Pesticide Risk Mitigation Engine

Dietary Exposure and Risk Index

White Paper

Table of Contents

Introduction and Summary

Pesticide dietary risk to humans is a function of exposure and toxicity. Toxicity, in turn, is influenced by the timing of exposures, as well as by tissue-specific patterns of exposure. In PRiME, the "Dietary Risk Index" (DRI) value for a given pesticide in a specific crop/food is the ratio of an estimate of exposure via residues in food, relative to the chronic toxicity-driven, maximum amount of a pesticide that can be consumed by a person in a day without exceeding the Environmental Protection Agency's (EPA) general level of concern.

In short, the DRI for a pesticide-food combination is the average residue level in food divided by the maximum amount that can be in the food, based on EPA's current assessment of each pesticide's chronic toxicity.

The numerator in the DRI ratio is simply the mean residue level of a given pesticide in a food, based on all samples of the food found to contain a quantifiable level of the pesticide (otherwise referred to as the "mean of the positives"). Mean residue levels are expressed in milligrams of pesticide per kilogram of food, or parts per million (ppm).

The DRI denominator is the maximum concentration of a pesticide, also expressed in milligrams of pesticide per kilogram of food, that can be present in a daily serving (or servings) of a food, without exposing an individual to a dose of the pesticide that exceeds his or her personal maximum, limit. In the case of chronic exposures and risk, this dietary exposure limit is referred to as the "chronic Reference Concentration," or cRfC.[1]

Chronic Reference Concentrations are calculated using a formula driven by EPA-set chronic Reference Doses (cRfD), or chronic Population Adjusted Doses (cPAD). The cPAD for a pesticide is equal to the cRfD, adjusted to encompass any applicable, additional safety factors intended to reflect the heightened vulnerability of pregnant women, infants, and children to the toxic effects of pesticides. The 1996 "Food Quality Protection Act" directed the EPA to consider the need for added, ten-fold safety factors to better assure a "reasonable certainty of no harm" for all population groups.

The cRfD and/or cPAD for a given pesticide is expressed in milligrams of pesticide per kilogram of a person's bodyweight per day, and refers to the total amount of the pesticide that can be consumed in a day with a "reasonable certainty of no harm." The cRfC, on the other hand, is a measure of the concentration of a pesticide in a serving of food, sufficient to deliver a dose of

[1] The same concept – Reference Concentration – is used in the PRiME inhalation risk index, and measures essentially the same thing (amount of pesticide X that can be in air over a specified period of time without over exposing an individual). Throughout PRiME documents we will explicitly state whether we are referring to the dietary or inhalation exposure "Reference Concentration."

the pesticide equal to the cRfD or the cPAD for a person of known size, consuming a known amount of food.

Index Structure and Data Sources

The chronic Dietary Risk Index =
(Mean Residue Level Pesticide$_x$) ÷ (Chronic Reference Concentration Pesticide$_x$)

The mean residue level is the mean of the positive values reported by a residue-testing program, based in most cases on domestically grown samples. For most PRiME applications, pesticide residue data for a specific food is derived from the U.S. Department of Agriculture's "Pesticide Data Program" (PDP). The PDP is widely regarded as one of the highest quality pesticide residue datasets available worldwide. Moreover, the protocols of the PDP include a sampling scheme designed to reflect residues in food "as eaten," rather than at the farm-gate as is the case with most of the residue testing conducted by the Food and Drug Administration (FDA). For example, the PDP tests bananas after peeling them, but the FDA tests them with the peel. Obviously, PDP results are more reliable for purposes of dietary risk assessment.

Limited PDP data is available for 1991 and 1992, but the full, modern PDP started in 1993 and has been run continuously since. Each year 12-15 fresh foods, and another half-dozen to a dozen processed foods are selected for testing. Domestically grown and imported samples are selected roughly proportional to market share, allowing analysts to assess risk levels and trends in domestically grown food versus imports.

Raw PDP data files have been downloaded for each year. Using a series of queries within Microsoft Access, basic residue data files are constructed by crop/food, country of origin, and year, and used to calculate the mean residue levels among all positive samples. This is the "mean of the positives" used in the DRI formula.

Other Sources of Residue Data

PRiME is structured so that other residue datasets can be drawn upon in calculating DRIs. But given the Congressional mandate governing the selection of foods for testing via the PDP, we are confident that PDP results encompass most foods and crops that contribute significantly to pesticide dietary exposure and risk in the U.S.

Many grower groups, processors, retailers, and food companies periodically or routinely test samples of food grown in a specific region or from a given supplier for pesticide residues. These usually proprietary residue datasets may also be used in calculating DRI values, which would allow PRiME users to compare pesticide dietary risks among a specific set of growers, suppliers, or producers in a defined region (including abroad) to the DRI values calculated from PDP results for domestically grown samples only, or combined imports or imports by country.

The pesticide residue program of the State of California could be used in calculating DRI values for crops grown in the state. For states accounting for a significant share of the national production of a given crop, say grapes, we can extract from the PDP dataset all New York or California grape samples, calculate mean residue levels for just these samples, and report a New York or California-specific DRI. The ability to calculate state-crop specific DRIs is limited to those state-crop combinations in the PDP for which an adequate number of samples are available for a given year.

The U.K.'s Food Standards Agency carries out an extensive, high-quality residue program, which could be used to calculate DRIs. The FSA's program often does extensive testing of imports into the U.K. of a specific type of foods, including imports from the U.S. For some imported foods on the U.S. market, the best source of residue data is actually the U.K. FSA. Examples include tea, spices, and exotic fruits, foods that have been tested in recent years by the FSA.

Certain ecolabel programs have also compiled extensive datasets on residue levels in certain foods. These data could also be used to develop DRI values.

Accounting for Pesticide Toxicity

The DRI is calculated using a pesticide's "chronic Reference Concentration" (cRfC). Put most simply, the cRfC is the maximum level of a pesticide that can be present in or on a given food without violating the Food Quality Protection Act's basic "reasonable certainty of no harm" standard.

The cRfC is a relative measure or indicator of a pesticide's dietary risk potential. Values will differ based on the weight of a given individual, as well as on how much of a given food the person consumes in a day. A person's bodyweight matters because pesticide chronic PADs and reference Doses are set per kilogram of bodyweight. The amount of a specific food a person consumes in a given day is important, because the total weight of the pesticide ingested is a function of the concentration in the food, expressed in milligrams per kilogram, and the amount of food consumed.

Accordingly, cRfC values will vary as a function of the size of person used in the basic formula, as well as assumptions regarding typical serving sizes. In the case of a relative risk assessment tool like PRiME, it matters little what combination body weight and serving sizes are used, as long as the same assumptions are embedded in the calculation of cRfCs for all pesticides.

Given the EPA's conclusion that pesticide dietary risks are typically greatest for infants and children, cRfC calculations used to estimate PRiME DRI values are based on the diet of a child weighing 16 kilograms. The selection of 16 kilograms (35.2 pounds) corresponds to children

around 3.5 years old, based on the 50th percentile of growth (see CDC growth chart noted in "References").

This body weight was chosen in order to reflect the age and size when most children are consuming a mix of foods close to that consumed by adults. It is also a time of rapid growth and significant food intake relative to body size. By or around age 3.5 years, children are consuming their largest portions of individual foods per kilogram of body weight. For this reason, cRfCs based on children weighing 16 kilograms are conservative, in that most other population groups consume less of individual foods per kilogram of body weight than 3.5-year old children.

