Fax-On-Demand
Fax Number: (202) 401-0527
Item: 6040

Guidance for the Conduct of Bridging Studies for Use in Acute Dietary Probabilistic Risk Assessment

Executive Summary

This document provides additional guidance to registrants, other test sponsors, interested parties, and data reviewers on the extent and quality of "bridging data" needed to support the use of typical application rates in acute dietary probabilistic exposure and risk assessments. Bridging data (generally from side-by-side field trials) are 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 pre-harvest interval) and residues which would result from more typical application application rates. This guidance provides information on how risk-mitigation activities (e.g., lowered use rates) can be considered in Office of Pesticide Programs (OPP) risk assessments and used to adjust tolerance levels. Additional specific desirable elements in an assessment and details (as well as illustrative examples) are described. By following this guidance, registrants and other sponsors may generate pesticide-specific data that can be used by the Agency to produce highly refined, acute dietary probabilistic exposure and risk assessments. While the data developed in accordance with this guidance are preferred, EPA will also consider other data or information as long as they would provide a scientifically sound basis for estimating residues at typical application rates for risk mitigation purposes.

Background

In October, 1998, the Agency made available for comment its "Guidance for Submission of Probabilistic Human Health Exposure Assessments to the Office of Pesticide Programs" (63 FR 59780). The stated purpose of the guidance document was to establish performance standards for probabilistic human health exposure assessments done for, and by, the Office of Pesticide Programs. The document was not intended to provide step-by-step instructions on conducting probabilistic assessments. Instead, the intent of the document was to provide a conceptual framework which would establish which approaches are appropriate for consideration in probabilistic assessments.

The document stated that probabilistic exposure assessments submitted to OPP's Health Effects Division could include data based on the range of "typical" application scenarios that may be more restrictive (lower rates, fewer applications, longer PHI's) than the maximum label conditions provided that certain conditions are met. OPP stated that residue data must be available to support the inclusion of more typical use patterns and that assumptions of linear or other relationships between application rates and resulting residue levels may not be made

automatically: data correlating measured residue values to application rates must be provided.

Additional details concerning this probabilistic incorporation of typical application scenarios were provided in an April, 1999, Federal Register notice entitled “Data for Refining Anticipated Residue Estimates Used in Dietary Risk Assessments for Organophosphate Pesticides.” This notice described the types of data that can be used to refine residue estimates, outlined the basic characteristics of useful data, discussed how residue data and usage data are linked, and explained how OPP would use these types of data in its dietary exposure assessments. Bridging studies, which are used to quantify the difference in residues resulting from various application rates, were described in some detail and residue decline studies, which can be used to quantify the differences in residues resulting from various pre-harvest intervals (PHIs) were briefly discussed. The document stated that OPP was preparing two related technical guidance documents, "Guidance for the Conduct of Bridging Studies for Use in Acute Dietary Probabilistic Risk Assessment" and "Guidance for the Conduct of Residue Decline Studies for Use in Acute Dietary Probabilistic Risk Assessment," that will provide more detailed information.

This document provides additional guidance to registrants and other sponsors on the extent and quality of “bridging data”needed to support the use of typical application rates in probabilistic risk assessments. Bridging data refer to data (generally from side-by-side field trials) which are 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 pre-harvest interval) and residues expected at the range of more typical rates. This guidance also provides information on how risk-mitigation activities (e.g., lowered use rates) can be considered in OPP risk assessments and used to adjust tolerance levels. Additional details (as well as illustrative examples) are described as well. 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 EPA 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.

Purpose, Required Location, and Number of Field Trials

Side-by-side field trials should be designed to compare residues resulting from maximum label conditions (i.e., those conditions used to derive a tolerance) to the range of more typical application rates. 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 OPPTS Test Guidelines, Residue Chemistry, 860.1500 for this and other basic information on the conduct of field trials). Specifically, the minimum number of field trials recommended for bridging studies is as follows:

Number of Residue Field Trials Recommended by OPP Guidelines for Tolerance-setting purposes	Minimum Recommended Number and Location of Sites for Side-by-Side Field Trials Required to Establish Reduced-Use (Bridging) 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] The "HAFT" refers to the Highest Average Field Trial. If no HAFT has 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 should be derived from side-by-side (i.e., conducted at the same site and the same time) field trials because of the potential impact that environmental conditions and variability in study conduct have on the results. Therefore, only data from controlled field trials specifically designed and collected to monitor the effects of application rate on residue can be used. As an example, it would 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 California in 1992 and residues from another application rate were obtained from field trial at the same or another location three years later. Data provided should include weather and precipitation records to enhance the evaluation of a study and its results. In addition, an untreated area which receives no pesticide application should be established to serve as the "control.".

