Organisation de Coopération et de Développement Économiques
Organisation for Economic Co-operation and Development

07-Sep-2016

English - Or. English

ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

OECD GUIDANCE DOCUMENT ON CROP FIELD TRIALS

SECOND EDITION
Series on Pesticides - No. 66
Series on Testing & Assessment - No. 164

JT03400223

ENV/JM/MONO(2011)50/REV1
Unclassified
English - Or. English

OECD Environment, Health and Safety Publications

Series on Pesticides

No. 66

and

Series on Testing and Assessment

No. 164

Guidance Document on Crop Field Trials

SECOND EDITION

IOMC

INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS

A cooperative agreement among FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD

Environment Directorate
ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT
Paris 2016

About the OECD

The Organisation for Economic Co-operation and Development (OECD) is an intergovernmental organisation in which representatives of 35 industrialised countries in North and South America, Europe and the Asia and Pacific region, as well as the European Commission, meet to co-ordinate and harmonise policies, discuss issues of mutual concern, and work together to respond to international problems. Most of the OECD's work is carried out by more than 200 specialised committees and working groups composed of member country delegates. Observers from several countries with special status at the OECD, and from interested international organisations, attend many of the OECD's workshops and other meetings. Committees and working groups are served by the OECD Secretariat, located in Paris, France, which is organised into directorates and divisions.

The Environment, Health and Safety Division publishes free-of-charge documents in twelve different series: **Testing and Assessment**; **Good Laboratory Practice and Compliance Monitoring**; **Pesticides**; **Biocides**; **Risk Management**; **Harmonisation of Regulatory Oversight in Biotechnology**; **Safety of Novel Foods and Feeds; Chemical Accidents; Pollutant Release and Transfer Registers; Emission Scenario Documents; Safety of Manufactured Nanomaterials;** and **Adverse Outcome Pathways.** More information about the Environment, Health and Safety Programme and EHS publications is available on the OECD's World Wide Web site (www.oecd.org/chemicalsafety/).

This publication was developed in the IOMC context. The contents do not necessarily reflect the views or stated policies of individual IOMC Participating Organizations.

The Inter-Organisation Programme for the Sound Management of Chemicals (IOMC) was established in 1995 following recommendations made by the 1992 UN Conference on Environment and Development to strengthen co-operation and increase international co-ordination in the field of chemical safety. The Participating Organisations are FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD. The purpose of the IOMC is to promote co-ordination of the policies and activities pursued by the Participating Organisations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

This publication is available electronically, at no charge.

For this and many other Environment, Health and Safety publications, consult the OECD's World Wide Web site (www.oecd.org/ehs)

or contact:

OECD Environment Directorate,
Environment, Health and Safety Division
2, rue André-Pascal
75775 Paris cedex 16
France

Fax : (33-1) 44 30 61 80

E-mail : ehscont@oecd.org

FOREWORD

This Guidance Document is an update of the first *Guidance Document on Crop Field Trials* published in 2011. It has been developed by the Residue Chemistry Expert Group of the OECD Working Group on Pesticides (WGP).

Crop Field Trials (CFT, also referred to as supervised field trials) are conducted to determine the magnitude of the pesticide residue in or on raw agricultural commodities, including feed items, and should be designed to reflect pesticide use patterns that lead to the highest possible residues. While the *OECD Guideline for the Testing of Chemicals on Crop Field Trial* (TG 509 published in September 2009) provides a harmonized approach to conducting and reporting crop field trials in OECD countries, this *Guidance Document on Crop Field Trials* helps in planning the trials in OECD countries and in interpreting the results.

Around the time the first Guidance Document was published, outstanding issues related to the CFT studies were raised following an OECD survey on Maximum Residue Level (MRL) policies in member countries (survey results published in 2010, Series on Pesticides, No. 51). Further work on these issues was discussed and agreed upon at the September 2011 Pesticides Registration Steering Group (RSG) Meeting (Ottawa, Canada) and then endorsed by the RSG's parent body, the WGP.

The Ottawa RSG Meeting agreed that the 2011 CFT Guidance Document should be updated with respect to the following points: i) crop groups and representative commodities; ii) considering the use of the proportionality principle for adjusting crop field trial values relative to application rate; iii) the independence of trials; iv) the composition of data sets; and v) further direction on the collection and preparation of field trial samples.

After two rounds of comments in 2014-2015 among the WGP and the Working Group of National Co-ordinators of the Test Guidelines Programme (WNT), the updated CFT Guidance Document was approved by the WGP and WNT in April 2016.

This publication is organised into two parts: the core document on guidance for conducting crop field trials ENV/JM/MONO(2011)50/REV1 and the three Annexes that are published together in ENV/JM/MONO(2011)50/REV1/ANN.

This document is being published under the responsibility of the Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology, which has agreed that it be declassified and made available to the public on 29 August 2016.

TABLE OF CONTENTS

INTRODUCTION

1. Crop field trials (also referred to as supervised field trials) are conducted to determine the magnitude of the pesticide residue in or on raw agricultural commodities, including feed items, and should be designed to reflect pesticide use patterns that lead to the highest possible residues. Objectives of crop field trials are to:

1. quantify the expected range of residue(s) in commodities following treatment according to the proposed or established Good Agricultural Practice (GAP);

2. determine, when appropriate, the rate of decline of the residue(s) of plant protection product(s) on commodities of interest;

3. determine residue values such as the Supervised Trial Median Residue (STMR) and Highest Residue (HR) for conducting dietary risk assessment and calculation of the dietary burden of livestock; and

4. derive maximum residue limits (MRLs).

2. The purpose of these trials is described in the OECD Test Guideline 509 on Crop Field Trials. While the TG 509 provides a harmonized approach to conducting and reporting crop field trials in OECD countries, this Guidance Document on Crop Field Trials will help in planning the trials in OECD countries and in interpreting the results.

3. The document will discuss some aspects that need to be considered while evaluating crop field trials. Topics include:

- Principles of crop grouping and selection of appropriate representative commodities as a prerequisite for extrapolation of results from residue trials used in national/regional approaches as well as in Codex;

- Proportionality, the relationship between application rate and resulting residues;

- Equivalency of formulations;

- Use of conversion factors for converting residues measured using the residue definition for MRL/Tolerance enforcement to residues corresponding to the residue definition for risk assessment;

- Conversion of residues in whole commodity to the residue in edible parts of the commodity;

- Geographical distribution of the residue trials;

- The number of residue trials required using national/regional approaches, the Codex approach and comprehensive data submissions in OECD countries;

- The selection of residue data for MRL determination; and

- The Use of the OECD MRL Calculator.

4. After publication of the first version of this OECD Guidance Document in 2011, new developments took place and it was decided to take them into account in this revision.

- In 2013 the Codex Alimentarius Commission adopted the "Principles and Guidance for Application of the Proportionality Concept for Estimation of Maximum Residue Limits for Pesticides". According to Codex, the proportionality concept can be applied to data from field trials conducted within a rate range of between 0.3X and 4X the GAP rate. The OECD considered whether it is appropriate to restrict this range and decided to recommend the same range as Codex. The range is based on the decision that a deviation of ±25% between actual and estimated concentration of residues is acceptable.

- In the 2011 version of this OECD Guidance Document it was stated that "current evidence suggests that residue data generated at a similar GAP in different geographical regions/climatic zones may be used as a consolidated global dataset for MRL setting. Additional exploration is recommended to define the extent of applicability of the concept". These data are now available and the results and the recommendations are included in this revision.

- It was decided to streamline this OECD Guidance Document by concentrating on conclusions and recommendations. As the background is important for the understanding of conclusions and recommendations, it was decided to provide it into annexes.

- Some additional information and editorial changes were also included in this revision.

1. Crop Grouping

Background

5. National authorities use targeted data sets and data extrapolation to provide sufficient data for exposure assessment or for setting MRLs for both individual major and minor commodities, and commodity groups. Data extrapolation provides the mechanism for extending field trial data from several (typically two or three) representative commodities to related commodities in the same commodity group or subgroup. Crop grouping and the identification of representative commodities are also critical for maximizing the ability to use a targeted data set determined for representative commodities to support minor uses. The representative commodity (within the group) has the following properties:

a) major commodity in terms of production and consumption; and

b) most likely to contain highest residue.

6. Representative commodities are those designated commodities from which extrapolations of residue data sets can be made to one or more related commodities or to an entire group of commodities. Commodity group schemes are intended to classify commodities into groups and subgroups that have similar characteristics and residue potential (Codex Alimentarius Commission, 1993). For example, the Codex pome fruit group contains inter alia apple, pear, crab-apple, loquat, medlar, quince, and Japanese Persimmon. As an example for representative commodities apple and pear would be suitable.

7. One use of the crop grouping approach is to establish a maximum residue limit (MRL, tolerance) for the entire group based on field trial data for several of the commodities, designated representative commodities, within the group. In the pome fruit group, residue data for apples and/or pears would be used to establish a MRL for pome fruit. This MRL would apply to all members of the group provided the GAP is comparable within the crop group.

8. All the OECD Countries use a certain crop grouping scheme in their national authorisation system. The classification systems in North American Free Trade Agreement (NAFTA), European Union (EU), and Codex are currently under revision and expansion. The NAFTA system is being revised and expanded based on petitions to the US EPA from the Interregional Research Project No. 4 (IR4). IR4 creates the petitions based on work with the International Crop Grouping Consulting Committee (ICGCC), USDA, and EPA/OPP. The ICGCC is a voluntary association of international experts with interests in plant physiology, residue research, regulation, and the growth/export/import of minor crops. Simultaneously, Codex via a CCPR (Codex Committee on Pesticide Residues) workgroup chaired by the Netherlands is working on the revision of the Codex Classification of Foods and Feeds. The work of the ICGCC/IR4 is a very important input for this revision.

9. Annex 1 of this Guidance Document describes the current situation and contains a table of the groups, subgroups, representative commodities, and extrapolations in Codex, EU, Australia, Japan, and NAFTA.

10. Like the EU, Codex uses commodity codes to facilitate proper identification of commodities. Note that in the classification there are crops with multiple commodities (e.g. radish root and tops), with these commodities being in different classification groups.

11. Crop grouping in this guidance document will emphasize the criteria for classification, issues related to representative commodities, and opportunities for additional extrapolations. Guidance will be provided on the use and combination of data sets for group MRLs.

Conclusion and Recommendation on Crop Grouping

12. The OECD decided not to work on its own crop grouping system. It recommends the adoption of the Codex commodity groups and examples of representative commodities as they are adopted by the Codex Alimentarius Commission.

13. Currently the Codex commodity groups for all fruits were adopted by the Codex Alimentarius Commission in July 2012, REP12/CAC (for details see Table 1, in Section 10). Further Codex commodity groups are under discussion in the Codex Committee on Pesticide Residues (http://www.codexalimentarius.org/codex-home/en/) and will be adopted by the Codex Alimentarius Commission at a later stage.

2. Extrapolations

14. Extrapolation means that a residue data set from one or more commodities is extrapolated to establish a group MRL if the GAP for the members within the commodity group is the same. Extrapolation is closely connected to crop grouping. A pre-requisite is the selection of representative commodities which is described in Chapter 1 on Crop Grouping. Additional information on national approaches, statistical approaches and possibilities on wider extrapolations are given in Annex 2.

Conclusion and Recommendation on Extrapolations

15. Different datasets from (representative) commodities belonging to the same commodity group or subgroup treated according to the same GAP should be inspected by the risk assessor, preferably using statistical means to decide whether these datasets can be combined. Statistical tools that may be used are Mann-Whitney U-test or Kruskal-Wallis H-test (such test could be found for example at http://ec.europa.eu/food/plant/docs/pesticides_mrl_guidelines_mann-whitney_2015_en.xls and http://ec.europa.eu/food/plant/docs/pesticides_mrl_guidelines_kruskal-wallis_2015_en.xls). However, such

tools may not be useful with small data sets (< 5) except using an alpha value of 0.1 or higher. Other statistical tools may be accepted to compare datasets provided they are scientifically justified.

16. Provided that datasets belong to the same population the results can be combined. In that case the combined dataset is used for MRL estimation and the estimate is used for MRL setting for the whole group or subgroup.

17. If the datasets do not belong to the same population a pragmatic approach is recommended. It is proposed to calculate specific MRLs for the data sets, and take the higher estimate for the group MRL and the other estimates for single commodity MRLs within the commodity group, or to calculate and set specific sub-group MRLs when there is sufficient data. With this approach the risk of MRL exceedances for the remaining (minor) crops residue behaviour is minimized.

18. Wider extrapolations may be possible on a case-by-case basis.

3. Proportionality

19. Proportionality means that when increasing or decreasing the application rate the residue level increases or decreases in the same ratio. In an ideal situation it means that doubling the application rate results in doubling the residue. Proportionality implies that the relationship between application rates and residues is linear.

20. A proposal to predict the level of residues in plant matrices on the basis of the assumption that residues will increase linearly with the application rate was considered by experts within JMPR and OECD. The quantity of a pesticide initially deposited and retained on a crop surface depends upon many factors, including the physical-chemical properties of the active substance and especially the spray liquid, the nature of the (leaf) surface, growth stage and the application method used. The crop canopy is also important for determining spray deposits. Therefore, the extrapolation of residues usually was not accepted as a waiver for residue trials in the past. However, in a small number of cases, the approved label application rate may ultimately be different from the field trial study rate due to various reasons (regulatory action, local restrictions, changing environmental requirements, etc.). Residue studies in plants are usually not conducted as parallel trials using different application rates under otherwise identical conditions. A proposal on predicting residues was recently considered which may save time, money and resources while avoiding significant uncertainty.

Background

21. In a publication by MacLachlan and Hamilton (2010) a proposal was made to use day zero data and residue decline studies to estimate median and highest anticipated residues in foliar-treated crops. In this model the residue levels were "normalised" for application rates, which assumes proportionality between application rates and residues. This and other tools may be developed in the future to assist MRL estimation.

22. In the JMPR Report 2010 (FAO, 2011a) a general item on proportionality reported the results of an analysis by MacLachlan and Hamilton (2011) of a large number of side-by-side trials in which application rates were compared. The MacLachlan and Hamilton approach was based on an analysis of slope and intercept of the $\ln(C_2)$ plotted as a function of $\ln(C_1)$, where C_2 is the residue from the higher application rate and C_1 is the residue from the lower application rate. It was also based on the evaluation of the ratio $[R_2/R_1]/[C_2/C_1]$ where R is the application rate and C is the residue concentration. In case of true proportionality, this ratio would be 1.0.

23. The main conclusions of this analysis were:

- Residues of insecticides and fungicides in plant commodities do scale with application rate, allowing prognosis on residue levels resulting from field trials conducted using variable application rates.

- Proportionality was found to be independent of the ratio of application rates (at least for the range 1.3× to 10× or their reciprocal) formulation type, application type (foliar spray, soil spray and seed treatment), PHI, residue concentration or crop.

24. The 2010 JMPR recommended:

- Principles of proportionality should not be used for herbicides and plant growth regulators applied to growing plants or for granular applications since these types of uses were not sufficiently investigated (based on lack of data).

- While residues are generally proportional in the whole commodity (e.g., citrus fruit), careful application of proportionality is required for the corresponding protected parts (e.g., fruit pulp).

- A use may be supported by up-scaling residue data from trials conducted at rates below the GAP or by down-scaling residue data from trials conducted at rates above the GAP; up-scaling of residues should be limited to a factor of 3, down-scaling to a factor of 5.

25. The Codex Committee on Pesticide Residues 2011 agreed that the 2011 JMPR could elaborate MRLs proposals with and without making use of the concept of proportionality so that the result could be compared and discussed at the next session of the Committee. It was noted by the Codex Committee that:

- This situation usually applied to minor crops and should therefore be limited to these crops.

- When applying proportionality, all data points under consideration, i.e. within/outside the acceptable range of ±25%, should be adjusted to 1X to prevent issues of bias.

- The concept of proportionality should be further tested to ensure reliable results before the Committee endorse this approach for use by JMPR.

26. In 2011 the JMPR elaborated the proportionality approach for five active substance / commodity-combinations in General Considerations 2.3 (FAO, 2011b). CCPR 2012 considered a number of MRLs proposed by JMPR based on proportionality and agreed to advance them to Step 5 (for further consideration). There were concerns by some countries that clear guidance on how and when to apply proportionality had not been finalised, and an electronic working group was established by the Committee to develop principles and guidance for use of proportionality to estimate maximum residue levels. The 2012 JMPR further defined criteria for use of proportionality, noting that proportionality based on spray concentrations can only be applied to residue trial data following consideration of both spray concentration and spray volume applied per area on a case by case basis (JMPR Report 2012, General Item 2.9, FAO, 2013). The JMPR again applied the principle in several cases where MRL estimates could not otherwise be made.

27. To this end, industry and regulatory authorities were asked to provide residue data from further side-by-side residue data conducted at different rates which had not been reviewed previously by MacLachlan and Hamilton (i.e. that were not included in the JMPR evaluations issued between 2000 and 2009). Data were provided (as Excel spreadsheets) by the governments of China and Japan, as well as by BASF, Bayer CropScience, Dow AgroSciences, DuPont, and Syngenta. The data were distinct from (i.e., supplemental to) that used by MacLachlan and Hamilton.

