Global Zoning and Exchangeability of Field Trial Residues Between Zones: Are There Systematic Differences in Pesticide Residues Across Geographies?

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ABSTRACT

Mixed-effects models were used to evaluate the global zoning concept using residue data from a comprehensive database of supervised field trials performed in various countries and regions on a variety of pesticide–crop combinations. No statistically significant systematic differences in pesticide residues were found between zones among the pesticide uses examined. In addition, we conducted a simulation to assess the impact of using regional versus global datasets for calculating maximum residue limits (MRLs). The conclusion of this assessment supports the concept of exchangeability of pesticide residue values across geographic regions and opens the possibility of improving harmonization of pesticide regulatory standards by establishing more globally aligned MRLs. Supplemental material for this article is available online.

1. Introduction

1.1. Policy Background

Pesticide residue data obtained from crop field trials have been used for about four decades to support setting maximum residue limits (MRLs, also called tolerances in the United States) on pesticides. MRLs are maximum legal limits for residues of pesticides on crops and have been established to assure that pesticide residues in food are safe for consumers and to enforce compliance with pesticide label instructions regarding application. They represent levels which, if exceeded when measured in channels of commerce, allow the crop to be seized as “adulterated” by government regulatory or enforcement authorities. It is widely accepted that MRLs are not necessarily set at the maximum safe toxicological limits, and exceedances are not necessarily a health concern. More information concerning MRLs and the implications of exceeding these limits can be found in references listed in the bibliography (ECPA 2005; Crop Life America 2014).

In the United States, the Environmental Protection Agency (U.S. EPA) has published MRLs (tolerances) for more than 900 pesticides registered for domestic uses or for imported produce. These pesticide tolerances are established on more than 700 crop commodities and can be found online on the website of the U.S. Government Publishing Office’s electronic code of federal regulations (Electronic Code of Federal Regulation 2017) and in other publicly available online MRL databases (Bryant Christie Inc. 2017). The U.S. EPA MRLs are derived from field trials conducted by pesticide manufacturers that wish to obtain a “registration,” or license, to manufacture and sell the pesticide in the United States (Whitford et al. 1999). The field trials submitted to the U.S. EPA to determine a tolerance and obtain a registration are required to follow guidelines published by the U.S. EPA (1996). Among other things, the U.S. EPA guidelines require a specific number of field trials to be conducted in specified crop growing areas within the United States, and the pesticide concentration data in the crop are submitted to the U.S. EPA for review and for determination of an appropriate MRL. Specifically, the field trial data are reviewed by U.S. EPA for conformance with the guidelines. The measured pesticide concentrations in the crop from each field trial are used to calculate the U.S. MRL, or tolerance, using the OECD-developed MS Excel-based MRL calculator (OECD 2011a, 2011b). The U.S. MRL is published in the Federal Register and becomes a legally permissible pesticide residue concentration in the crop of interest. Compliance of harvested crops with U.S. tolerances is expected if pesticide applications to those crops are in accord with U.S. approved label instructions.

In the same way, other countries have national regulations that require MRLs to be set based on local data or by adopting other standards. Countries that do not set their own country-specific standards most often use the Codex Alimentarius (Codex) (FAO 2017). Codex was created by the World Trade Organization (WTO) in 1965 as a means to enable trade by setting standards like MRLs. The World Health Organization (WHO) and Food and Agriculture Organization (FAO) cooperate at two levels in order to establish Codex MRLs. One is the Codex Committee on Pesticides Residues (CCPR) that approves a work schedule and formally approves MRLs; the other is the Joint Meeting for Pesticides Review (JMPR). JMPR...
has one panel to review toxicity data and the second panel to review pesticide residue data to propose Codex MRL values to be approved by CCPR. The United States has a delegation to both CCPR and JMPR and has been active in supporting alignment of requirements between countries for harmonized MRLs. Codex evaluation criteria follow the Organization for Economic Cooperation and Development (OECD) Guidelines, which were developed to facilitate global harmonization of pesticide regulation among OECD countries (OECD 2008).

One of the significant steps toward harmonization of pesticide MRLs was the publication of OECD guideline 509 (OECD 2009) that set the framework for comprehensive global residue programs where registrants are encouraged to conduct field trials in at least two regions of intensive production for each crop using the same or similar agricultural practices, or good agricultural practices (GAP). The consolidated data could thus be used to propose a global MRL that would be inclusive of a wide range of variability. Another example supporting harmonization is the OECD MRL calculator (described above) that was published in 2014 as a tool unifying all previously existing models and is used by many OECD countries—and non-OECD countries for calculating MRLs from the pesticide registrant-submitted field trial data.