Extrapolation of Results Between Similar Crops

Extrapolation of data between similar crops (e.g., in the same crop group) may be allowed on a case-by-case basis, considering similar cultural practices and application patterns.

Number of Application Rates to be Tested

Since the purpose of the 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 must be at the maximum label rate (i.e., that rate used to

establish the tolerance); 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 must 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 <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 (1x) rate in addition to two other (exaggerated) rates (e.g., 2x and 3x) to ensure that quantifiable residues result.

Number of Composite Samples to Collect at each Application Rate

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., ½x, 3/4x, and 1x (maximum label-permitted rate) , a total of at least nine composite samples (three at each rate) should be collected. Furthermore, the test sponsor should demonstrate that reduced rates result in quantitatively reduced residue levels and that the postulated mechanistic structure (e.g., a linear relationship between rate and residue level) 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 do result in differing residue levels and that it is appropriate to postulate that a linear relationship between application rate and residue level exists. The Agency believes that if lower application rates 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, that the analytical method is sufficiently 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 field trials (for insertion into a probabilistic assessment) unless sufficient analytical and sample collection resources are provided to demonstrate that reduced use rates do result in quantitatively reduced residues. An illustration of the determination of the relationship between application rate and the resulting residue level is provided in Boxes 1 through 5. It is this relationship which will be used to adjust the 1x residue levels (as determined in the tolerance field trials) to more typical actual application rates.

BOX 1

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 WA while the other was conducted in VA. The label permits application rates of from 1.0 to 2.0 lb ai/A applied 3 days prior to harvest. Each of the two reduced-use field trials were conducted at 2.0 lb ai/a, 1.5 lbs ai/A, and 1.0 lbs ai/A (these represent relative application rates of 1.0x, 0.75x, and 0.5x, respectively) with three composite samples (24 individual items per composite) collected at each rate from each trial (with a 3 day PHI). A total of 18 composite samples were analyzed.

Data obtained by OPP indicate that 25% of the U.S. bell pepper crop is treated with the pesticide of interest. Of the bell pepper crop which is treated, 20% is treated at the 1.0 lb ai/A rate, 50% is treated at the 1.5 lb ai/A rate, and 30% is treated at the 2.0 lb ai/A rate.

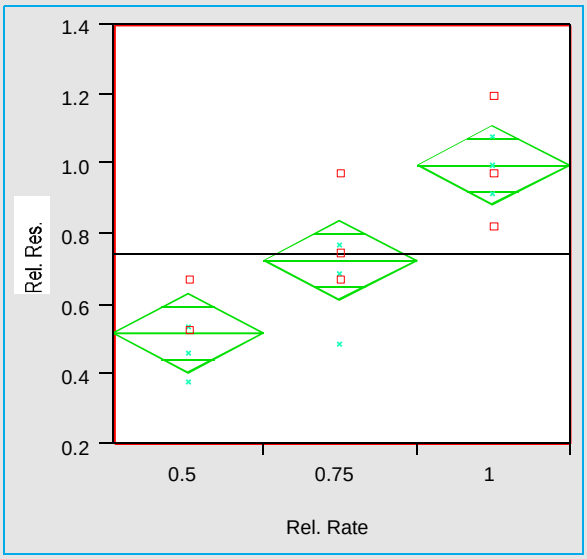
The results from the registrant's two reduced-use field trials are as follows:

WA
2.0 lb ai/A: 1.2 ppm, 1.4 ppm, 1.3 ppm
1.5 lb ai/A: 0.9 ppm, 1.0 ppm, 0.7 ppm
1.0 lb ai/A: 0.6 ppm, 0.7 ppm, 0.6 ppm

VA
2.0 lb ai/A: 1.1 ppm, 1.3 ppm, 1.6 ppm
1.5 lb ai/A: 0.9 ppm, 1.0 ppm, 1.3 ppm
1.0 lb ai/A: 0.6 ppm, 0.7 ppm, 0.9 ppm

BOX 2

Given the results of the field trials presented in BOX 1, OPP would conduct exploratory data analysis 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 (described in the last paragraph of this Box) to verify that the assumptions for linear regression are satisfied.