28. Details of data evaluation are given in Annex 3.

Conclusion and Recommendation on Proportionality

29. In May 2013 the Codex Committee on Pesticide Residues decided to propose the following principles and guidance for application of the proportionality concept for estimation of maximum residue limits for pesticides for inclusion into the Procedural Manual as an Annex to the Risk Analysis Principles Applied by the Codex Committee on Pesticide Residues:

a) Use of the concept for soil, seed and foliar treatments has been confirmed by analysis of residue data. Active substances confirmed included insecticides, fungicides, herbicides, and plant growth regulators, except desiccants.

b) The proportionality concept can be applied to data from field trials conducted within a rate range of between 0.3x and 4x the GAP rate. This is only valid when quantifiable residues occur in the dataset. Where there are no quantifiable residues, i.e. values are less than the limit of quantitation, the residues may only be scaled down. It is unacceptable to scale up in this situation.

c) The variation associated with residue values derived using this approach can be considered to be comparable to using data selected according to the ±25% rule for application rate.

d) Scaling is only acceptable if the application rate is the only deviation from critical GAP (cGAP). In agreement with JMPR practice, additional use of the ±25% rule for other parameters such as PHI is not acceptable. For additional uncertainties introduced, e.g. use of global residue data, these need to be considered on a case-by-case basis so that the overall uncertainty of the residue estimate is not increased.

e) Proportionality cannot be used for post-harvest situations at this time. It is also recommended that the concept is not used for hydroponic situations due to lack of data.

f) Proportionality can be applied for both major and minor crops. The main difference between minor and major crops is the number of trials required by national/regional authorities, which has no direct relevance to the proportionality of residues. If scaling is applied on representative commodities, there is no identified concern with extrapolation to other members of an entire commodity group or subgroup.

g) Regarding processed commodities, it is assumed that the processing factor is constant within an application rate range and resulting residues in the commodity being processed. Therefore existing processing factors can also be used for scaled datasets.

h) With respect to exposure assessments, no restrictions appear to be necessary. The approach may be used for distribution of residues in peel and pulp, provided the necessary information for scaling is available from each trial. Scaled datasets for feeds may also be used for dietary burden calculations for livestock.

i) The approach may be used where the dataset is otherwise insufficient to make an MRL recommendation. This is where the concept provides the greatest benefit. The concept has been used by JMPR and different national authorities on a case-by-case basis and in some cases MRLs may be estimated from trials where all of the data (100%) has been scaled.

j) Although the concept can be used on large datasets containing 100% scaled residue trials, at least 50% of trials at GAP may be requested on a case-by-case basis depending for example on the

range of scaling factors. In addition, some trials at GAP might be useful as confirmatory data to evaluate the outcome in cases where the uses result in residue levels leading to a significant dietary exposure.

30. The principles and guidance were adopted by the Codex Alimentarius Commission in July 2013.

31. For the proportionality concept, while the MacLachlan and Hamilton analysis covered a large range of pesticides, formulation types, application methods and crops, some pesticides and uses were less well represented. Hence, additional data was reviewed for herbicides, soil applications, seed treatments and post-harvest applications to expand the scope of the proportionality principle to these situations over the range of 0.3X to 4X. The OECD decided to use the principles and guidance as adopted by the Codex Alimentarius Commission. The following explanations are added as a follow-up to comments received during the drafting of the text:

- When using the proportionality concept both up- and downscaling within one dataset (mixed approach) is possible and acceptable. The scaling has to be within a rate range of between 0.3x and 4x the GAP rate.

- When scaling is used for a residue definition that includes metabolites (e.g. parent + metabolite A + its conjugates expressed as parent) it should be done on the residue values as normally reported as "calculated as", and not on the individual components of the residue definition.

32. All data points under consideration, i.e. data points corresponding to application rates within/outside the acceptable range of ± 25% of the nominal application rate, should be adjusted to the nominal (1x) application rate to prevent issues of bias.

4. MRL Enforcement and Risk Assessment – Conversion Factors

33. In some countries authorities responsible for enforcement have to fulfil two objectives:

- Enforcing compliance with MRL legislation.

- Assessing consumer risk.

34. The laboratories must analyse as many active substances as possible. This is only possible by using up-to-date multi-residue methods. Analysing for complex residue definitions which are sometimes set for enforcement often requires more sophisticated work-up steps and a single residue method. This is not always feasible for the laboratories.

35. When conducting consumer risk assessments, several factors must be taken into account:

1. Conversion from the residue definition for enforcement to the residue definition for risk assessment.

2. Residue in the edible part of the commodity (distribution peel/pulp).

3. Processing factors.

36. The derivation of processing factors (PF) (No. 3 above) is described in the OECD Guidance Document No. 96 on Magnitude of Pesticide Residues in Processed Commodities (OECD 2008).

Conversion of Residue Definition for Enforcement to Risk Assessment

37. The conversion factor for the conversion from the residue definition for enforcement to the residue definition for risk assessment (CF_{risk}) should be derived from supervised residue trials data. In these trials all components of both residue definitions have to be addressed by the applicant using appropriate pre-registration methods. Therefore, they are the best source to derive CF_{risk}. This factor is used in cases where a risk assessment is conducted on the basis of enforcement residue data.

38. Plant metabolism studies give indications and can be used to derive conversion factors for the crop investigated if the study parameters match the intended PHI but should not be used on regular basis as their main purpose is to identify the nature rather than the magnitude of the residue which may vary from crop to crop. In most cases conversion factors should be calculated using data from supervised field trials supported by metabolism data.

39. In order to obtain the CF_{risk} the value of the measured residue for risk assessment is divided by the value of the measured residue for enforcement for each pair of residues for a set of residue trials data with a comparable GAP. From this set of individual CF_{risk} values, the median is selected as the representative CF_{risk}. In addition, for calculation the different residue definitions have to be expressed in the same way (e.g. both "calculated as parent"). For the calculation of CFs residue trials resulting in residue levels below the LOQ should not be taken into account.

40. An example (Spinetoram in lettuce, residue values from FAO, 2009a) to calculate CF_{risk} is given in the following table.

Trial number	Residue in compliance with residue definition for enforcement[a)]	Residue in compliance with residue definition for risk assessment[b)]	Individual CF_{risk}[c)]
1	0.31	0.64	2.1
2	0.15	0.28	1.9
3	0.34	1.35	4.0
4	0.32	0.56	1.8
5	0.55	1.16	2.1
6	7.80	9.55	1.2
median value of individual CF_{risk}			2.0

[a)] parent only.

[b)] parent Spinetoram and N-demethyl and N-formyl metabolite of the major Spinetoram component.

[c)] In view of the overall variation of the CFs the factors should be rounded to two significant figures.

41. Even so, it is unlikely that the trials data sets will cover all the likely permutations of ratios of analytes (including parent and metabolites) over the various timescales that uses permitted under the GAP allow or in relation to the time period before which treated crop items are consumed. Residues evaluators, in recognising the time dependent nature of the changing ratios of the levels of the analytes (which may include parent and metabolites) should consider the variations observed in the CF_{risk} from individual trials and consider the potential for estimates of CF_{risk} being particularly uncertain. If the metabolism data or the trials data have considered the formation of different analytes over various timings (different timing of application or harvest in relation to application) then such studies may be useful for considering this. Anyhow any derivation of CF_{risk} should ideally be supported by a statement of possible uncertainty

associated with a derived value and should ensure that the scope of relevance of using the conversion factor is clear (the crop or crops to which the CF_{risk} factor would be applicable).

42. For illustration the following example is provided for spirotetramat (European Food Safety Authority 2013). For this active substance, an overall CF for risk assessment of two has been proposed in the EFSA conclusion considering the CF derived for a total of 19 crops at various PHIs. Note: This example shows dependency on the PHI. However PHI is normally only the minimum waiting period of a GAP, and CF may significantly increase for periods beyond PHI.

CF for spirotetramat at different PHIs								**Total samples**
PHI (days)	0-	0+	3	7	14	21	28	
Citrus	1.7	1.2		1.4	1.6	1.7	1.8	87
Pome fruit	1.7	1.2		1.4	1.6	1.7	1.9	124
Peach	1.7	1.3		1.5	1.7	2.1	2.4	68
Plum	1.6	1.3		1.4	1.8	2.2	2.7	60
Cherry	1.7	1.3		1.3	1.6	1.8	2.1	58
Grape	1.5	1.4	1.2	1.4	1.6	1.9		40
Strawberry (Out)	1.8	1.4	1.3	1.4	1.7			39
Strawberry (In)	1.3	1.1	1.2	1.2	1.3			36
Onion	1.7	1.6	1.6	1.6	1.6	1.6		72
Tomato	1.4	1.3	1.4	1.5	1.9			50
Pepper	1.2	1.2	1.2	1.2				80
Cucumber	2.4	2.1	2.3	2.4				58
Melon	2.4	2.3	2.4	2.4				65
Brassica flowering	2.0	1.8	2.0	2.4	2.2	1.6		65
Brassica head	2.1	1.7	1.9	1.8	1.8	1.8		114
Brassica leafy	1.4	1.2	1.3	1.5	1.5	1.7		42
Kohlrabi	1.2	1.2	1.2	1.2	1.2	1.3		23
Lettuce (Out)	1.7	1.2	1.5	1.7	2.5			32
Lettuce (In)	1.4	1.1	1.1	1.3	1.8			78
Bean (with pods)	2.1	1.7		1.9	1.8	1.8		40
Hops				1.9	1.7	1.7		20
Overall mean CF	1.7	1.4	1.5	1.6	1.7	1.8	2.2	1251

Explanations

- Residue definition for enforcement: Sum of spirotetramat and spirotetramat-enol expressed as spirotetramat.

- Residue definition for risk assessment: Sum of spirotetramat, spirotetramat-enol, spirotetramat-ketohydroxy, spirotetramat-monohydroxy and spirotetramat-enol-Glc, expressed as spirotetramat.

- CF at requested PHI are greyed.

43. The above described approach can also be used for feed commodities when calculating dietary burden, if the residue definition for monitoring differs from the residue definition that should be used for exposure of animals to residues in the feed commodities.

Conversion Factor for Edible Parts

44. The conversion factor for the conversion from whole product to the edible part should be derived from supervised residue trials data (based on the residue definition for enforcement) and is in principle a processing factor. For this reason it should be abbreviated as a processing factor (PF_{edible}). In order to obtain the PF_{edible} the value of the measured residues in the edible commodity is divided by the value of measured residues in the whole commodity for each pair of residues for a set of residue trials data with a comparable GAP. From this set of individual PF_{edible} values, the median is selected as the representative PF_{edible}.

5. Formulations

45. Most types of formulations can be divided into two groups – those which are diluted with water prior to application and those which are applied intact. Emulsifiable concentrates (EC) and wettable powders (WP) are examples of the first type whereas granules (GR) and dusts (DP) are the most common examples of the latter. Some special types of formulations are described in paragraphs 52-53. A description of the various types of formulations including coding is given in the Manual of the Joint Meeting on Pesticide Specifications (JMPS) (FAO, 2010) [see also Table 2, in Section 10].

Formulations Diluted in Water

46. The most common formulation types which are diluted in water prior to application include EC, WP, water dispersible granules (WG), suspension concentrates (SC) (also called flowable concentrates), and soluble concentrates (SL). Residue data may be translated among these formulation types for applications that are made to seeds, prior to crop emergence (i.e., pre-plant, at-plant, and pre-emergence applications) or just after crop emergence. Data may also be translated among these formulation types for applications directed to the soil, such as row middle or post-directed applications (as opposed to foliar treatments).

47. In a recent publication by Maclachlan and Hamilton (2010) it was shown by evaluation of side-by- side trials with the same application rate and similar spray volumes that WP, EC, CS (capsule suspension) and SC formulations do not show a significant difference in day-zero residues after foliar treatment (JMPR data from 2000 to 2004). The evaluation includes trials with PHIs of less than seven days. If the PHI is exceeding 7 days, for mid-season and late-season foliar applications of formulations diluted in water, those formulations not containing oils or organic solvents (e.g., WG, SC) are considered equivalent and those containing oils or organic solvents (e.g., EC, OD) are also considered equivalent. Some authorities may require bridging data between the two formulation types (to demonstrate similarity of residue levels) where a complete data set exists for one type.

48. The publication by Maclachlan and Hamilton (2010) was available after the publication of OECD Test Guideline No. 509; for this reason the above paragraph appears in contradiction of paragraph 27 of the Test Guideline. Consequently it is recommended that paragraph 27 of the OECD TG 509 be further revised accordingly.

Water Soluble Bags

49. Placing a formulation (typically WP) in a water soluble bag does not require additional residue data provided adequate data are available for the unbagged product and the formulation chemistry data

provided show acceptable dissolution of the water soluble bag will be expected under practical conditions of use.

Formulations Applied Intact

50. Granular formulations applied intact will generally require a complete data set regardless of what data are already available for other formulation types. This is based on several observed cases of residue uptake being quite different for granules versus other types of formulations of the same active ingredient.

Formulations Designed for Seed Treatments

51. Some formulations are often designed specifically for seed treatment use such as DS powder for dry seed treatment use and ES emulsion for seed treatment. Residue data for seed treatment uses may be translated between such formulations. Nevertheless, it may be necessary to consider the chemical loading data for assurance on translation of the residue data for these formulations.

Controlled Release Formulations

52. Controlled release formulations (e.g., certain microencapsulated products) normally require a complete data set tailored to that particular use. Since these formulations are designed to control the release rate of the active ingredient, different residues are possible compared to other formulation types.

Formulations that Contain Active Substances as Nanomaterials

53. In general it is expected that if active substances were to be formulated as nanomaterial they would have different properties compared to normal sized material. At present no definitive statement can be made as to whether or not current data requirements are sufficient to carry out risk assessments for nanopesticides. For the time being a complete data set is needed for plant protection products containing nanomaterials in order to compare residue behaviour with conventional products.

6. Geographical Distribution of Residue Trials

54. In response to one of the recommendations of the workshop in York in 1999 (OECD 2003) on "Developing Minimum Data Requirements for Estimating MRLs and Import Tolerances", the OECD Working Group on Pesticides and the FAO Pesticide Management Group invited a small group of residue experts from OECD and FAO Member countries to develop the concept of a global zoning scheme to define areas in the world where pesticide trials data could be considered comparable, and therefore where such trials could be used within each zone for MRL-setting purposes, irrespective of national boundaries (OECD 2003).

55. On the basis of the underlying assumption that residues depend on climatic conditions and that it might be possible to develop a climate-based residue zoning scheme, an extensive database of residue trials data from the FAO/WHO Joint Meeting on Pesticide Residues (JMPR) Residue Evaluations was collected and then analysed by an independent statistician. The outcome from this analysis was that:

- There was sufficient information to indicate that a residue zoning scheme, based on climatic differences alone, could not be proposed because of the high variation in residues reported from comparable trials even within the same climatic zone.

- Pre-harvest climatic conditions were not major factors influencing residue variability in comparable residue trials.

- Most of the residue variability at harvest reported from comparable trials was associated with variability in residues at 'zero-days' (assumed to be largely unaffected by pre-harvest climatic conditions).

- Many of the factors possibly contributing to residue variability in comparable residue trials have already been recognised, to a greater or lesser extent, in the MRL assessment procedures established at the national, regional and international level, with residue trials being designed to reflect the range of production systems and climate situations that might be expected during the commercial use of the product.

56. The main point addressed in the OECD report was that national boundaries are not a barrier to acceptance of supervised field trials from other regions. This point was used by JMPR and some national/regional authorities at the time of publication. Unfortunately, the recommendations of this report were not considered further and the results were not much used by national or regional evaluation or legislation.

57. The results of the above project were used to support the proposal that for comprehensive OECD submissions (see paragraphs 68 to 79) the number of residue trials can be reduced by 40%. The EU now allows to a certain extent to replace the number of trials necessary by trials from outside Europe, provided that they correspond to the critical European GAP (within the ± 25% rule) and that the production conditions (*e.g.* cultural practices) are comparable (European Commission 2013). Canada and the United States allow substitution of some US/Canadian trials by trials from outside the US/Canada on a case-by-case basis provided the crop cultural practices, climatic conditions, and use pattern are substantially similar to those of the subject US/Canada region(s).

58. The analysis of the above mentioned project also forms the basis of the recommendations in OECD Test Guideline 509 (OECD, 2009) to generally accept data from only one season, rather than requiring data sets to be conducted typically over two or more seasons, provided that crop field trials are located in a wide range of crop production areas such that a variety of climatic conditions is taken into account. Despite this, where there is evidence of particular seasonal variations in data, it is reasonable to require more data.

59. In an earlier discussion in the OECD Residue Chemistry Expert Group it was recommended to confirm the results by evaluating five different major crops (e.g., grain, leafy vegetable, fruiting crop, root crop, oilseed) with realistic non-zero PHI residues data (difficult to achieve meaningful data for root crops) from different OECD countries/regions laying emphasis not only on foliar applications but also taking other applications techniques into account. Results from other application techniques should complete that project. Different types of pesticides (insecticides, herbicides, etc.) with both systemic and non-systemic properties should be represented.