The formula to calculate a cRfC for a given food is:

cRfC Pesticide$_x$ (mg/kg food) x Serving Size Food$_x$ (grams/day) =

Weight of Person (kg) x cPAD for Pesticide$_x$ (mg/kg bw/day)

cRfC Pesticide$_x$ (mg/kg food) = Weight of Person (kg) x cPAD for Pesticide$_x$ (mg/kg bw/day)

Serving Size Food$_x$ (kg/day)

Chronic "Population Adjusted Doses" or cPADs, are calculated by the EPA for purposes of dietary risk assessment for all pesticides registered for use on food crops. The cPAD for a given pesticide equals the pesticide's chronic Reference Dose (cRfD) divided by the applicable, additional safety factor (if any) imposed in the course of implementing the 1996 Food Quality Protection Act (FQPA). FQPA safety factors are usually set at three or ten and are intended to more fully protect pregnant women, infants, and children from pesticide risks.

The current EPA-set cRfD or cPAD for pesticide active ingredients are obtained from routine EPA data sources including Federal Register (FR) notices and Reregistration Eligibility Documents. For newly registered pesticides, these data are extracted from FR "Final Rules" announcing EPA approval of pesticide tolerance levels.

A table with sample cRfC calculations follows:

Sample Calculations of Chronic Reference Concentrations (cRfC) for a Child Weighing 16 Kilograms

Pesticide	Food	(Column D) Serving Size (grams/day)	(Column E) Serving Size (kgs/day)	(Column F) cRfD or cPAD (mg/kg/day)	cRfC (mg/kg)
Diazinon	Apple juice	248	0.248	0.0002	0.0129
Thiabendazole	Apple juice	248	0.248	0.1	6.4516
Carbaryl	Apple juice	248	0.248	0.014	0.9032
DPA	Apple juice	248	0.248	0.03	1.9355
AZM	Apple juice	248	0.248	0.00149	0.0961
O-phenylphenol	Apple juice	248	0.248	0.02	1.2903
Methamidophos	Cantaloupe	223.4	0.2234	0.0001	0.0072
Endosulfan	Cantaloupe	223.4	0.2234	0.006	0.4297
Dicofol	Cantaloupe	223.4	0.2234	0.0004	0.0286
Chlorpyrifos	Cantaloupe	223.4	0.2234	0.00003	0.0021

Notes: The formula used to calculate the cRfC in mg/kg (values in Col. G) is: the weight of person (Col. B) multiplied by the pesticide's chronic Reference Dose (cRfD) or chronic Population Adjusted Dose (cPAD) (Col. F) divided by serving size in kg/day.

Note that PRiME is currently basing its dietary risk index on chronic exposures and risks – hence the use of cRfDs or cPADs. Given our focus on chronic risks, it is also appropriate to base DRI values on typical or average (mean) residues.

Some users of PRiME may be interested in comparing relative acute dietary risk levels, or risks associated with applications of oncogenic (cancer causing) pesticides. In such cases, DRI values could be recalculated using a different toxicological endpoint. The option to provide alternative methods for calculating Reference Concentrations based on acute or cancer risks is among the PRiME enhancements under consideration.

Analytical Issues and Options

A number of factors must be taken into account in order to produce the most accurate and reliable set of DRIs for a given application of PRiME. Some impact the exposure side of the DRI equation, while others reflect issues involving pesticide toxicity and how cRfCs are calculated. A number of such issues are discussed in this section.

Residues Not Linked to Field Applications

Some of the pesticide active ingredients detected in a given food may not stem from applications of pesticides in the field during the growing season. For many fruits and vegetables, one-third to one-half of the residues found are from fungicides applied post-

harvest, typically in storage facilities.[2] Clearly, farmers have no control over these applications and residues and they would not be a part of a typical PRiME assessment of in-field pest management options.

Chlorinated hydrocarbon insecticides (e.g., DDT, toxaphene, chlordane) that were banned some 30 years ago still account for the majority of residues found in many animal products and some root and leafy green crops. There is nothing farmers can do to avoid these residues when crops are grown that are prone to taking up soil-bound organochlorine residues , other than testing soils and avoiding contaminated fields. For this reason, residues of banned organochlorines insecticides, and their breakdown products are not typically included in an assessment of dietary risks in PRiME.

A significant share of the residues found in organic food samples are from drift, contaminated fog or water, or residues bound in the soil (Baker et al., 2000; Benbrook, 2008). Growers have little or no control over these classes of residues. In applying PRiME to an organic cropping system, users would presumably only enter those pesticide applications allowed for use by organic farmers and listed in a farm's "Organic System Plan" (OSP). If the PDP has detected residues of such pesticides in the crop, PRiME would report a DRI value.

If there are 10 or more organic samples tested for the pesticide and at least three positives, PRiME can be directed to report a DRI based on the mean residue level in just the organic samples. In most cases though, there will not be at least three positives among 10 or more organic samples and the DRI reported by PRiME will, by necessity, reflect applications to conventional and organic acreage. In all likelihood, the residue profile from an application of a pesticide on an organic field will closely match the profile from the same use pattern on a conventional farm, so this assumption does not introduce significant bias into PRiME DRI estimates.

Country of Origin

PRiME DRI values have been calculated for all crops/foods tested for pesticide residues since 1993 by the U.S. Department of Agriculture's "Pesticide Data Program," or PDP.[3] The DRI for a given food-pesticide combination can be calculated in four ways drawing upon different sets of PDP residue data – (1) those samples reflecting residues in domestically grown food only, (2) all imported samples, (3) imports by country, and (4) all samples combined.

PRiME can be instructed to use any of the four country-of-origin dataset options, and can also calculate DRIs and total pesticide dietary risks by year, although data will be available for a

[2] For example, imazalil, thiabendazole, iprodione, and diphenylamine.

[3] For information on the PDP and to access annual reports and data files, go to www.ams.usda.gov, to "Science and Laboratories," and click on "Pesticide Data Program" under "Data Programs."

given crop only for those years when the crop was included in the PDP. These options allow users to carry out dietary risk trend analyses for a given crop, and/or assessments of differences in dietary risk levels by country of origin, over time.

Unless otherwise specified, PRiME will report DRIs based on the most recent year a crop was tested by PDP and for domestically grown samples only. In future enhancements, we plan on providing users the option to select which of the four residue data sets they want to use, as well as the PDP year.

Treatment of Imports

PRiME calculates relative pesticide risks across a set of risk indices based on data on pesticide use patterns, field-specific soils, water, and weather data, and toxicological data pertinent to individual pesticide active ingredients. Currently, PRiME indices that depend on soil, weather, water, and field-specific input variables can only be calculated for pesticide uses in the U.S. Other PRiME indices can be calculated for pesticide uses anywhere in the world, as long as the use pattern information needed to run the PRiME model are available (i.e., formulation; rate, method, and timing of application; and pre-harvest and field re-entry intervals). The DRI is one of the PRiME indices that can be calculated for food from any country, as long as pesticide residue data are available reflecting pesticide residues in food grown abroad.

