Pesticide Risk Mitigation Engine

Dermal Risk Index

White Paper

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Dermal Risk Index

Introduction

The PRiME dermal risk index provides a quantitative estimate of the potential risk associated with worker dermal exposure that occurs when workers reenter a treated field after a pesticide application. Exposure for pesticide applicators is not considered as part of this index. Dermal exposure is estimated based on skin surface area exposed, application rate and foliar half-life (contributors to dislodgeable foliar residue), and the amount of pesticide absorbed through the skin into the body. The estimated absorbed dose is then compared to a level of concern—the non-cancer dermal Reference Dose (RfD_{dermal}). The ratio of estimated absorbed dose to RfD_{dermal} is the hazard quotient, a value that provides the fraction of the RfD_{dermal} to which a worker is likely to be exposed if he or she works in the field after a specified time interval. The risk index is based on the value of the hazard quotient.

Data Sources

Reference Doses

The RfD used in the PRiME dermal risk index is based on the Level of Concern (LOC) for dermal exposure determined by US EPA, which we will refer to as the RfD_{dermal}, adapted to include FQPA safety factors, since pregnant women frequently do farm work. As part of the registration process, US EPA requires a number of *in vivo* toxicity tests on laboratory animals to obtain a dermal reference dose. The RfD_{dermal} serves as a concentration threshold below which adverse effects are not anticipated from dermal exposure.

Dermal LOCs are typically available in EPA Reregistration Eligibility Decision (RED) documents and/or the supporting materials for the REDs.[1] The RfD_{dermal} values are derived from the human-equivalent No Observed Adverse Effect Level (NOAEL) determined from an animal or human toxicity study, as well as any Uncertainty Factors (UFs), as described in equation (1).

$$RfD_{dermal} = \frac{\text{NOAEL (mg/kg - day)}}{UF_{intra} \times UF_{inter} \times UF_{other} \times UF_{FQPA}} \quad (1)$$

The UFs typically include an interspecies 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 Lowest Observed Adverse Effect Level (LOAEL) is obtained from a study, an additional uncertainty factor of 3–10 may be applied. Yet another uncertainty factor, the Food Quality Protection Act (FQPA) factor of 3–10, may be used for pesticides that are more toxic to developing organisms than to adults. Because the PRiME dermal risk index is

based on a reference dose for the most sensitive worker population—a 64-kg woman who may be pregnant—the FQPA safety factor is included in calculating the RfD_{dermal} used in PRiME.

For evaluation of dermal risk, it is preferable to use an RfD_{dermal} derived from exposure of laboratory animals via the dermal route; however, dermal exposure studies are not available for all pesticides. For pesticides for which a dermal exposure study is missing, US EPA uses the oral RfD to estimate RfD_{dermal}, corrected by the dermal absorption factor (AF) for that pesticide, according to equation (2). If no dermal absorption studies are available to determine AF, US EPA may make assumptions about what AF is likely to be. Some default assumptions that EPA has used in the past include AF = 0.2, 0.5 and 1.0.

$$RfD_{dermal} = \frac{RfD_{oral}}{AF} \quad (2)$$

Some pesticides are highly irritating or corrosive to eyes and skin; for these pesticides, US EPA generally does not determine an RfD_{dermal}, assuming that severe localized irritation effects of the chemical on the skin would be self-limiting. These pesticides are flagged to the PRiME user as corrosive and irritating, but unless there is also systemic toxicity, no RfD_{dermal} was determined by US EPA.

Cancer risks are not currently accounted for by the PRiME dermal risk index.

Foliar Half-Lives

The foliar half-lives (DT_{50}) used to estimate degradation of pesticides on plant surfaces were calculated according to the algorithm in equation (3), derived by Mineau *et al.*,[2]

$$\text{Log}(DT_{50}) = 0.51 \times \log(\text{Soil } DT_{50}) + 0.11 \quad (R^2 = 0.4) \quad (3)$$

where Soil DT_{50} is the "typical" soil half-life from the EU Footprint Database.[3]

Surface Area Exposed

The US EPA Exposure Factors handbook[4] 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) of 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 additional exposure through clothing is not currently accounted for by the PRiME dermal 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 by the worker.

Application Rates

The application rates used to test the dermal risk index algorithm are an average of the application rate for the particular active ingredient used on grapes in California in 2007, as reported in the 2007 CA Pesticide Use Reporting (PUR) data.[5] In normal use of the PRiME tool, the application rate will be entered by the user.

Restricted Entry Intervals

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 dermal risk index algorithm were taken from the CA product database published by the California Department of Pesticide Regulation.[6] 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 was used in the test data set.

PRiME Dermal Index Structure

Introduction

The PRiME dermal risk index provides a quantitative estimate of the risk of dermal exposure, using readily available data. Prediction of worker exposure is based on the pesticide application rate and foliar half-life, workplace parameters (hours in field, field entry 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 redefined by the user to evaluate alternate application scenarios of application rate, surface area and field entry times. This approach permits extension of the index to other workplace settings where PPE and other safety precautions are not necessarily utilized.

The estimated dose provided by the algorithm is divided by the RfD_{dermal} to give a hazard quotient. This structure allows comparison of different pesticides and application

scenarios, facilitating the assessment of the relative worker reentry risks for different pesticides.

In developing the index, we evaluated US EPA, [7, 8, 9, 10] USFS[17] and European Union[15] 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. The method provides an estimate of pesticide exposure without the need for post-application residue data, task-, crop- and chemical-specific transfer coefficients. Measured dermal absorption factors are used to estimate dermal uptake of the pesticide from US EPA data.

Overview

Estimation of the dose of a pesticide received from dermal exposure 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

These processes are characterized by equation (4).

$$D_{int} = (D_{pot}\,(\mu g) * AF * 0.001\ mg/\mu g)/64\ kg \qquad (4)$$

D_{pot} represents the potential dose in μg available from the chemical that is transferred to the skin from the crop. The absorption fraction, AF represents the fraction of pesticide on the skin that penetrates the skin surface and is absorbed into the body. The product of D_{pot} and AF provides an estimate of the internal dose, D_{int}, that is absorbed into the bloodstream in μg. A dose in units of mg of pesticide per kilogram of body weight is calculated using a conversion factor (μg to mg) and a body weight of 64 kg for a woman farm worker. The PRiME dermal index calculation involves determination of D_{int} and comparison to RfD_{dermal} as an indicator of potential risk.

Transfer: Determination of Potential Dose, D_{pot}

The potential dose, D_{pot}, is a function of the transfer rate from crop to skin (TR), the surface area of the exposed skin (SA), and the amount of time the worker spends in the field (WT), as described in Equation (5):

$$D_{pot} = SA * TR * WT \qquad (5)$$

where

D_{pot} = potential dose, in μg

SA = surface area of exposed skin (cm^2). Hands, face and neck are assumed to be the only exposed skin area (1,730 cm^2).[11, 12]

TR = transfer rate (μg/cm^2-hr), the rate at which pesticide is transferred from the treated crop to the skin.

