Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Science Policy Notice

SPN2003-05

Guidance for Refining Anticipated Residue Estimates for Use in Acute Dietary Probabilistic Risk Assessment

The following document is a policy/guidance document that reflects the United States Environmental Protection Agency's (USEPA) recent dietary risk assessment science policy/guidance paper entitled, *Guidance for Refining Anticipated Residue Estimates For Use in Acute Dietary Probabilistic Risk Assessment* (June 15, 2000).

The following policy document is intended to provide guidance and information to PMRA personnel and decision-makers, and to the public. As a guidance document, the policy in this document describes the process used by PMRA scientists in dietary risk assessments. Stakeholders remain free to comment on the application of the policy to individual pesticides. The Pest Management Regulatory Agency (PMRA) will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to the Publications Coordinator at the address below.

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Executive Summary

The Pest Management Regulatory Agency (PMRA) regulates pesticides to ensure that their use does not pose unreasonable risks to human health or the environment and that exposure to pesticide residues in food is safe. In assessing risk, the Agency considers all sources of exposure (e.g., food, drinking water, incidental exposure in and around the home, school, etc.) and the inherent toxicity of the pesticide.

The PMRA is responsible for regulating the nature and amount of pesticide residues in food under the *Food and Drugs Act* (FDA) and Regulations. Section 4 (a) and (d) of the FDA authorizes the PMRA to set a maximum residue limit (MRL) under Regulation B.15.001 of the Food and Drugs Regulations (FDR), or an exemption from the requirement of an MRL under Regulation B.15.002(2) of the FDR. The PMRA performs dietary risk assessments (DRA) that include estimations of human exposure to pesticide residues in foods over a single day and lifetime exposures. Exposures are determined for general and regional populations, as well as many subpopulations (infants, children, teenagers, adults, seniors, etc.). These estimates require the use of magnitude of residue (MOR) data for imported as well as domestically grown foods, since large amounts of foods consumed in Canada are imported from foreign countries.

The purpose of this document is to provide guidance to registrants, other test sponsors, other stakeholders and PMRA personnel and on the extent and quality of pesticide residue and ancillary data needed to support the use of more refined "anticipated residues" in acute dietary probabilistic exposure assessments[1]. The document outlines the types of data that can be used to refine residue estimates for pesticides and explains when and how the PMRA may use these data. Such data can include information from cooking studies, processing studies, and market basket surveys conducted on individual produce items. In addition, such data can include information from "bridging" studies used to support the use of typical application rates or residue decline data used to support the use of typical pre-harvest intervals (PHI) in probabilistic risk assessments. This guidance also provides information on how risk mitigation activities (e.g., increasing PHIs, lowering maximum label rates) can be considered in risk assessments and used to adjust MRL levels.

The United States Environmental Protection Agency (USEPA) has taken the lead in developing science policies related to the U.S. *Food Quality Protection Act* (FQPA). Such policies play an increasingly important role in the evaluation and assessment of risks posed by pesticides, and improve the regulator's ability to make decisions that fully protect public health and sensitive subpopulations. These policies are vetted by the North American Free Trade Agreement (NAFTA) Technical Working Group on Pesticides and have been approved for adoption only after extensive consultation by scientific experts from governmental, academic and all non-governmental interested parties.

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[1] Although the guidance and examples provided in this document are specific to the refinements of acute dietary risk assessments, the principles discussed are also applicable to chronic assessments.

The PMRA has utilized, to the greatest extent possible, the policy and guidance outlined in the USEPA document, *Guidance for Refining Anticipated Residue Estimates Used in Acute Dietary Probabilistic Risk Assessment* (USEPA, 2000). Harmonization of DRA methodologies and science policies is part of the NAFTA goals within the Pesticides Technical Working Group Subcommittee and is key to our ability to do joint reviews. The consultation process utilized by the PMRA for science policy notices is outlined in a memo entitled *Memorandum to Registrants, Applicants and Agents,* (January 25, 2001), and may be obtained from the PMRA Web site at:

http://www.hc-sc.gc.ca/pmra-arla/english/pdf/fqpa/fqpa_memo-e.pdf

It should be noted that the guidance in this document is not intended to limit or restrict the type of data that may be submitted in support of risk mitigation measures, and that the PMRA will consider other data or information as long as they would provide a scientifically sound basis for determining residues at typical application rates for risk mitigation purposes.

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I. Introduction

This document is not intended to provide step-by-step instructions on conducting probabilistic dietary risk assessments, but rather to discuss how residue data and usage data are linked, outline the basic characteristics of data that can be used to refine residue estimates and explain how the PMRA would use these types of data in its dietary risk assessments. Information that can be used to refine estimates of dietary exposure and risk include (as is further discussed in the document) data from cooking studies, processing studies, and market basket surveys conducted on individual produce items. In addition, data based on the "typical" application scenarios, that may be more restrictive than maximum label conditions, may be incorporated into probabilistic risk assessments, provided supporting residue data are available, such as "bridging" studies to support the use of typical application rates, or residue decline data used to support the use of typical pre-harvest intervals (PHIs).

This guidance will also serve to provide information on how risk mitigation activities (e.g., increasing PHIs, lowering maximum label rates) can be considered in PMRA risk assessments and used to adjust MRL levels. It should be noted that the guidance in this document is not intended to limit or restrict the type of data that may be submitted in support of risk mitigation measures, and that the PMRA will consider other data or information as long as they would provide a scientifically sound basis for determining residues at typical application rates for risk mitigation purposes.

This document is specifically intended to provide additional guidance to registrants, other test sponsors, interested parties and data reviewers on the extent and quality of pesticide residue and ancillary data needed to support the use of more refined "anticipated residues" in acute dietary probabilistic exposure assessments. The principles discussed can however be readily applied to chronic exposure assessments as well. As a guidance document and not as a rule, the guidance presented here provides a starting point for PMRA risk assessments and is not binding on either the PMRA or outside parties.

This document is divided into seven sections. The first section is this introduction. Section II provides an overview of the PMRA's tiered approach to risk assessment and the value of refined anticipated residue data. Sections III, IV, V and VI provide further, more detailed information of cooking/processing studies, market basket surveys, residue degradation studies, and bridging and residue decline studies, respectively. The last section (Section VII) provides a list of references. Finally, two appendices are included. Appendix 1 provides illustrative sample statistical and other calculations for bridging studies while Appendix II provides comparable information for residue decline studies (which would also be applicable for residue degradation studies).

II. The PMRA's tiered approach and value of refined anticipated residue data

A. The PMRA's tiered approach to exposure evaluation

The PMRA has typically used a tiered approach to acute dietary risk assessment. Generally speaking, the level of resources and data needed to refine exposure estimates increase with each tier. Lower tier (Tiers 1 and 2) exposure assessments use residue levels derived from guideline crop field trial data (MRL levels) and can (for certain crops) use readily available usage information such as the percentage of the crop that has been treated (%CT) with a particular pesticide. These estimates tend to overestimate actual pesticide residues in food at the point of consumption. Generally, if dietary risks from pesticide residues in food are not of concern using lower tier exposure estimates, no further refinements are made. With aggregate and cumulative assessments it is likely that higher tier (Tiers 3 and 4) exposure estimates will be needed. These higher tier assessments may involve probabilistic techniques (i.e., Monte Carlo analyses for acute assessment), often incorporating processing factors (e.g., washing, cooking data), degradation data (for stored commodities), market basket survey information, and other information that allows the PMRA to more fully consider distributions of residue values. These tiered approaches are more fully described below and in the USEPA document, *Classification of Food Forms With Respect to Level of Blending. HED Standard Operating Procedure 99.6* (USEPA 1999d).

1. Tier 1 and Tier 2 assessments

Residue information submitted to the Agency to support registrations and determine MRLs represents maximum labelled application rates and minimum labelled PHIs. These "worst-case" conditions are used to ensure that MRLs are set at levels that encompass the highest residues that could be found. In the absence of reliable monitoring data, current procedures call for the use of these controlled field trial residue values (derived from maximum application rates and minimum PHIs) in exposure and risk assessments. Often, this is the only information that is available to the Agency for use in these assessments.

The PMRA recognizes that these residues do not necessarily reflect (in these tiers) real-world use practices nor declines in residue due to time between harvest and consumption nor typical commercial and consumer practices such as washing, peeling, cooking, etc. The Agency recognizes that using residue data from only the maximum application rate and the minimum PHI in risk assessments may overestimate the actual residue on foods for a number of reasons. Chief among these are that not all applications occur at the maximum label rate, and some crops are treated long before harvest, in effect resulting in a longer PHI.

2. Tier 3 and Tier 4 assessments

In cases where the registrant believes that the range of real-world use rates is significantly lower than maximum application rates or the range of real-world PHIs is significantly greater than the minimum label PHI, it may be advantageous to incorporate this information into probabilistic (i.e., Tier 3 and Tier 4) acute exposure and risk assessments. This information can be incorporated, however, only if reliable usage data are available for determining what percentage of the crop is treated at which rate (and/or what percentage is harvested at which PHIs). Together, residue data collected from a series of reduced-use or multi-PHI field trials and information on real-world application rates or PHIs would enable the PMRA to incorporate the residue values resulting from the entire range of application rates and/or PHIs in the exposure assessment. The PMRA emphasizes that both multi-rate and/or multi-PHI residue data specifically collected for this purpose and appropriate use-related data are recommended to implement this refinement; neither one, by itself, is sufficient. The reader is referred to a companion paper from the USEPA entitled *The Role of Use-Related Information in Pesticide Risk Assessment and Risk Management* (USEPA 1999e) for further discussion of the sources of use data and how the PMRA and USEPA employ these data in their assessments.