New Data Evaluation

60. In an example of a global residue program provided by Dow AgroSciences (C. Tiu, 2011, 2012) quantifiable residue data were generated at critical GAP for foliar application of the active substance sulfoxaflor over a 2-3 years period in four different regions of the world (Europe, North America, Australia, New Zealand and Brazil) for 39 crops, to support OECD global joint review, Codex-MRLs and multiple national registration processes. Residues data were analysed for commodities representing leafy vegetables, Brassica vegetables, fruiting vegetables, fruit trees, oilseeds and cereal grains. Root crops were not considered due to very low or no detectable residues. Residue datasets for this active substance showed the best goodness of fit for log normal distribution (68%), followed by normal distribution (21%) and unknown distributions (11%). Results for all crops showed that data analysed by ANOVA is

statistically similar across the different regions/zones ($p > 0.05$). The results of the Turkey test (one possible ANOVA post-hoc analysis) showed no significant difference between the means of the residue data by regions. Variability between trials within a zone was higher than the variability between regions (2-20x). It represented in average 78% *versus* 12% average contribution from zone. The remaining 10% variation is assumed as a residual effect proceeding from duplicate samples, analytical variability, etc.

61. In order to further explore and extend the findings from the OECD workshop report (OECD, 2003) described above in Paragraphs 54 - 56 and the global residue program information provided by Dow Agrosciences for sulfoxaflor described in Paragraphs 60, a broader and deeper analysis of crop field trial data and putative systematic differences between zones was initiated by US EPA, PMRA, IR-4 and CLA which attempted to apply more recently developed statistical models (linear mixed models) to the issue. As part of this more recent update, data made available by CLA and IR-4 and used in this analysis totaled more than 700 field trials and 36 crop pesticide combinations among four geographic zones (Australia-New Zealand, Europe, North America, and South America) for which application scenarios between zones were either identical or corrected for proportionality. The analysis found no systemic statistically significant differences in field trial residues between the four zones examined using both a non-parametric rank sum test (a Kruskal-Wallis test for clustered data) and by using a linear mixed effects model. More specifically, the analysis found that residues between zones did not systematically differ more than about 30%, with confidence intervals of ranging from 0.496 (on the low end) to 1.991 (on the high end) which implies that the estimated residue ratios at 95% confidence are within about 2-fold. This updated analysis and associated material was presented as a side-event at the CCPR48 conference held in April 2016 in Chonqinq, China. The draft technical support document entitled "Global Zoning and Exchangeability of Field Trial Residues Between Zones" is available on the Codex CCPR48 website[1]. This analysis supports the previous findings of the Dow Agroscience global field trial work with sulfoxaflor with respect to within vs. between zone differences; it is also similar to the conclusion in the OECD workgroup report (OECD, 2003) with respect to minimal to non-existent systematic differences between (climatic-based) zones which found no systematic statistically significant differences in field trial residues between zones.

Conclusion and Recommendation for Geographical Distribution of Residue Trials

62. Current evidence suggests that residue data generated at similar GAP in different geographical regions/climatic zones may be used as a consolidated global dataset for MRL setting. Like for application of the proportionality principle, the associated uncertainty is interpreted within the ±25% deviation of supervised field trials. The distribution of the trials should be in at least two different regions or 50% of the number of regions pursuing registration, in order to provide the minimum number of trials required and a representative distribution for comprehensive global programs. At a later stage the number of trials as described below and given in Table 3 in Section 10 should be carefully reconsidered in light of future regulatory requirements in different countries.

63. The overall aim is to define for a given GAP that is used in more than one Country or region – a Global GAP (not necessarily meaning that it is used all over the world) – a number of acceptable trials and how to distribute them in more than two regions in order to be accepted as a common data set for this Global GAP.

[1] See link here or go to

http://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FMeetings%252FCX-718-48%252FStatistical%2BReport%2Bof%2BGlobal%2BZoning%2BAnalysis%2BApril%2B18%2B2016%2BDRAFT%2BFINAL_send2.pdf

7. Number of Trials

National/Regional Approach to Number of Trials

64. National/regional requirements concerning number of residue trials per crop remain in place. To a certain extent the total number of trials required by a regulatory authority may include trials conducted in another region provided that these trials correspond to the critical GAP and the production conditions, i.e. with comparable cultural practices. Before combining residue data, the protocols should be studied carefully as to whether they met these criteria.

Codex Approach to Number of Trials

65. JMPR performs the evaluation of the submitted information and estimates maximum residue levels if the database is considered sufficient, regardless of whether it represents worldwide use or is limited to a region. The number of trials (generally minimum 6-10) and samples is dependent on the variability of use conditions, the consequent variation of the residue data, and the importance of the commodity in terms of production, trade and dietary consumption.

Recommendations for Comprehensive Data Submissions

66. In the case of a comprehensive submission to all OECD countries where the desired GAP is uniform, a 40% reduction in the total number of trials is feasible, compared to the total number of trials determined by summation of individual country requirements. The residue trials chosen are those conducted independently. The assumption is that the number of trials specified in each crop production region reflects the economic (acreage) importance and/or dietary significance of the representative commodity(ies) within that production region.

67. The reduction in the total number of trials within any OECD country or crop production region is compensated for by the total number of crop field trials making up the comprehensive submission data set and the wider geographic distribution of these data. With this 40% reduction, regulatory authorities may receive fewer crop field trials conducted in their specific country or region; however they will actually receive a greater number of trials in total with a more comprehensive geographical distribution. There are precedents in OECD countries and regions for this approach.

68. To qualify for this comprehensive submission approach, all crop field trials as requested by national/regional authorities should meet the following criteria:

- Field trials are conducted according to the *c*GAP (within ± 25% of the nominal application rate, number of applications or PHI). For comprehensive submission at least 50% of the trials should be conducted at or above (within 25%) the *c*GAP. For this purpose, trials whose intended application rates match the cGAP but actual rates fall down to 10% below the cGAP (e.g., due to the normal variability in preparing spray solutions) are considered acceptable. If more than 50% of the trials were conducted at actual rates below that of the cGAP (but within 25%), the proportionality approach can be used by the scaling of the entire dataset to the nominal dose.

- Although it is possible to use results from residue trials that are not conducted according to cGAP but calculated according to the proportionality principle, the combining of both concepts – reduction of number of trials and proportionality – should be used with caution due to the lack of experience in both concepts.

- Some authorities request up to 50% of the trials to be decline studies;

- The trials should cover a range of representative crop production practices for each crop including those likely to lead to the highest residues (e.g., irrigated vs. non-irrigated, trellis *vs.* nontrellis production, autumn-planted *vs.* spring-planted, etc.).

- Trials that are substituted by trials from another country should not be used for across the board reduction. For example, a trial can be considered only one time and cannot count toward the total number of trials both in the country where conducted and a second time in another country or region where it would be substituted for a local trial.

69. The minimum total number of trials for any crop in a comprehensive submission is eight. In addition, the total number of trials to be conducted must not be less than the requirement for any given individual region. For example, upon calculation of the 40% reduction, some crops such as dried lima beans have fewer total trials [14] than required in one region [16 in the EU]. Therefore, at least 16 trials are needed for dried lima beans in a comprehensive submission.

70. Any reduction in the number of crop field trials should be distributed proportionally among the crop production regions as shown in the example for a 40% reduction for barley below. Table 3 gives the trial numbers for crops grown throughout OECD countries. If the number of required trials changes in any given region, Table 3 should be adjusted accordingly.

71. In the example given below the total number of trials is 31, which represents a 40% reduction compared to 52.

Country or Region	NAFTA	EU	JP	AUS	NZ	Total
Number without reduction	21	16	3	8	4	52
Number with 40% reduction	12	10	2	5	2	31

72. This means that for a global submission, instead of a total of 52 trials a total of 31 trials is sufficient. These trials should meet the requirements defined in paragraph 69. The total of 31 trials should be distributed across the regions as indicated in the table.

73. In no case the number of trials in a given crop production region may be reduced below two. Thus, the 40% reduction does not apply to a crop for which the required number of trials is two. In such a case the number of trials is two before and after reduction.

74. It is important to keep in mind that this comprehensive strategy would only apply to an OECD wide submission. If, for example, the MRL submission is originally submitted to the US and Canada, the crop field trial guidelines, with respect to the number of trials, for those countries should be followed. Subsequently, if MRLs in additional OECD countries are pursued, the regulatory authorities in the additional countries should be consulted to determine what residue data are required. For example, following establishment of an MRL in the US and Canada, if an MRL for the same use is pursued in the EU, the applicant may consult with EU regulatory authorities about the possibility of using residue data from the US/Canadian data submission and performing fewer crop field trials in the EU.

75. The table of trial numbers in the Table 3 addresses only outdoor crop field trials and not greenhouse (glasshouse) or post-harvest treatments. For a comprehensive submission to OECD countries, concerning greenhouse uses, a minimum of eight greenhouse trials is needed, but not less than the

requirement for any given individual region. For such greenhouse trials, geographic distribution typically is not an issue; however for active ingredients which are susceptible to photodegradation, consideration should be given to locations at different latitudes and winter/summer periods.

76. The number of post-harvest trials on a commodity should be at least four, but no less than the requirement for any given individual region, taking into consideration the application techniques, storage facilities, and packaging materials used. Changes in the mentioned conditions may require additional trials.

77. As stated in paragraph 62 further considerations are useful in the light of experience gained in future.

8. Results from Residue Trials to be used in MRL Estimations

78. In principle all data from residue trials conducted according to cGAP and considered valid should be taken into account for MRL setting. Nevertheless a few questions often arise and some of the main ones are discussed in the following paragraphs.

Handling of Outliers

79. Residue values above the majority of the data population are always suspicious and therefore are often characterised as outliers. Nevertheless, before disregarding a result as an outlier the study should be carefully examined to see if there is adequate information and/or experimental evidence to justify its exclusion. The exclusion of an apparent outlier must be justified by agricultural practice or other evidence deriving from the experimental set up or analytical conditions. Statistical results, in and of themselves, are generally not sufficient to exclude data from the MRL-setting process.

Multiple Component Residues

80. Where the active substance and at least one metabolite, degradation or reaction product is included in the residue definition two cases have to be considered: either the components are converted to a single component or analyte by the analytical method or the components are determined separately.

81. In the first case the total residue is measured as a single compound and expressed as the parent compound or in some circumstances as a metabolite or degradation product. As in any other case the LOQ is usually determined by the lowest validated level of analyte. The MRL estimate is based on the measured residues for the total residue.

82. In the second case residue components are determined separately by the method of analysis. The concentrations of measurable residues are adjusted for molecular weight and summed, and their sum (normally parent equivalent residues) is used for estimating the maximum residue level. Nevertheless, some guidance is necessary if the residues for some or all the components are at or below the LOQ. This is explained using the following example.

General Example

83. Note: example based on the FAO Manual for bentazone with fictive values. The residue definition is given as "parent, metabolite 1 and metabolite 2 expressed as parent". The LOQ of the method of analysis for the single components of the residue definition is 0.02 mg/kg. The different situations are described in the following table.

Example	Maximum levels (mg/kg) detected for components (supervised residue trials)			Recommended total residue (mg/kg)
	Parent	metabolite 1	metabolite 2	(expressed as Parent)
(a)	<0.02	<0.02	<0.02	<0.06
(b)	0.04	<0.02	<0.02	0.08
(c)	0.04	0.03	<0.02	0.09
(d)	<0.02	0.04	0.05	0.11

84. This recommendation in the table is based on the assumption that it might be possible to improve the method of analysis to achieve for example a LOQ of 0.01 mg/kg. Re-examination of the results may then give residues only slightly below 0.02 mg/kg for each of the single compounds and 0.06 mg/kg for the sum. The recommended total residues from the table should be used in MRL estimations. Referring to example (a) it is important to maintain the "<", since the individual components were all <LOQ and the number of censored data is relevant for the calculation.

85. A problem arising from this recommendation is discussed as follows: a MRL of 0.06 mg/kg would allow any residue component to be present at 0.06 mg/kg, or all of the three at 0.02 mg/kg, without exceeding the MRL. Consequently, individual residue components could be three times those which should arise from GAP-compliant use of the compound but would be within the MRL.

86. It is recommended that decisions on the levels of MRLs at or about the practical limit of quantification should particularly take into account the following factors:

- Toxicity of the active ingredient as indicated by the ADI or the ARfD. Normally, low ADIs or ARfDs should be accompanied by relatively low limits of quantification. The lower limit used may also have implications for risk assessment calculations.

- In principle, the lower the residue arising from GAP, the lower the limit of quantification should be.

- The limit used in the supervised residue trials is also a consideration which should be taken into account. A LOQ may not normally be established at a level lower than that used in the generation of the data. However, should other factors be considered determinant, regeneration of the data using a more appropriate lower limit may be required.

- Evidence from metabolism studies, chromatograms and other information on the relative concentrations of the various residue components.

Independent Supervised Residue Trials

87. As a principle only one result from each residue trial that is within cGAP should be used for the estimation of MRLs. In addition, selected results should only be used from independent supervised residue trials. When considering independence of supervised residue trials OECD recommends that each of the following factors should be considered separately:

- Geographical location and site – Trials at different geographic locations are considered independent.

- Dates of planting (annual crops) and treatments – Trials involving ~~significantly~~ different planting dates or treatment dates (> 30 days apart) are considered independent.

88. Additional factors may influence the independence and may be taken into consideration on a case by case basis:

- Crop varieties – Some varieties may be sufficiently different (e.g. different size at maturity, rough *vs.* smooth surface, different amount of foliage) to influence the residue and could be considered independent.

- Formulations – Trials conducted with different formulations should not be considered independent. Exceptions can be derived from chapter 5, i.e. granular formulations, controlled release formulations and formulations based on nanomaterials that need a separate dataset. In this case a statistical test is required to see whether residues from these formulations differ from those with water diluted formulations. If they differ, they can be considered independent.

- Application rates and spray concentrations – Trials at different application rates and spray concentrations should not be considered independent.

- Treatment operations – Trials using the same spray operation are not considered independent.

- Application equipment – Trials using different equipment are not considered independent.

- Addition of adjuvants – A trial with the addition of an adjuvant should not be considered independent. If an adjuvant will be routinely recommended or included in the marketed formulation, then the trials should use the adjuvant. If the use pattern includes mid-season to late-season foliar application, consideration should be given to including appropriate adjuvants in a portion of the trials.

89. Only one field trial would normally be selected per trial site if multiple plots/trials are conducted in parallel, unless one or more of the conditions outlined above apply, e.g., significantly different varieties in the replicate plots. For trials at the same location there should be convincing evidence that additional trials are providing further independent information on the influence of the range of farming practices on residue levels.

90. For trials being considered independent the measured residue is used in MRL estimates. For those trials being considered as not independent the measured residues should be treated as being replicates (see below).

Replicates

91. Various scenarios may apply when several residue values are described as "replicates" such as when there are:

- Replicate analysis samples from one laboratory sample (duplicate analysis).

- Replicate laboratory samples obtained with sub-division from one field sample.

- Replicate field samples analysed separately (each sample is taken randomly from a plot which was treated as a whole).

- Replicate plots or sub or split-plot field samples are analysed separately (the whole trial is subject to the same spraying treatment, but it is divided into two or more areas that are sampled separately).

- Replicate trial samples are analysed separately (trials from the same site that are not independent may be considered as replicate trials).

92. In all cases the type of replicate should be specified when assessing the data. The average or mean value of replicates should be used as the representative value for that field trial in exactly the same fashion that is done for analytical replicates of the same composite sample. From a statistical point of view, the mean or average residue value of replicate samples provides the basis for setting MRLs targeted at the p95 of the underlying distribution. However, there may be situations where single valid results from replicate samples may exceed the MRL estimated from the use of average or mean values. In such situations and in view of consumer safety, consideration may be given by some regulatory authorities to the use of these single values as the HR in dietary risk assessment.

93. Also JMPR has checked this approach in 2010 and concluded to use the average of replicate field samples in establishing the data set for statistical calculation of maximum residue level estimates. However, JMPR also noted that the interpretation of the estimate must take into account individual replicate values contributing to the data set that exceed the estimate. For such situations JMPR will still use the HR, to avoid missing the HR value for dietary risk assessment. JMPR continues to select the highest residue value for MRL derivation in case of two or more trials that are not considered independent.

Residues at Harvest

94. Normally, the residue at the PHI specified in the cGAP should be used for the MRL estimation. Nevertheless, the residue trial data should be assessed carefully and higher residues at longer PHIs should be used instead of the residue at the cGAP as this safety interval is defined as the shortest possible meaning that harvest at later stages may take place. In case of replicates take first a decision on handling as recommended (see paragraphs 91-93).

95. In some cases the time of application is well defined by the growth stage (BBCH; a decimal code system, which is divided into principal and secondary growth stages[2]). In this case setting of a PHI is not necessary. The selection of the results from residue trials then depends on the use of the plant protection product at the correct growth stage and the normal harvest of the product.