WT = work time (hr). The amount of time worker is in the field, potentially accumulating chemical on skin from the crop surface

The transfer rate, TR, is a function of the application rate and the amount of dislodgeable foliar residue (DFR), the leaf density of the crop in the area touched by workers, and the type of task performed. The DFR decreases over time as the pesticide is washed off the leaves by rain or irrigation water, absorbed by the plant or degraded.

Surface Area

Using only the exposed surface area will likely result in an underestimate of exposure, since clothing is not fully protective. In the 1997 Exposure Factors Handbook,[11] US EPA notes:

> *"A common assumption is that clothing prevents dermal contact and subsequent absorption of contaminants. This assumption may be false in cases where the chemical may be able to penetrate clothing, such as in a fine dust or liquid suspension. Studies using personal patch monitors placed beneath clothing of pesticide workers exposed to fine mists and vapors show that a significant proportion of dermal exposure may occur at anatomical sites covered by clothing (U.S. EPA, 1992b).[7] In addition, it has been demonstrated that a "pumping" effect can occur which causes material to move under loose clothing (U.S. EPA, 1992b). Furthermore, studies have demonstrated that hands cannot be considered to be protected from exposure even if waterproof gloves are worn (U.S. EPA, 1992b).[7] This may be due to contamination to the interior surface of the gloves when donning or removing them during work activities (U.S. EPA, 1992b). Depending on the task, pesticide workers have been shown to experience 12 percent to 43 percent of their total exposure through their hands, approximately 20 percent to 23 percent through their heads and necks, and 36 percent to 64 percent through their torsos and arms, despite the use of protective gloves and clothing (U.S. EPA, 1992b)[7]."* (abstracted from section 6.2.5 in reference 11)

In the current draft 2009 Exposure Factors Handbook,[4] EPA notes:

> *"It is reasonable to assume that clothing reduces the contact area. However, while it is generally assumed that adherence of solids to skin occurs to only the areas of the body not covered by clothing, it is important to understand that soil and dust particles can get under clothing and be deposited on skin to varying degrees depending on the protective properties of the clothing. Likewise, liquids may soak through clothing and contact covered areas of the skin. Assessors should consider these possibilities for the scenario of concern and select skin areas that are judged appropriate."*

Earlier work by Krieger[13] provides an estimate of a clothing penetration factor of 10%. While the current PRiME dermal risk index does not account for this additional exposure, we are evaluating potential methods for doing so.

Transfer Rate

Durkin[14] showed that the transfer rate (TR) from vegetation to the skin significantly depends on the amount of dislodgeable foliar residue (DFR). Measured values of hand residues collected from 15 diverse studies using different vegetation types, activities and exposure durations produced an R^2 of 0.78 ($p < 0.00001$) for transfer rate as a function of dislodgeable foliar residue. This highly significant correlation indicates that a robust estimate of the amount of chemical transferred to the skin from multiple activities can reliably be obtained from the amount of dislodgeable foliar residue present on the crop. The PRiME dermal index uses the generic algorithm derived from these studies to estimate the transfer rate (TR) as a function of dislodgeable foliar residue (DFR), described by equation (6):

$$\text{Log TR} = 1.09 * \text{Log DFR} + 0.05 \quad (6)$$

With algebraic manipulation and the laws of logarithms, equation (6) is transformed to equation (8):

$$\text{Log TR} = \text{Log}(\text{DFR}^{1.09}) + 0.05 \text{ in } (\mu g/cm^2\text{-h}) \quad (7)$$

$$\text{TR} = \text{DFR}^{1.09} * 1.12 \text{ in } (\mu g/cm^2\text{-h}) \quad (8)$$

Dislodgeable Foliar Residue

The DFR on the day of the application (DFR_0) is proportional to the application rate, as described by equation (9),

$$DFR_0 = AR * DF * 11.21\ \mu g/cm^2 \text{ per lb/acre} \quad (9)$$

where:

DFR_0 = DFR of chemical on the plant surface at t = 0 days, the time of application ($\mu g/cm^2$), after spray residue has dried

AR = application rate (lb/acre)

DF = dislodgeable fraction, or fraction of application rate that is dislodgeable (assumed to be 20% of application rate)

Over time, the DFR will decrease, due to plant absorption of the pesticide, volatilization, photolysis, and wash-off from rain or irrigation water. The foliar half-life (DT_{50}) provides an estimate of DFR remaining at a particular time t, using the equation for first-order degradation, equation (10),

$$DFR_t = DFR_0 * (0.5^{\,t/DT50}) \quad (10)$$

where:

DFR_t = DFR of chemical on the plant surface at time = t in days, ($\mu g/cm^2$)

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

t = time at which exposure is being estimated, typically the REI specific to the product and crop (days).

Thus, to obtain the transfer rate at a particular time after an application (TR_t), we use DFR_t in the calculation, as shown in equation (11).

$$TR_t = (DFR_t)^{1.09} * 1.12 \quad (11)$$

Fraction of Foliar Residue That Is Dislodgeable

The fraction of the foliar residue that is dislodgeable (DF) is a significant risk driver, and different values are used by different groups. The EUROPOEM II Re-entry Working Group surveyed the literature for experimental measurements of initial dislodgeable foliar residue and determined a 90th percentile value for DF of 3 $\mu g/cm^2$ per kg applied/ha,[15] which translates to a DF of 30%.[16] The US Forest Service (USFS) used a DF of 10% for vegetation management work.[17] US EPA typically uses transfer coefficients to estimate crop- and task-specific dermal exposure (see Appendix 1), but when transfer coefficients are not available, they use the same methodology discussed in this paper. For example, in their estimate of worker dermal exposure for bifenthrin use on berries,

they utilized a DF of 20% for the day the restricted entry interval expires.[18] We decided to use a value of 20% to estimate an average level of risk for workers re-entering a field after treatment.

Worker contact with the crop varies substantially by crop, with the highly mechanized field crops such as grains, cotton, rice and soybeans leading to far less post-application worker dermal exposure compared to high-contact crops. In contrast, crops that require hand harvesting, pruning, thinning and inspection have high exposure potential. To account for these crop differences, the algorithm applies a crop-specific adjustment factor (see Variable Parameters section below).

Absorption: Absorbed Fraction, AF

The amount of pesticide on the skin that is absorbed into the body is primarily a function of the polarity of the chemical and its molecular weight. The skin's outermost layer, the stratum corneum, is highly lipophilic, which is responsible for rapid initial absorption of non-polar compounds with high K_{ow} values. In contrast, polar compounds with low K_{ow} values penetrate the outer layer more slowly initially.

The absorbed fraction (AF) of pesticide can be measured experimentally using time-series urine samples from animal or human exposure studies. Alternatively, cadaver skin or rat skin models are also used to estimate AF. The US EPA utilizes such studies to estimate occupational and residential dermal risks. When an absorption factor is not available from the registrants, US EPA often assumes a default value for this term. Default values that have been noted in various risk assessments include 0.2, 0.5 and 1.0.