B. Potential anticipated residue refinements

The tiered approach described above permits a number of anticipated residue refinements to be made that may prove valuable when used to obtain better estimates of exposure for use in risk assessment. Such studies can include, for example, cooking/processing studies, bridging (or reduced use) studies, residue decline studies and residue degradation studies. Each of these studies is described to a limited degree below. Additional, detailed specifics regarding the design and conduct of these studies are provided subsequently in sections III, IV, V and VI of this document.

1. Cooking/processing studies

Cooking and other home processing information is currently incorporated into PMRA risk assessments only to the extent that this information is made available to the PMRA. If a PMRA risk assessment uses residue data generated from field trials as one component of the input file, then the effects of cooking and home preparation/processing are not typically factored into the assessment unless additional studies or information that quantifies the degree of reduction are provided by the data submitted.

Data generated as part of the U.S. Department of Agriculture's (USDA) Pesticide Data Program (PDP), on the other hand, do implicitly incorporate the effects of home preparation in that the produce sampled by PDP is prepared in the laboratory as if for consumption. This generally includes, for example washing and, when appropriate, peeling, trimming, coring or pitting, depending upon the commodity sampled. Thus, the effects of normal home preparation (except for cooking) are implicitly incorporated into the PMRA risk assessment when PDP data are used. The USDA PDP residue data is

considered pertinent to commodities consumed by Canadians since most of the foods imported into Canada are from the US.

The effects of commercial processing are included in the risk assessment by use of default processing factors included in the Dietary Exposure Evaluation Model (DEEM™) exposure and risk assessment software used by the PMRA. If information is available that indicates that a different processing factor is more appropriate, then this revised processing factor is incorporated. PMRA Guidelines specifically recommend that processing studies be performed on certain commodities (e.g., corn into corn oil, soybean into soybean meal, etc.) in which case these experimentally determined factors are incorporated into PMRA risk assessments. However, if a registrant or other data-submitter chooses to provide additional studies for other commodities for which PMRA guidelines do not recommend processing studies, this information will be used and incorporated into the dietary risk assessment.

2. Bridging studies

Data from bridging (or reduced use) studies can be used to establish a relationship among residues from field trials conducted at the maximum application scenario (e.g., maximum application rate, highest application frequency and shortest PHI) and residues expected at the range of more typical rates. This type of study is intended to "bridge" pesticide residue concentrations between maximum application rates used to determine MRLs and the range of more typical rates at which the pesticide is actually applied. Generally, bridging studies consist of one or more field trials using several different application rates. The applications should occur at the same location and at the same time. They are used to establish the relationship between application rate and resulting residue level. This information, together with use information on what fraction of the crop is treated at each rate, permits the Agency to refine its estimates of exposure by incorporating residues resulting from the full range of application rates in its probabilistic assessments. This information, together with information on what fraction of the crop is treated at what rate, could be used to produce a distribution of residue values for use in a probabilistic assessment. Bridging studies and related usage information will influence the dietary risk assessment most when there are large differences between the maximum and typical application rates, and when a large percentage of the applications occur at less than the maximum rate.

3. Residue decline studies

Similar to data from "bridging studies", residue decline data refer to data that can be used to establish a relationship between residue levels at the time of application (or at the label PHI) and residue levels at the range of typical harvest times. These studies recognize that not all crops are harvested at the labeled minimum PHI and are used to establish the relationship between the time of harvest (relative to the last pesticide application) and the level or amount of residues found on the commodity. Because pesticides degrade and dissipate at different rates over time, it cannot be assumed that this relationship is linear,

e.g., that doubling the PHI would result in half the residue. In a residue decline study, samples from a single field trial are collected at multiple PHIs and analyzed to determine rates of residue dissipation. A minimum of three intervals is recommended, although at least five are preferable. This information, together with use-related information on what fraction of the crop is harvested at each interval, would permit the Agency to refine its estimates of exposure by incorporating the full range of PHIs. This kind of information is most useful when there are large differences between the minimum labelled and typical PHIs and when these pesticidal compounds are relatively short-lived.

4. Residue degradation studies

Residue degradation is a concept that is similar to residue decline, except residue *decline* is considered to occur between pesticide application and harvest while residue *degradation* is considered to be a post-harvest process (i.e., occurring between harvest and consumer purchase). This information may be particularly useful when a substantial period of time elapses subsequent to harvest but prior to consumption if, for example, extended transportation or storage times are involved.

III. Cooking/processing studies

Cooking and processing data permit better estimates of pesticide exposure by incorporating information on actual consumer and industry food preparation practices, such as washing, peeling and various cooking methods.

The Agency recognizes that home processing (including washing, peeling, cooking, etc.) can significantly reduce exposure to pesticides. For example, potatoes would probably be cooked prior to consumption and oranges and bananas would be peeled. If information is available on how these practices affect residue levels in the consumed item, the Agency is willing to consider data that quantify these reductions. In a home processing/cooking study, residue measurements in the raw agricultural commodity are made prior to cooking/washing/peeling and again after cooking/washing/peeling. This reduction factor can then be incorporated into the risk assessment if there is additional information concerning the prevalence of these practices or if the relevant food form is reported in the USDA's Continuing Survey of Food Intakes by Individuals (CSFII) (e.g., peeled orange; raw potato vs. baked potato vs. fried potato). These U.S. consumption data are considered to accurately reflect the eating habits of Canadians and are part of the DEEM database used to calculate residue exposures from the various foods consumed.

Information on the effects of commercial food processing on pesticide residues can also be considered by the PMRA in its risk assessment process. In commercial processing studies, samples are collected from at least two points in the processing procedures (e.g., before processing/cooking, after washing, after peeling, at the end of processing, etc.) and a processing factor (typically a large reduction) is calculated. The processing practices used in the study should reflect typical commercial practices (e.g., whether the raw agricultural commodity is typically washed, peeled, cooked or otherwise treated before

canning, freezing, drying or other types of processing) and the PMRA's risk assessment should reflect how prevalent these practices are and whether these practices represent the industry as a whole or their variation by region. Ideally, for comparison purposes, residue data would be available to compare residues on commodities at various stages of processing, as they come into the plant, after washing, and after peeling or cooking.

IV. Market basket data

Market basket data are intended to characterize the difference between the level of residue that is found on commodities in the field and the residues that remain at the time of purchase by the consumer. Market basket surveys use statistically defined sampling procedures designed to produce residue data that can be directly used in a probabilistic assessment. Generally, samples are collected at the point of sale to the consumer (e.g., supermarkets or convenience stores).

Samples may be prepared for consumption (e.g., peeled or washed) and generally follow the USDA's PDP sample preparation protocol (see the USDA web site: http://www.ams.usda.gov/science/pdp/Labop03.pdf for the preparation protocol for a variety of fruits, vegetables, and grains). These types of data are particularly useful in characterizing the actual residues on commodities that are typically consumed fresh as a single serving, for example, apples, oranges and tomatoes.

V. Residue degradation studies

Similar to residue decline studies (see below), residue degradation studies seek to improve the PMRA's assessment of exposures. The PMRA recognizes, for example, that some crops such as apples and potatoes can be typically stored for relatively long periods of time after harvest and before purchase by the consumer. Other items (e.g., tomatoes and bananas) may be typically picked green for ease of transport; of necessity, many days can, therefore, pass between harvest and consumption. Residue degradation studies are designed to characterize the decreasing amounts of pesticide residues over time on commodities *during storage or transportation* (in contrast to residue decline studies that seek to characterize the decreasing concentration of residues between pesticide application and harvest); residue degradation studies incorporate aspects of both residue decline and processing studies. In a residue degradation study, samples are collected before storage or transportation begins and at different points in the "process" that correspond to times that consumers may purchase the food.

VI. Bridging and residue decline studies

Bridging and residue decline data can be useful in that they permit the PMRA to incorporate a range of residues resulting from various application rates or PHIs that are used in actual practice. This section discusses some of the specific issues that are associated with these studies. The PMRA notes, importantly, that this information is

valuable and can be used only when PDP or other monitoring data (USDA Agricultural Research Service, USFDA, and/or the Canadian Food Inspection Agency (CFIA) and Agriculture and Agri-Food Canada (AAFC)) are not available. If PDP or other monitoring data are available, this monitoring information will generally supercede data resulting from bridging or residue decline studies.

A. Purpose, recommended location, and number of field trials

For bridging (or reduced-use) studies, side-by-side field trials should be designed to compare residues resulting from maximum label conditions (i.e., those conditions used to derive an MRL) to the range of more typical application rates. Similarly, residue decline studies should be designed to compare residues resulting from harvest at the minimum label PHI (i.e., those conditions used to derive an MRL) to the range of more typical PHI. Generally, such comparative data should be obtained from between one and three field trials depending on the number of recommended field trials established in the Residue Chemistry Guidelines—see Tables in the PMRA's *Residue Chemistry Guidelines*, DIR98-02, for this and other basic information on the conduct of field trials (PMRA 1998).

Specifically, the minimum number of field trials recommended for the residue decline studies is as follows:

Number of residue field trials recommended by the PMRA's guidelines for MRL-setting purposes	**Recommended minimum number and location of sites for side-by-side field trials to establish bridging or residue decline data**	
	Recommended number	**Recommended region(s)**
more than 12 trials	3 sites	1 in region with largest production of the commodity 1 in region with second largest production 1 in region in which largest HAFT was found[1]
6 to 12 trials	2 sites	1 in region with largest production of the commodity 1 in region in which largest HAFT was found[2]
3 to 5 trials	1 site	1 in region with largest production of the commodity

[1] HAFT refers to the highest average field trial. If no HAFT has previously been determined (as, for example, with a new chemical or new use of an old chemical), this trial should instead be performed in the region with the largest production.