9. MRL Estimations

Considerations for MRL-setting based on specific Use Patterns

96. The post-harvest use of a persistent, non-volatile active substance in stored products will lead to residues that can be calculated on the basis of the amount used to treat the stored commodity for short waiting periods. The MRL should not be set at a higher level than the application rate equivalent, but higher maximum residue levels may need to be considered on a case by case basis to account for inhomogeneous distribution of the pesticide during application or sampling difficulties (especially bulk commodities). Any variation in residues depends on the precision of the application especially concerning the deposition of the active substance on the surface of the treated commodity. Environmental and commodity related factors (like metabolism) will only have limited influence. Residue trials are necessary to reflect storage locations with variable conditions regarding temperature, humidity, aeration, etc. Once

[2] A description in German, English, French, or Spanish can be downloaded from: http://www.jki.bund.de/en/startseite/veroeffentlichungen/bbch-codes.html

the relationship between application rate and residue level has been shown, additional trials with other application rates are not necessary. This relationship is based on special environmental and commodity factors independent from the conditions of the proportionality principle.

97. The OECD MRL calculator may not be a suitable tool to propose MRL for post-harvest application. In such a case, the estimate calculated as "CF X3 mean" should normally be disregarded and the MRL proposal based on the estimates calculated as "Mean + 4 SD" or "Highest residue" and considering the nominal application rate.

98. For seed treatments a situation could be imagined, where the worst-case MRL based on the ai-content in the seed, the known seed density and the known yield of the commodity would be estimated being below the LOQ or below an already existing MRL. In that case and assuming that possibly formed metabolites are adequately covered, a waiver for additional residue trials with a new application rate might be acceptable (e.g. for cereals or carrots). Seed treatments for such a consideration exclude potato seed treatments: This is related to the different growing situations. In case of potatoes distribution into the daughter tubers has been taken into account.

Selecting of Data for Using the OECD Calculator in MRL Estimations

99. A statistical calculator has been developed by OECD for determination of MRLs from valid field residue data. The calculation process is based on "mean + 4SD" methodology. A White Paper and related user guide are available as additional resources (OECD 2011). The OECD Calculator itself is provided as an excel spreadsheet either for single data set or for multiple data sets.

100. For the OECD calculator method of MRL calculation, it has been determined that the mean or average residue value, when replicate sample data have been generated per field site, should be used in the calculation process (see paragraph 93).

101. Several examples of criteria, used in selecting data to be considered in the MRL calculation, require expert judgement and consultation with national/regional authorities:

- Use of censored data (i.e. <LOQ). The default inputs to the calculator for these values are the respective LOQ values with an asterisk designation for censored data. The calculator uses a censoring factor to correct for residues reported at the LOQ that were less than the LOQ. Care must be taken when large parts of the data set consist of censored data. In such cases the calculator indicates less reliability of results.

- Proposing MRLs lower than 0.01 mg/kg. The calculator's lowest accepted residue value is 0.001 mg/kg. The calculator will work with values below 0.01 mg/kg and will display statistical values below 0.01 mg/kg including unrounded MRL. The proposed MRL will be always the lowest MRL class of 0.01 mg/kg. On the basis of these data it is possible to round the results to an appropriate MRL class below 0.01 mg/kg if guaranteed. Nevertheless, MRLs below 0.01 mg/kg are an exception for the moment and routine MRL setting below this value should be discussed in the light of future developments in analytical methods.

- Small datasets: If the dataset consists of less than three values the message "MRL calculation not possible. [Too small dataset]" is displayed at the bottom of the spreadsheet. The choice of three values was made based on the minimal requirement common among OECD countries. With a single residue value, it is impossible to compute an estimator for the standard deviation of the dataset, which is needed in the calculation procedure. If the dataset consists of 3-7 residue values, the message "High uncertainty of MRL estimate, [Small dataset]" is displayed to remind the user

of the considerable level of uncertainty surrounding the calculation of any statistical quantity for such small datasets. [For information: NAFTA countries on rare occasions for a very minor crop must make an MRL estimate from 2 independent field trials (n = 2). Various options were considered, and it was found that 5 X Mean provides the best estimate for outdoor trials and 3 X Mean provides the best estimate for greenhouse trials. This is based on simulations.]

- Data selection from dependent residue trials (those that are not assessed as independent from one another) – In case of dependent data the average of the residue values from the dependent trials should be used in the OECD Calculator if provided these trials are statistically not different. Otherwise the highest measured residue is used.

- Combining of datasets for the same commodity treated at closely related GAP (i.e., cGAP within maximum 25% deviation in one of the key parameters) – The term closely related GAP will exclude data sets that differ, for example, in application type (broadcast foliar versus ground application) or in kind of production (indoor versus outdoor production). Closely related GAPs are for example those where high volume and low volume spray is used. In this case, it should be determined if the residues are comparable, that is, if they belong to the same residue population (see paragraph 15), or if they should be handled separately. If the data sets are not comparable, the MRL should be calculated for each dataset separately and the MRL from the highest residue population should be used.

- Combining/separating datasets for the same ai/crop/GAP combination generated with different LOQs and containing some censored data – Combine the data sets.

- Combining/separating datasets for the same ai/crop/GAP combination generated with different LOQs and all measured residues are below the LOQ – Where there are two or more data sets consisting of residue data with different LOQ levels, the set with the lowest LOQ should be preferred for MRL setting (given it is sufficient as such) as it usually reflects state-of-the-art analytical methods.

- Combining datasets from different regions (e.g. NAFTA and EU) for the same commodity treated at the same GAP (see paragraph 15) – Northern and southern residue region in Europe are considered in the first step as different regions. It should be determined if the residues are comparable, or if they should be handled separately. If the data sets are not comparable, the MRL should be calculated for each dataset separately and the MRL from the highest residue population should be used.

- Combining of datasets from different commodities for the same commodity group treated at the same GAP. – Values should not be combined for morphologically different commodities.

- Combining data sets from the same species differing in size – Sometimes authorities differentiate between small size and large size varieties. For example Codex will in future require trials on sweet pepper; and one cultivar of chili pepper or one cultivar of large variety of eggplant and one cultivar of small variety eggplant for extrapolation to the entire commodity group. Though requiring trials on varieties of different size, the data will normally be combined in one population (with probably high variability) since the same MRL is applicable for all varieties and statistical tools are normally not applicable for such very small data sets.

102. The OECD calculator is useful to determine whether an MRL estimate is appropriate on the basis of a particular data set. However, a reviewer is aware of other factors which may influence the values at which MRLs are set. It is therefore important to note that although the calculator is a beneficial tool, the

decision about the most appropriate MRL should be made by the reviewer, who is in possession of all the relevant information.

10. References

Australian Pesticides and Veterinary Medicines Authority 2000. Residue Guideline No. 24. http://www.apvma.gov.au/publications/guidelines/rgl_24.php#top

Codex Alimentarius Commission, 1993. Codex Alimentarius, Volume 2 Pesticide Residues in Food. 2nd Ed. Section 2 Codex Classification of Food and Animal Feeds. Food Joint FAO/WHO Food Standards Programme, Rome, 1993.

Codex Alimentarius Commission, 2004. Report of the Thirty-Sixth Session of the Codex Committee on Pesticide Residues. Alinorm 04/27/24, para 248 – 258. New Delhi, India, 19 - 24 April 2004.

Codex Alimentarius Commission, 2004. Twenty-seventh Session. Report Alinorm 04/27/41, Appendix VI. Centre International de Conférences de Genève, Geneva, *Switzerland,* 28 June – 3 July 2004.

Codex Alimentarius Commission, 2006. Report of the Thirty-Eighth Session of the Codex Committee on Pesticide Residues. Alinorm 06/29/24, para 160 – 171.Fortaleza, Brazil, 3 - 8 April 2006.

Codex Alimentarius Commission, 2006. Twenty-ninth Session. Report Alinorm 06/29/41, Appendix VIII. Centre International de Conférences de Genève, Geneva, *Switzerland,* 3 – 7 July 2006.

Codex Alimentarius Commission, 2007. Report of the Thirty-Ninth Session of the Codex Committee on Pesticide Residues. Alinorm 07/30/24, para 142 – 152 and CX/PR 07/39/4, Beijing, China, 7-12 May 2007.

Codex Alimentarius Commission, 2008. Report of the Fortieth Session of the Codex Committee on Pesticide Residues. Alinorm 08/31/24, para 107 – 115 and CX/PR 08/40/4, Hangzhou, China, 14-19 April 2008.

Codex Alimentarius Commission, 2009. Report of the Forty-First Session of the Codex Committee on Pesticide Residues. Alinorm 09/32/24, para 131 – 155, CX/PR 09/41/4 and CX/PR 09/41/4 Add. 2, Beijing, China, 20 - 25 April 2009.

Codex Alimentarius Commission, 2010. Report of the Forty-Second Session of the Codex Committee on Pesticide Residues. ALINORM 10/33/24, para 73, 86 – 118, Xian, China, 19 - 24 April 2010.

Codex Alimentarius Commission, 2011. Report of the 43rd Session of the Codex Committee on Pesticide Residues. REP11/PR, para 24, 82 – 86, Beijing, China, 4 - 9 April 2011.

Codex Alimentarius Commission, 2012. Report of the Forty-fourth Session of the Codex Committee on Pesticide Residues. REP12/PR, Shanghai, China, 23 - 28 April 2012.

Codex Alimentarius Commission, 2012. Report of the Thirty-fifth Session of the Codex Alimentarius Commission. REP12/CAC, Rome, Italy, 2 - 7 July 2012.

Codex Alimentarius Commission, 2013. Report of the 45th Session of the Codex Committee on Pesticide Residues. REP13/PR, Beijing, China, 6 - 11 May 2013.

Environmental Protection Agency 1996. Residue Chemistry Test Guidelines – OPPTS 860.1000 Residue Chemistry Test Guidelines and 860.1500 Crop Field Trials. http://www.epa.gov/opptsfrs/publications/OPPTS_Harmonized/860_Residue_Chemistry_Test_Guidelines/Series/860-1000.pdf

European Commission, 2013. Commission Regulation (EU) 283/2013 of 1 March 2013 setting out the data requirements for active substances, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market. OJ L 93, 03.04.2013, p. 1-84.

European Commission, 2015. Guidance Document, Guidelines on comparability, extrapolation, group tolerances and data requirements for setting MRLs. SANCO 7525/VI/95 – rev. 10.1. Revision 10.2 under review.

European Food Safety Authority, 2013. Conclusion on the peer review of the pesticide risk assessment of the active substance spirotetramat. EFSA Journal 2013;11(6):3243, 90 pp.

FAO, 2009a. Pesticide residues in food—2008. Evaluations Part I – Residues. FAO Plant Production and Protection Paper, 194, 2009.

FAO, 2009b. Submission and evaluation of pesticide residues data for the estimation of maximum residue levels in food and feed (FAO Manual, 2nd Edition). FAO Plant Production and Protection Paper, 197, 2009.

FAO 2010. Manual on development and use of FAO and WHO specifications for pesticides. Prepared by the FAO/WHO Joint Meeting on Pesticide Specifications (JMPS) November 2010 – Second Revision of the First Edition. FAO, WHO, Rome 2010.

FAO, 2011a. Pesticide residues in food—2010. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group. FAO Plant Production and Protection Paper, 200, 2011.

FAO, 2011b. Pesticide residues in food—2011. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group. FAO Plant Production and Protection Paper, 211, 2011.

FAO, 2013: Pesticide residues in food—2012. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group. FAO Plant Production and Protection Paper, 215, 2013.

FAO 2014: Pesticide residues in food—2013. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group. FAO Plant Production and Protection Paper, 219, 2014.

FAO 2015: Pesticide residues in food—2014. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group. FAO Plant Production and Protection Paper, 221, 2015.

MacLachlan, D. J. and Hamilton, D., 2010. A new tool for the evaluation of crop residue trial data (day-zero-plus decline', Food Additives & Contaminants: Part A. First published on: 05 January 2010 (iFirst), DOI: 10.1080/19440040903403024, http://dx.doi.org/10.1080/19440040903403024.

MacLachlan, D. J. and Hamilton, D., 2011. A review of the effect of different application rates on pesticide residue levels in supervised residue trials, Pest Manag Sci 2011; 67: 609–615, Published online in Wiley Online Library: 30 March 2011. http://onlinelibrary.wiley.com/doi/10.1002/ps.2158/pdf.

National Registration Authority for Agricultural and Veterinary Chemicals, 2000. Information sheet – Residues and minor crops.

Nguyen, J., Miller, D. and Tiu, C., 2015: Power between Kruskal-Wallis Test, Rule of X factor between Maximum values, and Rule of X factor between Median values.

OECD, 2003. Report of the OECD/FAO Zoning Project. Series on Pesticides Number 19, Paris.

OECD, 2008. OECD Guidance Document on Magnitude of Pesticide Residues in Processed Commodities. Series on Testing and Assessment No. 96, OECD, Paris.

OECD, 2009. OECD Guidelines for the Testing of Chemicals – Crop Field Trial. No. 509, OECD, Paris.

OECD MRL Calculator at:
http://www.oecd.org/env/chemicalsafetyandbiosafety/agriculturalpesticidesandbiocides/oecdmaximumresiduelimitcalculator.htm

OECD 2011. OECD MRL Calculator: User Guide. Series on Pesticides No. 56. OECD, Paris.

OECD 2011. OECD MRL Calculator: Statistical White Paper. Series on Pesticides No. 57. OECD, Paris

OECD 2011. OECD MRL Calculator: Spreadsheet Single Data Set. OECD, Paris 2011.

OECD 2011. OECD MRL Calculator: Spreadsheet Multiple Data Sets. OECD, Paris 2011.

Pest Management Regulatory Agency 1998. Residue Chemistry Guidelines Section 9, Crop Field Trials, Regulatory Directive 98-02.
http://www.pmra-arla.gc.ca/english/pdf/dir/dir9802b-e.pdf

Tiu, C. and Barnekow, J., 2011. Crop Residues Homogeneity Across Global Regions. Dow AgroSciences, 21st September 2011, submitted to the OECD RCEG Meeting November 27 and 28 2012, Queenstown/New Zealand, presented during the Global Minor Use Summit 2, FAO, Rome 21- 23 February 2012 (GMUS-2 Booklet available on the internet at: http://www.gmup.org/GMUS2_webversion.pdf

Tiu, C., 2012. Residue Data: Addressing extrapolation between global regions. Fall 2012 Philadelphia ACS National Meeting (August 19-23, 2012), Division of Agrochemicals, Syposium/Session MRLs and Ag Chemicals.

Table 1: New Codex Commodity Groups, Examples of Representative Commodities and Extrapolations (adopted July 2012)

Codex Commodity Groups	Codex Subgroups	Codex Examples of Representative Commodities (for group or subgroup)	Extrapolation
001 Citrus fruits	001A, Lemons and Limes	Lemon or Lime	to subgroup 001A
	001B, Mandarins	Mandarin	to subgroup 001B
	001C, Oranges, Sweet, Sour	Orange	to subgroup 001C
	001D, Shaddock and Pomelos	Pummelo or Grapefruit	to subgroup 001D
		Lemon or Lime; Mandarin; Orange and Pummelo or Grapefruit	to whole group 001
002 Pome fruits		Apple or Pear	to whole group 002
003 Stone fruits	003A, Cherries	Cherry, Sweet or Cherry, Sour	to subgroup 003A
	003B, Plums	Plum or Prune Plum	to subgroup 003B
	003C, Peaches	Peach or Apricot	to subgroup 003C
		Cherry, Sweet or Cherry, Sour; Plum or Prune Plum or Peach or Apricot	to whole group 003
004 Berries and other small fruits	004A, Cane berries	Blackberry or Raspberry	to subgroup 004A
	004B, Bush berries	Blueberry or Currants, black, red or white	to subgroup 004B
	004C, Large shrub/tree berries	Elderberry	to subgroup 004C
	004D, Small fruit vine climbing	Grapes	to subgroup 004D
	004E, Low growing berries	Strawberry	to subgroup 004E
		Blackberry or Raspberry; Blueberry or Currants, black, red or white; Elderberry; Grape and Strawberry	to whole group 004
005 Assorted tropical and sub-tropical fruits – edible peel	005A, Assorted tropical and sub-tropical fruits – edible peel – small	Olive	to subgroup 005A
	005B, Assorted tropical and sub-tropical fruits – edible peel – medium to large	Fig or Guava	to subgroup 005B
	005C, Assorted tropical and sub-tropical fruits – edible peel – palms	Date	to subgroup 005C

Codex Commodity Groups	Codex Subgroups	Codex Examples of Representative Commodities (for group or subgroup)	Extrapolation
		Olive; Fig or Guava and Date	to whole group 005
006 Assorted tropical and sub-tropical fruits – inedible peel	006A, Assorted tropical and sub-tropical fruits – inedible peel – small	Litchi (lychee) or Longans or Spanish Lime	to subgroup 006A
	006B, Assorted tropical and sub-tropical fruits – inedible smooth peel - large	Avocado; Pomegranate or Mango; Banana and Papaya	to subgroup 006B
	006C, Assorted tropical and sub-tropical fruits – inedible rough or hairy peel – large	Atemoya and Pineapple	to subgroup 006C
	006D, Assorted tropical and sub-tropical fruits – inedible peel – cactus	Pitaya and Prickly pear	to subgroup 006D
	006E, Assorted tropical and sub-tropical fruits – inedible peel – vines	Kiwifruit or Passionfruit	to subgroup 006E
	006F, Assorted tropical and sub-tropical fruits – inedible peel – palms	Muriti or Palmyra Palm	to subgroup 006F
		Litchi (lychee) or Longans or Spanish Lime; Avocado; Pomegranate or Mango; Banana and Papaya; Atemoya; Pineapple; Dragonfruit; Prickly pear; Kiwifruit or Passionfruit and Muriti or Palmyra Palm	to whole group 006

Table 2: Formulations and their definition/description

From CropLife International Technical Monograph no 2, 6th Edition. Revised May 2008. Catalogue of pesticide formulation types and international coding system (reproduction of Appendix E from the Manual of the Joint Meeting on Pesticide Specifications (JMPS) (FAO, 2010).