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 1x 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 WA trials and residues generated in the VA trials (as indicated by X's and boxes, respectively). We note that there appears to be a trend (as expected) toward increasing residues with increasing application rate.

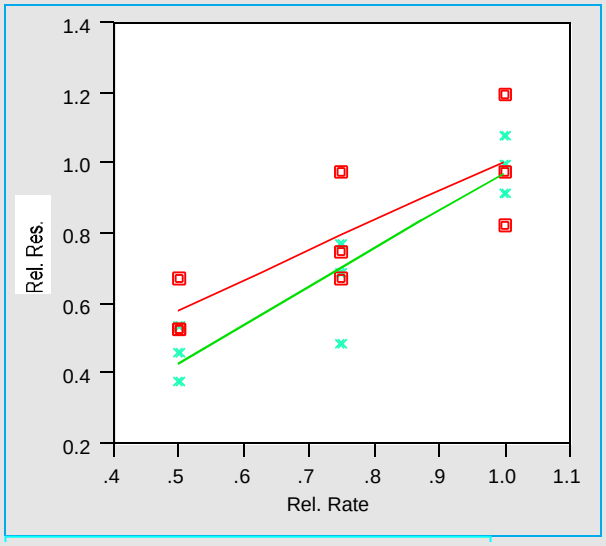
Prior to performing any linear regression to develop a quantitative relationship between relative residue and relative application rate, it would be necessary to verify that the variances do not differ significantly among treatment rates and trials (i.e., to test for homogeneity of variance). Although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

---

[1] 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 which is produced there.

BOX 3

Given the results of the field trials presented in Box 1, the _initial exploratory analysis shown in Box 2, and confirmation of the homogeneity of variance (not shown) as discussed in Box 2, OPP would hypothesize as a preliminary assumption that there was a linear relationship between application rate and residue and conduct a linear regression analysis. Specifically, relative residue concentration (i.e., residue concentration at any given application divided by the average residue at the 1x rate) would be regressed on relative application rate (i.e., application rate divided by maximum application rate). The linear regression and parameter estimates for the sample data for each site are shown below.



VA

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|	Lower 95%	Upper 95%
Intercept	0.1605556	0.175489	0.91	0.3907	-0.254414	0.5755253
Rel. Rate	0.8466667	0.225773	3.75	0.0072	0.3127936	1.3805398

CA

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|	Lower 95%	Upper 95%
Intercept	-0.106667	0.135693	-0.79	0.4576	-0.427533	0.2141998
Rel. Rate	1.08	0.174574	6.19	0.0005	0.667194	1.492806

Note from the graph and "Parameter Estimates" blocks that a linear relationship between the relative residue and relative application rate appears reasonable and the slopes between the CA and VA are not significantly different. A specific test for parallel slopes is provided in Box 4.

BOX 4

Given the results of the field trials presented in Box 1 and the results of the preliminary analyses in Boxes 2 and 3, HED 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 1x 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 CA(0) or VA(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 below in the "Analysis of Variance" and "Parameter Estimates" blocks.

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	3	0.74448889	0.248163	16.2497
Error	14	0.21380556	0.015272	Prob>F
C Total	17	0.95829444		<.0001

Sequential (Type 1) Tests

Source	Nparm	DF	Seq SS	F Ratio	Prob>F
Rel. Rate	1	1	0.69600833	45.5747	<.0001
Location	1	1	0.03827222	2.5061	0.1357
Location*Rel. Rate	1	1	0.01020833	0.6684	0.4273

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|	Lower 95%	Upper 95%
Intercept	0.1605556	0.156859	1.02	0.3234	-0.175872	0.4969829
Rel. Rate	0.8466667	0.201804	4.20	0.0009	0.4138411	1.2794923
Location[WA]	-0.267222	0.221832	-1.20	0.2483	-0.743002	0.2085579
Location[WA]*Rel. Rat	0.2333333	0.285394	0.82	0.4273	-0.378774	0.8454411