The absorption factor is not always necessary to estimate a dose that will be compared to an RfD. If the RfD_{dermal} is determined from a dermal study, the AF is already accounted for, i.e., AF=1. Alternatively, if an oral study is the basis for the RfD_{dermal}, the AFs are typically less than one and are used by US EPA to calculate the internal dose, D_{int} according to equation 4.

For a few pesticides, studies have been done that show differences in dermal penetration for human skin compared to experimental animals. This absorption difference (AD) is also taken into account when determining the internal dose. For example: 1) *In vitro* studies with carbaryl have been done comparing dermal penetration through rat and human skin that showed that rat skin was more permeable to carbaryl.[19] 2) *In vivo* studies comparing dermal absorption of radiolabeled tribufos between monkeys and rabbits showed that primate skin absorbed less than rabbit skin.[20] In both of these cases an additional factor accounting for the absorption difference (AD) was included when calculating the internal dose (equation 12).

$$D_{int} = (D_{pot}\,(\mu g) * AF * AD * 0.001\ mg/\mu g)/64\ kg \quad (12)$$

Measured AFs are not available for all pesticides; however, the current data set used in PRiME includes 410 of the most commonly used active ingredients. Many of the chemicals with missing data are low toxicity compounds for which US EPA waived data requirements.

In the absence of a measured AF, approaches have been developed by other groups to estimate AF based on the octanol-water distribution coefficient (K_{ow}) of the chemical and its molecular weight. We evaluated this approach and found it to be inadequate for the broad collection of registered pesticides currently in use, with little correlation between US EPA's measured values of AF and the values calculated using K_{ow} and molecular weight. See Appendix 2 for additional detail on this method.

Risk Index Values

The dermal risk index is expressed as a hazard quotient— the ratio of the estimated internal dose (D_{int}) in mg/kg-day to the RfD_{dermal}. For pesticides with RfDs determined via dermal studies, the comparison is between D_{pot} (in mg/kg-day) and the RfD_{dermal}; for pesticides with RfDs determined via oral studies, the comparison is between D_{int} and the RfD_{oral}. For dermal RfDs based on oral studies, $RfD_{dermal} = RfD_{oral}$. Hazard quotients less than one represent low risk; between one and 10 are of concern and ratios greater than 10 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: Risk Score Bins for Dermal Index

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

Table 2: Dermal Hazard Quotients (HQ) for a Subset of Pesticides Used on Grapes

Chemical	Avg Application Rate (lbs/acre)[a]	Calc'd Foliar DT_{50} (days)[b]	Avg REI (days)[c]	Dermal RfD (mg/kg-day)[d]	Type of study as basis for RfD	AF (EPA)[e]	D_{int} using EPA AF (mg/kg-day)	HQ using EPA AF[f]
Carbofuran	2.87	5.68	2.00	0.0001	Oral	0.06	0.040	847.72
Azinphos-methyl	1.00	3.35	2.33	0.0056	Dermal	1	0.22	61.63
Diazinon	1.02	3.19	0.74	0.0100	Dermal	1	0.33	50.03
Endosulfan	1.69	7.46	0.75	0.0125	Oral	0.45	0.32	34.54
Chlorpyrifos	2.02	7.46	1.00	0.0500	Dermal	1	0.68	22.75
Glufosinate-ammonium	0.50	2.89	0.50	0.0063	Oral	0.51	0.12	19.38
Dicofol	1.13	9.45	1.00	0.0400	Oral	1	0.48	15.38
Fenamiphos	1.74	1.03	2.00	0.0250	Dermal	1	0.46	9.87
Dichlobenil	2.00	8.84	0.14	0.2500	Dermal	1	1.06	4.92
Carbaryl*	2.18	4.22	0.28	0.3000	Dermal	1	1.22	4.33
Phosmet	1.25	1.89	0.60	0.1500	Dermal	1	0.61	3.92
Propyzamide	0.51	7.23	1.00	0.0846	Oral	1	0.20	2.99
Dimethoate	1.85	1.74	1.86	0.1867	Dermal	1	0.52	2.73
Oxydemeton-methyl	0.38	1.11	0.75	0.0500	Dermal	1	0.12	2.44
Propargite	1.81	7.90	1.02	0.0600	Oral	0.14	0.12	2.37
Naled	0.63	1.11	1.00	0.1000	Dermal	1	0.13	1.78
Fenpropathrin	0.28	6.15	1.00	0.0300	Oral	0.333	0.032	1.46
Diquat dibromide	0.62	33.99	1.00	0.0100	Oral	0.041	0.012	1.40
Pendimethalin	1.99	10.03	0.96	0.1000	Oral	0.1	0.073	1.15
Fenbutatin-oxide	0.90	20.38	2.00	0.0510	Oral	0.1	0.045	0.95
Malathion	3.02	0.52	0.34	1.2700	Dermal	1	1.63	0.94
Acephate	0.97	1.86	0.69	0.5000	Dermal	1	0.45	0.85
2,4-D, dimethylamine salt	0.54	3.35	2.00	0.0250	Oral	0.1	0.019	0.77
Dichloran	1.42	21.37	0.61	1.2000	Dermal	1	0.66	0.70
Pyrimethanil	0.33	7.83	1.00	0.2310	Oral	1	0.096	0.68
Thiram	0.43	4.12	1.00	0.3000	Dermal	1	0.15	0.65
Simazine	1.13	8.18	0.46	0.0625	Oral	0.06	0.036	0.61
Tebuconazole	0.12	8.32	0.55	0.0293	Oral	0.231	0.012	0.44
Methomyl	0.85	2.81	0.86	0.9000	Dermal	1	0.27	0.43