[2] If this coincides with the region with the largest production or no HAFT has been determined (e.g., for a new chemical or new use of an old chemical), this trial should instead be performed in the region with the second largest production.

Data establishing relationships between residues and application rates or PHIs should be derived from field trials conducted at the same site and at the same time because of the potential impact of environmental conditions and variability in study conduct on results. Therefore, only data from controlled field trials specifically designed and collected to monitor the effects of application rate or PHI on residues can generally be used. As an

example, it would generally NOT be appropriate to attempt to derive a relationship between application rate and resulting residues if data from one application rate were obtained from a field trial conducted in Ontario in 1992 and residues at another application rate were obtained from field trials conducted at the same location or elsewhere three years later. Similarly, it would generally NOT be appropriate to attempt to derive a relationship between PHI and resulting residues if data from different PHIs were obtained from field trials conducted at different locations or at different times. In all cases, data provided should include weather and precipitation records to enhance the evaluation of a study and its results.

B. Number of application rates or PHIs to be tested

1. Bridging studies

Since the purpose of the bridging (reduced-use) field trials is to compare (or "bridge") the residues resulting from the maximum application rate to those representing typical rate(s), one application rate in each field trial should be at the maximum label rate (i.e., that rate used to establish the MRL); residues at other rates will be compared to residues at this maximum rate to establish the relationship between application rate and resulting expected residue concentrations. At least two other (preferably lower) application rates should be selected (for a total of at least three rates) so that a relationship between application rate and residue level can be calculated and used. The registrant or other sponsor should ideally include in its field trials the maximum label rate, the minimum label rate, and at least one additional intermediate rate (preferably a "typical" rate or a rate mid-way between the maximum and minimum rates).

In some cases, when studies are to be conducted to determine the relationship between application rate and residue level, it may be preferable (particularly if less than limit of quantification (LOQ) residues are expected) for the registrant or other sponsor to use exaggerated rates in its bridging studies in an attempt to calculate a relationship between application rate and resulting residue level. For example, if minimal residues are expected at the maximum label rate, it may be advisable that the bridging study application rates consist of the full (1×) rate in addition to two other (exaggerated) rates (e.g., 2× and 3×) to ensure that quantifiable residues result.

2. Residue decline studies

Since the purpose of the residue decline trials is to develop a relationship between residue concentration and time, the data submitter should submit a sufficient number of residue measurements such that this relationship can be established over the time period of interest (i.e., the range of typical PHIs). Generally, this would involve measuring residues at at least three time intervals with five generally recommended. These times should be selected such that more residue measurements are made in the time period of the steepest residue declines such that a reliable relationship can be established.

In some cases when studies are to be conducted to determine the relationship between the time of harvest and residue level, it may be preferable (particularly if less than LOQ residues are expected) for the registrant or other sponsor to collect samples prior to the labeled PHI (especially if the decline curve is steep and residues at the PHI and beyond are not clearly in the range of reliable quantification). For example, if minimal residues are expected at the PHI, it may be advisable that the residue decline studies collect samples at time periods both before and following the label PHI to ensure that measurable residues are found and that quantifiable residues result.

C. Recommended sampling protocol

1. Number of composite samples to collect at each application rate or PHI

For each of the bridging study trials conducted, at least three independent samples should be obtained at each application rate. For example, if reduced use field trials are being conducted with three potential application rates (e.g., ½×, ¾×, and 1× (maximum label-permitted rate)), a total of at least nine composite samples (three at each rate) should be collected. Similarly, for each of the residue decline field trials, at least three composite samples should be obtained at each PHI, with samples collected at a minimum of three intervals (with at least five preferable).

For example, if residue decline field trials are being conducted with five potential PHIs (e.g., one, two, three, five and seven days), a total of at least fifteen composite samples (three at each PHI) should be collected at each trial. In addition, for both bridging study and residue decline field trials, control samples should be collected prior to any application of pesticide.

Furthermore, the test sponsor should demonstrate that reduced rates or increased PHIs result in quantitatively reduced residue levels and that the postulated mechanistic structure (e.g., a linear relationship between rate and residue level in the case of a bridging study or a first order decay in residue level with time in a residue decline study) is an adequate representation of reality. The purpose of this effort is to ensure, prior to using probabilistic techniques to refine exposure estimates, that differing application rates or PHIs do result in differing residue levels and that it is appropriate (for example) to postulate that either a linear relationship between application rate and residue level exists or that a residue decay is first-order with time. The Agency believes that if lower application rates or increased PHIs are not demonstrated to result in lower residue levels in crops, then incorporation of any purported resulting lower residues in a probabilistic assessment is not appropriate.

The consequence of this policy is as follows: the registrant or other test sponsor should ensure that a sufficient number of field trial samples are collected at each application rate or PHI, that the analytical method is sufficiently specific and precise, and that the results are sufficiently consistent such that the residue data generated by this exercise can be used in a Monte Carlo assessment. There is little point in conducting reduced-use or

residue decline field trials (for insertion into a probabilistic assessment) unless sufficient analytical data and sample collection resources are provided to demonstrate that reduced use rates or longer PHIs do result in quantitatively reduced residues. An illustration of the determination of the relationship between application rate or PHI and the resulting residue level is provided in Appendices I and II for bridging and residue decline data, respectively. It is this relationship that will be used to adjust the 1× residue levels (as determined in the MRL-setting field trials) to more typical actual application rates or the residues at the label minimum PHI to residues typical of the range of longer PHIs.

2. Single-serving vs. composite sampling

It is important that the bridging (reduced-use) study or residue decline field trials be directly comparable to the trials used to establish MRLs as it is this relationship that will be used to "adjust" the measured residues from the field trials used to establish MRLs. Thus, the sample sizes collected during the reduced-use field trials should be the same as those collected during the trials used to establish MRLs. Ordinarily, this means that the sample sizes should be the same as those indicated in the PMRA's Residue Chemistry Guidelines relating to conduct of field trials (see *Residue Chemistry Guidelines*, Section 9, Crop Field Trials).

Nevertheless, while the PMRA would prefer that *composite* samples be collected as part of reduced-use or residue decline field trials to retain comparability with earlier maximum rate/minimum PHI field trials conducted to support MRL decisions, the PMRA still has concerns (shared by the USEPA OPP, the UK's Department for Environment, Food and Rural Affairs (DEFRA), and WHO/FAO) about the effect compositing may have on variation in the measured units. When residue estimates are generated from maximum application rates and minimum PHIs (worst-case conditions), the PMRA believes that there is an adequate degree of compensating overestimation such that individual unit variation is not of concern. That is, due to the fact that composite field trial data do not take into account residue reduction due to home processing, cooking, and residue degradation during transportation/storage or the fact that few farmers apply at the maximum rate or minimum PHI, *composite* sample residues from field trials were viewed as adequate for assessing potential *single serving* residues for acute dietary analyses.

By incorporating the range of application rates and PHIs in a probabilistic scenario, the conservatism built into the use of worst-case field trial data is eroded and the PMRA may decide to compensate for this with statistically valid data on individual samples and/or unit-to-unit variation. That is, the methods described in this paper necessitate the use of composite samples to "adjust" the residues found in the original field trials conducted to establish the MRL. However, if the adjustment factors obtained from the bridging or residue decline studies are incorporated into the risk assessment, the PMRA would be concerned about the use of composite samples that potentially underestimate high-end residues in single-serving samples.

To account for and consider this in the risk assessment, the PMRA will thus evaluate chemical-specific considerations to determine whether the use of composite data from bridging or residue decline field trials is acceptable. This will include consideration of the systemic nature of the pesticide, application type and timing, and the stability of the pesticide (especially post-harvest and during precessing or cooking), as these factors influence the likelihood that data on composited samples at harvest may underestimate residues in single-serving sized samples at the time of consumption.

If examination of these and other factors leads the PMRA to determine that composited samples from reduced-rate field trials may underestimate risks to one or more subgroups, then other options would be pursued. These could include use of a "decompositing" procedure that would attempt to simulate single-serving samples. As indicated previously, the USDA PDP provides data that assists in adequately describing the relationship between residues in single-serving vs. composited samples. Alternatively, these could include: performing a single-serving sized Tier 4 market basket survey, reverting to an exposure assessment based only on maximum label conditions, or calculation of worst-case residues in a single-serving sized component by assuming all residues of the composite sample can be attributed to a component single-serving sized sample. If a registrant or other test sponsor has concerns about this issue, it may be beneficial for them to incorporate an investigation of composite vs. single-serving variability in their reduced-use field trials. Guidance for the conduct of such a study (which may be run as part of the reduced use field trials) can be provided.

The Agency recommends that registrants who wish to perform bridging or residue decline studies for use in acute dietary probabilistic assessments contact the Agency prior to initiation of these studies to ensure that the use of composite samples will not substantially underestimate residues in single-serving samples. The PMRA anticipates that for many non-systemic, surface-type residues that decay rapidly, composite samples from residue decline studies will be acceptable.

D. Generation of adjusted data for incorporation into the probabilistic analysis

For bridging field trials, once a determination is made that it is appropriate to adjust residue levels from maximum rate/minimum PHI field trials with information obtained from reduced-rate field trials, it becomes necessary to incorporate these data into a Monte Carlo analysis. The first step of this incorporation is to adjust the field trial data that would have been developed earlier for MRL-setting purposes to residues that would have been found had lower application rates been used. A key consideration is that the *variability* inherent in the multitude of MRL field trials be *retained* while at the same time the data are *adjusted* to account for lower application rates. This is best illustrated with the example provided in Appendix I. Here, a regression equation is developed from the reduced rate field trials and used to establish a relationship between relative residue and relative application rate. This equation is then used to adjust the original (MRL-determining) field trial residues.