The ability to assess dietary risks in imported food is important because imports account for a substantial share of U.S. consumption, especially of fresh produce during the winter months when there are no or limited supplies of fresh produce grown in North America. The frequency and levels of pesticide residues vary markedly in imports compared to domestically grown produce and more often than not pose greater pesticide dietary risk per serving. For this reason, users of PRiME may wish to pursue the option of comparing pesticide dietary risks in domestically grown versus imported food, and can do so as long as there are appropriate residue datasets available to calculating DRI values. Such data are accessible in the PDP results for most major fruits and vegetables for which imports dominate fresh consumption during off season months (e.g., fresh grapes, spinach, tomatoes, pears, peaches, strawberries).

State-Level Residue Data

State-specific DRI values can also be calculated for some crop-state combinations using PDP data, since PDP enumerators are supposed to record the packing and production state for each sample. In the early years, data on where samples came from were not consistently recorded, although these data are now more routinely accessible.

Criteria and a method will have to be established to determine the minimum number of samples that PDP must test in a state (or a region) in a given year, prior to estimating state or region-specific DRI values. Initially, we will not compute state-level DRIs for crop-state

combinations with fewer than 50 samples. For most crops in recent years, there will be 50 or samples in one to three states.

Based on analyses done in the past using state-specific residue profiles, DRI values do vary markedly when comparing, for examples, residues of fungicides on food grown in a wet, humid region versus a dry, desert location. Allowing users to utilize state or region-specific DRI values is a valuable refinement that can be made now via interaction with the PRiME team. Creating the ability to select different state-specific residue datasets is among the refinements planned for future PRiME enhancements.

Crops Not Tested by PDP

In the event a user of PRiME is evaluating a food/crop not tested by the PDP, DRI values can be computed if there is another source of residue data that meets the user's minimal criteria for statistical rigor and accuracy. In some cases, the PDP residue data available on one crop can be used in estimating DRIs in a similar crop that falls in the same crop grouping.[4] For example, PDP data on sweet cherries could be used in estimating DRIs for sour cherries; or data on oranges could be used to calculate lemon DRIs.

Key factors in deciding whether PDP data on a crop can be used in approximating DRI values in a related crop include whether a similar set of pesticides and use patterns are applied on both crops, at about the same stage of crop development, with comparable pre-harvest intervals. When no acceptable residue data are available on a crop/food, no DRI values will be reported in PRiME output for that crop/food.

Dealing with Multiple Applications

Multiple applications of a given pesticide are often made on a crop in a single growing season, and each would be entered in PRiME as a separate application. Across most PRiME risk indices, impacts are additive across applications, but additively is usually not a valid assumption in the case of dietary risks.

If a user of PRiME wishes to estimate season long relative dietary risks in cases with multiple applications of a pesticide, a DRI value will be reported only for the last application of the pesticide (i.e., the application with the shortest pre-harvest interval). This approach is likely to result in, at most, modest underestimation of dietary risks. This is because multiple applications of a pesticide are typically required only in cases in which earlier applications have broken down, dissipated, or washed off a crop, and hence are no longer effective. In such cases, the pesticide is also not likely to persist to harvest and be present at any more than negligible levels in the harvested crop.

[4] Crop groupings are set forth in C.F.R. Section 180.41.

Exceptions to this general rule will arise. For example, if two applications of the same pesticide are made in different ways, times, or formulations, it may be appropriate to treat them as separate applications for purposes of projecting relative dietary (or other) risks. For example, suppose an insecticide is applied to potatoes in two primary ways – in furrow applications at planting, and liquid sprays during the growing season. Dietary risks may vary markedly between these two use patterns, leading to different treatment within PRiME.

In general, persistent, systemic pesticides are the most likely to result in additivity of residues when two or more applications are made in a growing season. This version of PRiME, however, does not provide the option to explore this possibility or alter DRI values in light of full or partial additivity.

Dealing with Isomers and Metabolites

The PDP tests foods for parent pesticide active ingredients, as well as major metabolites and/or isomers. For dozens of active ingredients, the PDP reports results separately for two or more isomers or metabolites of a pesticide active ingredient, as well as the parent compound. In a smaller number of cases, the PDP also reports results for "Total" or multiple residues (e.g., "Total Endosulfans" and "Endosulfans," or "Total Permethrins" or "Permethrins") and/or all metabolites/isomers combined. In such cases, special care must be exercised to avoid double counting residues and risk in estimating DRIs.

In cases where the PDP reports results for individual isomers and metabolites, as well as "total" residues of the pesticide, DRI values are based just on the "total" residue results. This is necessary to avoid double counting of residues present in a given food.

When PDP reports values for the parent compound and one or more isomer or metabolite, a DRI value is calculated for each based on the residue data specific to the parent compound, isomers, and metabolites, and then added together to equal the total pesticide DRI.

For example, the 2008 PDP reports residues of endosulfan I, endosulfan II, and endosulfan sulfate. DRI values are calculated for each of these three forms of endosulfan and the values are added together to form the final, total endosulfan DRI value for a given food.

In the case of permethrin, the PDP reports results for "Permethrin Total," as well as permethrin's two stereoisomers, permethrin cis and permethrin trans. In this case, DRI values are computed based on the residue data reported for "Permethrin Total."

One of the most complex challenges in using the PDP dataset for assessment of dietary exposure/risk levels over time arises from the fact that the PDP has changed over the years

how it tests for and reports residues for pesticide parent active ingredients, isomers, and metabolites. A few dozen pesticides, including endosulfan and permethrin, have been handled differently over time in the PDP. In some years, results are reported just for parent compounds, while in other years, the results cover parent compounds plus one or more isomer and metabolite. The nature of and number of isomers/metabolites varies over time in some cases. Sometimes values are reported for the parent compound alone and in other cases they are not.

Each method for reporting pesticide-specific PDP results has been evaluated to determine the appropriate basis to calculate DRIs for a given pesticide-food combination in each year of PDP testing, beginning in 1993. Accordingly, PRiME DRI values for a given pesticide-crop combination reflect the outcome of the above described approach for avoiding the double counting of certain residues when PDP reports results in multiple, overlapping ways.

Apple Pilot Case Study

For the pilot case study involving fresh apples, DRI values are based on the crop year 2009 fresh apple residue dataset compiled by the PDP. This is the most recent fresh apple residue data available; 700 samples of domestically grown apples were tested. With the exception of tropical fruits and vegetables not grown in the continental U.S., all PRiME DRI values are based on residue data for domestically grown crops only. These residue data represent sampling across the United States, with the number of samples collected in a given state roughly proportional to that state's contribution to total domestic harvest. The samples are prepared for testing "as eaten." In the case of apples, "as eaten" means washed, but not peeled.

Table 1 reports DRI values for fresh apples in 2009. It includes the data required to calculate DRI values – mean residue levels and cRfCs. In addition, the table includes the number of samples tested, the percent of samples reported as positive, the pesticide's cPAD, and the size of the average daily serving (in grams) used to calculate the cRfC.

Residues of 51 pesticides, isomers, and breakdown products were detected by PDP during its apple testing in 2009. A total of 3,553 residues were detected, or 5.95 per sample tested.[5] Just under 30% were residues of the post-harvest fungicides diphenylamine (DPA, 526 positives) and thiabendazole (532 positives).

Chlorpyrifos has the highest DRI, with a positive-sample mean residue level DRI of 15.8. But there were only three positive samples out of 700. This means that about one out of every 233 servings of apples will expose a person to relatively high risks from chlorpyrifos. The Centers for

[5] This relatively high number of residues per sample is largely why apples top the "Dirty Dozen" list of foods issued by the Environmental Working Group.