Due to efforts by various government agencies and international organizations such as the OECD, there is a high degree of harmonization in both the data necessary to establish pesticide MRLs and in the general process for determining the appropriate value for the MRL. However, in spite of these efforts, MRLs are still often dis-harmonized across countries for the same pesticide active ingredient—crop commodity combination, even when the agricultural practices (GAP) are the same. Although there are many reasons for this, the most common reason is that MRLs established in countries are largely (still) set by national authorities based on country-specific datasets of pesticide residues.

### 1.2. Why Do National Agencies Continue to Use National Datasets?

Given the above, a very relevant question is: Why do national agencies continue to use national datasets even when use practices are common among countries? One reason is that many national requirements have not been updated to acknowledge OECD promotion of global programs. Another reason is that there are not enough opportunities for global joint reviews, where the active ingredients are regulated at a supra-national level. Last to be mentioned—but not least in importance—is the fact that residue levels from different regions were suspected by many regulatory authorities to be significantly influenced by region or location. That is, commodities grown in one region, location, or country were suspected to potentially contain systematically different concentrations of pesticides than those in the same commodity grown in a different region, even if the application scenarios (e.g., application methods, rate, and timing) were exactly the same. These assumed systematic differences in pesticide residue concentrations were thought to be due to variations in climate, microclimates, local weather, soil conditions, rainfall, sunlight, etc. that are expected to differ regionally or locally. The exchangeability/interchangeability of residue data between zones, regions, or locales was not sufficiently validated, thus leading to a reluctance to combine or exchange (substitute) residue data from different geographic regions in the belief that, application parameters being equal, differences in such location- or region-specific factors could result in systematic differences in pesticide concentration study results.

The global zoning concept for field trial residues relates to the degree to which pesticide residues resulting from a given application scenario in one geographic, climatic, political, or other zone differ systematically (and predictably) from those in another zone under those (exact) same pesticide application practices. To the extent that pesticide residues do not systematically differ across geographic, climatic, political, or other zones, crop field trials conducted in one zone could be “exchanged” for or combined with those in another zone with no or minimal effect on the level of the MRL. This means, for example, field trials conducted in citrus-growing regions in the United States (e.g., AZ, CA, FL, and TX) for a given pesticide on oranges could be combined with those conducted in citrus-growing regions in Europe (Portugal, Spain, and Greece) and South America (Brazil and Chile), provided that the label-prescribed application scenarios among these locations are all the same. And instead of having separate MRLs in the United States (based on the U.S. data), Europe (based on European data), Brazil (based on Brazilian data), and Chile (based on Chilean data) the datasets could be combined to produce a single (global) MRL for oranges. A further advantage to broader acceptance of field trials conducted across the globe is that the number of field trials required within a given country to establish an MRL is generally small, and combining such trials into a larger dataset would result in a better and more representative (robust) MRL (OECD 2011b).

From 2003 to 2014, several attempts were made by various agencies and organizations to investigate the effect of geographic region or zone on pesticide residue levels from supervised field trials to determine the extent to which systematic differences in pesticide residues may or may not exist between zones. For example, the OECD and UN FAO in 2003 published the results of their first evaluation of global zoning using the JMPR residue database (OECD/FAO 2003). This report was produced as a follow-on to work conducted several years earlier in York, UK in 1999 by the OECD Working Group on Pesticides and the FAO Pesticide Management Group. To develop recommendations for field trials, they began work on the concept of a global zoning scheme to define areas in the world where trials could be considered comparable for MRL-setting purposes, irrespective of national boundaries. The objective of the OECD/FAO work was to “define and design world-wide geographic zones for conducting pesticide residue field trials, where, within each zone, pesticide residue behavior would be expected to be comparable, and therefore, where residue trial data would be considered equivalent and therefore acceptable for regulatory purposes.”