Similarly for residue decline field trials, it is necessary to incorporate these residue decline data into a probabilistic analysis such that residue levels from maximum rate/minimum PHI field trials is adjusted using information obtained from the specially conducted residue decline field trials. Briefly, this involves mathematically adjusting (or normalizing) the residues found in the original field trials performed for MRL-setting purposes to appropriately account for residue decline with time and using the time-adjusted residue values in the appropriate proportions in the exposure and risk assessment. This is best illustrated with the example provided in Appendix II.

E. Incorporation of adjusted data into a probabilistic analysis

Once the field trial data have been adjusted to incorporate either the use of lower application rates (in the case of bridging studies) or the use of longer-than-label PHIs (in the case of residue decline studies), it is necessary that these residues be inserted into the probabilistic analyses such that the probabilistic analyses select these values in the appropriate proportions. This is illustrated in Appendices I and II, where the actual input values for the Monte Carlo analyses are derived for the case of bridging studies and residue decline studies, respectively.

F. Additional information

1. Incorporation of "less than limit of quantification" values into a regression relationship

In some instances, test sponsors may find that residues are "not detected" or, alternatively, are detected but at levels that are less than the LOQ. The question arises, then, if these values should be incorporated into the regression relationship and if so, in what manner. Ideally, the PMRA believes that only quantitative residue measurements should be used to establish a quantitative relationship between the application rate (or PHI) and the resulting residue concentration. Therefore, the sponsor should ensure, through proper selection of application rates (including exaggerated rates) and/or postapplication sampling times, that quantitatively measurable residues will result during these field trials. The sponsor is not limited to using the enforcement analytical methods, and the use of more specific and sensitive analytical methods, if available, is encouraged. Due to significant quantitative uncertainties, the PMRA will generally not incorporate less than LOQ measurements into its regression analyses (but see below).

Ordinarily (for residue decline field trials), this will mean repeated frequent sampling during the time period immediately following application (e.g., one, two, three, five and seven days) and less (if any) sampling during the later time periods. In many cases, this will mean that initial sampling will have to occur at time points prior to the label-specified minimum PHI (but note that these concentrations will only be used to establish a decay rate and will generally not be used directly as part of the risk assessment).

In the case of bridging studies, it may in some cases be useful to conduct the field trials at an exaggerated rate (e.g., 2×) such that all residue measurements will be at greater than LOQ levels and can be used in the regression analysis. Application rates, however, should not be excessively exaggerated (e.g., no more than 5×) since doing so may fundamentally alter decay parameters and processes and this should not be used to compensate for a generally inadequate analytical method.

This limitation is not expected to present a serious impediment to widespread use of the method: if non-quantitative residues are found at a 5× exaggerated rate then the risk assessment would generally be conducted by assuming residues are present at 1/10 the LOQ and it is unlikely that the tested commodities would be a significant risk driver or that a data submitter would have found it necessary to conduct bridging or residue decline field trials in the first place. Again, the residue values obtained from any shorter-than-label-PHI or exaggerated rate level will generally not be used directly in the risk assessment, but will only be used to establish the appropriate decay parameters or proportionate application rate factors.

The purpose of the policy guidance recommendation that measurements below the LOQ not be used in quantitative regression analysis in determining the effect application rate (or PHI) has on residue levels is to encourage the use of exaggerated rates, such that residue measurements can be adequately quantified. The PMRA will nevertheless consider and evaluate the data generated from field trials in which below detection limit (BDL) or below quantification limit (BQL) measurements are obtained. As always, the PMRA reviewer can use his or her judgement and conclude that incorporation of BQL or BDL measurements into quantitative estimates of this relationship is appropriate, depending on the specifics of the case. In these situations, the PMRA will probably investigate the robustness of the regression analysis by performing a sensitivity analysis of the regression relationship. That is, the sensitivity of the final estimated relationship to assumptions regarding the value associated with the BQL or BDL can be assessed to determine if incorporation of BQL or BDL measurement might significantly affect the outcome of the study or assessment.[2]

The PMRA, however, believes that the concern about a potential preponderance of BQL or BDL values when field trials are conducted at 1× and lower rates is misplaced. BDL and BQL values generally do not significantly affect PMRA dietary risk estimates and it is doubtful that bridging or residue decline studies would be conducted on crops for which BQL or BDL residues are expected.

[2] In any case, if it is determined that it is appropriate to incorporate BQL limits into a quantitative regression relationship, then it is important that the actual estimated value (and not a default value of one-half LOQ) be incorporated.

2. Extrapolation of results between similar crops

Extrapolation of data between similar crops may be allowed on a case-by-case basis, considering similar cultural practices and application patterns. At a minimum, the PMRA would expect that the crop grouping system used in establishing MRLs (Section 15, *Residue Chemistry Guidelines*) would be extended to bridging/residue decline studies. That is, studies conducted on three representative crops (as listed in the RCGs, Section 15) within a crop group could be readily extended to the entire crop group.[3]

3. Use of multiple linear regression techniques in the simultaneous adjustment of rate and residue decline data

The PMRA recognizes that in some cases it may be advantageous to simultaneously adjust maximum rate/minimum PHI field trial values for both typical lower-than-label application rates and typical longer-than-label PHIs. In these instances, the test sponsor should consider performing field trials in which both application rate and residue decline information is *simultaneously* collected. This information on both the effects of application rate and residue decline with time can then be combined and analyzed using multiple linear regression techniques and could be used to adjust the original field trial data for any combination of use rate and PHI. In fact, this information could also be used to mathematically "test out" a variety of rate–PHI combinations to determine which combinations are most advantageous in terms of minimizing risk (or maximizing risk reduction) consistent with prudent agricultural practices. Thus, from a resource standpoint, sponsors may want to consider performing field trials in which both application rate and PHI are varied simultaneously and use multiple linear regression to determine bridging factors (for application rate) and residue decline factors (for PHI).

4. Field trial requirements for pesticides with various chemical and/or physical forms

As noted in the RCGs (Section 9) the relationship between residue level and application rate may vary among chemical forms of the active ingredient (e.g., the acid, salt, and ester chemical forms of a given pesticide). A representative of each major chemical form of the active ingredient should be compared for several representative crops to determine if there is an effect of chemical form on the relationship between application rate and residue level. The relationship may also vary among formulation classes (and other aspects of the use pattern associated with the application of these formulations), for example, emulsifiable concentrates (EC), wettable powders (WP), granulars (G), dusts (D), or microencapsulated (Mcap) formulations. The PMRA has divided these into

[3] As additional data from these bridging/residue decline trials are provided to and analyzed by the PMRA and the PMRA is able to further investigate the putative similarities and differences that exist among and between crop groups, more guidance on extrapolation to additional crop groups or classifications may be possible.

groups of formulation classes based on potential differences in the residue/rate relationship:

- Solid formulations not diluted (e.g., D or G);
- Formulations diluted with water (e.g., WP or EC);
- Formulations diluted with oil/organic solvents (e.g., EC or invert emulsions);
- Microencapsulates or time-release granules.

The residue decline trials should be conducted in separate locations, as described in this document, for a major chemical or physical form in each formulation class group listed above. The Agency will consider arguments for lesser numbers of trials depending on market share. If any registrant or interested party is uncertain about translating residue data from one formulation to another, these concerns should be raised with the Agency prior to initiation of field trials.

List of abbreviations

AAFC	Agriculture and Agri-food Canada
a.i.	active ingredient
BC	British Columbia
BDL	below detection limit
BQL	below quantification limit
CFIA	Canadian Food Inspection Agency
CFR	Code of Federal Regulations
CSFII	Continuing Survey of Food Intakes by Individuals (USDA)
D	dust
DEEM™	Dietary Exposure Evaluation Model
DEFRA	Department for Environment, Food and Rural Affairs
DRA	dietary risk assessment
EC	emulsifiable concentrates
FAO	Food and Agriculture Organization
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
FDR	Food and Drug Regulations
FDA	*Food and Drugs Act*
FR	Federal Register
FQPA	*Food Quality Protection Act* (1996)
G	granulars
ha	hectare
HAFT	highest average field trial
HED	Health Effects Division (Office of Pesticide Programs)
kg	kilogram
LOD	limit of detection
LOQ	limit of quantification
Mcap	microencapsulated
MOR	magnitude of residue
MRL	maximum residue limit
NAFTA	North American Free Trade Agreement
ON	Ontario
OPP	Office of Pesticide Programs (USEPA)
OPPTS	Office of Prevention, Pesticides, and Toxic Substances (USEPA)
PDP	Pesticide Data Program (USDA)
PHI	pre-harvest interval
PMRA	Pest Management Regulatory Agency
RCG	*Residue Chemistry Guidelines*
SAP	Scientific Advisory Panel (FIFRA)
SOP	Standard Operating Procedure
UK	United Kingdom
USDA	United States Department of Agriculture
USEPA	United States Environmental Protection Agency
USFDA	United States Food and Drug Agency
WHO	World Health Organization

WP	wettable powders
%CT	percent of crop treated

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USEPA 1999e. *The Role of Use-Related Information in Pesticide Risk Assessment and Risk Management*; draft document. June 29, 1999.
http://www.epa.gov/fedrgstr/EPA-PEST/1999/July/Day-14/p17318.htm (64 FR 37977).