Code	Term	Definition
AE	Aerosol dispenser	A container-held formulation which is dispersed generally by a propellant as fine droplets or particles upon the actuation of a valve.
AL	Any other liquid	A liquid not yet designated by a specific code, to be applied undiluted.
AP	Any other powder	A powder not yet designated by a specific code, to be applied undiluted.
BR	Briquette	Solid block designed for controlled release of active ingredient into water.
CB	Bait concentrate	A solid or liquid intended for dilution before use as a bait.
CP	Contact powder	Rodenticidal or insecticidal formulation in powder form for direct application. Formerly known as tracking powder (TP).
CS	Capsule suspension	A stable suspension of capsules in a fluid, normally intended for dilution with water before use.
DC	Dispersible concentrate	A liquid homogeneous formulation to be applied as a solid dispersion after dilution in water. (Note: there are some formulations which have characteristics intermediate between DC and EC).
DP	Dustable powder	A free-flowing powder suitable for dusting.
DS	Powder for dry seed treatment	A powder for application in the dry state directly to the seed.
DT	Tablet for direct application	Formulation in the form of tablets to be applied individually and directly in the field, and/or bodies of water, without preparation of a spraying solution or dispersion
EC	Emulsifiable concentrate	A liquid, homogeneous formulation to be applied as an emulsion after dilution in water.
EG	Emulsifiable Granule	A granular formulation, which may contain water-insoluble formulants, to be applied as an oil-in-water emulsion of the active ingredient(s) after disintegration in water.
EO	Emulsion, water in oil	A fluid, heterogeneous formulation consisting of a solution of pesticide in water dispersed as fine globules in a continuous organic liquid phase.
EP	Emulsifiable powder	A powder formulation, which may contain water-insoluble formulants, to be applied as an oil-in-water emulsion of the active ingredient(s) after dispersion in water.
ES	Emulsion for seed treatment	A stable emulsion for application to the seed either directly or after dilution.
EW	Emulsion, oil in water	A fluid, heterogeneous formulation consisting of a solution of pesticide in an organic liquid dispersed as fine globules in a continuous water phase.
FS	Flowable concentrate for seed treatment	A stable suspension for application to the seed, either directly or after dilution.

Code	Term	Definition
FU	Smoke generator	A combustible formulation, generally solid, which upon ignition releases the active ingredient(s) in the form of smoke.
GA	Gas	A gas packed in pressure bottle or pressure tank.
GE	Gas generating product	A formulation which generates a gas by chemical reaction.
GL	Emulsifiable gel	A gelatinized formulation to be applied as an emulsion in water.
GR	Granule	A free-flowing solid formulation of a defined granule size range ready for use.
GS	Grease	Very viscous formulation based on oil or fat.
GW	Water soluble gel	A gelatinized formulation to be applied as an aqueous solution.
HN	Hot fogging concentrate	A formulation suitable for application by hot fogging equipment, either directly or after dilution.
KK	Combi-pack solid/liquid	A solid and a liquid formulation, separately contained within one outer pack, intended for simultaneous application in a tank mix.
KL	Combi-pack liquid/liquid	Two liquid formulations, separately contained within one outer pack, intended for simultaneous application in a tank mix.
KN	Cold fogging concentrate	A formulation suitable for application by cold fogging equipment, either directly or after dilution.
LN	Long-lasting insecticidal net	A slow- or controlled-release formulation in the form of netting, providing physical and chemical barriers to insects. LN refers to both bulk netting and ready-to-use products, for example mosquito nets.
LS	Solution for seed treatment	A clear to opalescent liquid to be applied to the seed either directly or as a solution of the active ingredient after dilution in water. The liquid may contain water-insoluble formulants.
MC	Mosquito coil	A coil which burns (smoulders) without producing a flame and releases the active ingredient into the local atmosphere as a vapour or smoke.
ME	Micro-emulsion	A clear to opalescent, oil and water containing liquid, to be applied directly or after dilution in water, when it may form a diluted micro-emulsion or a conventional emulsion.
OD	Oil dispersion	A stable suspension of active ingredient(s) in a water-immiscible fluid, which may contain other dissolved active ingredient(s), intended for dilution with water before use.
OF	Oil miscible flowable concentrate (oil miscible suspension)	A stable suspension of active ingredient(s) in a fluid intended for dilution in an organic liquid before use.
OL	Oil miscible liquid	A liquid, homogeneous formulation to be applied as a homogeneous liquid after dilution in an organic liquid.
OP	Oil dispersible powder	A powder formulation to be applied as a suspension after dispersion in an organic liquid.
PA	Paste	Water-based, film-forming composition.
PR	Plant rodlet	A small rodlet, usually a few centimetres in length and a few millimetres in diameter, containing an active ingredient.
PS	Seed coated with a pesticide	Self defining.
RB	Bait (ready for use)	A formulation designed to attract and be eaten by the target pests
SC	Suspension concentrate(= flowable concentrate)	A stable suspension of active ingredient(s) with water as the fluid, intended for dilution with water before use.

Code	Term	Definition
SD	Suspension concentrate for direct application	A stable suspension of active ingredient(s) in a fluid, which may contain other dissolved active ingredient(s), intended for direct application, to rice paddies, for example.
SE	Suspo-emulsion	A fluid, heterogeneous formulation consisting of a stable dispersion of active ingredients in the form of solid particles and fine globules in a continuous water phase.
SG	Water soluble granule	A formulation consisting of granules to be applied as a true solution of the active ingredient after dissolution in water, but which may contain insoluble inert ingredients.
SL	Soluble concentrate	A clear to opalescent liquid to be applied as a solution of the active ingredient after dilution in water. The liquid may contain water-insoluble formulants.
SO	Spreading oil	Formulation designed to form a surface layer on application to water.
SP	Water soluble powder	A powder formulation to be applied as a true solution of the active ingredient after dissolution in water, but which may contain insoluble inert ingredients.
ST	Water soluble tablet	Formulation in form of tablets to be used individually, to form a solution of the active ingredient after disintegration in water. The formulation may contain water-insoluble formulants.
SU	Ultra-low volume (ULV) suspension	A suspension ready for use through ULV equipment.
TB	Tablet	Pre-formed solids of uniform shape and dimensions, usually circular, with either flat or convex faces, the distance between faces being less than the diameter.
TC	Technical material	A material resulting from a manufacturing process comprising the active ingredient, together with associated impurities. This may contain small amounts of necessary additives.
TK	Technical concentrate	A material resulting from a manufacturing process comprising the active ingredient, together with associated impurities. This may contain small amounts of necessary additives and appropriate diluents.
UL	Ultra-low volume (ULV) liquid	A homogeneous liquid ready for use through ULV equipment.
VP	Vapour releasing product	A formulation containing one or more volatile active ingredients, the vapours of which are released into the air. Evaporation rate is normally controlled by using suitable formulations and/or dispensers.
WG	Water dispersible granules	A formulation consisting of granules to be applied after disintegration and dispersion in water.
WP	Wettable powder	A powder formulation to be applied as a suspension after dispersion in water.
WS	Water dispersible powder for slurry seed treatment	A powder to be dispersed at high concentration in water before application as a slurry to the seed.
WT	Water dispersible tablet	Formulation in the form of tablets to be used individually, to form a dispersion of the active ingredient after disintegration in water.
XX	Others	Temporary categorization of all other formulations not listed

Code	Term	Definition
		above.
ZC	A mixed formulation of CS and SC	A stable suspension of capsules and active ingredient(s) in fluid, normally intended for dilution with water before use.
ZE	A mixed formulation of CS and SE	A fluid, heterogeneous formulation consisting of a stable dispersion of active ingredient(s) in the form of capsules, solid particles, and fine globules in a continuous water phase, normally intended for dilution with water before use.
ZW	A mixed formulation of CS and EW	A fluid, heterogeneous formulation consisting of a stable dispersion of active ingredient(s) in the form of capsules and fine globules in a continuous water phase, normally intended for dilution with water before use.

For record keeping purposes, the suffix "SB" should be added to the formulation code, if the material is packaged in a sealed water soluble bag (e.g. WP-SB).

Table 3: Proposed Number of Residue Trials for Comprehensive Submissions

Minimum number of Supervised Field Trials Conducted at cGAP									
Crop[1]	US	Additional Canadian (where US trials do not overlap)	EU[2]	JP[3]	AUS	NZ	Other	Total	After 40% reduction[4]
Acerola (Barbados cherry)	1		4	2				7	8
Alfalfa	12	6	F	2		4		24	15
Almond	5		4	2	6	2		19	13
Apple	16	4	16	6	8	6		56	35
Apple, Sugar	2		4	2				8	8
Apricot	5	2	12	2	6	2		29	20
Arracacha	2		4	2				8	8
Artichoke, Globe	3		4	2		2		11	8
Artichoke, Jerusalem	3		4	2		2		11	8
Asparagus	8	1	6	2	4	4		25	16
Atemoya	1		4	2		2		9	8
Avocado	5		4	2	8	2		21	14
Banana	5		4	2	8			19	12
Barley	12	9	16	3	8	4		52	31
Bean, Dried	12	3	16	2		2		35	23
Bean, Edible Podded	8		16	2		4		30	19
Bean, Lima, Dried	3		16	2		2		23	16
Bean, Lima, Green	8		16	2	8	2		36	24
Bean, Mung	3			2		2		7	8
Bean, Snap	8	2		2		2		14	11
Bean, Succulent Shelled	8		16	3		2		29	19
Beet, Garden	5	1	12	2		2		22	15
Blackberry	5	1	4	2		2		14	10
Blueberry	8	3	4	2	4	2		23	15
Bok choi	2			2		2		6	8
Boysenberry	2		4	2		2		10	8
Broccoli	8	4	6	3	8	4		33	20
Broccoli, Chinese (gai lon)	2			2		2		6	8
Brussels Sprouts	3	2	6	2	4	2		19	14
Buckwheat	5		6	2		2		15	11
Cabbage	8	4	12	6	8	4		42	25
Cabbage, Chinese	3		4	6		2		15	10
Cacao Bean (cocoa)	3			2				5	8
Calabaza	2			2				4	8
Calamondin (Codex: mandarin)	1			2				3	8
Canola	8	9	16	2	8	2		45	29
Cantaloupe	8		12	2	8	2		32	21
Capsicum (pepper)					8				8
Carambola	2		4	2		2		10	8
Carob	3		4	2				9	8
Carrot	8	4	16	6	8	4		46	28
Cassava, bitter or sweet	2		4	2		2		10	8
Cauliflower	8	3	16	2	8	2		39	26
Celery	8	4	6	3	4	4		29	17
Cherry, Sweet	8	1	12	2	3	4		30	19

Minimum number of Supervised Field Trials Conducted at cGAP									
Crop[1]	US	Additional Canadian (where US trials do not overlap)	EU[2]	JP[3]	AUS	NZ	Other	Total	After 40% reduction[4]
Cherry, Tart (Sour)	8	1	12	2	3	2		28	19
Chestnut	3		4	2	4	2		15	10
Chickpea (garbanzo bean)	3		6	2	4	2		17	12
Chicory	2		4	2		2		10	8
Clover	12		F	2		4		18	12
Coconut	5		4	2				11	8
Coffee	5			2	4			11	8
Collards	5		6	2		2		15	11
Corn, Field	20		16	2	2	4		44	28
Corn, Pop	3			2				5	8
Corn, Sweet	12	3	6	3	6	2		33	21
Cotton	12		8	2	8			30	19
Cowpea (dried shelled bean)	5		6	2		2		15	11
Cowpea (forage/hay)	3		F	2		2		7	8
Cowpea (succulent shelled bean)	3		6	2		2		13	10
Crabapple	3		6	2		2		13	10
Cranberry	5	1	4	2		2		14	10
Cress, Upland	1		4	2				7	8
Cucumber	8	3	12	6	4	4		37	22
Currant	2		6	2		2		12	10
Dandelion	1		6	2		2		11	9
Dasheen (taro)	2		4	2		2		10	8
Date	3		4	2				9	8
Dill (dill seed, dillweed)	2		6	2		2		12	10
Eggplant	3		6	6		2		17	12
Elderberry	3		4	2		2		11	8
Endive (escarole)	3		6	2		2		13	10
Fennel			6	2				8	6
Fig	3		4	2		2		11	8
Filbert (hazelnut)	3		4	2		2		11	8
Flax	5	5	6[3]	2		2		20	14
Fodder beet			16	2		4		22	14
Garlic	3	2	6	2		2		15	12
Genip (Codex: Spanish lime)	1		4	2				7	8
Ginger	2		4	3				9	8
Ginseng	3		4	2				9	8
Gooseberry	3		6	2		2		13	10
Grape	12	3	16	3		6		40	25
Grape, table			16	3	8	4		31	19
Grapefruit	8		4	2	2	2		18	13
Grasses	12		F	2		4		18	11
Guar	3			2				5	8
Guava	2		4	2		2		10	8
Herbs			6	2				8	6
Hops	3		6	2		2		13	10
Horseradish	3		6	2		2		13	10

[3] Flax is known for fibre production, value given is for seed production

Minimum number of Supervised Field Trials Conducted at cGAP									
Crop[1]	US	Additional Canadian (where US trials do not overlap)	EU[2]	JP[3]	AUS	NZ	Other	Total	After 40% reduction[4]
Huckleberry	3		4	2		2		11	8
Kale	3		12	2		2		19	13
Kiwi fruit	3		6	3		6		18	12
Kohlrabi	3		6	2		2		13	10
Kumquat	1		4	2		2		9	8
Leek	3		12	6	4	2		27	17
Lemon	5		8	2	6	2		23	15
Lentil	3	6	4	2		2		17	12
Lettuce, Head	8	5	16	6	8	3		46	29
Lettuce, Leaf	8		16	2	8	3		37	24
Lime	3		4	2		2		11	8
Loganberry	2		6	2		2		12	10
Longan	1		4	2				7	8
Lotus Root	1		4	3				8	8
Lychee	1		4	2	2			9	8
Macadamia Nut	3		4	2	6	2		17	12
Mamey Sapote	2		4	2				8	8
Mandarin (tangerine)	5		8	6	8	4		31	19
Mango	3		4	2	8			17	11
Melon			12	3		2		17	11
Melon, Casaba	3					2		5	8
Melon, Crenshaw	3					2		5	8
Melon, Honeydew	5	5				2		12	8
Millet, Proso	5	1	6	2		2		16	12
Mint	5		6	2		2		15	11
Mulberry	3		6	2				11	8
Mushrooms	3		4	2	6	2		17	12
Muskmelons	8					2		10	8
Mustard Greens	8		6	2		2		18	13
Mustard, Chinese	2			2		2		6	8
Nectarine	8	2	12	2	8	2		34	23
Oat	16	8	16	2	6	2		50	33
Okra	5		4	2		2		13	9
Olive	3		8[4]	2		2		15	11
Onion, Dry Bulb	8	4	16	6	8	4		46	28
Onion, Green	3	2	8	6	4	2		25	17
Orange, Sour and Sweet	16		8	2	8	4		38	24
Papaya	3		4	2				9	8
Parsley	3		4	2	2	2		13	10
Parsnip	3		6	2		2		13	10
Passion Fruit	2		4	2		2		10	8
Pawpaw	3		4	2				9	8
Pea, Chinese	1			2		2		5	8
Pea, Dried Shelled	5	8	16	2	8	2		41	27
Pea, Edible podded	8		6	2	6	2		24	17
Pea, Edible Podded	3			2		2		7	8

[4] Number of trials for olives for oil production; otherwise 4 trials

Minimum number of Supervised Field Trials Conducted at cGAP									
Crop[1]	US	Additional Canadian (where US trials do not overlap)	EU[2]	JP[3]	AUS	NZ	Other	Total	After 40% reduction[4]
Pea, Field (Austrian Winter) (forage/hay)	3		F	2	8	2		15	11
Pea, Succulent Shelled (Pea, Garden, Succulent)	8	4	16	2		2		32	21
Peach	12	4	12	3	8	4		43	25
Peanut	12	3	4	2	8			29	18
Peanut, Perennial	3			2				5	8
Pear	8	4	16	6	8	4		46	28
Pecan	5		4	2	4	2		17	11
Pepper, (other than bell)	3			2		2		7	8
Pepper, Bell	8	4	16	3		2		33	21
Persimmon	3		4	6		4		17	10
Pimento	2		4	2		2		10	8
Pineapple	8		4	2				14	9
Pistachio	3		4	2				9	8
Plantain	3		4	2				9	8
Plum	8	1	16	2	8	2		37	25
Pomegranate	3		4	2				9	8
Potato	16	10	16	6	8	4		60	37
Pumpkin	5	4	6	2	4	2		23	15
Quince	3		6	2		2		13	10
Radish	5	1	6	2		2		16	12
Radish, Oriental (daikon)	2			6		2		10	8
Rapeseed	3		16	2		2		23	16
Raspberry, Black and Red	5		6	2		2		17	11
Rhubarb	2	1	6	2		2		13	11
Rice	16		8	6	6			36	23
Rice, Wild	5	4		2				11	8
Rutabaga	3	2	6[5]	2		2		13	11
Rye	5	2	16	2		2		27	19
Safflower	5	2	4	2		2		15	11
Sainfoin	3		F	2		2		7	8
Salsify	3		6	2		2		13	10
Sesame	3		4	2				9	8
Shallot	1		6	2		2		11	9
Sorghum, Grain	12		8	2	6	2		30	20
Soybean (dried)	20	1	16	6	8	4		55	34
Spices			6	2				8	6
Spinach	8	3	6	6		2		25	17
Squash, Summer	8	4	12	2		4		30	18
Squash, Winter	5		6	3		2		16	11
Strawberry	8	3	16	3	8	4		42	26
Sugar Beet	12	6	16	3	2			39	25
Sugarcane	8			3	8			19	12
Sunflower	8	2	16	2	8	2		38	26
Sweet Potato	8		4	6		2		20	13

[5] See turnip

Minimum number of Supervised Field Trials Conducted at cGAP									
Crop[1]	US	Additional Canadian (where US trials do not overlap)	EU[2]	JP[3]	AUS	NZ	Other	Total	After 40% reduction[4]
Swiss Chard	3		6	2		2		13	10
Tangelo	3		4	2		2		11	8
Tanier (cocoyam)	2			2				4	8
Tea				6				6	8
Tobacco	3	5	4	2		2		16	11
Tomato	16	11	16	6	8	4		61	38
Triticale			16	2	4	2		24	16
Turnip, root	5		6	3		4		18	11
Turnip, tops (leaves)	5		6	3		2		16	11
Walnut, Black and English	3		6	2		2		13	10
Watercress	2		6	2		2		12	10
Watermelon	8		16	6	4	2		36	23
Wheat	20	13	16	6	12	4		71	43
Yam, True	3		4	3		2		12	8

[1] Crops to be reconsidered after Codex classification is finalised.