In this OECD/FAO analysis, zones were defined based on Köppen classification of climate made up of five zones: polar, cold, temperate (wet), temperate (dry), and tropical. The Köppen climate zone classification approach and the ancillary information the Group decided to explore to define zones in this
project led to some practical limitations for use. In addition, the decision to incorporate random factors such as rainfall, temperature, and sunshine hours related to the month of harvest for each crop, etc. as independent variables led to difficulties with developing and supporting a reasonable and practical path forward or any quantitatively supported judgment as to whether field trial residues in zones were comparable. In the end, the OECD/FAO report indicated that “there was a higher level of residue variability within zones than between zones” and concluded that “the differences in residue behavior between the proposed residue zones were inconsistent, and that the use of a residue zoning scheme based on refinements of existing climate maps could not be validated using the available data.” Importantly, the analysis did not attempt to quantify estimated differences in field trial residues between zones but only stated that the variability within zones was greater than that between zones. Due in part to limitations of the selected statistical approaches, the investigation did not provide relevant conclusions or sufficient information for regulatory agencies to make decisions regarding the hypothesized exchangeability of field trial residues between zones.

In 2014, OECD again published the results of another investigation of global zoning conducted by Dow AgroSciences as part of its OECD Draft Guidance Document on Crop Field Trials (OECD 2014). In this analysis, residue data from field trials following common agricultural practices of one chemical (sulfoxaflor) for 22 crops conducted in four different continents (North America, South America, Europe, and Australia and New Zealand) during 2008–2010 were analyzed on a crop-by-crop basis using a mixed-effects model with zone as a fixed factor and trial as a random factor. Two major improvements for this analysis over the earlier OECD analysis were that (i) zones were classified using geographical boundaries or continents rather than based on Köppen classification of climate made up of five zones (polar, cold, temperate wet, temperate dry, and tropical) which was used in 1999 and 2003 OECD analyses and (ii) a more sophisticated mixed-effects model was used to analyze the data. The analysis indicated that “variability within zones was greater than between zones” which was consistent with the finding reported in the earlier OECD/FAO analysis in 2003 (OECD/FAO 2003). The analysis indicated that of the total variability in the data, 78% was within zones and 12% was between zones, with the remaining 10% being attributed to other sources such as field variability and analytical variability. The result of the analysis was that “variability within zones was greater than between zones.” However, the 2014 analysis in the OECD document (OECD 2014) did not quantify or report the estimated ratios of the field trial residue concentrations between zones, and the utility of simply knowing that variability within zones was greater than between zones—even when quantified as between versus within variability—is likely insufficient evidence for combining crop field trials across zones. Furthermore, the 2014 approach of performing separate, individual analyses for each crop–pesticide combination would likely lead to problems with lack of power and possibly the inability to come to an overall single general conclusion for all crop–pesticide combinations, considered collectively.

Overall, the results of these earlier investigations agreed that location was likely not a principal factor in defining residue variability. However, these investigations either lacked statistical strength or adequate scale or scope; as a result, they have not been considered by regulatory agencies when making decisions regarding the exchangeability of field trial residues between zones, or whether field trial residues from different zones should be combined to calculate a global MRL.

2. Objective

Given that the previous analyses have not provided sufficient support for regulatory decisions, the U.S. EPA, Pest Management Regulatory Agency of Health Canada (PMRA), the USDA-supported Interregional Project-4, and CropLife America (CLA) collaborated to gather a field trial residue database suitable for determining if systematic differences in residue concentrations from supervised field trials conducted in different geographic zones existed. The objective of this project was to expand upon and improve earlier work investigating whether systematic overall differences between various global zones exist in pesticide residues resulting from supervised field trials conducted under the same agricultural practices (i.e., application rate, method of application, time interval for harvesting after the last application, etc.) of any crop–pesticide combination (e.g., field trial location, or zone is trivial with respect to establishing MRLs), and to determine the extent to which crop field trials conducted in one zone can be “exchanged” for or combined with those in another zone without minimal consequences for the level of the MRL. If there are no systematic statistically significant differences in residue levels attributable to global zones, then residue data from supervised trials conducted in multiple zones worldwide could be used to estimate global MRLs when global residue data are available. As indicated earlier, such combining of field trials would produce a larger dataset that would be expected to result in a more robust MRL—per the OECD MRL calculator.