Appendix I Example analysis of bridging data and generation of appropriately weighted input residue file for probabilistic analysis

Introduction

In an attempt to refine residue estimates as part of a probabilistic assessment, a registrant has conducted two reduced-use field trials with bell peppers. One side-by-side crop trial was conducted in British Columbia (BC) while the other was conducted in Ontario (ON). The label permits application rates from 1.0 to 2.0 kg a.i./ha applied three days prior to harvest. Each of the two reduced-use field trials were conducted at 2.0 kg a.i./ha, 1.5 kg a.i./ha, and 1.0 kg a.i./ha (these represent relative application rates of 1.0×, 0.75×, and 0.5×, respectively) with three composite samples (24 individual items per composite) collected at each rate from each trial (with a three-day pre-harvest interval or PHI). A total of 18 composite samples were analyzed.

Data obtained by the PMRA indicate that 25% of the Canadian bell pepper crop is treated with the pesticide of interest. Of the bell pepper crop that is treated, 20% is treated at the 1.0 kg a.i./ha rate, 50% is treated at the 1.5 kg a.i./ha rate, and 30% is treated at the 2.0 kg a.i./ha rate.

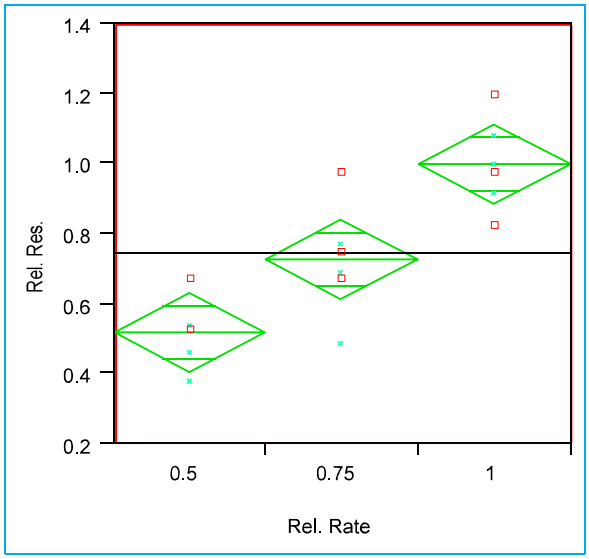
The results from the registrant's two reduced-use field trials are as follows:

Rate (kg a.i./ha)	Residue Level (ppm)
British Columbia	
2	0.2, 1.4, 1.3
1.5	0.9, 1.0, 0.7
1	0.6, 0.7, 0.6
Ontario	
2	1.1, 1.3, 1.6
1.5	0.9, 1.0, 1.3
1	0.6, 0.7, 0.9

Step 1

Given the results of the field trials presented in above, the PMRA would conduct exploratory data analyses to ensure that there are not systematic differences between the residue results from each of the two locations. This would include tests for homogeneity of variance to verify that the assumptions for linear regression are satisfied[4].

A plot of relative application rate vs. relative residue level is shown to the right. Specifically, the relative residue level (i.e., residue concentration at any given application rate divided by the average residue at that trial's 1× rate) is plotted against relative application rate (i.e., the application rate divided by the maximum application rate). We would note that there is no indication of *systematic differences* between residues generated in the BC trials and residues generated in the ON trials (as indicated by Xs and boxes, respectively)[5]. We note that there appears to be a trend (as expected) toward increasing residues with increasing application rate.



4 Prior to performing any linear regression to develop a quantitative relationship between relative residue and relative application rate, it would be necessary to verify that the variances do not differ significantly among treatment rates and trials (i.e., to test for homogeneity of variance). Although not specifically illustrated here, Bartlett's and Levine's test for determining homogeneity of variance are among several tests that can be performed. These are more fully described in the USEPA's publication *Guidance for Data Quality Assessments: Practical Methods for Data Analysis* (USEPA 1998). This determination is a prerequisite to performing a valid linear regression (i.e., linear regression assumes that variances are equal).

5 If the rate of residue increase is significantly impacted by location, then alternatives could include use of the smaller slope for all locations or use of each regional-specific relationship in a proportion appropriate for the percent of the crop that is produced there.

Step 2

Given the results of the field trials presented in the introduction and the results of the preliminary analyses in STEPS 1 and 2, the PMRA would verify that data from the reduced-use field trial studies can be legitimately combined. This would be done by conducting a linear regression and analysis of variance (ANOVA) with the following equation:

$$C_{rel} = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2 + \varepsilon$$

where C_{rel} is the relative pesticide concentration (compared to the 1× rate) β_o is the y-intercept, β_1 is the slope (and represents the increase in the relative concentration given an increase in the relative application), β_2 is the coefficient of the indicator variable "STATE" (a 0-1 variable signifying location—either BC (0) or ON (1)), β_3 is the coefficient for the interaction term, and ϵ is the error term. The linear regression results for the sample data are shown in the "Analysis of Variance" and "Parameter Estimates" blocks to the right.

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	3	0.72037222	0.240124	16.5490
Error	14	0.20313889	0.014510	Prob>F
C Total	17	0.92351111		<.0001

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	0.1116667	0.152896	0.73	0.4772
Rel. Rate	0.9	0.196706	4.58	0.0004
STATE	-0.163889	0.216227	-0.76	0.4611
Rel. Rat*STATE	0.1266667	0.278184	0.46	0.6559

To determine if the two regressions differ, the null hypothesis that $\beta_2=\beta_3=0$ is tested against the alternative that β_2 and β_3 are not both equal to 0. This is appropriately performed by using the *partial F test.* The calculation is as follows:

$$F^* = \frac{0.0213 + 0.00301}{2} \div \frac{0.2031}{18-4} = 0.838$$

To control alpha at 0.05 (for example), we require F (0.95,2,14) = 3.7. Since F = 3.7 > F* = 0.838, there is no reason to conclude that the two regression functions are different (this can also be done with a Sequential (Type 1) test shown in the box labeled "Sequential (Type 1) Tests" below. This analysis indicates that relative residues **do** increase with increasing application rate, but that the relative rate of residue increase is **not** significantly impacted by the

Sequential (Type 1) Tests

Source	Nparm	DF	Seq SS	F Ratio	Prob>F
Rel. Rate	1	1	0.69600833	47.9678	<.0001
STATE	1	1	0.02135556	1.4718	0.2451
Rel. Rate*STATE	1	1	0.00300833	0.2073	0.6559

location.[6] Thus, the regression analysis can be performed legitimately after removing the location (β_2) and interaction (β_3) terms and, in effect, adopting a single (uniform) value for the relative rate of increase in residue concentration.

Step 3

In STEP 2, it was found that the location and interaction terms (β_2 and β_3 in the regression equation) were not significant and could be eliminated from the regression equation. Given this result, the regression equation would be re-written as follows:

$$C_{rel} = \beta_0 + \beta_1 X_1 + \varepsilon$$

Summary of Fit

RSquare	0.753655
RSquare Adj	0.738258
Root Mean Square Error	0.119243
Mean of Response	0.752222
Observations (or Sum Wgts)	18

Note from the "Parameter Estimates" block for this new regression formula that the "t-ratio" for Rel Rate (β_1) is significant ($p<0.0001$) which confirms that residues do increase with increasing relative application rate. Importantly, the parameter estimate for Rel. Rate (β_1) is 0.9633. This is the estimate for the relative increase in residue that will later be used to adjust the residues obtained from the field trial data. From the F-ratio of 0.1781 in the "Lack of Fit" block ($p=0.6790$), there is no reason to conclude that the linear model does not adequately describe the data.

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	0.0297222	0.107024	0.28	0.7848
Rel. Rate	0.9633333	0.13769	7.00	<.0001

Lack of Fit

Source	DF	Sum of Squares	Mean Square	F Ratio
Lack of Fit	1	0.00266944	0.002669	0.1781
Pure Error	15	0.22483333	0.014989	Prob>F
Total Error	16	0.22750278		0.6790
				Max RSq
				0.7565

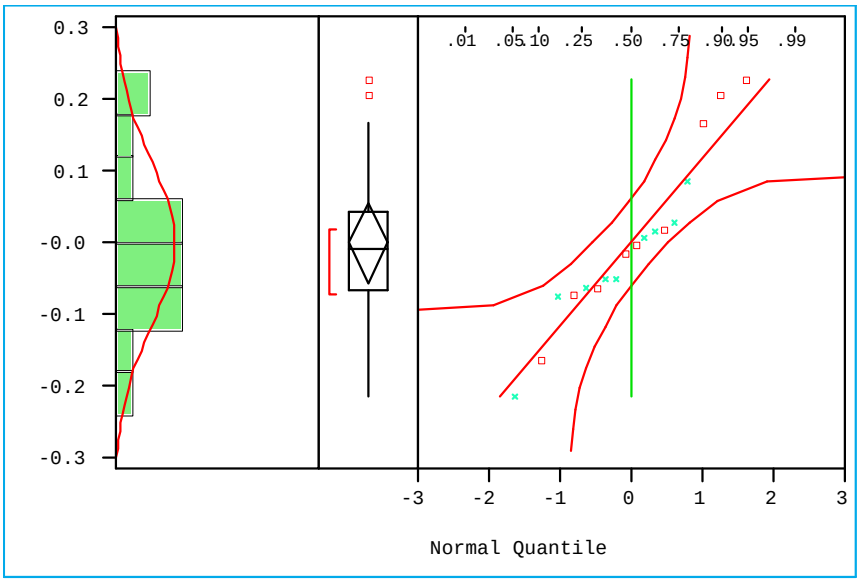
At this point, the PMRA would examine graphical plots of the residuals against either the fitted values or the application rate predictor variable to confirm that no patterns were evident. The PMRA would also produce a normal plot and a box plot of the residuals to verify that the residuals had an approximately normal distribution (see Figure A.1.1). All of these plots should support the appropriateness of the regression model for the data.

