolation, and therefore TD_{50} values are not used in our assessment.

Appendix 2: US EPA Determination of Pesticide Tolerances

US EPA is responsible for regulating the pesticides that are used by growers and for setting limits on the amount of pesticides that may remain in or on foods marketed in the US. These limits on pesticide residues left on foods are called tolerances in the US. Anticipated residue data are commonly drawn from crop field trial or food processing studies, and actual residue data come from monitoring studies that sample food to test for the presence of pesticide residues.[7, 8]

For anticipated residue data, Magnitude of Residue studies are conducted using the maximum legal pesticide application rate according to the EPA-approved label and registration. Crop field residue studies are conducted in several locations that are representative of the variety of growing conditions in areas where the crop is grown, and reflect the maximum application rates and number of applications as well as the minimum duration after application that a crop may be harvested (pre-harvest intervals, or PHIs). All of this information is defined by the pesticide product's registration and label. Residue levels are determined immediately upon harvest of the crop commodity.

For certain pesticides, we identified conflicting information among the available EPA literature on tolerances, residues levels determined from field trials, and PHIs. For example, the tolerance for iprodione on grapes is 60 ppm (40 CFR 180.399) despite the fact that EPA's 1998 Reregistration Eligibility Decision (RED) states that the tolerance for iprodione on this commodity was changed to 10 ppm.[32] The label for Rovral, an iprodione-based fungicide product for grapes, states that grape plants may be treated up to 7 days before harvest (wine grapes) or at early to mid-bloom (table grapes).[33] However, field studies of iprodione on grapes, which are used to validate the established tolerances, have been conducted with iprodione applications up to the day of harvest.[34] Although the cancer risk algorithm is designed to calculate R_{MAX} from the tolerance and PHI, we decided to designate the official tolerance (60 ppm) as R_{MAX} for iprodione on grapes (PHI = 0 days), in agreement with the field trial residue data.

The only tolerance listed for use of iprodione on peaches is 20 ppm for postharvest applications (40 CFR 180.399). Because pre-harvest treatments on peaches may not be made after petal fall,[33] iprodione residues on peaches should not result from this manner of treatment. EPA's 1998 RED for iprodione states that "the tolerance for iprodione on all stone fruit and strawberries will be reduced to the limit of quantification (0.05 ppm)," reflective of the pre-harvest use pattern of iprodione.[32] EPA and other literature indicate that postharvest iprodione applications on peaches will eliminate most of the pre-harvest residues due to the rinsing step preceding the postharvest dip.[35] Residues of iprodione on peaches range from 0.025–12 ppm (average

= 1.76 ppm) in 2008, the most recent year of data for peaches.[2] Based on the available information, it is apparent that the bulk of the residues on peaches correspond to postharvest treatments. The consumer cancer risk index thus includes a preset residue level of 1.76 ppm for postharvest application to stone fruit that bypasses the algorithm's residue calculation.

In addition to iprodione, the tolerance for thiophante-methyl was determined using residue data that is not always reflective of the allowed use pattern. Specifically, field studies that generated this data documented application rates outside of the acceptable range up to the day of harvest despite the established 7 day PHI.[36] Therefore, the official tolerance (5 ppm) was used as R_{MAX} for thiophanate-methyl and a number of other pesticides when the field trial application methods were unavailable or contradictory to label use patterns.

Appendix 3: US EPA Carcinogenicity Classifications

The US EPA Office of Pesticide Programs maintains a *List of Chemicals Evaluated for Carcinogenic Potential*, which classifies pesticides by their role in causing cancer in humans and laboratory animals. A panel of scientists reviews the available data, including both epidemiological studies on humans exposed to the chemicals in the course of their daily lives and studies on laboratory animals, and make a decision about a cancer ranking based on the weight of the evidence. US EPA's classification of carcinogenicity has changed three times between 1986 and the present. The following is a discussion of the three classification schemes US EPA used from 1986 to 1996,[37] 1996 to 1999, and 1999 to the present.[38]

US EPA used the following carcinogenicity categories between 1986–1996:

- **Category A: Known to cause cancer in humans.** This classification is generally based on epidemiological data showing sufficient evidence to support a causal association between exposure to the substance and cancer.
- **Category B: Probable human carcinogen.** Chemicals in this category are known to cause cancer in animals but not yet definitively shown to cause cancer in humans. Category B is further split into the following sub-categories:
    - **B1:** This sub-category is for chemicals with sufficient evidence of carcinogenicity from animal studies and limited evidence of carcinogenicity from epidemiological studies in humans.
    - **B2:** This subcategory is for chemicals with sufficient evidence of carcinogenicity from animal studies but inadequate or no data from epidemiological studies in humans.
- **Category C: Possible human carcinogen.** The toxicological data for chemicals in this category show limited evidence of carcinogenicity in laboratory animal studies but lack human data.
- **Category D: Not classifiable as to human carcinogenicity.** This category is for chemicals for which the toxicological data is incomplete, inadequate or ambiguous and is labeled as "not classifiable," or "cannot be determined." For these chemicals, tumor effects or other key data are suggestive, conflicting, and/or limited in quantity. Further studies are generally required for the accurate description of human carcinogenic potential.
- **Category E:** No evidence of carcinogenicity in at least two adequate animal tests in different species and in available epidemiological studies.