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.

$$F^* = \frac{0.0383 + 0.0102}{2} \div \frac{0.2138}{18-4} = 1.59$$

To control α at 0.05 (for example), we require F(0.95,2,14) = 3.7. Since F = 3.7 > F* = 1.59 , there is no reason to conclude that the two regression functions are different. This indicates that relative residues **do** increase with increasing application rate, but that the relative rate of residue increase is **not** significantly impacted by the location.[1] 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.

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

BOX 5

In Box 4, the location and interaction terms (β_2 and β_3 in the regression equation in Box 4) were not significant and could be eliminated from the regression equation. Given this result, the regression equation would be re-written as follows:

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

Note from the "Parameter Estimates" block for this new regression formula that the "t-ratio" for Rel Rate (β_1) is significant ($p<0.001$) 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 which will later be used to adjust the residues obtained from the field trial data. From the F-ratio of 0.2719 in the "Lack of Fit" block ($p=0.6097$), 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|	Lower 95%	Upper 95%
Intercept	0.0269444	0.114915	0.23	0.8176	-0.216663	0.2705514
Rel. Rate	0.9633333	0.147842	6.52	<.0001	0.6499244	1.2767422

At this point, OPP would examine graphical plots of the residuals against the either the fitted values or the application rate predictor variable to confirm that no patterns were evident (not shown). OPP would also produce a normal plot and a box plot of the residuals to verify that the residuals had an approximately normal distribution (not shown). All of these plots should support the appropriateness of the regression model for the data.

Lack of Fit

Source	DF	Sum of Squares	Mean Square	F Ratio
Lack of Fit	1	0.00466944	0.004669	0.2719
Pure Error	15	0.25761667	0.017174	Prob>F
Total Error	16	0.26228611		0.6097
				Max RSq
				0.7312

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) were not significant, OPP could conclude that there is no statistically significant relationship between relative residue level and application rate. In this situation, the residue decline data provided by this study might *not* be used and the probabilistic analysis conducted by OPP could revert to using the residue data obtained from the maximum rate and minimum PHI bell pepper field trials originally developed to establish the tolerance. 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 were significant : in this case, OPP 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.

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	0.69600833	0.696008	42.4580
Error	16	0.26228611	0.016393	Prob>F
C Total	17	0.95829444		<.0001

Incorporation of "Less than Limit of Quantitation (<LOQ)" Values into A Regression Relationship

In some instances, test sponsors may find that residues are "not detected" or, alternatively, are present (i.e., are detected), but at levels that are less than the quantitation limit. OPP believes that only *quantitative* residue measurements should be used to establish a *quantitative* relationship between application rate and resulting residue concentration--use of <LOQ residue levels in establishing this relationship may introduce excessive uncertainty into the regression equation. Therefore, the sponsor should ensure through proper selection of application rates (including exaggerated rates) and conditions that quantitatively measurable residues will result during reduced used field trials. Due to significant quantitative uncertainties, OPP will not incorporate <LOQ measurements into its regression analyses.

In some cases, it will be useful to conduct the field trials at an exaggerated rate (e.g., 2x) such that all residue measurements will be at >LOQ levels and can be used in the regression analysis. Application rates, however, should not be excessively exaggerated (e.g., no more than 5x) since doing so may fundamentally alter decay parameters/processes and this should not be used to compensate for a generally inadequate analytical method. Again, the residue values obtained from any exaggerated rate level will not be used directly in the risk assessment, but will only be used to establish the appropriate decay parameters.

Single-serving vs. Composite Sampling

It is important that the reduced-use residue trials be directly comparable to the trials used to establish tolerances as it is this relationship which will be used to "adjust" the measured residues from the field trials used to establish tolerances. Thus, the sample sizes collected during the reduced-use field trials should be the same as those collected during the trials used to establish tolerances. Ordinarily, this means that the sample sizes should be the same as those indicated in the OPPTS Test Guidelines relating to conduct of field trials (see Residue Chemistry Test Guidelines, OPPTS 860.1500, Crop Field Trials).