Chemical	Avg Application Rate (lbs/acre)[a]	Calc'd Foliar DT_{50} (days)[b]	Avg REI (days)[c]	Dermal RfD (mg/kg-day)[d]	Type of study as basis for RfD	AF (EPA)[e]	D_{int} using EPA AF (mg/kg-day)	HQ using EPA AF[f]
Spirodiclofen	0.27	2.81	0.50	0.0065	Oral	0.02	0.0026	0.38
Thiophanate-methyl	0.79	0.88	0.31	1.0000	Dermal	1	0.42	0.35
Oryzalin	2.08	4.72	0.85	3.3333	Dermal	1	1.10	0.34
Bifenazate	0.54	1.11	0.35	0.8000	Dermal	1	0.27	0.29
Myclobutanil	0.11	25.32	0.86	0.1000	Oral	0.5	0.018	0.26
Thiamethoxam	0.13	7.46	0.38	0.0120	Oral	0.05	0.0031	0.25
Fluazifop-P-butyl	0.12	1.11	0.14	0.0200	Oral	0.09	0.0050	0.24
Pyridaben	0.46	7.83	0.50	1.0000	Dermal	1	0.17	0.24
Flumioxazin	0.16	4.72	0.50	0.3000	Dermal	1	0.061	0.24
Quinoxyfen	0.10	10.42	0.58	0.2000	Oral	1	0.040	0.22
Oxyfluorfen	0.51	6.24	0.65	0.3000	Oral	0.18	0.042	0.16
Paraquat dichloride	1.10	20.38	0.25	0.0125	Oral	0.003	0.0018	0.15
Ziram	2.07	5.78	2.00	0.0750	Oral	0.01	0.0077	0.13
Pyraclostrobin	0.10	5.97	0.50	0.0500	Oral	0.14	0.0062	0.12
Chlorothalonil	1.23	4.95	0.00	6.0000	Dermal	1	0.73	0.12
Maneb	1.09	1.11	1.00	3.0000	Dermal	1	0.49	0.11
Norflurazon	0.71	10.03	0.50	3.7500	Dermal	1	0.36	0.10
Cyprodinil	0.41	6.42	0.50	0.6200	Oral	0.3	0.052	0.10
Indoxacarb, S-isomer	0.11	4.35	0.50	0.5000	Dermal	1	0.047	0.10
Bifenthrin	0.10	5.38	0.50	0.4700	Dermal	1	0.042	0.10
Triflumizole	0.17	3.81	0.50	0.0283	Oral	0.035	0.0024	0.094
Acetamiprid	0.05	1.86	0.50	0.0597	Oral	0.3	0.0059	0.089
Glyphosate	1.25	3.66	0.25	10.0000	Dermal	1	0.70	0.071
Boscalid	0.20	15.02	0.50	0.2180	Oral	0.15	0.013	0.066
Triclopyr, triethylamine salt	0.30	5.78	0.00	0.0500	Oral	0.02	0.0032	0.063
Rotenone	0.01	1.53	0.50	0.0050	Oral	0.1	0.0003	0.059
Avermectin	0.02	5.78	0.45	0.0012	Oral	0.01	0.0001	0.059
Clofentezine	0.22	12.13	0.50	0.0200	Oral	0.01	0.0011	0.055
Cyfluthrin	0.05	6.06	0.19	0.0236	Oral	0.05	0.0010	0.045
MSMA	0.74	15.02	0.50	10.0000	Dermal	1	0.37	0.041

Chemical	Avg Application Rate (lbs/acre)[a]	Calc'd Foliar DT_{50} (days)[b]	Avg REI (days)[c]	Dermal RfD (mg/kg-day)[d]	Type of study as basis for RfD	AF (EPA)[e]	D_{int} using EPA AF (mg/kg-day)	HQ using EPA AF[f]
Imidacloprid	0.10	14.68	0.44	0.1000	Oral	0.072	0.0030	0.033
Trifloxystrobin	0.08	2.81	0.75	1.0000	Dermal	1	0.030	0.029
Fenarimol	0.04	16.82	0.50	0.1167	Oral	0.2	0.0029	0.029
Buprofezin	0.53	7.46	0.50	10.0000	Dermal	1	0.22	0.028
Cyfluthrin, beta	0.03	3.81	0.50	0.0236	Oral	0.05	0.0005	0.021
Fenhexamid	0.50	1.11	0.50	10.0000	Dermal	1	0.25	0.020
Triadimefon	0.13	5.38	0.50	3.0000	Dermal	1	0.051	0.019
Fenpyroximate	0.12	7.39	0.25	3.0000	Dermal	1	0.052	0.018
Captan	1.68	1.00	2.41	0.1000	Oral	0.004	0.0024	0.007
Clethodim	0.05	0.85	0.79	1.0000	Oral	0.3	0.0048	0.0030
Spirotetramat	0.01	1.11	0.67	0.1000	Oral	0.1	0.0004	0.0025
Hexythiazox	0.14	5.78	0.50	2.4000	Oral	0.02	0.0013	0.0006

Table Notes:

[a] Based on 2000–2007 California Pesticide Use Reporting data for grapes in California.

[b] Calculated using equation 3.

[c] Average of all REIs for grapes for products containing the active ingredient.

[d] The RfD is the NOAEL (or LOAEL) divided by the uncertainty factors used by US EPA. Absorption factors are accounted for in the dose, not in the RfD.

[e] From US EPA risk assessments. AF = 1 when the toxicity endpoint is from a dermal study.

[f] Calculated by dividing D_{int} by the dermal RfD.

[g] This pesticide is longer registered for use on grapes.

[h] The RfD_{dermal} was divided by an additional factor of 0.36 for carbaryl to account for the differences in permeability between rat and human skin.

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[15] 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 15.

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 Dermal 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.[10]

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: How the PRiME Approach Compares to US EPA's Approach

There are several differences between the PRiME and US EPA approaches to estimating dermal risk from re-entry into a field after a pesticide has been applied.

1) For many pesticides, US EPA uses a proprietary database of transfer coefficients (Tc) that provide an estimate of potential dose based on dislodgeable foliar residue (DFR) for the specific crop and task:

   D_{pot} (mg) = DFR ($\mu g/cm^2$) * 0.001 mg/μg * Tc (cm^2/h) * ET (h)

   where:
   DFR = dislodgeable foliar residue
   Tc = transfer coefficient
   ET = exposure time

   Because access to the data set of transfer coefficients is restricted, we utilize the approach taken by the US Forest Service (and by US EPA when data are missing) and estimate dermal exposure based on the dislodgeable fraction (DF) of foliar residue, as defined in equation 9,

   D_{pot} (mg) = SA (cm^2) * TR ($\mu g/cm^2$-h) * WT (h) (9)
   where:
   SA = surface area of skin exposed
   TR = [$DFR^{1.09}$ * 1.12] ($\mu g/cm^2$-h)
   WT = work time
   DFR = AR (lb/acre) * 11.21 $\mu g/cm^2$ per lb/acre * DF
   AR = application rate
   DF = dislodgeable fraction

2) US EPA only estimates risk from dermal exposure at the time the re-entry interval (REI) expires. PRiME allows the user to estimate risks for any period of time after the REI has expired by using the dislodgeable foliar half-life (DT_{50}) of the pesticide to calculate the reduction in residues over time as the pesticide degrades and/or dissipates from foliar surfaces.

Appendix 2: Calculated Absorption Factors (AF)

Measured AFs are not available for all pesticides; however, approaches have been developed to estimate AF based on the octanol-water distribution coefficient of the chemical and the molecular weight.[21] We evaluated the computational method described below as a potential tool for estimating the AF when data were not available; however, correlations of calculated AF with measured AF from US EPA data were not statistically significant, so we decided to utilize only the measured absorption factors utilized by US EPA. We include this calculation below for reference.

The AF can be calculated using equation (13):

$$AF = 1 - e^{-Ka * ET} \quad (13)$$

where:

K_a = first-order dermal absorption coefficient (see equation (14 below), in units of h^{-1}

ET = total exposure time = work time plus time elapsed between end of work and removal of the pesticide from the skin. A value of 24 hours is used for ET, according to the exposure model developed by the USFS.