Disease Control reports that Americans eat about 120 apples per capita per year, or about 36 billion apples, each of which is about one serving. Accordingly, in 2009 there were over 150 million servings of apples with chlorpyrifos residues associated with a DRI value of 15.8 – clearly well above EPA's "level of concern."

Dicofol had a DRI of 11.2, but this was based on just one positive sample out of 700. Diazinon had a DRI of 0.6 based on 8.7% positives (61 samples) and azinphos methyl had a DRI of 0.2 with 130 positives.

Table 2. Derivation of Dietary Risk Index Values for Pesticides Applied to Apples in 2009 (Most Recent Year of PDP Testing) Based on Mean PDP Residue Levels (DRI-Mean) (see notes)

	Pesticide Type	Number of Samples	Number of Positives	Percent Positive	Mean Residue (ppm)	cPAD	Chronic Reference Concentration	DRI-Mean
Chlorpyrifos	I	700	3	0.4%	0.0592	0.0000	0.00375	15.7778
Dicofol p,p'	I	700	1	0.1%	0.5600	0.0004	0.05	11.2000
Diazinon	I	700	61	8.7%	0.0148	0.0002	0.025	0.5931
Fenpropathrin	I	700	25	3.6%	0.0881	0.0025	0.3125	0.2820
Azinphos methyl	I	700	130	18.6%	0.0412	0.0015	0.18625	0.2211
Dimethoate	I	700	2	0.3%	0.0305	0.0022	0.275	0.1109
Diphenylamine (DPA)	PGR	700	526	75.1%	0.3571	0.0300	3.75	0.0952
Cyhalothrin, Lambda	I	196	3	1.5%	0.0100	0.0010	0.125	*0.0800*
Cyhalothrin, Lambda epimer R157836	I	196	1	0.5%	0.0100	0.0010	0.125	*0.0800*
Cyhalothrin Total								**0.1600**
Fludioxonil	F	700	67	9.6%	0.2148	0.0300	3.75	0.0573
Phosmet	I	700	100	14.3%	0.0637	0.0110	1.375	0.0463
Pyridaben	I	196	1	0.5%	0.0250	0.0050	0.625	0.0400
Endosulfan I	I	700	51	7.3%	0.0293	0.0060	0.75	*0.0391*
Buprofezin	I	700	3	0.4%	0.0143	0.0033	0.4125	0.0346
Carbendazim (MBC)	F	504	103	20.4%	0.0343	0.0080	1	0.0343
Formetanate hydrochloride	I	700	109	15.6%	0.0027	0.0007	0.08125	0.0333
Endosulfan sulfate	I	685	53	7.7%	0.0236	0.0060	0.75	*0.0315*
Endosulfan II	I	696	94	13.5%	0.0234	0.0060	0.75	*0.0311*
Endosulfan Total								**0.1017**
Thiabendazole	F	700	532	76.0%	0.3877	0.1000	12.5	0.0310
Omethoate	I	700	2	0.3%	0.0080	0.0022	0.275	0.0291
Pyrimethanil	F	700	406	58.0%	0.4860	0.1700	21.25	0.0229
Methomyl	I	700	2	0.3%	0.0200	0.0080	1	0.0200
Esfenvalerate+Fenvalerate Total	I	504	5	1.0%	0.0486	0.0200	2.5	0.0194
Tetrahydrophthalimide (THPI)	F	700	111	15.9%	0.2623	0.1300	16.25	0.0161
Carbaryl	I	700	23	3.3%	0.0267	0.0140	1.75	*0.0152*
Thiacloprid	I	700	48	6.9%	0.0069	0.0040	0.5	0.0139
Fenpyroximate	I	504	69	13.7%	0.0154	0.0100	1.25	0.0123
1-Naphthol	PGR	196	1	0.5%	0.0200	0.0140	1.75	*0.0114*
Carbaryl Total								**0.0267**
Diflubenzuron	I	700	23	3.3%	0.0252	0.0200	2.5	0.0101
Captan	F	196	17	8.7%	0.1461	0.1300	16.25	0.0090
Acetamiprid	I	700	231	33.0%	0.0212	0.0230	2.875	0.0074
Pyraclostrobin	F	700	118	16.9%	0.0201	0.0340	4.25	0.0047
Propargite	I	700	4	0.6%	0.0208	0.0400	5	0.0042
Hexythiazox	I	196	6	3.1%	0.0113	0.0250	3.125	0.0036
O-Phenylphenol	F	700	9	1.3%	0.0080	0.0200	2.5	0.0032
Chlorpropham	H	700	3	0.4%	0.0170	0.0500	6.25	0.0027
Fenbuconazole	F	700	6	0.9%	0.0100	0.0300	3.75	0.0027
Piperonyl butoxide	I	687	1	0.1%	0.0310	0.1600	20	0.0016
Boscalid	F	700	134	19.1%	0.0408	0.2180	27.25	0.0015
Myclobutanil	F	700	23	3.3%	0.0045	0.0250	3.125	0.0015
Spinosad A	I	196	4	2.0%	0.0039	0.0268	3.35	0.0011
Trifloxystrobin	F	700	27	3.9%	0.0049	0.0380	4.75	0.0010
Flonicamid	I	700	4	0.6%	0.0086	0.0730	9.125	0.0009
Spinetoram	I	489	18	3.7%	0.0031	0.0268	3.35	0.0009
Etoxazole	Acaricide	504	18	3.6%	0.0047	0.0460	5.75	0.0008
Imidacloprid	I	700	126	18.0%	0.0050	0.0570	7.125	0.0007
5-Hydroxythiabendazole	F	196	4	2.0%	0.0083	0.1000	12.5	0.0007
Methoxyfenozide	I	700	81	11.6%	0.0075	0.1000	12.5	0.0006
Pendimethalin	H	700	11	1.6%	0.0070	0.1000	12.5	0.0006
Permethrin cis	I	700	1	0.1%	0.0040	0.2500	31.25	0.0001
Chlorantraniliprole	I	504	152	30.2%	0.0096	1.5800	197.5	0.0000

Placing DRI Values Into Perspective

The higher the DRI value, the greater the relative risk, but how can DRI values be placed into perspective in light of EPA's determination of the maximum residue level that meets – or exceeds -- the FQPA's "reasonable certainty of no harm" standard?

Whenever the mean residue level of a particular pesticide in a given food equals or exceeds the applicable chronic Reference Concentration, individuals consuming a single serving of the food with such residues will ingest, on average, the maximum amount of the pesticide that EPA regards as consistent with the FQPA's "reasonable certainty of no harm" standard. The size of each pesticide-specific "risk cup" is determined by EPA's assessment of the toxicology data submitted by manufacturers in support of tolerance petitions.

When a DRI value equals one, this means that the average residue level will fill the risk cup. This implies, of course, that about 50% of the individuals consuming the food will ingest residues above the maximum level that is consistent with the FQPA's safety standard, while the other half will consume residues and risks below the FQPA threshold.

It is also important to recognize that the DRI value for a given food use of a pesticide, say on apples, is a measure of relative dietary risks from residues in apples compared to residues found in a serving of any other food. The DRI does not take into account how frequently a particular food is consumed, but it does take into account daily average consumption levels from one or more servings.