[2] Number of trials for fodder crops (marked F) in Europe not yet harmonised, although criteria are available that allow specifying number of trials i. e. cultivation area (ha) and production (t).

In case no number is given the mentioned crop is not widely grown in Europe. The number of trials necessary depends on criteria described in the EU Guidelines on comparability, extrapolation, group tolerances and data requirements for setting MRLs.

In addition, the new data requirement as described in Regulation (EU) No 283/2013 allow a reduction of the number of trials for minor crops that are growing in both European residue zones and where the GAP is the same. In this case six trials are sufficient instead of eight which is reflected in the above table.

[3] The Japanese government revised the requirements for the number of trials of residue data, depending on the production volume and consumption of each commodity, within the review of pesticide registration scheme. From 1st April in 2014, the minimum number of trials is six for major crops and three for semi-major crops, respectively. The minimum number of trials remains two for minor crops.

[4] To take into account that no reduction on two trials in an OECD country is possible and that a minimum of eight trials for a comprehensive submission is required.

ANNEXES

Three Annexes are provided in a separate publication ENV/JM/MONO(2011)50/REV1/ANN

Annex 1: Background Information to Chapter 1. Crop Grouping (including two Appendices)

Annex 2: Background Information to Chapter 2. Extrapolations

Annex 3: Background Information to Chapter 3. Proportionality (including four Appendices)

Organisation de Coopération et de Développement Économiques
Organisation for Economic Co-operation and Development

07-Sep-2016

English - Or. English

ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

OECD GUIDANCE DOCUMENT ON CROP FIELD TRIALS: ANNEXES WITH ADDITIONAL INFORMATION

SECOND EDITION
Series on Pesticides - No. 66
Series on Testing & Assessment - No. 164

JT03400235

Complete document available on OLIS in its original format

ENV/JM/MONO(2011)50/REV1/ANN
Unclassified
English - Or. English

OECD Environment, Health and Safety Publications

Series on Pesticides

No. 66

and

Series on Testing and Assessment

No. 164

Guidance Document on Crop Field Trials

SECOND EDITION

IOMC

INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS

A cooperative agreement among FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD

Environment Directorate
ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT
Paris 2016

About the OECD

The Organisation for Economic Co-operation and Development (OECD) is an intergovernmental organisation in which representatives of 35 industrialised countries in North and South America, Europe and the Asia and Pacific region, as well as the European Commission, meet to co-ordinate and harmonise policies, discuss issues of mutual concern, and work together to respond to international problems. Most of the OECD's work is carried out by more than 200 specialised committees and working groups composed of member country delegates. Observers from several countries with special status at the OECD, and from interested international organisations, attend many of the OECD's workshops and other meetings. Committees and working groups are served by the OECD Secretariat, located in Paris, France, which is organised into directorates and divisions.

The Environment, Health and Safety Division publishes free-of-charge documents in twelve different series: **Testing and Assessment**; **Good Laboratory Practice and Compliance Monitoring**; **Pesticides**; **Biocides**; **Risk Management**; **Harmonisation of Regulatory Oversight in Biotechnology**; **Safety of Novel Foods and Feeds; Chemical Accidents; Pollutant Release and Transfer Registers; Emission Scenario Documents; Safety of Manufactured Nanomaterials;** and **Adverse Outcome Pathways.** More information about the Environment, Health and Safety Programme and EHS publications is available on the OECD's World Wide Web site (www.oecd.org/chemicalsafety/).

This publication was developed in the IOMC context. The contents do not necessarily reflect the views or stated policies of individual IOMC Participating Organizations.

The Inter-Organisation Programme for the Sound Management of Chemicals (IOMC) was established in 1995 following recommendations made by the 1992 UN Conference on Environment and Development to strengthen co-operation and increase international co-ordination in the field of chemical safety. The Participating Organisations are FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD. The purpose of the IOMC is to promote co-ordination of the policies and activities pursued by the Participating Organisations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

This publication is available electronically, at no charge.

For this and many other Environment, Health and Safety publications, consult the OECD's World Wide Web site (www.oecd.org/ehs)

or contact:

OECD Environment Directorate,
Environment, Health and Safety Division
2, rue André-Pascal
75775 Paris cedex 16
France

Fax : (33-1) 44 30 61 80

E-mail : ehscont@oecd.org

FOREWORD

This Guidance Document is an update of the first *Guidance Document on Crop Field Trials* published in 2011. It has been developed by the Residue Chemistry Expert Group of the OECD Working Group on Pesticides (WGP).

Crop Field Trials (CFT, also referred to as supervised field trials) are conducted to determine the magnitude of the pesticide residue in or on raw agricultural commodities, including feed items, and should be designed to reflect pesticide use patterns that lead to the highest possible residues. While the *OECD Guideline for the Testing of Chemicals on Crop Field Trial* (TG 509 published in September 2009) provides a harmonized approach to conducting and reporting crop field trials in OECD countries, this *Guidance Document on Crop Field Trials* helps in planning the trials in OECD countries and in interpreting the results.

Around the time the first Guidance Document was published, outstanding issues related to the CFT studies were raised following an OECD survey on Maximum Residue Level (MRL) policies in member countries (survey results published in 2010, Series on Pesticides, No. 51). Further work on these issues was discussed and agreed upon at the September 2011 Pesticides Registration Steering Group (RSG) Meeting (Ottawa, Canada) and then endorsed by the RSG's parent body, the WGP.

The Ottawa RSG Meeting agreed that the 2011 CFT Guidance Document should be updated with respect to the following points: i) crop groups and representative commodities; ii) considering the use of the proportionality principle for adjusting crop field trial values relative to application rate; iii) the independence of trials; iv) the composition of data sets; and v) further direction on the collection and preparation of field trial samples.

After two rounds of comments in 2014-2015 among the WGP and the Working Group of National Co-ordinators of the Test Guidelines Programme (WNT), the updated CFT Guidance Document was approved by the WGP and WNT in April 2016.

This publication is organised into two parts: the core document on guidance for conducting crop field trials ENV/JM/MONO(2011)50/REV1 and the three Annexes that are published together ENV/JM/MONO(2011)50/REV1/ANN.

This document is being published under the responsibility of the Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology, which has agreed that it be declassified and made available to the public on 29 August 2016.

TABLE OF CONTENTS

ANNEX 1
Background information to chapter 1. Crop Grouping

Background

1. Annex 1 describes the background as provided by OECD member countries before September 2014 to illustrate where the discussion started and to make transparent why certain conclusions and recommendations were given in the OECD Guidance Document on Crop Field Trials. An update is not foreseen.

Principles for Crop Grouping

National/Regional Approaches to Crop Groups

2. NAFTA has made extensive use of the crop group/subgroup MRL concept. The EU has tended to use extrapolations rather than the broader crop grouping. Extrapolations rely upon the data from one commodity to support another, e.g., the MRL for tomato is extended to aubergine/eggplant. Upon closer examination, however, it seems that the EU extrapolations are often very similar to NAFTA crop sub groupings.

3. Subgroups are primarily indicative of form and growth habit, and normally at least one commodity would be needed from each subgroup to set a group MRL. For example, citrus fruits are divided in the US into three subgroups (10-10A orange or tangerine/mandarine, 10-10B lemon or lime and 10-10C grapefruit). One commodity from each subgroup (e.g., orange, lemon and grapefruit) would be needed for a group MRL.

4. Consideration of form and growth habit can also lead to differences in subgroups among countries. For example, NAFTA subdivides fruiting cucurbit vegetables into melons and pumpkins/ squashes/ cucumbers. The EU and Australia subdivide into edible peel and inedible peel. However, similar commodities are considered representative for the cucurbit vegetables (e.g. cucumber/ zucchini, melon/ watermelon/ winter squash).

5. The commodity consumed may also be reflected in the sub-grouping. For example, bulb vegetables are often grouped into subgroups 1: garlic, onion, shallot and 2: chives, spring onion, and leeks. The distinction is that only the bulbs of those in subgroup 1 are consumed, whereas the bulb and aerial portions of the subgroup 2 may be eaten. Different residue levels might be expected on the two sub-groupings for most pesticide applications. Thus, it might be possible to extrapolate from bulb onion to garlic and/or shallot, but not from bulb onion to spring onion.

6. Crop grouping, representative commodities, and extrapolations that were used in national/regional approaches are given in Appendix 1. Some of the criteria used by Japan, NAFTA, Australia and the EU in developing crop groups are summarized in Appendix 2.

Codex Approach to Commodity Groups

7. For the revision of the Codex commodity group/subgroup proposals the following principles used by the ICGCC/IR-4 are taken into account:

1. Botany and nomenclature of the commodity.

2. Geographical production and distribution of the commodity.

3. International trade of the commodity.

4. Cultural practices for the commodity.

5. Commercial importance of the commodity.

6. Possibilities of genetic improvement for the commodity.

7. Comparison of edible parts of the commodity.

8. If the commodity is used as a livestock feed item for beef and dairy cattle, poultry and swine.

9. If the commodity is used for processed products and/or fresh market as whole fruit/vegetable.

10. Comparison of pest problems of the commodity.

11. Comparison of potential residue levels on the commodity.

12. Existing classification of the commodity.

13. Justification for a Crop Group/Subgroup Definition.

Representative Commodities

National/Regional Approaches to Representative Commodities

8. When looking at national approaches for representative commodity (within the group) properties it seems that the following criteria are taken into account:

- major in terms of production and consumption; and
- most likely to contain the highest residue.

9. It is recognized that a major commodity may not have the highest residue. Although, there may be no definite resolution as there are no supervised residue trials data on all minor commodities of a crop group, it should not be acceptable that substantially higher residues in a minor commodity are ignored because residues of a major commodity from the same crop group support a lower MRL. In such cases, if appropriate data on the minor commodities are available, individual (higher) MRLs might be necessary. From a dietary exposure standpoint, using a major commodity as representative of the group is acceptable because of the small consumption of minor commodities. Nevertheless, one should bear in mind that this mainly refers to chronic exposure while large portion consumption relevant for acute exposure assessment is often in the same order of magnitude for minor commodities as for major commodities. Using major commodity residue situations which might not reflect highest residue in minor commodities might therefore result in an underestimation of the acute intake. In addition to dietary risk issues, there may be impacts on compliance with MRLs because a group/subgroup MRL may not reflect potential residues in one or more minor commodities. There exists the finite possibility of non-compliance for some commodities in the crop group. In such a case OECD countries have to take action on a case-by-case basis, a solution might be trials in some representative minor crops.

10. There may be some difference regionally in the desired representative crop/commodity. For example, aubergine (eggplant) is a major fruiting vegetable in Asia but not in NAFTA. In these situations, the selection of alternative representative commodities may be justified.

Codex Approach to Representative Commodities

11. Following the proposals made in Codex (CCPR 2010) representative commodities within each group and subgroup are selected and proposed, based on consideration of all available information. The following key principles are used for the selection of representative commodities:

- A representative commodity is most likely to contain the highest residues.
- A representative commodity is likely to be major in terms of production and/or consumption.
- A representative commodity is most likely similar in morphology, growth habit, pest problems and edible portion to the related commodities within a group or subgroup.

12. On the basis of these criteria one representative commodity for each group and subgroup may be sufficient. Nevertheless, to facilitate the global use of crop groups for MRL setting, alternative representative commodities may be selected giving flexibility for use of residue tests conducted in different countries or regions, given that representative commodities may vary due to regional differences in dietary consumption and/or areas of production for certain commodities.

13. The new proposed Codex commodity groups and subgroups together with proposed examples of representative commodities and the principles and guidance for selection of representative commodities were adopted by 35th Session of the Codex Alimentarius Commission in 2012 (July 2012, REP12/CAC) for fruits. A list of these commodities is given in table 1 of the main text. Further commodity groups are still under discussion and will be adopted by the Codex Alimentarius Commission at a later stage. They can be found in recent CCPR Reports and working papers.

Use of Crop Trial Data for Representative Commodities

14. Provided each authority uses the same representative commodities, crop trials which fulfil the data requirements of a regulatory authority may be used to the extent possible to replace trials required by another regulatory authority if the GAP and production conditions (e.g. cultural practices) are comparable. In those cases where the regulatory authorities in question have specified different representative commodities, the application of this approach will be made on a case-by-case basis.