The dermal absorption coefficient, K_a, is estimated based on the octanol/water partition coefficient and molecular weight of the chemical, according to equation (14).

$$\log K_a = 0.233 * \log K_{ow} - 0.00566 * MW - 1.49 \quad (14)$$

K_a = first-order dermal absorption coefficient (h^{-1})

K_{ow} = octanol/water partition coefficient (unitless)

MW = molecular weight (g/mol)

This approach was developed by the USFS for their pesticide risk assessments and is based exclusively on a data set of well-replicated exposure studies in humans.[22, 23, 24] These data provide an estimate of the effect of metabolism of the chemical in the skin and elimination of the pesticide from the skin through fugitive loss. Other methods to estimate absorption coefficients rely on steady state absorption rates (designated as K_p) from *in vitro* studies to estimate absorption and do not capture time-dependent skin absorption, skin metabolism or fugitive losses.[2] The AFs calculated according to equation 13 are not subject to the uncertainties of animal to human extrapolation and experimental variability associated with the dermal *in-*

vitro studies used in US EPA's risk assessments, but do suffer from the inability of the algorithm to accurately predict K_a for very polar or high molecular weight compounds.

The approach used to calculate AF follows that adopted by EPA to predict chemical absorption from liquids,[4] and analyses of the available data suggest that the effects of both molecular weight and K_{ow} on K_a may be linear only within certain limits.[7] The K_a prediction relies exclusively on permeability estimates from 29 human *in vivo* studies. Absorption rates obtained in these studies for compounds with log K_{ow} greater than 2.5 are consistently higher than the model-based estimates.

Another element of this model that introduces uncertainty into the prediction of the absorbed dose is the time scale over which absorption is modeled. The *in vivo* human studies used to derive equation 14 are based on measured pesticide concentrations in urine collected at 24 and 48 hours; thus, predicted absorption coefficients (K_a) represent quasi steady-state absorption where the skin compartment is saturated and the absorption rate determined by chemical leaving the compartment. Subsequent studies of pesticide absorption in humans over shorter exposure times (4 hours) have found a 10-fold higher absorption rate for shorter times when compared to that at 24 hours.[25] These differences from steady state absorption correlate with the physicochemical properties of the pesticide – more lipophilic pesticides are expected to initially be absorbed rapidly into skin through the lipophilic outer skin layer. For pesticides with high K_{ow} values where exposure is less than 8 hours, equation 14 may under-predict the absorbed dose.

In general, AFs calculated using equation 14 are lower than most of the EPA values; for the set of 71 pesticides used on grapes, the average AF from US EPA is 5.6 times higher than the calculated AF (see Table 2 and Figure 1), although there are some chemicals with lower EPA AF values, including, most notably, carbofuran, spiridaclofen, pendamethalin and simazine from the red and orange categories. The worst match between calculated AF and measured AF is for fenbutatin oxide, with a log K_{ow} of 5.15 (a factor of 7,553 difference). In contrast, fenpropathrin, with a log K_{ow} of 6.04 is only different from the measured AF by a factor of two. Also observed is that pesticides with very low K_{ow} values such as diquat and paraquat have substantial mismatches between the calculated AF and the measured AFs from US EPA.

The K_{ow} data used to calculate dermal absorption for conducting the evaluation of this method were obtained from the USDA Agricultural Research Services physical property data,[26] EPA Reregistration Documents for specific pesticides,[1] the European Union Footprint database,[3] and the WIN-PST physical properties database.[27] For pesticides for which K_{ow} data were not otherwise available, we utilized US EPA's Estimation Program Interface (EPI) Suite prediction routines.[28]

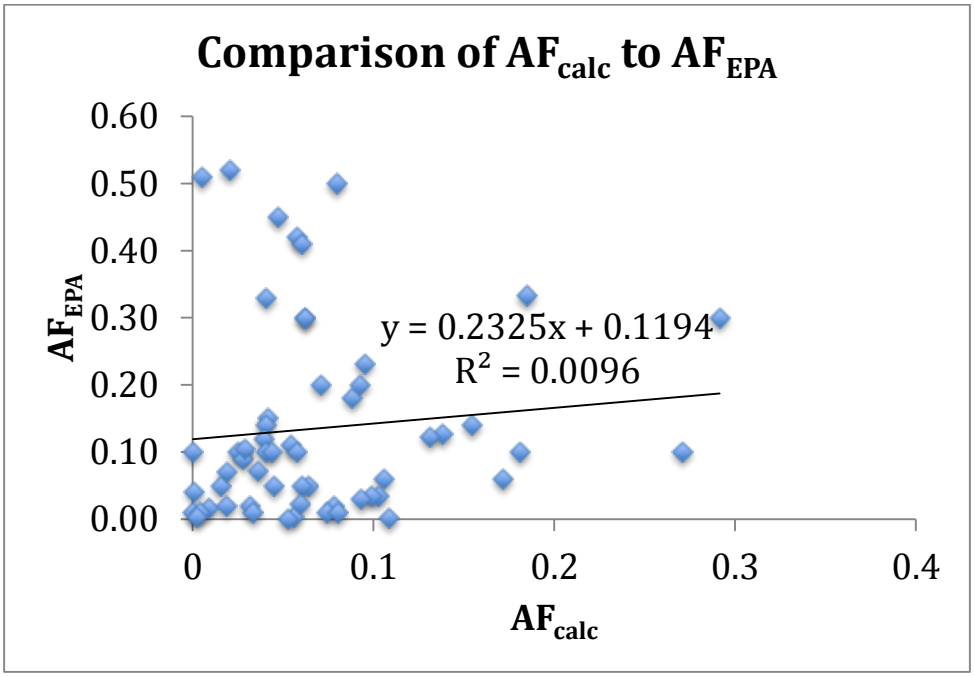

Figure 1: Correlation plot comparing measured absorption factors used by US EPA (AF_{EPA}) to absorption factors calculated using equation 14.

Appendix 3: Sensitivity Analysis

The absorbed dose (D_{int}) is a function of a number of different variables, as described in the text of this document. This appendix describes the sensitivity analysis that was conducted to determine which variables have the greatest effect on D_{int}.

In general, D_{int} is a function of the potential dose, D_{pot}, and the absorption factor, AF, as shown in equation A1.

$$D_{int} = D_{pot} * AF \quad \text{(A1)}$$

Effect of the Absorption Factor

For the PRiME index, many of the AF values used are taken from the experimentally measured values provided in US EPA risk assessments. As can be seen from the form of equation A1, D_{int} is directly and linearly proportional to AF; thus, for example, an increase in AF of 10% would result in an increase in D_{int} of 10%.

For chemicals for which no experimentally measured values of AF are available, the AF is calculated using equations A2 and A3, which insert some non-linear terms into the relationship. These dependencies are explored below.

$$AF = 1 - e^{-Ka * ET} \quad \text{(A2)}$$

$$\log K_a = 0.233 * \log K_{ow} - 0.00566 * MW - 1.49 \quad \text{(A3)}$$

Effect of the Potential Dose and Its Component Parameters

The potential dose, D_{pot}, is a function of surface area (SA), transfer rate (TR) and work time (WT), according to equation A4.

$$D_{pot} = SA * WT * TR \quad \text{(A4)}$$

As with AF, the relationship of D_{int} to both SA and WT is linear and directly proportional. However, the relationship of D_{int} to the transfer rate, TR, is non-linear and dependent on the dislodgeable foliar residue at the time of contact with the plant surface, DFR_t, as shown in equation A5.

$$TR_t = (DFR_t)^{1.09} * 1.12 \text{ in } (\mu g/cm^2\text{-h}) \quad \text{(A5)}$$

The DFR_t is a function of the application rate (AR) of the pesticide, the dislodgeable fraction (DF), and the half-life of the pesticide, DT_{50}, as shown in equation A6. The term CF is a conversion factor to reconcile units and is constant.

$$DFR_t = AR * 11.21 \ \mu g/cm^2 \text{ per lb/acre} * DF * (0.5^{\,t/DT50}) \quad \text{(A6)}$$

Analysis of Variables and Their Effects

Combining terms, we define D_{int} in equations A7 and A8 as a function of all of the contributing variables.