For example, the azinphos methyl (AZM) DRI value on apples in 2009 was 0.221 (see Table 1), about the same as in peaches in 2008 (0.255). But 18.6% of apples tested positive for AZM, compared to just 1.2% of peaches in 2008. Clearly, AZM residues in apples are a greater concern to regulators, parents, and health officials than in peaches, despite the comparable DRI scores.

The DRI is a measure of pesticide risk applied to individual pesticide-food combinations, although DRIs can be added together across foods. The EPA bases its dietary risk assessments on exposures via all the foods in which a given pesticide may be found, as well as drinking water. Accordingly, no one pesticide use (e.g., chlorpyrifos on apples) can "use up" the entire "risk cup" available for it.

Several widely used fungicides and insecticides are found by PDP in one-third to one-half or more of the foods tested by PDP annually. Twelve PDP-tested foods in 2009 contained chlorpyrifos residues, with apples posing the highest positive sample DRI value of 15.8. Aggregate chlorpyrifos DRI across the 12 foods was 32. In 2008, 19 foods were found to

contain chlorpyrifos, accounting for an aggregate DRI of 81. A very high DRI in collard greens in 2007 (DRI = 158) drove the aggregate chlorpyrifos DRI up to 208.

As a general rule of thumb, no single pesticide-food DRI should exceed 0.1. If residues are managed down to this level, aggregate DRIs across all foods in which a given pesticide is found are not likely to exceed 1.0.

DRI values greater than one do not mean inevitable toxic harm, but rather represents a reduction in the 100- to 1,000-fold margin of safety that EPA incorporates in its assessment of dietary risk and in the setting of pesticide tolerances. A positive sample "DRI = 10" means, in effect, that EPA's typical 100-fold safety factor has been reduced to 10-fold.

While the DRI is based on averages, the EPA strives to assure a "reasonable certainty of no harm" for nearly everyone by assessing distributions of pesticide exposure and risk levels. EPA dietary risk assessment policy strives to "protect" the person at the 99.9th percentile of the risk distribution curve. The agency deems this goal has been achieved when the exposure level for the person at the 99.9th percentile does not exceed that person's allowed dose of the pesticide. The person at the 50th percentile of the same risk distribution curve will be over-protected by several-fold when the person at the 99.9th percentile is at the maximum allowed exposure.

Accordingly, any pesticide-food combination posing DRI risks equal to or above one would, in general, exceed EPA's level of concern. Pesticide-food combinations with a DRI of less than 0.1 likely do not warrant EPA attention, at least not based on current knowledge and information. These benchmarks along the dietary risk continuum can serve as preliminary cutoffs for PRiME risk categories:

- Pesticide-food DRI values of 1.0 or higher – "Significant risk in need of mitigation"
- Pesticide-food DRI values between 0.1 and 1.0 – "Moderate risk"
- Pesticide-food DRI values below 0.1 – "Minimal risk"

Returning to the apple case study and the 51 residues found in PDP's 2009 testing, two pesticide-apple combinations have DRIs over 1.0 – chlorpyrifos (15.8) and dicofol (12.2). Four have values over 0.1 but below 1.0 – diazinon (0.6), AZM (0.2), fenpropathrin (0.28), and dimethoate (0.11). The other 45 residues fall in the "minimal risk" category with DRIs below 0.1.

UPAFs for the Human Dietary Risk Index

Farmers and pest management specialists have several options to alter likely exposure levels to specific non-target organisms following an application of a given pesticide. Indeed, in the case of dietary risks, a major focus of the EPA and pesticide industry in the implementation of the FQPA has been crafting label changes expected to reduce the frequency of residues in food at harvest time or residue levels, or both.

Pest management and pesticide risk tradeoffs can emerge, however, when EPA regulatory actions limit or prohibit the use of a particular pesticide. Many cases have emerged where food companies, growers, and farm organizations have urged the EPA to consider allowing continued use of a pesticide, despite the potential for exposures and risks above the EPA's "level of concern." The EPA is much more likely to allow such uses to continue if there are reliable and enforceable ways to lower overall dietary risks.

In working with pesticide users to assess whether and how a pesticide can be used without triggering excessive risks, the agency typically evaluates the impact of a variety of changes in pesticide labels and formulations and/or use patterns to determine if there are ways and conditions under which a pesticide can be applied safely.

PRiME also allows users to factor in the impact of steps taken by growers to reduce pesticide exposure levels, including steps that are adopted voluntarily, beyond those required on pesticide labels. This is done through "Use Pattern Adjustment Factors," or UPAFs. In the case of dietary risks, proven options to reduce expected residue levels include extending the Pre-harvest Interval (PHI) and/or reducing rates of application, or changing the way or timing of an application.

For example, apple growers in some states are using chlorpyrifos as a dormant application, painted onto tree trunks. This use pattern has essentially zero chance of producing measurable residues in the next season's harvest. A UPAF of 0.001 should be applied to all such dormant uses in apple orchards. Restricting a pesticide to only dormant uses is equivalent to expanding the PHI several-fold over the minimum PHI required on product labels.

In the case of a UPAF based on extension of the PHI or a reduced application rate, the magnitude of the reduction in expected residues should be relative to the typical use pattern in the region, rather than minimum or maximum label requirements. In this way, a UPAF based on extending PHIs or cutting rates will almost certainly lead to meaningful risk reduction compared to the typical use pattern for the pesticide in the region.

Time Lags in Monitoring Residue Levels

There is an approximate two-year lag between the availability of PDP residue data on a given crop and the present growing season. In some cases, label changes are phased in by EPA over a period of time to smooth transitions for growers. DRI values for pesticides in the midst of such a transition may warrant UPAFs reflecting mandatory changes in use patterns. In other cases, grower organizations or food companies may decide to impose limits on the use of a pesticide that has, in the past, been found in food at sometimes-worrisome levels.

Given the reliance on PDP data to estimate the PRiME DRI, there is no way to link specific data on pesticide use patterns with data on the resulting residues. Lacking such a connection, how can dietary UPAFs be set in a given PRiME application?

DRI scores for a given crop-pesticide combination reflect the average outcome in terms of detectable residues, following thousands of spray applications under conditions varying across multiple dimensions (rate, timing, weather, PHI, formulation, spray equipment, etc). Despite the number of variables at play, there are two ways to develop and support UPAFs in a given PRiME application.

First, through a survey or other mechanism, information can be gathered on the typical use pattern for a specific pesticide application. Suppose that such a survey shows that a significant share of all applications are made with a specific use rate, plus or minus 10%, or in accord with a specific pre-harvest interval in days, +/- 10%. These baseline values can then be considered as associated with the mean residue level reported by PDP. Reductions in the use rate or increases in the PHI from these baseline values could be linked to application of a UPAF.

For example, if the typical application of pesticide X on apples in 2009 was made with a 15-day PHI, resulting in a mean residue level of 0.01 ppm, a grower adhering to a PHI of no less than 20 days would likely warrant a UPAF. For some families of chemistry, field dissipation curves are known and can be used to estimate the percent of residues likely to degrade over a given period of time. These data can be used to provide an empirical basis for UPAFs.