3. Methods

3.1. Data Source

As a first step in this activity, field trial data—including information on agricultural practices, trial location, and residue levels—were provided by pesticide registrants, compiled into an electronic spreadsheet, and sent to U.S. EPA for review and statistical analysis. These data are freely available for distribution and can be accessed on the publisher’s website, but—due to the sensitivity of business information—the company names were coded as (A, B, C, etc.) and pesticide names were coded as (1, 2, 3, etc.). Data were provided worldwide for all continents (except Antarctica). Importantly, crop–pesticide combinations could only contribute to this analysis if application practices between regions were similar, and we took advantage of proportionality (OECD 2014; Limpert, Stahel, and Abbt 2001) to adjust the residues of field trials that had different application rates as long as the application rates ratios were between 0.3 and 4, the range in which proportionality has been demonstrated to be reasonable (CCPR 2013a, 2013b; OECD 2014; CLA 2014). Specifically, residues were adjusted or “normalized” to the application rate, by relying on an OECD analysis that demonstrated that residues...
on commodities will be proportional to the application rate (e.g., doubling the application rates will result in doubling the pesticide residue) (OECD 2014). U.S. EPA established a number of inclusion criteria in order for data of a given crop–pesticide combination to be included in the analysis. Specifically, (i) the crop–pesticide combination must have supervised field trial data from at least two zones; (ii) the associated residue data were required to have similar agricultural practices (such as same number of application and similar preharvest intervals (PHIs)); and (iii) the proportion of residues below the limit of detection (LOD) or limit of quantitation (LOQ) of the analytical method of a given crop–pesticide combination should not be too high which was necessarily a subjective judgment.\(^1\) Substantive differences in the agricultural practices for a given crop–pesticide combination between zones necessitated eliminating those crop–pesticide datasets from the analysis. If a crop–pesticide combination had multiple PHIs, then the PHIs that are closer to labeled (or common agricultural practices) PHIs, those with a larger number of field trials, and those that had a lower proportion of residues <LOD or <LOQ were selected to include in the analysis.

The final analysis included data from 700 field trials including 23 crops, 11 chemicals (3 fungicides, 1 herbicide, and 7 insecticides), and 36 different crop–pesticide combinations for which field trials existed in two or more zones among Europe, South America, North America, and Australia and New Zealand.\(^2\) Note that after removing datasets that did not meet the inclusion criteria described above, only a single herbicide trial remained. The regions of Europe and North America had the largest numbers of crop–pesticide combinations (34 combinations for each zone) while the Australia and New Zealand region had data reflecting 20 different crop–pesticide combinations. The South America region had data from nine crop–pesticide combinations. Table 1 summarizes the number of field trials available in the analysis for each zone and each class of pesticide (herbicide, insecticide, etc.). One field trial in Asia and 24 field trials in Europe (of a crop–pesticide combination) and 5 field trials in Africa and 7 field trials in Asia (of another crop–pesticide combination) were excluded from the analysis since there was an insufficient number of crop–pesticide combinations in Africa and Asia for reliable estimates for these two zones.

### 3.2. Statistical Methods

All statistical analysis was performed using SAS v9.3. The process used to conduct the analysis related to the objective followed a step-by-step procedure, beginning with a review of past attempts and methods to evaluate the effect zones might have—or not have—on pesticide residues, and then moving onto the selection of statistical methods appropriate for use. This included evaluation of these methods through synthetic residue datasets generated with known parameters as well as a “trial run” using actual field trial data from 2895 field trials of 219 datasets comparing the U.S. and Canadian field trial residues provided by Canada’s Pest Management Regulatory Agency (PMRA). A summary of this process is provided below with details and results presented in CCPR (2016), available online.

1. Review past attempts and methods to evaluate Global Zoning
2. Develop statistical methods appropriate for use in evaluating the Global Zoning concept
3. Evaluate the selected statistical methods using synthetic residue data (artificial data, representing typical residue distributions)
4. Evaluate the “exchange ability” of residues between the United States and Canada as a test case using a real residue database provided by PMRA
5. Extend the method to a global basis based on datasets collected from around the world EU-North versus EU-South Global (North America, Europe, South America, and Australia–New Zealand)
6. Internal/External Review
7. Review/Develop Policy

The residue distributions were assumed to be lognormal (or near lognormal) so log-transformation was applied to the residues prior to the analysis. Environmental data often display a lognormal distribution since they are nonnegative, right-skewed, and can typically arise from geometric (rather than arithmetic) growth (Ott 1995; Limpert, Stahel, and Abbt 2001). Since the mixed-effects model analysis performed here assumes the residue data follow lognormal distributions, a rank sum test for clustered data (Datta and Satten 2005) was used to evaluate the sensitivity of the conclusion to this assumption of log-normality. The rank-sum test for clustered data is a nonparametric test, and so does not make any assumptions about the distribution of the field trial residues. Thus, field trial residue data were used directly for the analysis without any transformation for this test. For both the mixed model and rank sum tests, no significant systematic differences were seen between zones. We note that different crop–pesticide combinations are expected to differ in their residue distributions (e.g., residues of Pesticide X on apples might differ systematically—and possibly quite dramatically from Pesticide Y on grapes). Similarly, pesticide residues derived from field trials from the same crop–pesticide combination are expected to be more similar to each other than the residues in field trials from different crop–pesticide combinations. To properly account for the similarity of residues from the

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\(^1\)The LOD is that concentration level at which the presence of a substance can be reliably determined and the LOQ is that concentration level at which the actual measured concentration—and not simply absence versus presence—can be reliably determined.