For pesticides with a measured AF, equation A7 is appropriate:

$$D_{int} = SA * WT * [1.12 * 10^{[1.09*\log(AR*CF*DF*(0.5\text{^}t/DT50))]}] * AF \quad (A7)$$

For pesticides where an AF is estimated using equation A3, equation A8 is appropriate:

$$D_{int} = SA * WT * [1.12 * 10^{[1.09*\log(AR*CF*DF*(0.5\text{^}t/DT50))]}] * (1-e^{-[(0.233 * Kow) / (1.01 * 10\text{^}MW * 30.90)] * ET}) \quad (A8)$$

A standard set of conditions was used to evaluate the variation in D_{int} with variation in the parameter of interest. The standard default parameters used that are not pesticide-dependent are shown in Table A1.

Table A1: Standard Default Parameters for Sensitivity Analysis

Parameter	Value	Unit
Surface area, SA	1,730	cm^2
Work time, WT	8	h
Dislodgeable fraction, DF	0.1	fraction dislodged
Exposure time, ET	24	h
Conversion factor, CF	11.21	$\mu g/cm^2$ per lb/acre

In order to evaluate the effect of pesticide-specific parameters on D_{int}, we selected four pesticides with substantially different parameters: Diazinon, methomyl, trifloxystrobin, and paraquat (see Table A2).

Table A2: Pesticide-Specific Default Parameters for Sensitivity Analysis

Parameter	Diazinon	Methomyl	Trifloxystrobin	Paraquat
Application rate, AR (lbs/acre)	1.02	0.85	0.08	1.1
Avg. REI for grapes, t (days)	0.74	0.86	0.76	0.25
Foliar half-life, DT_{50} (days)	0.96	1.08	3.42	2.78
Octanol-water partition coefficient, K_{ow} (unitless)	4,898	17.4	31,623	0.0000316
Molecular weight, MW (g/mole)	304.35	162.20	408.37	257.20

Table A3 summarizes the results for the sensitivity of D_{int} to each variable. Because some of the parameters are pesticide-specific, the results are slightly different for each chemical for variables that depend on these parameters.

Table A3: Change in D_{int} with a Change in Parameter for Selected Pesticides

Variable	Factor of Change in D_{int} with a factor of 2 increase in variable				Factor of Change in D_{int} with a factor of 10 increase in variable			
	Diazinon	**Methomyl**	**Trifloxystrobin**	**Paraquat**	**Diazinon**	**Methomyl**	**Trifloxystrobin**	**Paraquat**
AF (measured)	2	2	2	2	10	10	10	10
SA or WT	2	2	2	2	10	10	10	10
K_a or ET	1.90	1.83	1.96	2.00	6.49	5.03	8.32	9.89
AR or DF	2.13	2.13	2.13	2.13	12.30	12.30	12.30	12.30
t (REI)	0.56	0.55	0.85	0.93	0.0052	0.0045	0.22	0.54
DT_{50}	1.34	1.35	1.09	1.03	1.69	1.72	1.16	1.06

Figures A1–A4 provide a graphical display of the results of the sensitivity analysis for each of the four selected pesticides. The parameters that have the greatest effect on the absorbed dose are application rate (AR) and dislodgeable fraction (DF). For a given pesticide, the AR will not typically vary by much (ARs being determined by the efficacy of the pesticide), but they are quite different between the pesticides selected for analysis (trifloxystrobin at 0.08 lbs/acre and the other pesticides all approximately 1 lb/acre). This effect explains the large difference in D_{int} between trifloxystrobin and diazinon or methomyl.

Changes in the surface area exposed (SA), the work time (WT) and the absorption fraction (AF) have a slightly lower impact on the magnitude of impact on absorbed dose. The WT will change the dose at most by a factor of 2 (a 16-hour workday); an 8-hour day is typical and a 12-hour day is probably close to the maximum people will be working in one day.

Changes in K_{ow} are next in importance. For example, paraquat has a relatively low D_{int} due to its very low K_{ow}. The effect of calculated AF on D_{int} is somewhat less for compounds with moderate to high K_{ow} values.

Parameters having the least effect on the absorbed dose are foliar half-life (DT_{50}) and re-entry interval (REI).