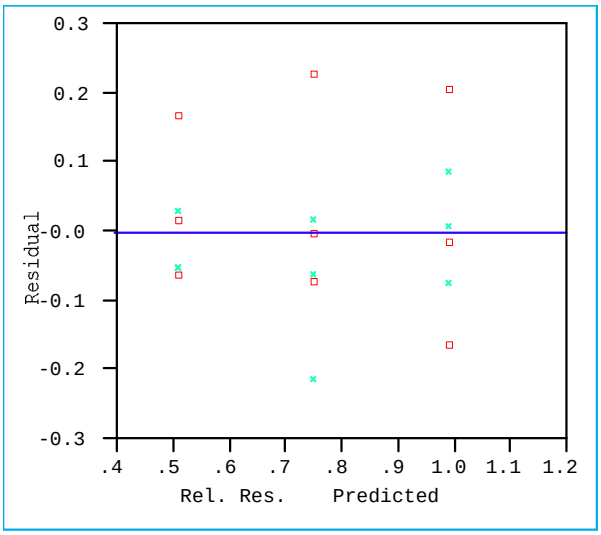
[6] Again, if the rate of residue increase is significantly impacted by location, then alternatives could include use of the smaller slope for all locations or use of each regional-specific relationship in a proportion appropriate for the percentage of crop that is produced there.

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	0.69600833	0.696008	48.9494
Error	16	0.22750278	0.014219	Prob>F
C Total	17	0.92351111		<.0001

Note that if the t-ratio for Rel. Rate from the "Parameter Estimates" block (or in this case the equivalent F-ratio from the "Analysis of Variance" Block) was not significant, the PMRA could conclude that there is no statistically significant relationship between relative residue level and application rate. In this situation, the residue data provided by this study might *not* be used and the probabilistic analysis conducted by the PMRA could revert to using the residue data obtained from the maximum rate and minimum PHI bell pepper field trials originally developed to establish the MRL. Information on "typical" application rates might not be quantitatively incorporated. A similar conclusion could be reached if the F-ratio in the "Lack of Fit" block was significant: in this case, the PMRA could conclude from these data that there was sufficient evidence against the hypothesis of a linear relationship between application rate and residue level and that it would be inappropriate to incorporate this information into a probabilistic analysis, and alternative means of analysis should be pursued.





Test for Normality

Shapiro-Wilk W Test

W	Prob<W
0.937965	0.2719

Figure A.1.1 Graphical plots of bridging study data analysis

Step 4

Initially, a total of five maximum rate/minimum PHI field trials was performed to establish MRLs; during these trials, a total of 10 composite bell pepper samples (i.e., two per trial) was collected and analyzed[7]. As per PMRA guidelines (RCGs), the trials were conducted in the appropriate geographic regions and in the appropriate numbers such that they are adequately representative of national production. The results were as follows:

Trial	Residue Level (ppm)
1	1.8,1.4
2	0.8,1.2
3	1.8,1.6
4	1.4,1.5
5	1.4,1.8

As a result of the newly submitted reduced-use field trials, the Agency has determined (see "Parameter Estimates" block in STEP 3) that the appropriate relationship between relative residue levels and relative application rate is as follows:

$$C_{rel} = 0.030 + 0.963 \; x \; relative \; application \; rate + \varepsilon$$

This is the relationship that would be used to adjust the results from the ten composite samples from the five maximum rate/minimum PHI field trials conducted earlier to establish MRLs (and listed above) to the results that would be expected to occur at the range of more typical application rates. As an example, if one of the maximum rate/minimum PHI residue values from a 1× application rate of 2 kg a.i./ha was 1.8 ppm (as in Trial 1 above), this value would be adjusted to a 1.5 kg a.i./ha (0.75×) rate by multiplying the 1.8 ppm value by 0.963 × 0.75 and adding 0.030. This would produce an adjusted residue value of 1.33 ppm. Each of the ten maximum rate/minimum PHI 1× values would be adjusted in this manner to yield a collection of ten residue values appropriate for a 0.75× rate. A similar operation would be used to adjust the same ten maximum rate residue values to a 0.5× (or 1.0 kg a.i./ha rate (which in the case of the 1.8 ppm value would produce an adjusted residue level of 0.90 ppm). In this manner, the PMRA would develop from the 10 composite samples originally collected for MRL-setting purposes, a series of ten comparable residue values that would reflect expected residues at a 0.75× rate as

[7] This is provided for demonstrative purposes only. PMRA Guidelines (RCGs) actually recommend eight crop field trials for bell peppers and a minimum of 16 samples; therefore it is unlikely that 10 composite bell pepper samples from five field trials would be adequate for use in a probabilistic risk assessment. The five field trials cited here are for illustrative purposes only.

well as a series of ten residue values reflective of expected residues at the 0.5× rate. These are illustrated below for the sample data:

Trial	Residue levels (ppm)	Adjusted residue levels (ppm)	
	1×	0.75×	0.5×
1	1.8, 1.4	1.33, 1.04	0.90, 0.70
2	0.8, 1.2	0.60, 0.89	0.41, 0.60
3	1.8, 1.6	1.33, 1.18	0.89, 0.80
4	1.4, 1.5	1.04, 1.11	0.70, 0.75
5	1.4, 1.8	1.04, 1.33	0.70, 0.89

Using the series of adjusted residue values that correspond to those application rates for which use data exist, it now becomes necessary to insert these values *(in the appropriate proportions*) into a probabilistic assessment. It is critical, for example, that if only 6% of the crop is treated at the maximum rate, that there only be a 6% probability of selecting a residue value that reflects this rate.

The Agency has determined from available use data that only 25% of the bell pepper crop is treated with the pesticide of interest (as originally stated in the introductory section to this example). Of those bell peppers that are treated, 20% are treated at the 1.0 kg a.i./ha rate, 50% are treated at the 1.5 kg a.i./ha rate, and 30% are treated at the 2.0 kg a.i./ha rate (these represent the 0.5×, 0.75×, and 1× rates, respectively). Thus, the maximum rate/minimum PHI field trial data conducted earlier for MRL-setting purposes will be adjusted to account for the lower residue levels (*as determined in STEP 3 and repeated in STEP 4*) in the appropriate proportions (*as determined by percent crop treated and treatment rate data presented in the introductory section to this example*). Given this information, 20%, 50%, and 30% of the treated commodity input file to any Monte Carlo analysis would be required to contain data representative of the 1-, 1.5-, and 2- kg a.i./ha treatment rates, respectively. In addition, the Monte Carlo file should be constructed such that there is only a 25% probability of selecting a treated commodity (and thus a 75% probability of selecting an untreated commodity with consequent residue levels of zero).

To do this, the ten original residue values representing the 1× rate from the maximum rate/minimum PHI MRL field trials would each be entered into the Monte Carlo file three times, the ten adjusted residue values representing the 0.75× rate would each be entered five times, and the ten adjusted residue values representing the 0.5× rate would each be entered twice in order to provide the appropriate 3:5:2 ratio for the 1×, 0.75×, and 0.5× application rates[8]. This would

[8] Alternatively (and equivalently), these residue values could be inserted into four separate files (one each representing values of 0 (for untreated), 1×, 0.75×, and 0.5× relative application rates) with associated probabilities of 75%, 7.5%, 12.5%, and 5%, respectively.

produce a file with a total of 100 positive residue values and would represent the number of "non-zeroes" in the file. To incorporate the untreated fraction of the commodity (i.e., that portion with residue values of true zero), 300 "zero" values would also be entered. Thus, there would be a total of 400 potential zero or non-zero residue levels from which to select, of which 300 (or 75%) represent zero for the untreated commodities, and 100 (or 25%) represent treated commodities in proportions appropriate to reflect the 3:5:2 ratios for the 2.0, 1.5, and 1.0 kg a.i./ha treatment rates, respectively.

The results of this analysis are shown in the table on the following page with exposures (as estimated by DEEM™ software) shown for the general Canadian population and children one to six at the 99.9th, 99th, and 95th percentiles for consumers only.

Method	**DEEM-estimated exposure (consumers only) mg/kg/day (relative exposure[a])**					
	General Canadian population			**Children one to six**		
	99.9th	**99th**	**95th**	**99.9th**	**99th**	**95th**
Assuming treatment at 1× rate of treated crop	0.0229 (1.00)	0.00830 (1.00)	0.00089 (1.00)	0.02986 (1.00)	0.01437 (1.00)	0.00233 (1.00)
Probabilistic treatment of distribution of treatment rates (1×, 0.75× and 0.5×)	0.01843 (0.81)	0.00638 (0.77)	0.00067 (0.75)	0.02484 (0.83)	0.01116 (0.77)	0.001807 (0.77)

[a] Expressed relative to estimated exposure assuming all applications occur at label-maximum rate.

As can be seen in the above table, the probabilistic use of a full distribution of treatment rates (i.e., 1×, 0.75×, and 0.5×) results in lower estimated exposures than would be calculated assuming that all application rates occur exclusively at the label rate. At the 99.9th percentile for the general Canadian population, for example, the probabilistic treatment of application rates, results in an estimated exposure at the 99.9th percentile that is only 81% of that exposure that would have been estimated without this probabilistic treatment. For children aged one to six, the corresponding percentage is 83%. Thus, the incorporation of a distribution of treatment rates into the exposure and risk assessment can result in significantly reduced exposure estimates.