\(^2\)Due to the small number of crop–pesticide combinations in Africa and Asia, the data from those zones were not included in the analysis.
same crop–pesticide combination in the database (clustering or intra-class correlation), statistical methods appropriate for nested/clustered data were used to analyze the data. Specifically, the method used to compare the residues between zones was a mixed-effects model (PROC MIXED, SAS 9.3) for an unbalanced, incomplete block study design, where each crop–pesticide combination was considered as a random block. Crop–pesticide combination and trial nested into crop–pesticide combination were set as random effects in the model. The mixed model with random zone effects was selected since it had a lower Akaike information criterion value than the model with common zone effects. The random zone effects of each crop–pesticide combination and the “average” (fixed effects) of random zone effects of all crop–pesticide combinations were estimated from the mixed-effects model. The systematic zone effects on residues in terms of ratios are the anti-logs of the estimates from mixed-effects model are presented in Table 2.

Below is the statistical equation of the mixed model:

\[ y_{ijkl} = \text{intercept} + \text{zone}_i + \text{pesticide}_j + \text{crop}_i + \epsilon_{ijkl}, \]

where \( y_{ijkl} \) is the log of residue of replicate \( l \) of field trial \( k \) of crop–pesticide \( j \) in zone \( i \); intercept is the fixed effect, a grand mean of all log(residue) of all crop–pesticide combinations in all zones; \( \text{zone}_i \) is the fixed effect of zone \( i \); \( \text{pesticide}_j \) is the random effect of crop–pesticide \( j \), \( \text{crop}_i \sim N(0, \sigma^2_{\text{cp}}) \) and \( \sigma^2_{\text{cp}} \) is the component variance of crop–pesticide combination (i.e., the variance of random intercept of experimental subject = crop–pesticide combination); \( \epsilon_{ijkl} \) is the random effect of replicate \( l \) of field trial \( k \) of crop–pesticide \( j \) in zone \( i \) = \( N(0, \sigma^2_{\text{cpz}}) \) and \( \sigma^2_{\text{cpz}} \) is the variance between zones; \( \epsilon_{ijk} \) = \( N(0, \sigma^2_{\text{cpz}}) \) is the variance of replicates within field trial.

### 4. Results and Discussion

#### 4.1. Mixed-Effects Model Results

The variance components of the random effects estimated from the mixed-effects model are presented in Table 2.

As can be seen, the between-zone variance (value 0.1925) accounts for only 20% of the total variance of within crop–pesticide combination while within-zone variance (value 0.7077 + 0.0672) accounts for more than 80% of the total variance (represented by the sum of 0.1925, 0.7077, and 0.0672). These values imply that within-zone variations are substantially larger than between-zone variations.

Estimated ratios of residues between zones with 95% confidence intervals (i.e., the anti-logs of the estimates from mixed-effect model) were considered with the expectation that these ratios would equal 1 if no systematic zonal differences existed. To the extent that systematic zonal differences do exist, these ratios of residues between zones would deviate from 1. The results are presented in Table 3. A nonparametric rank sum test for clustered data (Datta and Satten 2005) was also performed as described in the supporting technical document with a resulting p-value of 0.686 (CCPR 2016). However, this rank-sum analysis (by its nature) cannot estimate the pairwise estimated residue ratios between zones nor the confidence limits of the differences. Another disadvantage of the nonparametric rank-sum approach to this analysis is that it cannot identify the crop–pesticide combinations that have extreme (or outlier) estimated residue ratios.