Second, grower groups, food processors, and/or research teams can collect crop and region-specific residue data under a variety of use patterns, e.g., varying PHIs or application rates, or both. Based on the data from such controlled field residue trials, UPAFs can be developed to take into account the measured average reduction in residue levels between the typical use pattern and a modified one.

In applications of PRiME where there are alternative use patterns for the same pesticide, two or more DRI scores can be reported by PRiME, one reflecting the typical or unmodified use

pattern, the second a use pattern containing one or more changes known to reduce residues at harvest.

Future Refinements and Areas of Uncertainty

Acute versus Chronic Risk

In refining and expanding the scope of PRiME, we are exploring the option of calculating DRI values based on acute exposures and risks, in addition to chronic risk. (This cannot be done for all pesticide-food combinations because EPA has not calculated acute Reference Doses or acute PADs for all active ingredients.)

Once we have augmented PRiME to include an acute DRI index, users will be given the option of selecting DRI index values based on acute or chronic risks, or PRiME can be instructed to select and report the higher of the acute and chronic risk DRI values.

Cancer Risks

The current calculation of DRIs does not encompass cancer risks, which for some pesticides may arise at dose levels lower than chronic Reference Doses or cPADs. But given the focus of EPA over the last three decades on restricting food uses of cancer-causing pesticides, there are fortunately few pesticides still used on major food crops that pose significant dietary cancer risks.

One major exception is cancer risk associated with pesticide exposures via drinking water and beverages, which are part of the diet. Several pesticides found in drinking water are classified by EPA as possible or probable carcinogens, and one widely used corn herbicide, atrazine, is going through another re-evaluation by EPA, in part because of concern over cancer risks following exposures via drinking water.

The development of a drinking water human health risk index is under consideration for a possible future PRiME enhancement. A method can be developed to incorporate cancer risks into the DRI, either separate from or in conjunction with chronic and/or acute risks.

Transient Effects and Single versus Multiple Endpoints

DRI values reflect only a single toxicological endpoint and do not differentiate between a pesticide causing a relatively minor, reversible health impact at, for example, 0.01 ppm, compared to a pesticide that can cause a serious and irreversible health impact, also at 0.01 ppm. DRI values also do not take into account the number of adverse health impacts linked to exposures to a given pesticide.

This is a generic weakness shared by all pesticide dietary risk assessment methods and is also a source of bias in regulatory decisions. If and when toxicologists and regulatory authorities

reach consensus on better ways to account for the number of endpoints impacted by a pesticide and/or the severity and reversibility of impacts, we will assess whether some method or adjustment factor is warranted to take into account these differences.

National versus State or Region-Specific Residue Datasets

On the residue-exposure side of the DRI equation, the use of national residue datasets introduces a source of error in DRI calculations, to the extent that pesticide use patterns in one state differ markedly from those in other states. For most foods tested by the PDP, there are ample samples to calculate state-specific DRI values for one to four of the leading states growing the crop. In addition, regional DRI scores can be calculated by pooling the samples taken, for example, in all New England or all western states.

For some crops/foods, disaggregating PDP residue datasets down into four major regions, or even two (e.g., north versus south, or east versus west), could substantially improve the accuracy of DRI scores. This sort of manipulation of PDP residue data sets is not difficult, but does depend on consistent classification of PDP samples with respect to the state in which the food was grown. PDP enumerators do not always record this data. In some re-packing sheds, it is sometimes hard to determine exactly where a given fresh fruit or vegetable was grown.

Users of PRiME will have to determine, on a case-by-case basis, whether the added time and effort is justified to produce refined DRI values based on customized residue data sets. Based on past experience, only one to three pesticides used on a particular crop pose dietary risks of concern, and on many crops, none do. Moreover, the pesticide applications leading to high-end residues, and hence DRI values in the "significant risk" category, sometimes are clustered in one to a few states where a crop is grown. Disaggregation of PDP residue data by state and region will cause some DRI values to go up, and some markedly so, while others will fall, some precipitously from the "significant risk" to "low risk" category.

Impact of Gradually Falling Limits of Detection

The mean of all positive residues found by PDP in a given crop is a key variable in calculating DRIs. The limit of detection (LOD) embedded in residue chemistry methods and equipment is obviously important in determining mean residue levels. The more sensitive the analytical method (i.e. the lower the LOD), the more positives will be found, including more at progressively low levels. As a result, incrementally lower LODs will lead to lower mean residue levels and lower DRIs.

For many pesticides, the LODs in California Department of Pesticide Regulation (CDPR) residue testing are higher than the LODs in PDP testing. This is why DRI values calculated using CDPR residue data for a given crop will typically be higher than comparable calculations of DRIs using PDP samples.

Changes in LODs over time also impact DRI trends. In both the case of PDP and CDPR pesticide residue testing, incremental improvements in analytical methods have steadily reduced LODs, in some cases by 100-fold or more in the last 15 years. Such progress in the sensitivity of analytical methods will tend to lower mean residue levels, and as a result, DRI values, even in cases where the upper end of residue distributions have not changed.

For this reason, special procedures may need to be followed if and when multiple residue datasets with different LODs are used in an application of PRiME, or when DRI values are compared over time drawing on PDP data. One option to address this problem of variable LODs is to truncate datasets at some point in the distribution of values, e.g. at the highest LOD in all years of testing.

An example follows. Suppose for a given pesticide-food combination, the LOD was 0.01 ppm, in 1995, a year during which 32% of the samples tested positive, with mean residues of 0.05 ppm. Ten years later in 2005, the LOD has been reduced 10-fold to 0.001 ppm, 40% of the samples tested positive, and the mean residue was 0.015 ppm. In this example, have dietary risks gone up or down? One way to answer the question is to truncate the 2005 data set by setting all values below 0.01 ppm (the LOD in 1995) to zero.

After making this adjustment and re-running the statistics, only 20% of the samples might test positive, but the mean residue level might actually be higher than in 1995. These changes would suggest that a lower percent of acres are being treated, but on those acres that are treated, the use pattern resulted in somewhat higher residues than the case in 1995.

Truncating residue distributions in this way is not likely to seriously bias results as long as it is done consistently, since it is the upper end, not the lower end of residue distributions that account for most of the dietary risk.

Taking Into Account the Frequency of Residues

DRI values in PRiME for a given pesticide-food combination are based on the mean of all positive residues found in PDP testing. In some cases, this mean might be based on just five positive samples out of 600 tested, and in other cases, 350 positives out of 600 samples tested.

So, when a grower reports an application of azinphos-methyl (AZM) on apples, for example, PRiME will compute the DRI value based on the mean of all positive samples found to contain AZM residues. In doing so, there is an implicit assumption that residues at the mean level will be present following that farmer's application. In reality, the residues might be higher, lower, or even below the limit of detection.

It is common for pesticides to be used differently across the country on a given crop, in response to variable levels of pest pressure, climatic differences, and varying production

systems. As a result, residue profiles of a widely used insecticide like AZM tend to vary significantly. In regions with heavy insect pressure and relatively few cost-effective alternatives, residues tend to be found more often and mean residue levels are also typically higher, reflecting either shorter PHIs, higher application rates, or both.

In areas with relatively intense pest pressure, PRiME DRI values are likely to underestimate dietary risk levels compared to other parts of the country. In regions with relatively low pest pressure, DRI values will likely be inflated compared to other regions.