US EPA used the following carcinogenicity categories between 1996–1999:

- **Known/Likely:** This category of descriptors is appropriate when the available tumor effects and other key data are adequate to convincingly demonstrate carcinogenic potential for humans; it includes:
    - Agents known to be carcinogenic in humans based on either epidemiologic evidence of a combination of epidemiologic and experimental evidence, demonstrating causality between human exposure and cancer.
    - Agents that should be treated as if they were known human carcinogens, based on a combination of epidemiologic data showing a plausible causal association (not demonstrating it definitively) and strong experimental evidence.
    - Agents that are likely to produce cancer in humans due to the production or anticipated production of tumors by modes of action that are relevant or assumed to be relevant to human carcinogenicity.
- **Cannot be determined:** This category of descriptors is appropriate when available tumor effects or other key data are suggestive or conflicting or limited in quantity and thus, are not adequate to convincingly demonstrate carcinogenic potential for humans. In general, further agent-specific and generic research and testing are needed to be able to describe human carcinogenic potential. The descriptor 'cannot be determined' is used with a subdescriptor that further specifies the rationale:
    - Agents whose carcinogenic potential cannot be determined, but for which there is suggestive evidence that raises concern for carcinogenic effects.
    - Agents whose carcinogenic potential cannot be determined because the existing evidence is composed of conflicting data (e.g., some evidence is suggestive of carcinogenic effects, but other equally pertinent evidence does not confirm any concern), agents whose carcinogenic potential cannot be determined because there are inadequate data to perform an assessment.
    - Agents whose carcinogenic potential cannot be determined because no data are available to perform an assessment.
- **Not Likely:** This is the appropriate descriptor when experimental evidence is satisfactory for deciding that there is no basis for human hazard concern, as follows (in the absence of human data suggesting a potential for cancer effects):
    - Agents not likely to be carcinogenic to humans because they have been evaluated in at least two well conducted studies in two appropriate animal species without demonstrating carcinogenic effects.

  - Agents not likely to be carcinogenic to humans because they have been appropriately evaluated in animals and show only carcinogenic effects that have been shown not to be relevant to humans.
  - Agents not likely to be carcinogenic to humans when carcinogenicity is dose or route dependent. For instance, not likely below a certain dose range (categorized as likely by another route of exposure). To qualify, agents will have been appropriately evaluated in animal studies and the only effects show a dose range or route limitation, or a route limitation is otherwise shown by empirical data.
  - Agents not likely to be carcinogenic to humans based on extensive human experience that demonstrates lack of effect.

US EPA has been using the following carcinogenicity categories since 1999:

- **Carcinogenic to humans:** This descriptor is appropriate when there is convincing epidemiologic evidence demonstrating causality between human exposure and cancer. It is also appropriate when there is an absence of conclusive epidemiologic evidence to clearly establish a cause and effect relationship between human exposure and cancer, but there is compelling evidence of carcinogenicity in animals and mechanistic information in animals and humans demonstrating similar mode(s) of carcinogenic action. It is used when all of the following conditions are met:
  - There is evidence in a human population(s) of association of exposure to the agent with cancer, but not enough to show a causal association, and
  - There is extensive evidence of carcinogenicity, and
  - The mode(s) of carcinogenic action and associated key events have been identified in animals, and
  - The key events that precede the cancer response in animals have been observed in the human population(s) that also shows evidence of an association of exposure to the agent with cancer.
- **Likely to be carcinogenic to humans:** This descriptor is appropriate when the available tumor effects and other key data are adequate to demonstrate carcinogenic potential to humans. Adequate data are within a spectrum. At one end is evidence for an association between human exposure to the agent and cancer and strong experimental evidence of carcinogenicity in animals; at the other, with no human data, the weight of experimental evidence shows animal carcinogenicity by a mode or modes of action that are relevant or assumed to be relevant to humans.

- **Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential:** This descriptor is appropriate when the evidence from human or animal data is suggestive of carcinogenicity, which raises a concern for carcinogenic effects, but is judged not sufficient for a conclusion as to human carcinogenic potential. Examples of such evidence may include: a marginal increase in tumors that may be exposure-related, or evidence is observed only in a single study, or the only evidence is limited to certain high background tumors in one sex of one species. Dose-response assessment is not indicated for these agents. Further studies would be needed to determine human carcinogenic potential.
- **Data are inadequate for an assessment of human carcinogenic potential:** This descriptor is used when available data are judged inadequate to perform an assessment. This includes a case when there is a lack of pertinent or useful data or when existing evidence is conflicting, e.g., some evidence is suggestive of carcinogenic effects, but other equally pertinent evidence does not confirm a concern.
- **Not likely to be carcinogenic to humans:** This descriptor is used when the available data are considered robust for deciding that there is no basis for human hazard concern. The judgment may be based on:
    - Extensive human experience that demonstrates lack of carcinogenic effect.
    - Animal evidence that demonstrates lack of carcinogenic effect in at least two well designed and well conducted studies in two appropriate animal species (in the absence of human data suggesting a potential for cancer effects).
    - Extensive experimental evidence showing that the only carcinogenic effects observed in animals are not considered relevant to humans.
    - Evidence that carcinogenic effects are not likely by a particular route of exposure.
    - Evidence that carcinogenic effects are not anticipated below a defined dose range.

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