As can be seen, the analysis using a mixed-effects model found no significant differences between zones (p-value = 0.285) when these regional differences are considered jointly. Further information concerning the ratios in the residue concentrations between zones was also estimated. As seen in Table 3, the point estimates of these ratios range from a low of 0.724 for AU-NZ when compared to EU (indicating that AU-NZ is estimated to have residues that are systematically 27.6% lower than that of the EU) to a high of 1.207 for EU versus NA (indicating that residues in the EU are estimated to be systematically higher than those in NA by 20.7%). Neither of these differences, however, are statistically significant. The smallest estimated systematic difference between zones is 1.3% (with confidence intervals ranging from about 41% lower to 65% higher) based on eight trials representing the difference between NA versus SA. The smallest and largest values among the 95% confidence intervals of the estimated residue ratios are 0.496 (AU-NZ vs. SA) and 1.991 (EU vs. SA), which means that the estimated ratios at the 95% confidence level are within about 2-fold of each other. The following conclusions can be drawn from this analysis:

- there is not an overall statistically significant systematic difference in residues between the zones examined (\( p = 0.285 \));
- there are not statistically significant differences between pairs of zones examined (with p-values ranging from 0.074 for AU-NZ vs EU (estimated residue ratio of 0.724) to a p-value of 0.959 for NA vs SA (estimated residue ratio of 0.987)); and
- confidence intervals for the ratios range from about 2-fold lower to about 2-fold higher suggesting that we can be

**Table 2.** Variance and covariance estimated from the mixed-effects model.

| Covariance parameter   | Subject          | Estimate |
|------------------------|------------------|----------|
| Intercept              | Crop–pesticide   | 3.0788   |
| Zone                   | Crop–pesticide   | 0.1925   |
| Field trial (crop–pesticide) | Residual          | 0.7077   |
|                        | Residual         | 0.0672   |

**Table 3.** Results of comparisons from mixed-effects model.

| Comparison                          | No. crop–pesticide combinations with data available for both Zones | Ratio of residues between zones (unadjusted 95% CI) | ANOVA p-value | zone effect |
|-------------------------------------|-----------------------------------------------------------------|--------------------------------------------------|--------------|-------------|
| AU-NZ versus EU                     | 19                                                              | 0.724 (0.507, 1.033)                              | 0.074        | 0.285       |
| AU-NZ versus NA                     | 19                                                              | 0.874 (0.613, 1.246)                              | 0.449        |             |
| AU-NZ versus SA                     | 5                                                               | 0.862 (0.496, 1.499)                              | 0.593        |             |
| EU versus NA                        | 32                                                              | 1.207 (0.919, 1.585)                              | 0.172        |             |
| EU versus SA                        | 7                                                               | 1.191 (0.713, 1.991)                              | 0.498        |             |
| NA versus SA                        | 8                                                               | 0.987 (0.591, 1.649)                              | 0.095        |             |

NOTE: AU, Australia; NZ, New Zealand; EU, European Union; NA, North America; SA, South America.
reasonably confident that the [average] ratios—if different from 1—differ by no more than 2-fold.

The results from this analysis\(^3\) are in general agreement with what Dow AgroSciences found in 2014 when they stated that “variability within regions was greater than between regions,” measuring between—and within-zonal variation as 12% and 78%, respectively. What this means is that zone per se (be it North America, Europe, South America, or NZ/Australia) has a relatively small effect on the residues of a given crop–pesticide combination compared to the effects within a zone, and that the major effect on pesticide residues appears to derive from more local (within zone) conditions and statistical/experimental errors (field-specific and local idiosyncrasies, analytical error, statistical noise, etc.) than from larger macro-conditions which would be manifested through between-zone effects.

4.2. Regression Diagnostics—Model Fitness

The above conclusions depend upon the validity of the model that was generated. The validity was investigated graphically by reviewing the distribution of the residuals and by examining the outliers. Figures 1 and 2 present the histogram and Q–Q plot of the residuals of log(residue) of zones by crop–pesticide combination, where a residual was estimated by the mixed-effects model to be the estimated log(residue) of each zone per crop–pesticide combination minus the estimated log(residue) of each crop–pesticide combination from all zones together. Since one of the assumptions of mixed-effects models is that the errors follow a normal distribution, the histogram of the random effects in Figure 1 is expected to have a bell shape, and all the data points in the Q–Q plot in Figure 2 are expected to be on or close to the line in the figure. A residual of a zone-crop–pesticide combination that is located on the left tail or right tail of the normal curve in Figure 1 (or, equivalently, not close to the regression line in Figure 2) is an outlier and, ideally, there are at most only a few of these. As shown, the histogram in Figure 1 follows a bell shape and the majority of data points in Figure 2

\(^3\)Results and methods for this analysis comparing NA/SA/EU/AUS-NZ—and the two additional analyses discussed later comparing (i) Canada versus the United States and (ii) Northern Europe versus Southern Europe—are shown in the supplemental material (Table S1).
are located close to or on the line in the figure except for four high (or low) end data points. This provides some assurance that the selected mixed-effects model provides a reasonable fit to the data, and that gross departures of assumptions or violations are not apparent.