There are options to reduce or eliminate these patterns of bias in PRiME DRI values, but each step to narrow uncertainty or reduce bias, e.g. by compiling residue data sets specific to a region or UPAFs applicable to region-specific pesticide use patterns, will increase the costs of using PRiME.

In calculating PRiME DRI values, and indeed in all PRiME indices, methods can be devised to reduce any source of systemic bias, but doing so generally increases the costs and data required to complete a given PRiME application. Sometimes, reducing one source of bias or uncertainty can create or expand another.

In constructing PRiME indices, an effort has been made to avoid systemic underestimation of risks. This does not mean that PRiME indices reflect “worst case” scenarios, nor does PRiME encompass all sources and types of risk. But for those organisms and risks that are included in PRiME, an attempt has been made to limit the chances that risks have been systematically underestimated. The DRI within PRiME is structured consistent with this overall principle.

The DRI produces a reliable relative ranking of dietary risks associated with pesticides applied to a given crop tested by the PDP. The accuracy of PRiME output for a given food-pesticide combination is constrained by the number of samples tested in the PDP, the degree to which EPA toxicological datasets and evaluations accurately reflect relative toxicity to humans, and variability across the country in how and when a pesticide is applied.

References

Baker, B., Benbrook, C.M., Groth, E., and K.L. Benbrook. "Pesticide residues in conventional, integrated pest management (IPM)-grown and organic foods: insights from three US data sets," *Food Additives and Contaminants*, Vol. 19, No. 5: pages 427-446, (2002).

Benbrook, C. "Simplifying the Pesticide Risk Equation: The Organic Option," State of Science Review, The Organic Center, March, 2008. Access at: http://www.organic-center.org/reportfiles/OrganicOptionReport.pdf

Centers for Disease Control, "2 to 20 years: Boys Stature-for-age and Weight-for-age percentiles," http://www.cdc.gov/growthcharts/data/set1clinical/cj41l021.pdf

Appendix A -- Peer Review Comments and Responses

This white paper was reviewed by the following independent experts. Their specific comments follow, along with a summary of revisions made and further discussion of the issues raised.

- **Daniel L. Sudakin**, MD, MPH, FACMT, FACOEM, associate professor, Oregon State University
- **Nu-may Ruby Reed**, Ph.D., D.A.B.T., staff toxicologist, California DPR
- **Andy Hart,** leader, Risk Analysis Team, The Food and Environment Research Agency

General Comments (no response):

- The DRI concept is interesting and novel.
- The fact that organophosphate insecticides typically score relatively high using the DRI is consistent with EPA dietary risk assessments and "lends some face validity to the ranking system."

Detailed Comments and Responses:

Comment 1: Appropriate bodyweight to use in DRI formula – "…given EPA's regulatory conclusions about risks to children, I think consideration should be given to either 1). Using a lower body weight to reflect risks to infants…or 2). Providing some additional rationale behind the specific decision to use 16 kilograms."

> **Response:** The reviewer's comment is correct – many EPA dietary risk assessments identify the highest risk levels (and hence lowest margins of safety) among infants that are either less than one year old, or one to three years old. This occurs, of course, only for the relatively small number of solid foods that play a significant role in the diets of children under three years old (e.g., bananas, grapes, pears, sweet peas).
>
> Nonetheless, as pointed out in the revised text, there are several reasons to choose 16 kilograms as the benchmark weight for calculating the cRfCs used within the DRI. It is worth noting that we could have used a child weighing 14 or 18 kilograms, or an adult weighing 180 kgs. All these options would produce exactly the same relative ranking of pesticide dietary risk.

Comment 2: UPAFs associated with the DRI are interesting, but need to be characterized more fully; an example would be helpful.

> **Response:** The text has been expanded to more fully explain how UPAFs could be used, and examples are given of potential applications of a UPAF in the adjustment of dietary risks.

Comment 3: Given that the DRI is based on PDP residues, and there is no information or consideration in the PDP regarding how a pesticide was applied, how can UPAFs be used to adjust residue levels?

Response: This is a key question that is now addressed fully in the text.

Comment 4: Does PDP residue data really capture the distribution of pesticide residues that consumers are exposed to?

Response: Yes, and pretty well for many foods and most pesticides. The PDP typically tests 600-750 samples of a food per year, split between domestic production and imports, and by state, in accord to shares of national consumption. The PDP protocol calls for the testing of food "as eaten," which means samples are handled essentially how consumers would prior to consumption.

The weaknesses and gaps in the PDP program, however, are well known. While the 20 foods most frequently consumed by infants and children are covered over time, many foods have never been tested by the PDP (e.g., raspberries). PRiME DRI scores will be based on the most recent PDP data available, which might be five to eight or more years old; the "newest" PDP data is always about three years old. Hence, recent changes in pesticide product labels driven by the FQPA will not be reflected in the residue data sets used to calculate most DRI values.

Consider a scenario involving a pesticide covered by a label revision in 2009 that included a doubling of the PHI to reduce dietary exposures. When calculating a DRI score in 2010 based on the most recent PDP data for that crop (say from the 2006 season), consideration should be given to establishing a UPAF reflecting the expected impact of the now-extended PHI on mean residue levels.

Pesticide use patterns in crops like apples and potatoes vary tremendously across the country and as a function of production system. Residue levels and DRI scores for fresh tomatoes, for example, vary 10-fold or more depending on where the tomatoes are grown. Pest pressure, the emergence of a new pest, and weather conditions can, and moreover do routinely trigger the need for pesticide applications that drive residues and risk up or down by a factor of 10 or more.

When PDP samples are collected in regional warehouses, the individuals collecting the samples are supposed to record where each individual sample was collected (always done), where it was packed (done most of the time), and the state in which the product was grown (done some of the time). As a result, it is sometimes possible to disaggregate the PDP dataset into state or regional datasets, allowing region or state-specific DRI values to be calculated. This step, of course, requires additional

manipulation of the PDP dataset and hence will increase analytical costs. The results will show significant regional variation in pesticide dietary risks for most crops/foods.

Another minor weakness in the PDP is that not all pesticides are tested for in each crop. Some are not analyzed because they are generally recognized as safe, i.e. sulfur and copper. Others are not tested for because of very low use rates, use patterns unlikely to result in residues in harvested crops (i.e., soil incorporated herbicides and non-systemic insecticides), and/or a lack of evidence of toxicity (e.g., insect pheromones).

Comment 5: The DRI is currently based only on chronic risks; an indicator is also needed of acute risks.

Response: Ideally, all pesticide dietary risk assessments, as well as the DRI, should encompass acute, sub-chronic, chronic, and cancer risks. No regulatory authority in the world, however, has developed a system to simultaneously consider more than one of the above four types of risks in dietary risk assessments. The standard approach is to assess each type of risk individually, and then base regulations on that class of risk that poses the greatest concern at the lowest dose.

The PRiME team has considered calculating DRIs based on acute risks, but has not done so because the EPA has not established acute Reference Doses (aRFDs) or acute Population Adjusted Doses (aPADs) for all pesticide active ingredients. In fact, there are no aRfDs or aPADs for a significant share of active ingredients.