REFERENCE

USEPA 1998. *Guidance for Data Quality Assessment: Practical Methods for Data Analysis*; EPA QA/G9 QA-97 Version. Office of Research and Development. http://www.epa.gov/Region10/offices/oea/epaqag9.pdf (EPA/600/R-96/084)

Appendix II Example analysis of residue decline data and generation of appropriately weighted input residue file for probabilistic analysis

Introduction

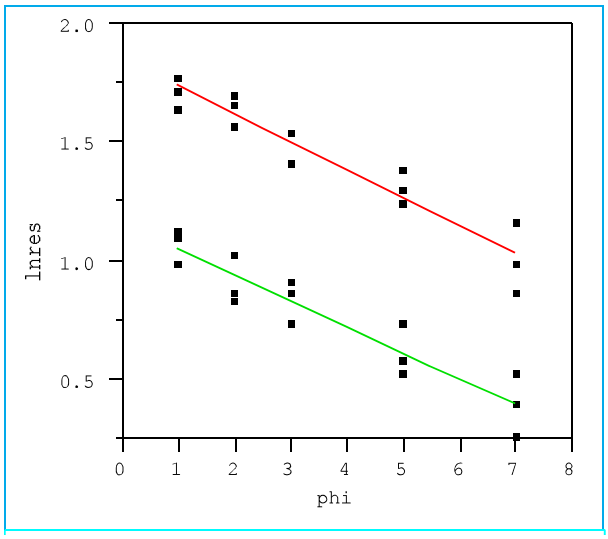
In an attempt to refine residue estimates as part of a probabilistic assessment, a registrant has conducted two field trials sampling bell peppers at various times following pesticide application. One side-by-side crop trial was conducted in BC while the other was conducted in ON. The label permits a pre-harvest interval (PHI) of three days. Samples were collected at one, two, three, five and seven days following application. Three composite samples (24 individual items per composite) were collected at each PHI from each trial. A total of 30 composite samples was analyzed.

PMRA data indicate that of the bell pepper crop that is treated, 20% is harvested three days following application (i.e., at the label PHI), 30% is harvested five days after application, and the remaining 50% is harvested 10 days following application. They have further estimated that only 25% of the bell pepper crop is treated.

The results from the registrant's two field trials are as follows:

PHI (day)	Residue level (ppm)
British Columbia	
1	3.1, 3.0, 2.7
2	2.8, 2.4, 2.3
3	2.5, 2.4, 2.1
5	2.1, 1.8, 1.7
7	1.7, 1.5, 1.3
Ontario	
1	5.9, 5.6, 5.2
2	5.5, 5.3, 4.8
3	4.7, 4.7, 4.1
5	4.0, 3.7, 3.5
7	3.2, 2.4, 2.7

Step 1



Given the results of the field trials presented above, the PMRA would conduct exploratory data analysis and hypothesize, as a preliminary assumption, that residue decline is first order with respect to concentration. This exploratory data analysis would also include tests for homogeneity of variance to verify that the assumptions for linear regression are satisfied. Specifically, prior to performing the linear regression analysis to estimate the residue decline rates in BC and ON, it would be necessary to verify that the variances do not differ significantly among the residue values across PHIs and trials (i.e., to test homogeneity of variance).[9]

A plot of the natural logarithm of residue (lnres) vs. PHI is shown above. The lower curve represents residue decline in BC while the upper curve represents decline in ON. There does not appear to be any indication of systematic differences between residue decline rates between these provinces (i.e., the slopes representing the decay rates appear to be similar)[10]. Furthermore, there is a statistically significant trend (as expected) in both trials toward decreasing residues with increasing PHI as evidenced by the PHI coefficients of -0.1092 day^{-1} and -0.1171 day^{-1} (p-value of <0.001) for the BC and ON sites, respectively:

9 Although not specifically illustrated here, Bartlett's and Levine's Tests for determining homogeneity of variance are among several tests that can be performed. These are more fully described in the USEPA's publication "Guidance for Data Quality Assessment: Practical Methods for Data Analysis;" (USEPA 1998). This determination is a prerequisite for performing a valid linear regression (i.e., linear regression assumes that variances are equal).

10 If there was any indication of significant differences in slope between the field trials, then analysis would proceed on a case-by-case basis; this could include use of the slowest degradation rate for all locations or use of each regional rate in proportion to percent of crop grown in that region.

ON Site:

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|	Lower 95%	Upper 95%
Intercept	1.8600116	0.042471	43.79	<.0001	1.7682588	1.9517643
phi	-0.117173	0.010124	-11.57	<.0001	-0.139044	-0.095302

BC Site:

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|	Lower 95%	Upper 95%
Intercept	1.1634715	0.046888	24.81	<.0001	1.0621762	1.2647669
phi	-0.109228	0.011176	-9.77	<.0001	-0.133373	-0.085082

Step 2

Given the results of the field trials and the results of the preliminary analysis presented above, the PMRA would typically verify if data from the residue decline studies could be legitimately combined. This could be done by conducting a linear regression and analysis of variance (ANOVA) with the following equation:

$$\ln C_t = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2 + \varepsilon$$

where β_o is the natural logarithm of the y-intercept (C_o), β_1 is the slope (and represents the first order decay rate), β_2 is the coefficient of the indicator variable "STATE" (a 0-1 variable signifying location—either ON (0) or BC (1)), and β_3 is the coefficient for the interaction term. The linear regression results for the sample data are shown to the right and below in the "Summary of Fit" and "Parameter Estimates" blocks.

Summary of Fit

RSquare	0.961453
RSquare Adj	0.957006
Root Mean Square Error	0.088958
Mean of Response	1.10422
Observations (or Sum Wgts)	30

We note from the "Parameter Estimates" block to the right that the t-ratio for PHI (β_1) is significant (t = -10.99; p<0.001) while the t-ratio for the β_3 interaction term (t= 0.53, p = 0.6027) is not.[11] This indicates that residues **do** decline with increasing PHI but that the rate of residue

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	1.8600116	0.044734	41.58	<.0001
phi	-0.117173	0.010663	-10.99	<.0001
State	-0.69654	0.063263	-11.01	<.0001
phi*State	0.0079454	0.01508	0.53	0.6027

[11] Note that the t-test is appropriate in this instance because there are only two trials. In the case of crops in which three trials are required, it is appropriate to test that no regression slopes are different and a second interaction term (β_4) would be necessary to properly code the variables. In this case, the more general *partial* F test (and not the t-test) would be the appropriate statistical procedure to apply.

decline is **not** significantly impacted by the location.[12] Thus, the regression analysis can be legitimately performed after removing this interaction term and, in effect, adopting a single (uniform) value for the rate of residue decline.

Step 3

Since we concluded above that the interaction term (β_3 in the above regression equation) was not significant and could be eliminated from the regression equation, the regression equation would be re-written as follows to exclude the nonsignificant interaction term:

$$\ln C_t = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \varepsilon$$

Note from the "Summary of Fit" block and "Parameter Estimates" block for this new regression formula that the correlation coefficient of 0.961 demonstrates that a substantial amount of the variation in residues is explained by the PHI, and the t-ratio for PHI (β_1) is significant ($p<0.001$), which confirms that residues decline with increasing PHI. Importantly, the parameter estimate for PHI (β_1) is -0.1132. This is the estimate for the common first-order decay constant for the two trials (i.e., the value for β_1 in the above equation) that will later be used to adjust the residues obtained from the field trial data. From the F-ratio of 0.2759 in the "Lack of Fit" block ($p = 0.9562$), there is no reason to conclude that the first-order decay model does not adequately describe the data.

Summary of Fit

RSquare	0.961042
RSquare Adj	0.958156
Root Mean Square Error	0.08776
Mean of Response	1.10422
Observations (or Sum Wgts)	30

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	1.8457099	0.035079	52.62	<.0001
phi	-0.113201	0.007438	-15.22	<.0001
State	-0.667937	0.032045	-20.84	<.0001

[12] Again, if the rate of residue decline is significantly impacted by location, then alternatives could include use of the slowest degradation rate for all locations or use of each region-specific degradation rate in a proportion appropriate for the percentage of crop that is produced there.

At this point, it would be appropriate to examine graphical plots of the residuals against either the fitted values or the PHI predictor variable to confirm that no patterns were evident. A normal plot and a box plot of the residuals might also be produced to verify that the residuals had an approximately normal distribution and a Shapiro-Wilk test for normality could be conducted for confirmation of residual normality. All of these plots and statistics should support the appropriateness of the regression model for the data. These plots and statistics are illustrated in Figure A.2.1.