The regression diagnostics also produced additional histograms of random effects of the ratio (i.e., zone effect) in the log-scale and actual scale on a pairwise comparison basis. These are not shown here, but more information on the regression diagnostics used to validate the model and analysis can be found in CCPR (2016), available online.

The two high-end and two low-end values shown in Figures 1 and 2 were from two crop–pesticide combinations (out of 36 combinations), and the estimated residue ratios (calculated from estimated random effects) associated with these four outliers were 4.73 and 3.90, which is not unexpected and can happen by chance given the nature of large variation of residues within a crop–pesticide combination.

The lack of a significant zonal effect as concluded from this analysis was also observed in the evaluations of field trial residue data from United States versus Canada and (separately) Northern Europe versus Southern Europe. Summaries of these comparisons are presented in the supplementary materials provided with this article, and a full description may be found in CCPR (2016).

- **For the United States and Canada:** The field trial residue database consisted of the U.S. and Canadian residue data from 2895 field trials consisting of 219 different crop–pesticide combinations, 21 different crop groups, and 37 different pesticides. We compared U.S. residues (representing one geographic region) with those from Canada (representing the second region). Both the rank-sum test for clustered data and the mixed-effects model indicate that field trial residues between the United States and Canada are not significantly different on a systematic basis (rank-sum test \( p \)-value = 0.268, mixed-effects model \( p \)-value = 0.281). The mixed-effects model shows that the residues of Canadian field trials are about 5% higher than the United States, but the difference is not statistically significant (see Figure S1). In part for this reason, both the United States and Canada were combined to create the “North American” zone in the current global analysis.

- **For EU-North versus EU-South:** The analysis included 702 field trials consisting of 64 different crop–pesticide combinations. Both rank-sum test and mixed-effects model analyses indicate that there were no systematic differences between field trial residues in Northern Europe and Southern Europe (\( p \)-values = 0.876 and 0.403 for the rank-sum and mixed effects models, respectively). On average, field trial residues in Northern Europe were estimated to be about 8% higher than field trial residues in Southern Europe, but the difference is not statistically different (see Figure S2). Similar to the North American case of the United States and Canada, EU-North and EU-South were combined and considered a single “EU” zone in the current global analysis.

### 4.3. Impact on Global and Zone-Specific MRLs

Ultimately, the relevance of this statistical analysis on the policies adopted internationally by trading partners relate to how pesticide residue data are used for regulatory decisions. For example, should residue datasets resulting from the same pesticide application practices be treated as specific to a region or zone and be used to develop MRLs specific for that area or, alternatively, should they be combined into a more broadly applicable global dataset and used to derive a globally applicable MRL? Furthermore, what are the consequences of combining data to develop a globally harmonized MRL from zones that may indeed (for a specific crop–pesticide combination) have systematically different pesticide residues? To what extent would combining these residues into a single harmonized global MRL result in an inappropriate MRL, both globally and for the zone/region in question? Although it is generally recognized that more robust MRLs are derived from larger datasets, there may be some concern about combining residues when large zonal systematic differences exist and their potential to erode the advantage of using a larger number of (global) trials to establish an MRL.

To determine if combining residues on a global scale might result in an inferior MRL if there existed a systematic difference in residues in one region, we performed a simulation to evaluate the extent to which a globally determined MRL might be less than optimal for the zone with systematically different residues. This is necessarily a balancing act and addresses the question: “To what extent does a relatively large, systematic between-zone difference in residue values undermine the benefits of using a larger dataset to derive a globally-based MRL?” Specifically, we created a synthetic dataset with four regions in which residues in one region were systematically lower than residues in the remaining regions by 30% (the largest difference found in Table 3 between AUS-NZ vs. the EU). This was done to evaluate the effects on MRLs if residue data were pooled from different zones when residues in one zone were systematically different from those in the other zones. For the simulation, field trial residues were randomly generated from lognormal distributions with \( CV = 1 \) (a reasonable assumption for field trial residues based on past work). The geometric mean of residues in Europe, North America and South America were arbitrarily selected to be 0.5 ppm while the geometric mean of residues in Australia-New Zealand was selected to be 0.35 ppm, 30% lower than for the other three zones. For each of 1000 iterations in the simulation, the MRLs were calculated using the OECD MRL calculator (i.e., MRL = the maximum of \( \left[ \text{the maximum residue value, } 3 \times \text{the average of residue values, the average of residue values} + 4 \times \text{standard deviation of residue values} \right] \) for each zone individually (EU, NA, SA, AU-NZ, with the latter calculated as 30% lower than the others) as well as pooled across all four zones using data from 9, 7, 5, or 3 field trials per zone (3 field trials is the lowest number of field trials required by the OECD MRL calculator (for details on the calculator, see OECD 2011a, 2011b)).
5. Simulation Results