APPENDIX 1
Crop Grouping, representative commodities, extrapolations

Existing Crop Groups and Extrapolations[1] (except Codex)

NAFTA Crop Group/ Subgroup	NAFTA Crop Group/ Subgroup (US numbering)[5]	NAFTA Crop Group/ Subgroup (Canadian numbering)[5]	NAFTA Representative Crop (for group or subgroup)	EU Groups of Crops	EU Representative Crop and Extrapolation[3]
10 Citrus Fruits	10-10 Citrus Fruits 10-10A Orange or tangerine / mandarine 10-10B Lemon or lime 10-10C Grapefruit	10- Revised Citrus Fruits 10-A Revised Orange subgroup 10-B Revised Lemon/Lime subgroup 10-C Revised Grapefruit subgroup	Sweet orange or tangerine / mandarine Lemon or lime Grapefruit Sweet orange or tangerine / mandarine Lemon or lime Grapefruit	1 Fruits (i) Citrus Fruits	Oranges or oranges and grapefruits (8 trials, with a minimum of four trials on oranges) and mandarins and/or lemons (8 trials)→ group
11 Pome Fruits	11-10 Pome Fruits	11-09 Pome Fruits	Apple Pear	1 Fruits (iii) Pome Fruit	Apples OR Pears (with a minimum of 4 apple trials) → group
12 Stone Fruits	12-12 Stone Fruits ——- 12-12A Cherry 12-12B Peach 12-12C Plum	12-09 Stone Fruits 12-09A Cherry subgroup 12-09B Peach subgroup 12-09C Plum subgroup	Cherry (sweet or tart) Peach Plum or prune plum Cherry (sweet or tart) Peach Plum or prune plum	1 Fruits (iv) Stone fruit	Peaches OR Apricots (with a minimum of 4 apricot trials) → nectarine, peach, apricot Sweet cherries ↔ Sour cherries plums
13-07 Berries			Blackberry	1 Fruit (v)	

NAFTA Crop Group/ Subgroup	NAFTA Crop Group/ Subgroup (US numbering)[5]	NAFTA Crop Group/ Subgroup (Canadian numbering)[5]	NAFTA Representative Crop (for group or subgroup)	EU Groups of Crops	EU Representative Crop and Extrapolation[3]
and Small Fruit			Raspberry Highbush blueberry, elderberry, or mulberry Grape Fuzzy kiwifruit Strawberry	Berries and small fruit	
13-07D Small fruit vine climbing subgroup			Grape and fuzzy kiwifruit	(a) grapes	Table ↔ Wine grapes
13-07E Small fruit vine climbing except grape, subgroup			fuzzy kiwifruit	(b) strawberries	None
13-07FSmall fruit vine climbing except fuzzy kiwifruit, subgroup			grape		
13-07G Low growing berry subgroup			strawberry	(c) cane fruit	Raspberries (4 trials) → blackberries
13-07H Low growing berry, except strawberry, subgroup			cranberry		Raspberries alone OR two representatives (6 trials) → Whole group
13-07A Caneberry subgroup			Blackberry or Raspberry	(d) Other small fruits and berries (except wild)	6 trials on currants (black, red or white) alone or 6 trials on two representatives (must also
13-07B Bushberry subgroup			Blueberry, highbush		

NAFTA Crop Group/ Subgroup	NAFTA Crop Group/ Subgroup (US numbering)[5]	NAFTA Crop Group/ Subgroup (Canadian numbering)[5]	NAFTA Representative Crop (for group or subgroup)	EU Groups of Crops	EU Representative Crop and Extrapolation[3]
13-07C Large shrub/ tree subgroup			Elderberry or mulberry		include a minimum of 4 trials on currants) or on grape and currant (must also include a minimum of 4 trials on currants)→ Whole group
tropical and subtropical fruits – edible peel[8]				1 Fruits (vi)(a) Miscellaneous fruit – edible peel	table olives ↔ olives for oil production Cherries → Surinam cherries
tropical and subtropical fruits – inedible peel[9]				1 Fruits (vi)(b) Miscellaneous fruit – inedible peel, small (c) Miscellaneous fruit – inedible peel, large	none none
3-07 Bulb vegetables 3-07A Onion, bulb subgroup 3-07B Onion, green subgroup			Onion, bulb Onion, green Onion, bulb Onion, green	2 Vegetables (ii) Bulb vegetables	 Bulb onion → garlic, shallots Spring/salad onions → Welsh onion, chives Leek ↔ spring/salad onions
5 Brassica			Broccoli OR	2 Vegetables	

NAFTA Crop Group/ Subgroup	NAFTA Crop Group/ Subgroup (US numbering)[5]	NAFTA Crop Group/ Subgroup (Canadian numbering)[5]	NAFTA Representative Crop (for group or subgroup)	EU Groups of Crops	EU Representative Crop and Extrapolation[3]
(Cole) Leafy Vegetables			Cauliflower Cabbage Mustard greens	(iv) Brassica vegetables	
5A Head and stem brassica subgroup			Broccoli OR Cauliflower Cabbage i	(a) Flowering brassicas.	Cauliflower, broccoli (4 trials each) → whole group
5B Leafy Brassica greens[6] subgroup			Mustard	(b) Head brassicas	Brussels sprouts, head cabbage → None
				(d) kohlrabi	None
				(c) Leafy brassicas	Kale → Whole group
9 Cucurbit vegetables			Cucumber Muskmelon Summer squash	2. Vegetables (iii) Fruiting vegetables	
9A Melon subgroup			Cantaloupes	(b) cucurbit edible peel	Cucumber or courgette (if courgettes alone 8 trials) → Whole group
9B Squash/ cucumber subgroup			Summer squash, Cucumber	(c) cucurbit inedible peel	Melons → Whole group
				(d) sweet corn	Immature maize → sweet corn
8-10 Fruiting Vegetables (except cucurbit)		8-09 Fruiting Vegetables (except cucurbits)	Tomato Bell pepper Non-bell pepper	2. Vegetables (iii) Fruiting vegetables	
8-10A Tomato subgroup		8-09A Tomato subgroup	Tomato (standard and one cultivar of small)	(a) Solanacea Tomatoes Peppers	Tomato → Aubergine Sweet peppers → Peppers

NAFTA Crop Group/ Subgroup	NAFTA Crop Group/ Subgroup (US numbering)[5]	NAFTA Crop Group/ Subgroup (Canadian numbering)[5]	NAFTA Representative Crop (for group or subgroup)	EU Groups of Crops	EU Representative Crop and Extrapolation[3]
8-10B Pepper/ eggplant subgroup 8-10C Nonbell pepper/ eggplant subgroup		8-09B Pepper/Eggplant subgroup 8-09C Nonbell pepper/eggplant subgroup	Bell pepper and one cultivar of nonbell pepper One cultivar of small nonbell pepper or one cultivar of small eggplant		
4. Leafy Vegetables (except Brassica)[6] 4A Leafy Greens subgroup 4B Leaf petioles[7] subgroup			Celery Head lettuce Leaf lettuce Spinach Head lettuce Leaf lettuce Spinach Celery	2. Vegetables (v) Leaf vegetables and fresh herbs (a)Lettuce and other salad plants including Brassicacea (b) Spinach and similar (leaves) (c)vine leaves (grape leaves)	 Lettuce (8 trials on open leaf varieties) → Whole lettuce and other salad plants group Spinach → whole group Spinach → rocket, red mustard, leaves and sprouts of Brassica sp. Lettuce (8 trials, with a minimum of 4 trials on open leaf varieties) → group Spinach and similar None

NAFTA Crop Group/ Subgroup	NAFTA Crop Group/ Subgroup (US numbering)[5]	NAFTA Crop Group/ Subgroup (Canadian numbering)[5]	NAFTA Representative Crop (for group or subgroup)	EU Groups of Crops	EU Representative Crop and Extrapolation[3]
				(d)Water cress (e) Witloof	None None
6 Legume Vegetables (Succulent or Dried) 6A Edible-podded legume subgroup 6B Succulent shelled pea and bean subgroup 6C Dried shelled pea and bean except soybean, subgroup			Bean (one succulent and one dried) Pea (one succulent and one dried) Soybean (dry) Edible-podded bean Edible-podded pea shelled succulent bean, garden pea dried bean, dried pea	2. Vegetables (vi) Legume vegetables (fresh) Beans, green with pods Peas, green without pod	Beans, green with pods ↔ Peas with pods Consideration should be given to possible contamination from mechanical harvesting None
See above 6C			See above 6C	3. Pulses, dry	Beans (dry) and/or peas (dry) → Whole group
1. Root and Tuber Vegetables 1A Root vegetable subgroup 1B Root vegetable except sugar beet, subgroup			Carrot Potato Radish Sugar beet Carrot, radish, sugar beet Carrot, radish	2. Vegetables (i)Root and tuber vegetables	Carrots Sugar beet Fodder beet Swedes and turnips Potato, carrot, and sugar beet (8 trials each) → Whole group (root and tuber vegetables)

NAFTA Crop Group/ Subgroup	NAFTA Crop Group/ Subgroup (US numbering)[5]	NAFTA Crop Group/ Subgroup (Canadian numbering)[5]	NAFTA Representative Crop (for group or subgroup)	EU Groups of Crops	EU Representative Crop and Extrapolation[3]
1C Tuberous and corm vegetables subgroup 1D Tuberous and corm vegetables except potato subgroup 2. Leaves of root and tuber vegetables (human food or animal feed)			potato Sweet potato Turnip tops Garden or sugar beet tops	(c)Other root and tuber vegetables except sugar beet (a)Potatoes (b)Tropical root and tuber vegetables 9. SUGAR PLANTS	Carrot Carrots → Whole "other root and tuber vegetables except sugar beet" Carrots → roots of herbal infusion, spices, Sugar beet → Beetroot, Swedes, turnips Swedes ↔ turnips Swede or turnip → celeriac, horseradish Potatoes →tropical root vegetables Sweet potato and/or yam → tropical root vegetables Carrot or sugar beet → chicory roots
see Group 4B			see Group 4B	2. Vegetables (vii) Stem vegetables	Leek ↔ spring/salad onions

NAFTA Crop Group/ Subgroup	NAFTA Crop Group/ Subgroup (US numbering)[5]	NAFTA Crop Group/ Subgroup (Canadian numbering)[5]	NAFTA Representative Crop (for group or subgroup)	EU Groups of Crops	EU Representative Crop and Extrapolation[3]
					Celery → Fennel (bulb), cardoon, rhubarb
15. Cereal grains			Corn (fresh sweet corn and dried field corn) Rice Sorghum Wheat For Canada: field corn and sweet corn wheat barley	5. Cereals	Barley Maize Oats Rice Rye Sorghum Triticale Wheat For treatments applied during inflorescence emergence and post-inflorescence emergence: Barley → oats Wheat →rye Maize → millet, sorghum Immature wheat → immature spelt
14-12 Tree nut		14-11 Tree Nuts	Almond Pecan	1.Fruits (ii)Tree nuts (shelled or unshelled)	Any two representative ("closed nuts" and "open nuts" e.g. cashew nuts, pistachios) with the exception of coconuts (6 trials) → Group Any "closed nut" with the exception of

NAFTA Crop Group/ Subgroup	NAFTA Crop Group/ Subgroup (US numbering)[5]	NAFTA Crop Group/ Subgroup (Canadian numbering)[5]	NAFTA Representative Crop (for group or subgroup)	EU Groups of Crops	EU Representative Crop and Extrapolation[3]
					coconuts (4 trials) → "closed nuts"
20. Oilseed 20A. Rapeseed subgroup 20B. Sunflower subgroup 20C Cottonseed subgroup			Rapeseed (canola varieties only), Sunflower, Cottonseed Rapeseed Sunflower cottonseed	4. Oilseeds and Oil fruits (i) Oilseeds (ii) Oil fruits	 Cotton seed Peanut Rapseed Soya bean Sunflower Any two of: Cotton seed, Rapeseed, Soya bean, Sunflower →, Minor unlisted oil seeds (oil seeds except those of previous column) Rapeseed → linseed, mustard seed, poppy seed, gold of pleasure Olives for oil production. Palm kernels olives for oil production ↔ table olives
				6 Tea, coffee, herbal infusions, and cocoa ii) Coffee (iv)cocoa (v) carob (St	 None None None

NAFTA Crop Group/ Subgroup	NAFTA Crop Group/ Subgroup (US numbering)[5]	NAFTA Crop Group/ Subgroup (Canadian numbering)[5]	NAFTA Representative Crop (for group or subgroup)	EU Groups of Crops	EU Representative Crop and Extrapolation[3]
				Johns bread)	
19. Herbs and Spices 19A. Herb subgroup			Basil (fresh and dried) Black pepper Chive Celery seed OR Dill seed Basil (fresh and dried) Chive.	2. Vegetables (v) Leaf vegetables and fresh herbs (f)Herbs (fresh)	Any crop of the herbs group (except bay leaves, sage, rosemary and thyme), spinach or lettuce (open leaf varieties → Whole group (other extrapolations can be considered on a case by case basis)
19B. Spice subgroup			Black pepper Celery seed OR Dill seed	8. Spices (i) Seeds: (ii)Fruits and berries	Anise, caraway, celery, coriander, cumin, dill, fennel, fenugreek, lovage, nasturtium Any single crop of previous column→ Whole group Any single cultivated crop → Fruits and berries of herbal infusions and spices

NAFTA Crop Group/ Subgroup	NAFTA Crop Group/ Subgroup (US numbering)[5]	NAFTA Crop Group/ Subgroup (Canadian numbering)[5]	NAFTA Representative Crop (for group or subgroup)	EU Groups of Crops	EU Representative Crop and Extrapolation[3]
				(iii)Bark (iv) Roots or rhizome	None Any single cultivated crop → roots of herbal infusions and spices Carrots or any root and tuber vegetable → roots of herbal infusions and spices
21. Edible fungi			White button mushroom and Oyster mushroom Or Shiitake mushroom	2.Vegetables (viii)Fungi (a)Cultivated (b) Wild	 Any single cultivated mushroom species → All cultivated mushrooms Any single wild mushroom species → All wild mushrooms
				7.Hops	None
				6 Tea, coffee, herbal infusions, and cocoa 6 (iii) herbal infusions (a) flowers (b) leaves (c) roots	Any single cultivated crop of (a), (b), or (c) → (a), (b), OR (c) of herbal infusions and spices

NAFTA Crop Group/ Subgroup	NAFTA Crop Group/ Subgroup (US numbering)[5]	NAFTA Crop Group/ Subgroup (Canadian numbering)[5]	NAFTA Representative Crop (for group or subgroup)	EU Groups of Crops	EU Representative Crop and Extrapolation[3]
					Carrots or any root and tuber vegetable → Roots of herbal infusions and spices
				(d)other herbal infusions	None
				6.Tea, coffee, herbal infusions and cocoa	
				(i) Tea	None
7 Foliage of legume vegetables (animal feed)	Any cultivar of bean, field pea, and soybean				
7A Foliage of legume vegetables except soybean, subgroup	Any cultivar of bean, field pea				
17 Grass Forage, fodder, and hay	Bermuda grass Bluegrass Bromegrass or fescue				
18 Nongrass animal feeds (forage, fodder, straw, and hay)	Alfalfa *Clover*				

Appendix 1 (continued): Existing Crop Groups and Extrapolations[1] (except Codex)

Australia Commodity Crops Groupings	Australia Possible Extrapolation From…	Australia Possible Extrapolation To…	Japan Crop Group[4]	Japan Representative Crop and Extrapolation
Subgroup 1 Lemon Lime Mandarin Subgroup 2 Grapefruit Oranges Tangelos	Oranges + Lemons Or Oranges + Limes Or Oranges + Mandarins	Whole group	Subgroup 1: Lemon and Limes Subgroup 2: Mandarins/orange Sweet, sour Subgroup 3: Pummelos	Satsuma Mandarin + Yuzu or Lime or Lemon + Natsudaidai → whole group
Apple Crab apple Loquat Nashi Pear Quince	Apples + Pears	Whole group	Pome fruits	Apple + Pears, or Apple + Persimmon, or Pears + Persimmon → whole group
Subgroup 1 Apricot Nectarine Peach Subgroup 2 Cherries Plums Prune	Peaches + Nectarines + Cherries Or Peaches + Plums + Cherries Peaches	Whole group Nectarines, plums	Subgroup 1: Peaches Subgroup 2: Apricots Subgroup 3: Plum/Nectarine Subgroup 4: Cherries	Peaches + Japanese Apricot + Cherries → whole group
Subgroup 1 Blackberry Boysenberry Cranberry Raspberry Subgroup 2 Blueberry Currants Gooseberry Other Grapes Strawberry	Grapes + strawberry and one other from subgroups 1 or 2 Raspberry Currants	Whole group Subgroup 1 Subgroup 2	Subgroup 1: Strawberry Subgroup 2: Grapes Subgroup 3: Currants/ Blueberry/ Rasberry	Strawberry + Grapes + Blueberries → whole group
Dates Figs	Olives + tamarillo (no	Whole group	Edible peel: Small:	Under consideration

Australia Commodity Crops Groupings	Australia Possible Extrapolation From…	Australia Possible Extrapolation To…	Japan Crop Group[4]	Japan Representative Crop and Extrapolation
Olives Persimmon Tamarillo Carambola Grumichan Jaboticaba	extrapolation from one crop to another is possible although if data from these crops are consistent, a group MRL may be possible)		Acerola/ Table Olives/ Kiwiberry/ Date Medium to Large: Chocolate Vine/Five leaf Akebia/ Fig	
Avocado Babaco Banana Custard apple Feijoa Guava Jackfruit Kiwifruit Litchi Longans Mango Mangosteen Pawpaw Passion fruit Persimmon Pineapple Rambutan Sapodilla Sapote	Banana Avocado Kiwifruit Mango Papaw Pineapple (no extrapolation from one crop to another is possible although if data from these crops are consistent, a group MRL may be possible)	Whole group	Inedible peel: Small: Litchi Smooth peel: Avocado/ Banana/ Papaya/ Mango Rough or hairy peel: Pineapple	Under consideration
Subgroup 1 Garlic Onions Shallots Subgroup 2 Chives Spring onions Subgroup 3 Leeks Subgroup 4 Fennel bulb	Onions + Spring onions Or Onions + shallots Or Onions + Leeks Onions (green) or shallots	Whole group Subgroups 1, 2 and 3	No Group has been established	N/A
Subgroup 1 Cauliflower Broccoli	Cauliflower + Cabbage + Brussels sprouts	Whole group	Brassica vegetables (edible flower buds and	Any two species →group

Australia Commodity Crops Groupings	Australia Possible Extrapolation From…	Australia Possible Extrapolation To…	Japan Crop Group[4]	Japan Representative Crop and Extrapolation
Subgroup 2 Cabbage Subgroup 3 Brussels sprouts	Or Broccoli + Cabbage + Brussels sprouts		stem): See Leafy vegetables (including Brassica leafy vegetables) (No other group has been established)	
Subgroup 1 Cucumber Chokos Bitter melon Zucchini Subgroup 2 Melons Marrow Pumpkin Squash Subgroup 3 Gherkin	Rock melon + Cucumber + Zucchini Melons	Whole group Subgroup 2	Cucurbits for pickles: Oriental pickling melon, Sponge grourd, Wax Grourd, Citron melon (No other group has been established)	Oriental pickling melon and any other one species →group Cucumber→ Zucchini
Subgroup 1 Egg plant Tomato Subgroup 2 Fungi Mushrooms Other Peppers Chilies Cape gooseberry Sweet corn Okra Roselle (Rosella)	Tomato + Capsicum (note it may be more appropriate to generate data as growing patterns and size vary widely) Maize	Whole group Sweet corn	Non-bell-shaped peppers: Chili pepper Long pepper Shishitou (*Capsicum annuum var.grossum* Sendth) (No other group has been established)	Shishitou (*Capsicum annuum var.grossum* Sendth) and any one other species →group Cherry tomato →Tomato