Nevertheless, while OPP would prefer that *composite* samples be collected as part of reduced-use field trials in order to retain comparability with earlier maximum rate/minimum PHI field trials conducted to support tolerance decisions, OPP still has concerns (shared by the FIFRA Scientific Advisory Panel, the UK's Ministry of Agriculture, Fisheries, and Food (MAFF), and WHO/FAO) about the effect compositing may have on unit-to-unit variation. When residue estimates are generated from maximum application rates and minimum PHI's (worst-case conditions), OPP believes that there is an adequate degree of compensating overestimation such that individual unit variation is not of concern. By incorporating the range of application rates and PHI's in a probabilistic scenario, the conservatism built into the use of worst-case field trial data is eroded and may require compensation for this with statistically valid data on individual samples and/or unit-to-unit variation. This issue has been considered and is presented in OPP's

Probabilistic Risk Assessment guidance document presented to the SAP in March, 1998 and announced in the Federal Register on November 5, 1998 (it was placed in Draft form on the OPP website at that time). Specifically, OPP will evaluate chemical-specific considerations to determine whether the use of composite data from reduced-rate 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 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 OPP 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: 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. In addition, a "decompositing" procedure could be applied in an attempt to simulate single-serving samples. As indicated previously, OPP has asked the USDA Pesticide Data Program to provide data that would assist in adequately describing the relationship between residues in single-serving vs. composited samples. 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 as study (which may be run as part of the reduced use field trials) can be provided.

Generation of Adjusted Data for Incorporation into the Probablistic Analysis

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 which would have been developed earlier for tolerance 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 tolerance 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 Box 6 in which the earlier regression equation developed from the reduced rate field trials and used to establish a relationship between relative residue and relative application rate is used to adjust the original (tolerance-determining) field trial residues.

BOX 6

Initially, a total of 5 maximum rate/minimum PHI field trials was performed to establish tolerances; during these trials, a total of 10 composite bell pepper samples (i.e., two per trial) was collected and analyzed[1]. As per OPP guidelines, 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
1	1.8 ppm, 1.4 ppm
2	0.8 ppm, 1.2 ppm
3	1.8 ppm, 1.6 ppm
4	1.4 ppm, 1.5 ppm
5	1.4 ppm, 1.8 ppm

As a result of the newly submitted reduced-use field trials, the Agency has determined (see Box 5) that the appropriate relationship between relative residue levels and relative application rate is as follows:

$$C_{rel} = 0.027 + 0.963 \; x \; relative \; application \; rate + \varepsilon$$

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 tolerances (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 1x application rate of 2 lb ai/A was 1.8 ppm (as in Trial 1 above), this value would be adjusted to a 1.5 lb ai/A (0.75x) rate by multiplying the 1.8 ppm value by 0.963 x 0.75 and adding 0.027. This would produce an adjusted residue value of 1.35 ppm. Each of the ten maximum rate/minimum PHI 1x values would be adjusted in this manner to yield a collection of ten residue values appropriate for a 0.75x rate. A similar operation would be used to adjust the same ten maximum rate residue values to a 0.5x (or 1.0 lb ai/A) rate (which in the case of the 1.8 ppm value would produce an adjusted residue level of 0.90 ppm). In this manner, OPP would develop from the 10 composite samples originally collected for tolerance setting purposes, a series of ten comparable residue values which would reflect expected residues at a 0.75x rate as well as a series of ten residue values reflective of expected residues at the 0.5x rate. These are illustrated below for the sample data:

Trial No.	Residue Values	Adjusted Residue Values	
	1x	0.75x	0.5x
1	1.8 ppm, 1.4 ppm	1.33 ppm, 1.04 ppm	0.89 ppm, 0.70 ppm
2	0.8 ppm, 1.2 ppm	0.60 ppm, 0.89 ppm	0.41 ppm, 0.60 ppm
3	1.8 ppm, 1.6 ppm	1.33 ppm, 1.18 ppm	0.89 ppm, 0.80 ppm
4	1.4 ppm, 1.5 ppm	1.04 ppm, 1.11 ppm	0.70 ppm, 0.75 ppm
5	1.4 ppm, 1.8 ppm	1.04 ppm, 1.33 ppm	0.70 ppm, 0.89 ppm

[1] This is provided for example purposes only. OPP Guidelines actually recommend 8 crop field trials for bell peppers and a minimum of 16 samples; therefore it is unlikely that 10 composite bell pepper samples from 5 field trials would be adequate for use in a probabilistic risk assessment. The five field trials cited here are for illustrative purposes only.