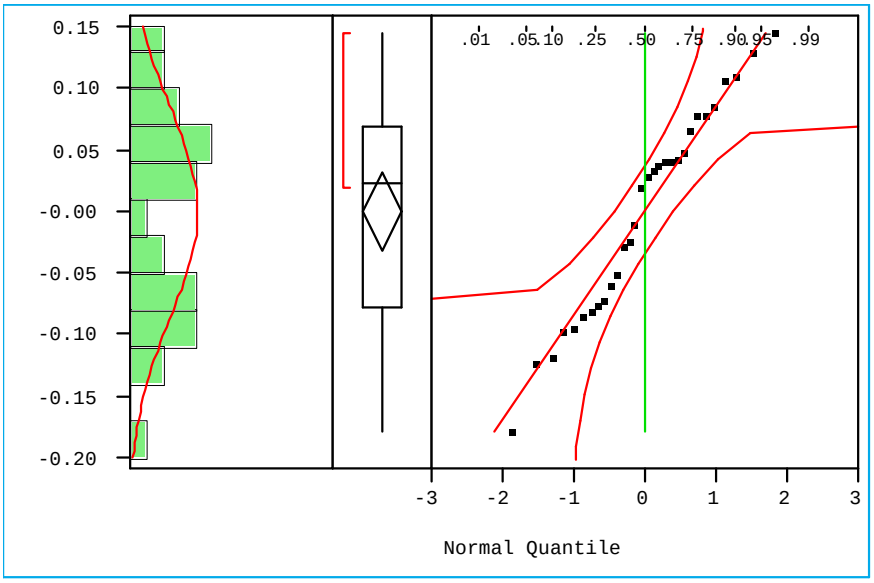
Lack of Fit

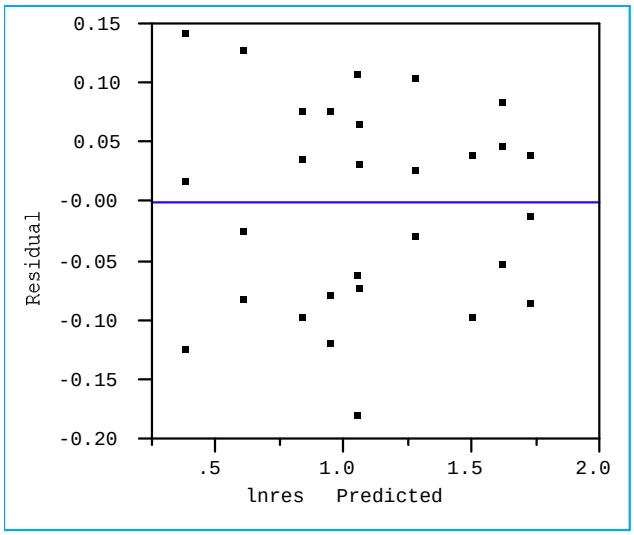
Source	DF	Sum of Squares	Mean Square	F Ratio
Lack of Fit	7	0.01831394	0.002616	0.2759
Pure Error	20	0.18963568	0.009482	Prob>F
Total Error	27	0.20794963		0.9562
				Max RSq
				0.9645

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	2	5.1298047	2.56490	333.0247
Error	27	0.2079496	0.00770	Prob>F
C Total	29	5.3377543		<.0001

If the t-ratios for PHI from the “Parameter Estimates” block (or in this case the equivalent F-ratio from the “Analysis of Variance” Block) were not significant, there would be no statistically significant relationship between residue level and PHI. In this case, the residue decline data provided by this study might *not* be used and the probabilistic analysis conducted by the PMRA could revert to using the residue data obtained from the maximum rate and minimum PHI bell pepper field trials originally developed to establish the MRL. Information on “typical” PHIs, in this instance, might not be incorporated, and an alternate method might be sought. A similar conclusion could be reached if the F-ratio in the “Lack of Fit” block was significant: in this case, the PMRA could conclude from these data that there was sufficient evidence against the hypothesis of first-order decay of residues with time such that it would be inappropriate to incorporate this into a probabilistic analysis, and alternative means of analysis should be pursued.





Test for Normality

Shapiro-Wilk W Test

W	Prob<W
0.961600	0.3842

Figure A.2.1 Graphical plots of residue decline study data analysis

Step 4

Previously, a total of five maximum rate/minimum PHI field trials was performed to establish MRLs. During these trials, a total of 10 composite bell pepper samples (i.e., two per trial) was collected and analyzed[13]. As per PMRA guidelines (RCGs), the trials were conducted in the appropriate geographic regions and in the appropriate numbers such that they are adequately representative of national production. The results were as follows:

Trial	Residue level (ppm)
1	5.2, 5.4
2	2.8, 3.2
3	1.8, 1.6
4	1.4, 1.5
5	1.4, 1.8

As a result of the residue decline field trials, the PMRA has determined previously (in STEP 3) that the appropriate estimate for residue decline (through a first-order decay process) is 0.1132 day^{-1}. Thus, the appropriate equation to adjust each (original) maximum rate/minimum PHI field trial value is as follows:

$$C_{t=T} = C_{t=minPHI} \times e^{(\beta_2)(n-minPHI)}$$

where $C_{t=minPHI}$ is the residue value to be adjusted (i.e., the residue sampled at the minimum label PHI in the original field trials), β_2 is the residue decline constant determined previously, and n is the number of days following application at which actual harvest occurs. This is the relationship that would be used to adjust the results from the ten composite samples from the five original field trials conducted earlier to establish MRLs to the results that would be expected to occur at the range of more typical application PHIs. As an example, if one of the maximum rate/minimum PHI residue values from a 1× application rate at the label PHI of three days was 5.2 ppm (as in Trial 1 above), this value would be adjusted as follows for 6- and 10-day PHIs:

6-day: $C_{t=6\ days} = 5.2\ ppm \times e^{(-0.113)(6-3)} = 5.2\ ppm \times 0.7125 = 3.70\ ppm$
10-day: $C_{t=10\ days} = 5.2\ ppm \times e^{(-0.113)(10-3)} = 5.2\ ppm \times 0.4534 = 2.36\ ppm$

Each of the ten maximum rate/minimum PHI 1× values would be adjusted in this manner to yield a collection of residue values reflecting any desired PHI. In this manner, one would develop from the 10 composite samples originally collected for MRL-setting purposes, a series of comparable

13 This is provided for example purposes only. PMRA Guidelines (RCGs) actually recommend eight crop field trials (and 16 samples) for bell peppers; therefore, it is unlikely that 10 composite bell pepper samples from five field trials would be adequate for use in a probabilistic risk assessment.

residue values that would reflect expected residues at various time intervals following residue decline. These are illustrated below for the sample data:

Trial	Residue level (ppm)	Adjusted residue level (ppm)	
	3 days	6 days	10 days
1	5.2, 5.4	3.7, 3.9	2.4, 2.4
2	2.8, 3.2	2.0, 2.3	1.3, 1.5
3	1.8, 1.6	1.3, 1.1	0.82, 0.73
4	1.4, 1.5	1.0, 1.1	0.63, 0.68
5	1.4, 1.8	1.0, 1.3	0.63, 0.82

Step 5

Given that the series of adjusted residue values (derived above) which correspond to those PHIs for which use-related data are available, it now becomes necessary to insert these values *(in the appropriate proportions*) into a probabilistic assessment. It is critical, for example, that if only 5% of the crop is harvested following the minimum (label) PHI, that there be only a 5% probability of selecting a residue value that reflects this PHI.

In this example, the PMRA has determined that only 20% of the treated bell pepper crop is harvested at the minimum label PHI of three days, that 30% is harvested five days following treatment, and the remaining 50% is harvested 10 days following treatment. Thus, the maximum rate/minimum PHI field trial data conducted earlier for MRL-setting purposes can be adjusted to account for the lower residue levels (*as determined by the above equation*) in the appropriate proportions (*as determined by the percent crop treated and treatment rate data*). Given this information, we note that 20%, 30%, and 50% of the treated commodity input file to any Monte Carlo analysis would be required to contain data representative of the three-, six- and 10-day PHIs, respectively. In addition, the Monte Carlo file should be constructed such that there is only a 25% probability of selecting a treated commodity to comply with the estimate of 25% crop treated (and thus a 75% probability of selecting an untreated commodity with consequent residue levels of zero).

To do this, the ten original residue values representing the three-day PHI from the maximum rate/minimum PHI MRL field trials would each be entered into the Monte Carlo file two times, the ten adjusted residue values representing the five-day PHI would each be entered three times, and the ten adjusted residue values representing the 10-day PHI would each be entered five

times.[14] This would produce a file with a total of 100 positive residue values and would represent the number of "non-zeroes" in the file. To incorporate the untreated fraction of the commodity (i.e., that portion with residue values of true zero), 300 "zero" values would also be entered. Thus, there would be a total of 400 potential zero or non-zero residue levels from which to select, of which 300 (or 75%) represent zero for the untreated commodities, and 100 (or 25%) represent treated commodities in proportions appropriate to reflect the 2:3:5 ratios for the three-, six- and ten-day PHIs, respectively.

The results of this analysis are shown below with exposures (as estimated by DEEM™ software) shown for the general Canadian population and children one to six at the 99.9th, 99th, and 95th percentiles:

Method	DEEM-estimated exposure (consumers only) mg/kg/day (relative exposure[a])					
	General Canadian population			Children one to six		
	99.9th	99th	95th	99.9th	99th	95th
Assuming harvest of treated commodity at label-prescribed minimum PHI of 3 days	0.0089 (1.00)	0.0024 (1.00)	0.00057 (1.00)	0.0138 (1.00)	0.00509 (1.00)	0.00116 (1.00)
Probabilistic treatment of distribution of PHIs (3-, 6- and 10-days)	0.0054 (0.61)	0.0014 (0.60)	0.00027 (0.47)	0.00992 (0.72)	0.00325 (0.64)	0.00069 (0.60)

[a] Expressed relative to estimated exposure assuming harvest occurs at label-minimum PHI of 3 days.

As can be seen in the above table, the probabilistic use of a full distribution of PHIs (i.e., three-, six-, and 10-days) results in lower estimated exposures than would be calculated assuming that all harvests occur exclusively at the label PHI of three days. At the 99.9th percentile for the general Canadian population, for example, the probabilistic treatment of PHI, in this example, results in an estimated exposure at the 99.9th percentile that is only 61% of which it would have been had it been estimated without this probabilistic treatment. For children one to six, the corresponding percentage is 72%. Thus, the incorporation of a distribution of PHIs into the exposure and risk assessment can result in significantly reduced exposure estimates.

REFERENCE

USEPA 1998. *Guidance for Data Quality Assessment: Practical Methods for Data Analysis*; EPA QA/G9 QA-97 Version. Office of Research and Development. http://www.epa.gov/Region10/offices/oea/epaqag9.pdf (EPA/600/R-96/084).

[14] Alternatively (and equivalently), these residue values could be inserted into four separate files (one each representing values of zero residues (for untreated), three days, six days and 10 days with associated probabilities of 75%, 5%, 7.5% and 12.5%, respectively).