The fraction of calculated MRLs that fell below the 95th percentile of the full zonal residue distributions was reported, as this is a critical measure of the appropriateness of the MRL. Specifically, MRLs are desired to exceed the 95th percentile of the distribution of underlying residue population, and MRLs which are consistently lower than the 95th percentile of the underlying residue population are considered problematic since they would underestimate what might be considered to be reasonably expected pesticide residue concentrations.

Figure 3 presents the boxplots of distributions of global and zone-specific MRLs from the simulation with 1,000 iterations.

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4 Additional details are presented in the technical paper published by CCPR-48 (CCPR 2016). Table S2 of the supplemental materials also provides further summary information on the proportion of MRLs below the 95th percentile of zone-specific residue distributions from this technical paper.
From Figure 3, we see that—regardless of the number of field trials used in the simulation—significantly fewer MRLs fell below the 95th percentile when the residues were pooled from all four zones. For example, less than 6% of the global MRLs calculated from pooling residues from four field trials from all four zones were below the 95th percentile of the zonal residue distributions (0.1% for the zone with the 30% lower residues and 5.6% for the other zones). However, 16–19% of the zone-specific MRLs with four field trials fell below the 95th percentile.

In each case, the distribution of global MRLs based on field trials from all four zones, including the AUS-NZ zone with residues that were 30% lower, was narrower than the zone-specific MRLs, indicating a more robust MRL. However, the zonal MRLs of Australia and New Zealand were generally lower than the global MRLs which is not ideal, but expected since the simulation modeled the extreme case in which supervised field trials in Australia and New Zealand were systematically generated to be 30% less than the corresponding supervised field trial residues in the other zones.

From the scenarios that were evaluated in the simulation, the global MRLs calculated from pooling zonal residues are generally better than zone-specific MRLs that are calculated for each individual zone from zone-specific supervised field trial data, defined as having a lower proportion of estimated MRLs below the true 95th percentile. This is true even when pesticide residues from one of the zones are 30% lower than those from the other zones.

6. Conclusion

This analysis indicates that there is no statistically significant systematic overall difference in pesticide residues resulting from supervised field trials conducted with the same agricultural practices in different global zones. Implicit in this conclusion is an assumption that the residue trials are conducted in areas that are conducive to growing a healthy crop. The importance of this outcome is that the effect of field trial location, or zone, is trivial with respect to establishing MRLs, and crop field trials conducted in one zone can be “exchanged” for those in another with no or minimal consequences for the level of the MRL. In fact, it is likely that the larger number of field trials that would consequently be available to establish a global MRL may result in a better, more robust MRL than would have been established on an individual zone basis.

When better performance in MRL estimation is defined as having a low proportion of estimated MRLs below the true 95th percentile, the MRLs calculated from pooling zonal residue data from the evaluated simulations are generally better than MRLs that are calculated from zone-specific data. Therefore, when global residue data are available (and appropriate), pooled residue data, rather than zone-specific residue data, are able to derive more robust MRLs. Furthermore, use of a common, global dataset by the various regulatory authorities will improve the prospects for achieving globally harmonized MRLs. Finally, even if there are differences in residues among zones that are systematic (up to 30% was tested here), MRLs obtained by pooling residues globally across zones are improved in that they are substantially less likely to produce MRLs that are below the 95th percentile of the residue distribution.

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Disclaimer

The analysis described in this article has been reviewed by the Office of Chemical Safety and Pollution Prevention (OCSPP), US EPA and approved for publication. Approval does not signify that the contents necessarily reflect the views, policies, or determinations of the Agency, nor does the mention of trade names of commercial products constitute endorsement or recommendation for use.

Supplementary Materials

Supplementary materials provide mixed effects model results and summary statistics comparing the exchangeability of field trial residues between U.S. and Canada and Northern and Southern Europe. Further technical documentation as part of a technical support document is also publicly available in CCPR (2016). The full raw dataset and SAS code are also provided, with the SAS code also appearing in CCPR (2016) (Section E of Part XI).

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