Incorporation of Adjusted Data into a Probabilistic Analysis

Now that the field trial data have been adjusted to incorporate the use of lower application rates, it is necessary that these residues be inserted into the probabilistic analysis such that the probabilistic analyses select these values in the appropriate proportions. This is best illustrated in Box 7 below in which the actual input values for the Monte Carlo analysis are derived.

BOX 7

Using the series of adjusted residue values which 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 which 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. Of those bell peppers which are treated, 20% are treated at the 1.0 lb ai/A rate, 50% are treated at the 1.5 lb ai/A rate, and 30% are treated at the 2.0 lb ai/A rate (these represent the 0.5x, 0.75x, and 1x rates, respectively). Thus, the maximum rate/minimum PHI field trial data conducted earlier for tolerance-setting purposes will be adjusted to account for the lower residue levels (*as determined by the equation in Boxes 5 and 6*) in the appropriate proportions (*as determined by BEAD percent crop treated and treatment rate data present in Box 1 and repeated above*). 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- lb ai/A treatment rates, respectively. In addition, the Monte Carlo file must 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 1x rate from the maximum rate/minimum PHI tolerance field trials would each be entered into the Monte Carlo file three times, the ten adjusted residue values representing the 0.75x rate would each be entered five times, and the ten adjusted residue values representing the 0.5x rate would each be entered twice in order to provide the appropriate 3:5:2 ratio for the 1x, 0.75x, and 0.5x application rates. 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 non-treated 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 non-treated 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 lb ai/A treatment rates, respectively.

Use of Multiple Linear Regression Techniques in the Simultaneous Adjustment of Rate and Residue Decline Data

OPP recognizes that in some cases it may be advantageous for the registrant or other sponsor 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 sponsor should consider performing field trials in which both application rate and residue decline information is collected *simultaneously*. Specifically, the registrant should perform its reduced-use field trials collecting samples at the label PHI (e.g., 3 days), but should also collect additional samples at a variety of other PHIs (e.g., 1, 2, 5, and 7 days) as per guidance released in a companion document entitled "Guidance for the Conduct of Residue Decline Studies for Use in Acute Dietary Probabilistic Risk Assessment." This information could 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 also could 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).

Field Trial Requirements for Pesticides With Various Chemical and/or Physical Forms

The relationship between residue level and application rate may vary with the chemical form 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 must 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 between 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. OPP has divided these into 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); and
- Mcap or time-release G.

The bridging study 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. OPP will entertain arguments for lesser numbers of trials depending on market share. If any test

sponsor is uncertain about translating residue data from one formulation to another, these concerns can be raised to OPP prior to initiation of field trials.

Questions for Public Comment

[*Due to the similarity in methods and techniques of the companion papers describing bridging studies and residue decline studies, the following questions relate to both of these papers*]

1. Is the guidance provided in these draft documents clear and complete? If not, why not and what additional guidance is needed?

2. Are the residue studies described in these documents adequate for generating refined acute dietary probabilistic exposure and risk assessments? If not, why not and how should they be modified?

3. OPP has proposed that between one and three field trials be conducted, that at least three application rates and/or five pre-harvest intervals (PHI) be tested, and that three composite samples be collected at each application rate or PHI. Do these recommendations appear to be reasonable and sufficient to establish a rate vs. residue or PHI vs. residue relationship? Are data available which indicate that these guidelines are adequate for the purposes intended? Explain.

4. OPP has stated that it believes that the field trials performed for bridging study/residue decline purposes should be conducted (at an exaggerated rate, if necessary) such that all residues are "quantifiable" (i.e., at or greater than the LOQ). We have stated that it would be considered inappropriate to derive a quantitative relationship between application rate and residue level on residues which were below the LOQ as this could introduce substantial uncertainty into the estimated relationship. Please comment on this proposed restriction. Please also comment on the recommendation that studies be conducted at an exaggerated rate, if necessary, to avoid the potential problem associated with non-detectable residues.