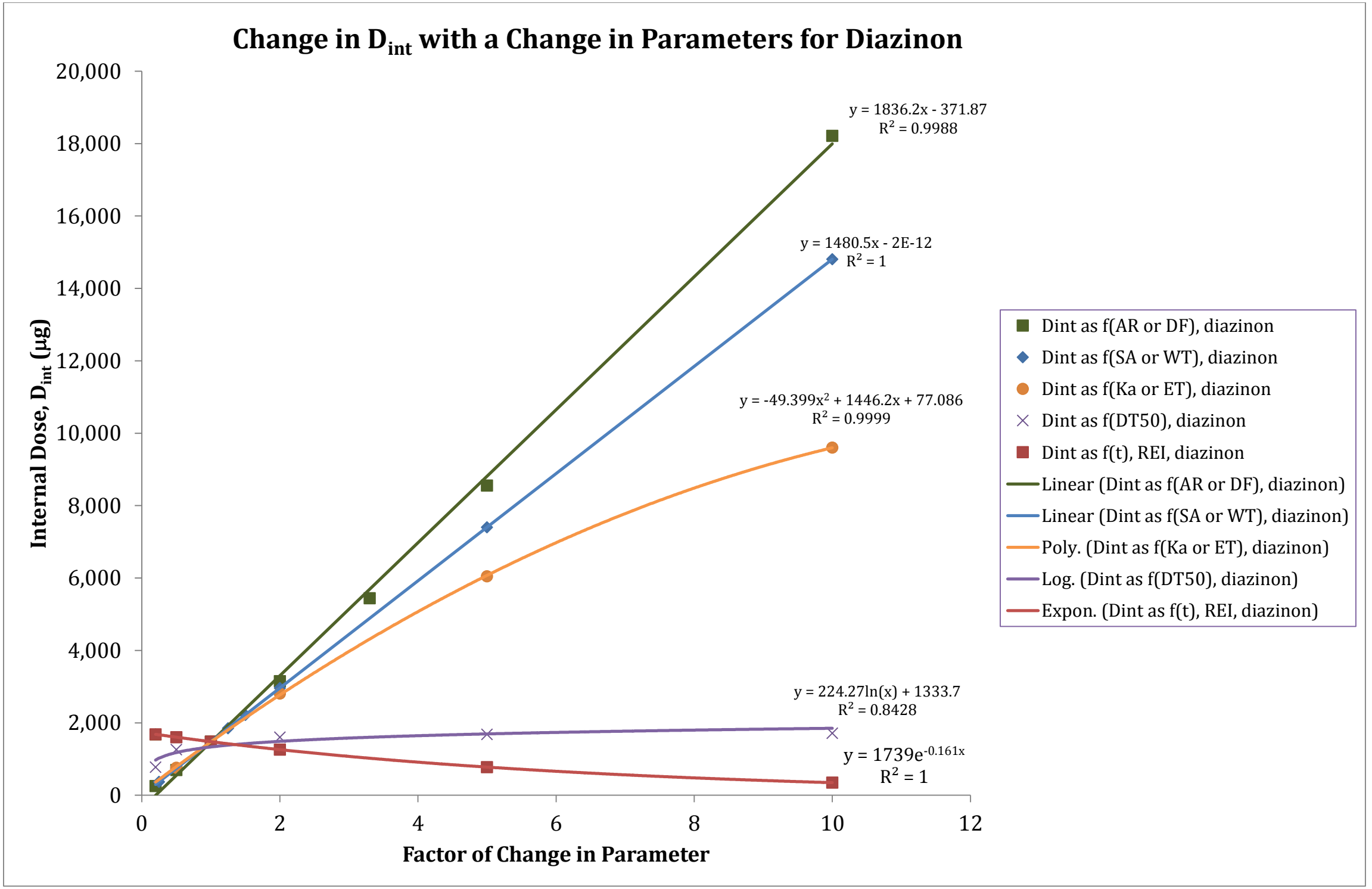

Figure A1: Summary plot showing how the absorbed dose (D_{int}) of diazinon changes as a function of various parameters used to calculate D_{int}.

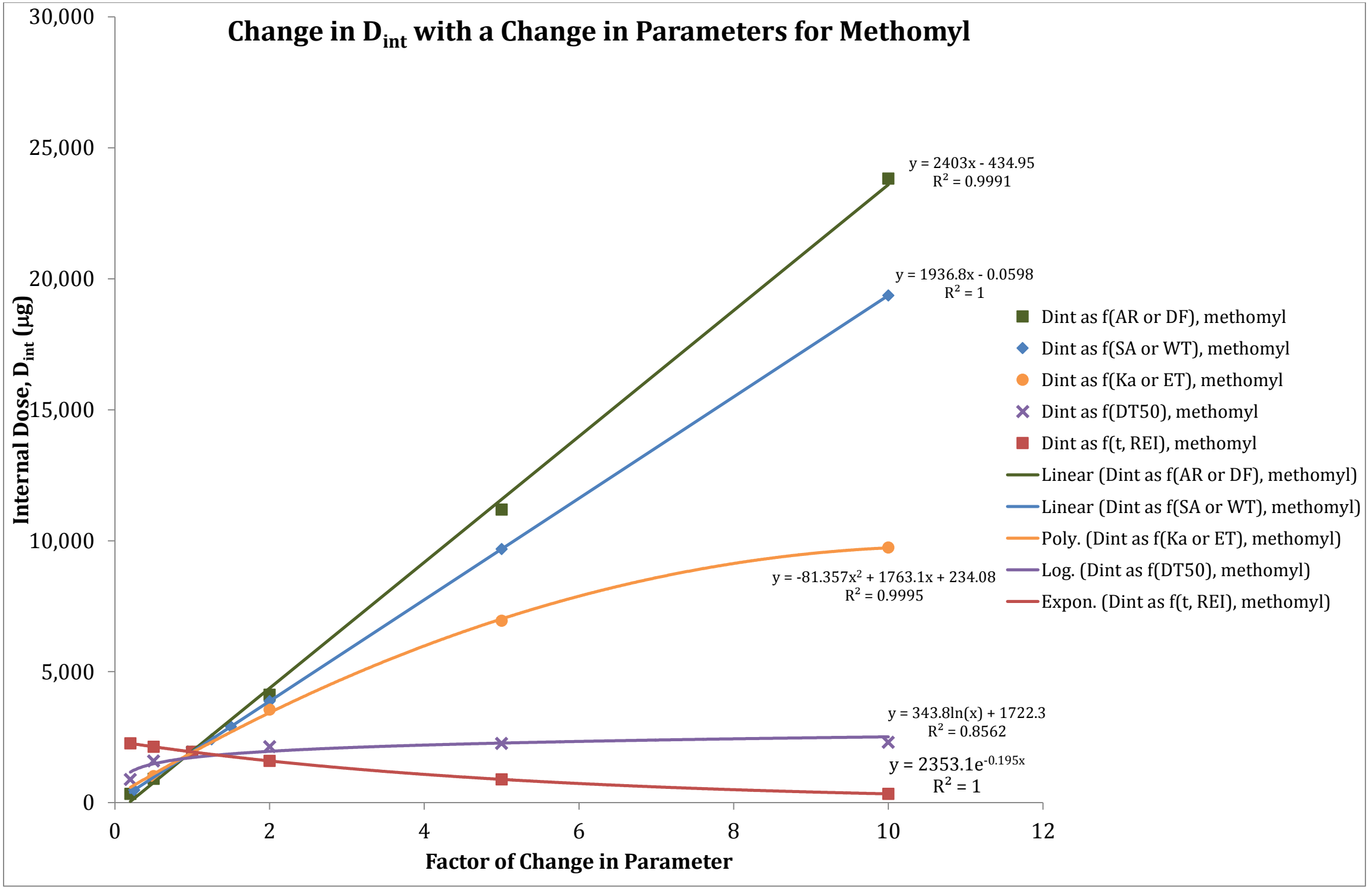

Figure A2: Summary plot showing how the absorbed dose (D_{int}) of methomyl changes as a function of various parameters used to calculate D_{int}.