The team has considered, and may in the future, record all acute and chronic RfDs/PADs and then select the one that is lowest for a given pesticide, or allow users to select the one they feel is most appropriate for a given application. The vast majority will remain chronic RfDs or PADs. A disadvantage of this approach is that the EPA calculates exposures differently when assessing acute or chronic risks. The PRiME DRI could mirror EPA exposure assessment policies for both acute and chronic dietary risks, producing an acute DRI and a chronic DRI, and then use the higher of the two values in PRiME output. The advantages in terms of greater accuracy and precision in relative risk estimates would have to be weighed against the computational costs. The costs would most likely be justified in crops for which PDP typically reports multiple residues in nearly all conventional samples (e.g., green beans, strawberries, spinach, peaches).

The challenge of incorporating cancer risks into the DRI and PRiME are now addressed in the text.

Comment 6: The DRI should be based on the mean of all samples tested by the PDP, not just the positive samples.

Response: One reviewer addressing this issue argues that "using only positives will mean the indicator exaggerates the chronic risk from pesticides used on small fractions of the crop, relative to pesticides used on large fractions."

The reviewer is correct in pointing out that in carrying out chronic risk assessments, regulatory bodies usually use mean residue levels counting all samples, including those with no residues. This approach is used because the goal in a chronic dietary risk assessment is to gauge average daily exposures over long periods of time.

The PRiME DRI, on the other hand, is designed to produce a relative ranking of pesticides a, b, c in terms of expected, average human dietary exposure, based on the assumption that a given acre of cropx was treated with pesticides a, b, and c. Any dietary risk index or metric should use the most robust and defensible residue and toxicology data, and strive by construction to avoid systemic bias and produce the lowest possible margins of error or uncertainty.

For reasons explained in the section "Acute versus Chronic Risks," the best measure of a pesticide's toxicity to humans that is available on all food-use pesticides is the chronic Reference Dose or Population Adjusted Dose. In calculating cRfDs and cPADs, the EPA takes into account many relatively short-term and subchronic effects, such as reproductive, liver, and immune effects. Many of these effects actually happen as a result of short-term exposures at periods of heightened vulnerability, e.g., during pregnancy or childhood. Plus, there are relatively few pesticides where the acute RfD or acute PAD is lower than the chronic RfD or PAD.

There are pros and cons associated with the use of mean residue levels among all positive samples versus the mean residue level across all samples. In PRiME a dietary risk index score is computed for each pesticide applied on a food crop. A DRI score is computed and included in PRiME ***only*** in cases where the pesticide was actually applied. But it is possible that in some regions and under some use patterns, an application of a pesticide will result in undetectable residues, despite the fact that PDP testing detected some positive samples. In such cases, the PRiME DRI will over-estimate risk. In a roughly equal number of instances for the same crop-pesticide combination, the PRiME DRI will underestimate risk, for basically the same reason – in some fields and food, residues will be higher than the mean of the positives from PDP data.

The problem with using the mean of all samples is markedly more serious. When using the mean of all samples, the residues found in the crop harvested from acres treated with a pesticide will be diluted downward by the inclusion of zero residue values for all samples of the crop that were grown on acres not treated with the pesticide. A review of high-DRI food pesticide combinations reveals many cases in which the pesticide was detected in 10% of less of samples. The two "high risk" apple-pesticide combinations were found in 1.5% and 0.7% of samples tested. If all samples were used in calculating mean residue levels, the DRI values for these two apple pesticide uses would be reduced

at 67 to 142 fold. This approach would, therefore, markedly underestimating risks for those children consuming the small percent of food with these residues.

The resulting downward bias in DRI values is the systemic and major shortcoming of this approach. A pesticide used on a small percent of acres could pose very large dietary risks, from relatively high mean residues level across all samples testing positive, but score low in the DRI because most samples were found to contain no residues. Further arguments in support of the use of the mean of the positives have been added in the White Paper.

Comment 7: Use of residue data on just raw commodities underestimates exposure and risks.

Response: For example, a DRI value based on residues in fresh apples will underestimate total risk from applications on apples, because possible residues in apple juice or sauce will not be taken into account. This point is valid, but is not a significant issue for the majority of crops. It is clear from PDP data that the vast majority of residues and risk from pesticide applications are present in, and consumed via raw food forms. With few exceptions, food processing reduces residue levels and risk by ten-fold or more; across almost all fresh food forms versus processed food forms, both DRI scores and the number and frequency of residues detected are far lower. Hence, calculating pesticide dietary risks based on residue data on raw food forms does not materially impact the validity of PRiME rankings.

Comment 8: By considering exposure and risk one commodity at a time, the DRI fails to take into account chronic exposures across multiple foods in which a pesticide might appear.

Response: Agreed, the PRiME DRI does not strive to reflect the results of cumulative dietary risk assessments across foods. Its focus is relative dietary risk from a single application of pesticide A versus pesticide B versus pesticide C, under known conditions of use. PRiME is not designed to support cumulative dietary risk calculations or judgments.

Comment 9: Several factors embedded in the DRI lead to the underestimation of risks, raising questions about how “low,” “medium” and “high risk” levels are determined.

Response: In structuring the DRI, an attempt has been made to avoid systemic bias in values, and to rely on the most defensible, robust data, recognizing that any measure will entail some degree of over estimation and under estimation. We believe the sources of over- and under estimation in the DRI are roughly equivalent across the pesticides applied to a given crop, hence reducing uncertainty and error in the relative ranking of risks. Nonetheless, the DRI, like all PRiME indicators, is a best-available approximation of relative risks and not necessarily an accurate reflection of actual risks. All the science issues plaguing quantitative risk assessment would have to be fully

resolved to assure that DRI-like relative rankings of risk are an accurate reflection of real-world risks.

Comment 10: Greater clarity is needed for users to understand which parameter values in PRiME are hardwired, and which can be modified by users, or selected from a list of options.

Response: Good suggestion; throughout this White Paper, revisions have been made to clarify whether a given value is set or subject to modification.

Comment 11: Use of the term "Reference Concentration" in the context of residues in food and dietary exposure opens the door to confusion since the term "Reference Concentration" is usually used in the context of inhalation exposure and risk.

Response: We agree that steps must be taken to avoid confusion between inhalation-based and dietary Reference Concentrations. In fact, the concept of reference concentrations is used in the estimation of other exposures and risks. We feel that the dual uses of the this term is appropriate in the case of inhalation and dietary risks, since the term refers to the same concept in both cases – the level of a toxic substance that can be present in a serving of food or the air over a period of time without over-exposing an individual of known size.

To avoid confusion, the PRiME team will be sure to clarify which Reference Concentration is being referred in each relevant section of PRiME documentation.

Comment 12: The cRfC is based on the amount of pesticide that can be in a single serving of food X, when actually it should be the amount of food X consumed in a day, recognizing that some foods are consumed on multiple occasions during a single day.

Response: Good point, agreed. The text of the White Paper has been modified to reflect this clarification.

Comment 13: Instead of using the most recent year of PDP data in estimating mean residues, the latest 3-5 years may better reflect the yearly variation in use patterns.

Response: Most crops are tested by the PDP for two consecutive years, once or twice per decade. There are usually at least three years between the time a crop drops out of the PDP and enters the program again. So, an attempt to average residues over 3-5 years of PDP data would entail including results over 10 years old for many crops. Passage of the Food Quality Protection Act in 1996 led to substantial changes in thousands of pesticide use patterns on food crops in the 2001-2006 period. These changes are reflected only in the most recent PDP data. For these reasons, attempts to average PDP data back over time are not likely to produce more accurate or robust estimates of contemporary mean residue levels.