5. OPP states that extrapolation of data between similar crops may be allowed on a case-by-case basis considering similar cultural practices and application patterns. Should these extrapolations be limited to crops within a crop subgroup/group or should more extensive extrapolations between groups be permitted? If so, on what basis should more extensive extrapolations be permitted?

6. For the relationship produced by bridging or residue decline data to be used in an exposure assessment, it is necessary to have reliable usage data concerning application rates and/or pre-harvest intervals. For example, if residues resulting from the full

(maximum) application rate, three-quarters of the maximum application rate, and one-half the maximum application are determined, it is necessary to also have information on the percentage (or fraction) of the time each of these application rates are used. A similar situation exists for pre-harvest intervals. Is this information available from either public or proprietary sources? If so, from which sources can this data be obtained and how readily available is it?

7. The proposed methodology uses what is believed to be the statistically more appropriate "lack of fit" test to determine if the hypothesized model (e.g., linear relationship between application rate and residue level, first order decay in residue concentration with time, etc) is adequate to describe the data. Please comment on this proposed approach and compare it with the more widely used coefficient of determination (r^2). Under what circumstances might the use of r^2 to judge a fit adequate be preferred to the "lack of fit" test? Should the two be used in conjunction with one another and if so, how? There may be instances where the lack of fit test reveals that the hypothesized linear association can be rejected, but the coefficient of determination shows that the linear relationship accounts for a significant portion of the variability. What statistical tests, if any, should be used to judge whether the r^2 is significant?

8 OPP will require that *composite* samples be collected as part of reduced-use field trials to retain comparability with earlier maximum rate/minimum PHI field trials conducted to support tolerance decisions. Nevertheless, OPP still has concerns about the effect compositing may have on unit-to-unit variation. When residue estimates are generated from maximum application rate and minimum PHI's (worst-case conditions), OPP believes that there is an adequate degree of compensating overestimation such that individual unit variation is not of concern. By incorporating the range of application rates and PHI's in a probabilistic scenario, the conservatism built into our use of field trial data is eroded and may require us to compensate for this with statistically valid data on individual samples and/or unit-to-unit variation. OPP is proposing that chemical-specific considerations be considered to determine whether the use of composite data from reduced-rate field trials is acceptable. Alternatively, a "decomposition" procedure may be judged appropriate. Please comment on whether these concerns are justified and, if so, how they should be addressed by OPP.

9. In performing the regression analysis for bridging studies, OPP has elected not to "force" the regression relationship through zero, despite the fact that an application rate of 0 lbs ai/A would be expected to result in a zero ppm concentration in the plant or plant part. Please comment on this decision and any required changes in interpretation of the statistical parameters which a decision to force the regression through zero would entail.

10. OPP intends to combine the bridging study and residue decline study guidance documents into one document. In doing so, would it be useful to expand the section on

multiple regression techniques? How useful would this expansion be and are there any recommendations on how this could best be done?

11. What other data or information similar to that described in this guidance document would provide a sound, empirical basis for determining residues at typical application rates for risk mitigation purposes?

References

U.S. EPA, Draft document entitled "Guidance for Submission of Probabilistic Human Health Exposure Assessments to the Office of Pesticide Programs" dated 11/4/98. FR 63 59780. Available on-line at:
http://www.epa.gov/docs/fedrgstr/EPA-PEST/1998/November/Day-05/6021.pdf

U.S. EPA. Draft document entitled "Data for Refining Anticipated Residue Estimates Used in Dietary Risk Assessments for Organophosphate Pesticides" dated 3/26/99. FR 64 (16967-16970). Available on-line at:
http://www.epa.gov/fedrgstr/EPA-PEST/1999/April/Day-07/6033.pdf

U.S. EPA, OPPTS Test Guidelines, Residue Chemistry guidelines (Series 860).

U.S. EPA, *Guidance for Data Quality Assessment: Practical Methods of Data Analysis* . EPA QA/G-9, EPA/600/R-96/084, July, 1996. Available on-line at:
http://Earth2.epa.gov/ncerqa/qa/docs/epaqag9.PDF