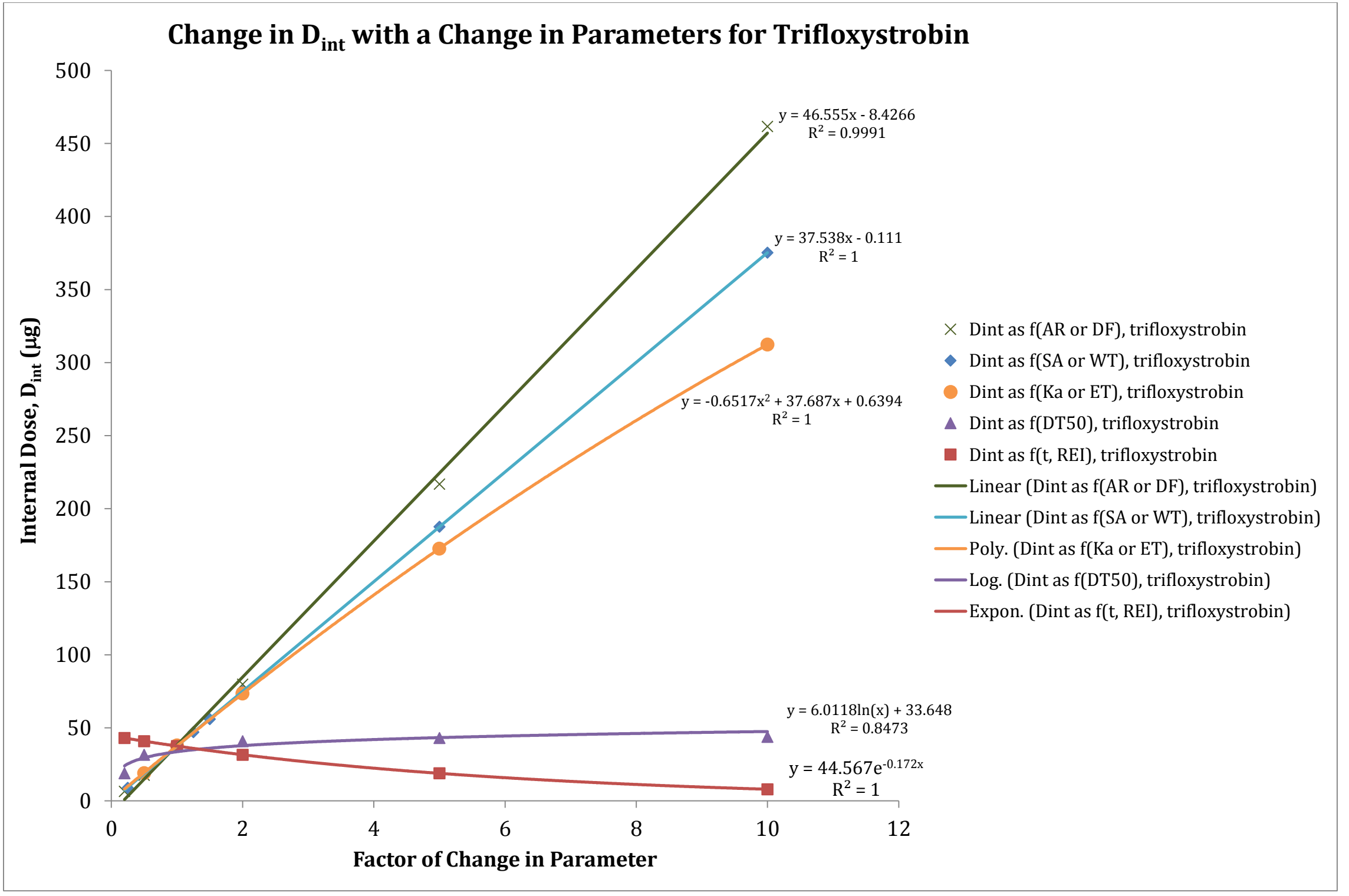

Figure A3: Summary plot showing how the absorbed dose (D_{int}) of trifloxystrobin changes as a function of various parameters used to calculate D_{int}.

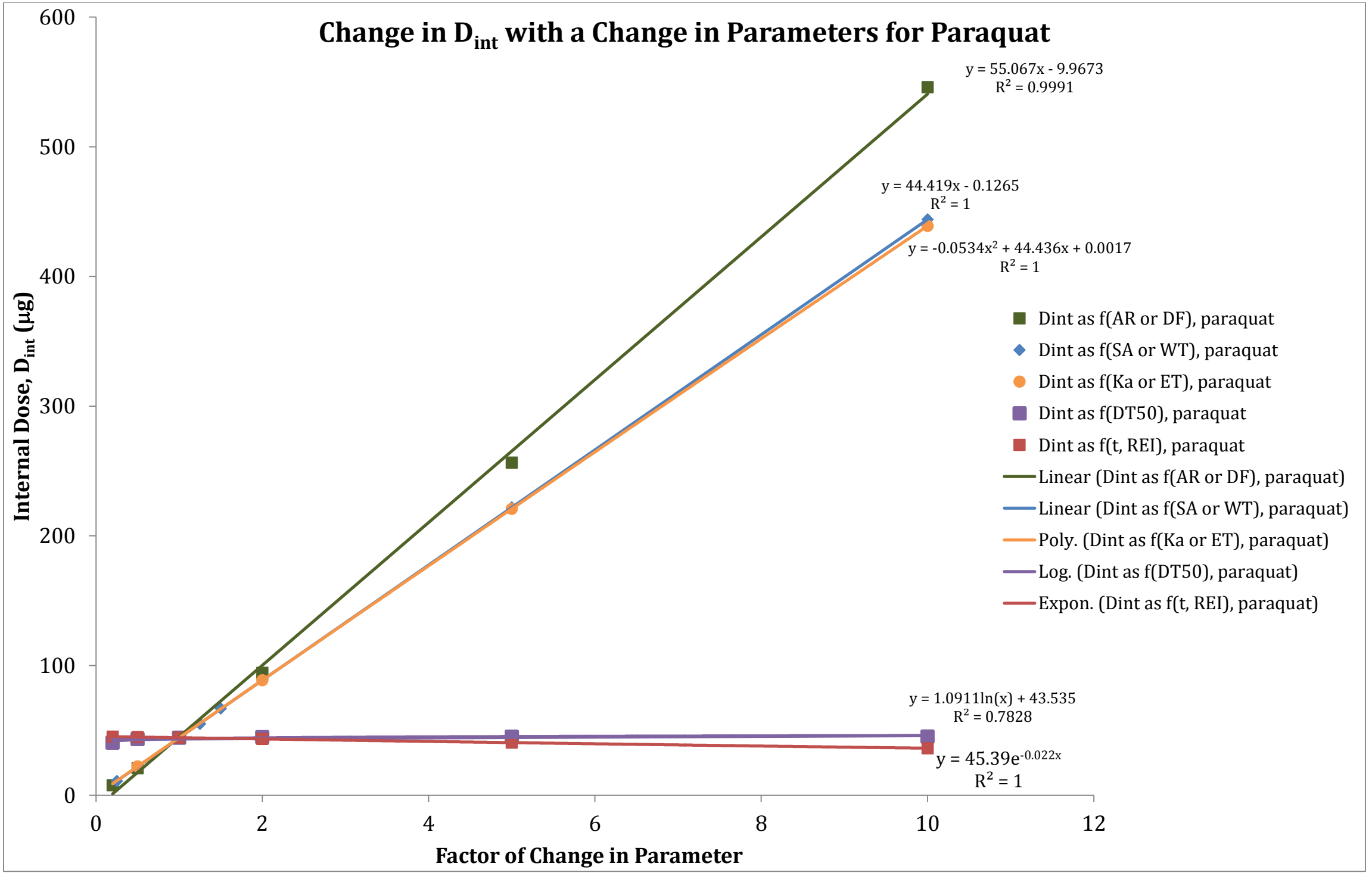

Figure A4: Summary plot showing how the absorbed dose (D_{int}) of paraquat changes as a function of various parameters used to calculate D_{int}.

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DF = (3.36 μg/cm^2 per lb/acre)/ (11.21 μg/cm^2 per lb/acre) = 0.30

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