Australia Commodity Crops Groupings	Australia Possible Extrapolation From…	Australia Possible Extrapolation To…	Japan Crop Group[4]	Japan Representative Crop and Extrapolation
Subgroup 1 Lettuce Mustard Cress Subgroup 2 Spinach Silverbeet Subgroup 3 Fennel Subgroup 4 Chinese cabbage Kale	Leafy lettuce + Spinach + Chinese cabbage Spinach Celery	Whole group Subgroup 2 Silverbeet	Brassica Leafy vegetables : Kale, Komatsuna, Mizuna, Pak Choi, Rucola Leaf Lettuce: Leaf Lettuce Labiate Leafy vegetables: Labiate, Sage, Mint, Basil Apiaceous Leafy vegetables: Celery, Coriander (leaf), Japanese honeywort Parsley, Soup celery	Komatsuna, Mizuna and one other species →group Any two species from the group →group Labiate, sage or mint; and one other species from the group →group Soup celery, coriander (leaf) or Japanese honeywort; and one other species from the group →group
Beans (green) Peas (green)	Beans (green) + Peas (green)	Whole group	Legume Vegetables (Succulent seeds and/or immature pods): Soy bean (immature seeds) Garden pea (young pods and immature seeds) Common bean (pods and immature seeds)	Soy bean, garden pea and common bean → whole group

Australia Commodity Crops Groupings	Australia Possible Extrapolation From…	Australia Possible Extrapolation To…	Japan Crop Group[4]	Japan Representative Crop and Extrapolation
Peas Beans Chickpea Lentils Lupin Soybean	Field peas (dry) + faba beans (dry) + lupins Or Field peas (dry) + chickpeas + lupins Or Field peas (dry) + navy beans + lupins	Whole group	Pulses (Dried): Soybean (dry) Groundnut	Soybean (dry), groundnut and one other species →whole group
Subgroup 1 Carrot Parsnip Subgroup 2 Beetroot Swede Turnip Subgroup 3 Sweet potato Potato Yam Subgroup 4 Radish Horseradish Subgroup 5 Chicory	Potato + carrot + beetroot Or Potato + carrot + swede Or Potato + carrot + radish	Whole group	No Group has been established	N/A
Artichoke Asparagus Celery Witloof Rhubarb	Celery, asparagus, artichoke Celery	Whole group Rhubarb	No Group has been established	N/A
Subgroup 1 Wheat Triticale Cereal rye Subgroup 2 Barley Oats Subgroup 3 Maize	Wheat + barley + oats Maize + sorghum Rice Wheat or barley	Subgroups 1 and 2 Subgroup 3 Subgroup 4 Oats, rye, triticale, durum wheat,	Cereals group 1 (only those below): Oats, Barley, Wheat and Rye (NB: rice is not included in this group)	Barley and Wheat →group

Australia Commodity Crops Groupings	Australia Possible Extrapolation From…	Australia Possible Extrapolation To…	Japan Crop Group[4]	Japan Representative Crop and Extrapolation
Sorghum Millet Subgroup 4 Rice	Wheat	(treatments applied before GS32 only) Whole group except rice for post-harvest treatment only	Cereals group 2: Millets (No other group has been established)	Awa*(Setaria italica)* →group
Sugar cane			No Group has been established	N/A
Almonds Cashew Chestnuts Hazelnuts Macadamia Pecan Pistachios Walnuts	Almonds + Macadamia	Whole group	No Group has been established	N/A
Subgroup 1 Mustard seed Linseed Rape seed Subgroup 2 Poppy seed Safflower seed Sesame seed Sunflower seed Subgroup 3 Peanut Subgroup 4 Soybean Subgroup 5 Olive Subgroup 6 Maize Subgroup 7 Cottonseed	Canola (safflower, linseed or linola may replace canola in case of winter crops depending on use –pattern), cottonseed, peanut (summer crops, sunflower, soybean may replace peanuts depending on use-pattern). Rape seed	Whole group Mustard seed, poppy seed, sesame seed, linseed	No Group has been established	N/A
Coffee			No Group has been established	N/A
Many	Parsley, mint (extrapolations	Whole group	See Labiate leafy vegetables and	

Australia Commodity Crops Groupings	Australia Possible Extrapolation From…	Australia Possible Extrapolation To…	Japan Crop Group[4]	Japan Representative Crop and Extrapolation
	to a group on a case-by-case basis)		Apiaceous leafy vegetables (No other group has been established)	
Many	Ginger (extrapolations to a group on a case-by-case basis)	Whole group	No Group has been established	N/A
See fruiting vegetable			Edible fungi: Shiitake mushroom Enokitake (*Flammulina velutipes)* Oyster mushroom Nameko (*Pholiota nameko)* Hen of the woods *(Grifola frondosa)*	Shiitake mushroom and one other species →whole group
			No Group has been established	N/A
			No Group has been established	N/A

[1] The current situation is fluid. Revisions are occurring in Codex and NAFTA. The table attempts to represent the official situation at the moment (before September 2014).

[2] For fruits according to adopted new Codex Classification, see Table 1 in the main text.

[3] Late season use. Separate criteria for early season use and for postharvest use.

[4] The work is currently ongoing as a part of the review of pesticide registration scheme in Japan on the classification of all food commodities/crops for which there are registered uses of pesticides and/or MRLs. The work uses the Codex Classification as a basis with some Japanese-specific situations taken into consideration. New classification of citrus fruits, pome fruits, stone fruits, berries and other small fruits, assorted tropical and sub-tropical fruits-edible peel and assorted tropical and sub-tropical fruits – inedible peel (as of October 2015) is included in the above table. Only important crops are shown. Other crop groups are currently considered pending Codex revision.

[5] The US EPA and Canadian PMRA numbering for some of the revised crop groups differ depending on the year they were established. In the second column only differences are indicated.

[6] Under revision. It is anticipated that leafy Brassica greens (5B) will be combined with and leafy non-Brassica vegetables (4) will be combined in a revised leafy vegetables group, as follows: 4A- 40 commodities; Representatives- Head and Leaf Lettuce and Spinach. 4B- 20 commodities; Representative – Mustard greens.

[7] A new crop group 22: Stalk, Stem, and Leaf Petiole Vegetable is anticipated. **17 commodities, 2 subgroups:**
22A Stalk and Stem Vegetable; Representative – Asparagus; 10 commodities (agave, asparagus, bamboo shoots, cactus, celtuce, florence fennel, edible fern, sea kale, kohlrabi, palm hearts).
22B Leaf Petiole Vegetable; Representative – Celery; 7 commodities (includes some commodities currently in 4B- Leaf petioles subgroup: Cardoon, celery, Chinese celery, fuki, rhubarb, udo, and zuiki).

[8] A new crop group 23, tropical and subtropical fruits – edible peel, is anticipated.

[9] A new crop group 24, tropical and subtropical fruits – inedible peel, is anticipated.

APPENDIX 2
Criteria for crop groups in national governments

Japan Criteria

Basis for Crop/Commodity Categorization in Japan:

The work is currently ongoing as a part of the review of pesticide registration scheme in Japan on the classification of all food commodities/crops for which there are registered uses of pesticides and/or MRLs. The work uses the Codex Classification as a basis with some Japanese specific situations taken into consideration.

NAFTA Criteria

The following 15 points are addressed in constructing rationale for a crop definition and/or group / subgroup proposal:

1. Botany and Nomenclature of Commodity:
    - Botanical Family and Family Characteristics of proposed commodities
    - Genus and Species
    - Common names and/or synonyms
    - Cultivars/hybrids where appropriate
2. Commodity Geographical Distribution and Production in the U.S.
3. Global Commodity Geographical Distribution and Production.
4. Commodity Imports/Exports.
5. Cultural Practices:
    - Planting Rate(s)
    - Planting Date(s)
    - Row or Broadcast Crop
    - Growing Season
    - Growth and development of crop and growth stages

- Irrigation
- Worker practices
- Harvesting practices
- Post-harvest activities
- Crop rotations
- Processing of commodity

6. Commercial Importance of Commodity (Current and Projected)

7. Possibilities for Genetic Improvement (Cultivars, Hybrids)

8. Comparison of Edible Part(s):

- Description of fruit/vegetable
- What is consumed?
- When harvested
- How harvested
- How often harvested
- Uses of commodity such as livestock feed, syrup, jelly, production, foods, shampoos, biodiesels, medicines, adhesives)
- Surface area to weight ratio of commodity
- Leaf shape and area
- Type of fruit/vegetable surface (smooth, hairy)
- Weight of fruit/vegetable
- Similarities to other commodities

9. Livestock Feed Item(s) for Beef and Dairy Cattle, Poultry, and Swine (include Importance of Feedstuffs (>250,000 tons) and Percent of Livestock Diet)

10. Processed Products (such as oil or flour) and/or Fresh Market as Whole Fruit/Vegetable

11. Comparison of Pest Problems:

- Insects
- Diseases

- Nematodes
- Weeds
- Vertebrates (such as moles, rodents)
- Other pests

12. Comparison of Potential Residue Levels (Tolerance/MRL)

13. Compare Codex Classification of Food and Feed Crops (Harmonization for International Considerations) with U.S.

14. Justification(s) for a Crop Group/Subgroup Definition

- Selection of Representative Crops Utilized for Residue Field Trials to Cover Entire Crop Group
- Selection of Representative Crops Utilized for Residue Field Trials to Cover Crop Subgroup

15. References Including:

- Scientific Literature, world complete literature search [USDA National Agricultural Library Agricola]
- Current Research Projects [USDA Current Research Information System (CRIS)]
- Scientific names [USDA GRIN (**http://www.ars-grin.gov/cgi-bin/npgs/htm/taxecon/pl**)]
- Specific Codex Classification of Foods and Animal Feeds.
- Previous IR-4 Petitions for Commodity or Crop Group
- Copies of Pertinent Reference Pages
- Classic Monograph Reference – Adapted from Foods and Feed Crops of the United States. 1998. George Markle, Jerry Baron, and Bernard Schneider. Second Edition. Meisterpro Publication.

Australian Criteria

For crop groups no own criteria:

- Crop groups used as defined by CODEX.

Crop group are further divided into subgroups:

- These are primarily indicative of form and growth habit.
- The subgroups are based on differences in the size of the commodity, whether there are any covering leaves to protect the edible part of the crop and the nature of the commodity.

- The subgroups are intended to reflect factors which may contribute to varying residue levels across the whole crop group.

- Other criteria which may contribute to the subgroups include the surface of the crop, i.e. curly leaf vs straight leaf or hairy surface vs wrinkled surface vs smooth surface.

European Criteria

European criteria are not described. Some of the criteria taken into consideration are given below:

- Botanical characteristics

- Morphological aspects

- Surface area to weight ratio of commodity

- Codex Classification of Food and Feed Crops

ANNEX 2
Background information to chapter 2. Extrapolations

Background

1. 1 Annex 2 describes the background as provided by OECD member countries before September 2014 to illustrate where the discussion started and to make transparent why certain conclusions and recommendations were given in the OECD Guidance Document on Crop Field Trials. An update is not foreseen.

National/Regional Approaches for Extrapolation and Establishment of Crop Group MRLs

2. In general, extrapolation and/or establishment of crop group MRLs in the EU occur only where there are registered uses for all members of the crop group or subgroup. This is based on the precautionary principle, known as the ALARA (as low as reasonably achievable) principle. The procedure for MRL estimations for crop group or subgroup is based on a sufficient number of trials conducted on one or more representative crops/commodities from the crop group or subgroup.

3. Nevertheless, this approach might be too restrictive. In view of global trade nearly all crop groups or sub-groups include commodities not grown in the respective countries. Therefore a situation with all members of the group being covered by national GAPs is unlikely to occur. In this situation EU introduced the concept of related varieties or other products in Regulation (EC) No 396/2005. For example the MRL for the commonly grown commodity radish also applies to black radish, Japanese radish, small radish and similar varieties as well as tiger nut, from which Japanese radish and tiger nuts are normally not covered by European GAPs.

4. The situation in NAFTA is slightly different. Extrapolations may be made for use on only a few crops when the registrant is not interested in registration on the entire crop group. For crop group MRLs, cases exist where not all the crops are registered due to the manufacturer having concerns over efficacy or phytotoxicity on particular plants. Therefore, although all necessary data may have been generated on all the representative commodities and regulatory authority may have established a crop group tolerance, the registrant may not permit use on certain members of the group. Extrapolations may also involve crops that do not belong to the group.

5. The original underlying assumption for extrapolation is that the same critical GAP exists for all crops of a crop group or subgroup and the supporting residue trials have been conducted according to this critical GAP (i.e. within 25% of the nominal application rate, number of applications or PHI). The description of the differences in application rates between “horizontal” and “vertical” crops can be found in OECD Guidelines for the Testing of Chemicals – Crop Field Trial. No. 509 (OECD, Paris 2009). In case of “vertical” crops the 25% rule should be applied to the most sensitive factor for residues in case different descriptions are used for the application rates in residue trials data.

6. Appendix 1 of Annex 1 contains a table of the groups, subgroups, representative commodities, and extrapolations in EU, Australia, Japan, and NAFTA while the information for adopted Codex commodity groups is given in Table 1 of the main text.

7. In estimating crop group MRLs, two methodologies are possible. In the simplest approach, the residue datasets with the highest residue levels for individual representative commodities are used to estimate group/subgroup MRL (called 'single crop approach'). In this case the MRL should be evaluated for each commodity data set and the highest result selected for the group or subgroup. There must be adequate data for each commodity without consideration of combinations. In the second approach used in some cases in Europe the data sets from the various commodities of a group/subgroup are combined, and an MRL proposal is made from the combined data. Data sets for different commodities within a group/subgroup are considered for combination to estimate group MRLs in EU only if residues are similar in magnitude (belonging to a similar residue distribution) and have similar GAPs. It is recommended that if it can be shown by using the Mann-Whitney or Kruskal-Wallis tests (paragraph 16) that the residues belong to the same residue population, the residue data should be combined. It is known from work with the OECD Calculator that the more residue data are used for MRL calculation, the less uncertainty there will be in the resulting MRL. If residue data for different representative commodities within a group are significantly different according to statistical testing and deviate beyond the usual variability accepted (see next paragraphs), group MRLs may not be appropriate, or exceptions to the group may need to be specified. Different approaches are in place in various countries on combining data for dietary risk assessments.

8. The single crop approach is utilized in NAFTA and also in the EU. Nevertheless, the EU Guidance Document SANCO 7525/VI/95 describes an approach to address the allowed variability in residues among crops for purposes of setting a group MRL. When using the proposed calculator model as described in the EU document, residue levels for relevant different raw agricultural commodities are considered to be comparable:

1. if assuming a standard (normal) distribution of data the respective 'mean to one-sigma-limit' ranges overlap; and

2. if the resulting recommended maximum residue limits when calculated for each single commodity according to the recommended calculation procedure fall into the same or a neighbouring MRL class after rounding up or down to the nearest MRL class.

9. The situation in NAFTA is different. The maximum residue limit estimates for the representative commodities should not vary by more than a factor of 5X of the maximum residue in order to establish a group MRL.

10. A statistical method for determining if data sets are from similar populations for possible combination is described in the FAO Manual 2009 (see paragraph 16) (FAO, 2009b).

Codex Approach for Extrapolation and Establishment of Codex Commodity Group MRLs

11. Residue extrapolation is the process by which the residue levels on representative commodities are utilized to estimate residue levels on related commodities in the same commodity group or subgroup for which trials have not been conducted.

12. The establishment of commodity group MRLs as opposed to MRLs for individual commodities has long been considered an acceptable procedure since economics may not justify residue trials on all of the individual crops in a group. In principle the approach recognizes that adequate data for the major commodities of a group may be sufficient to estimate maximum residue levels for the whole group.

13. Some pesticides may behave differently in different circumstances. Consequently, it is not possible to define precisely those commodities on which trials will always provide data that can lead to a group MRL. If the “highest residue” situation can be identified, however, the relevant data can be

extrapolated to other commodities with confidence, although it is recognised that this approach may result in an over-estimate of residues in some commodities.

14. Extrapolation requires a detailed knowledge of local agricultural practices and growth patterns. For example, wheat is generally grown under similar practices around the world, but tomatoes may be grown utilising widely varying practices. For the latter, care must be taken to ascertain if the relevant GAPs are comparable. In view of the large differences in commodity surface texture, shape, plant growth habits, rate of growth and seasonal cultivation and the significant role played by the surface/weight ratio, the JMPR has emphasized that decisions to extrapolate should be made on a case-by-case basis when adequate relevant information is available.

15. As a general precondition, for reliable estimation of residue levels an adequate number of independent trials is required. Under practical conditions the number of trials which can be performed for a given commodity is limited. On the other hand, a larger data set representing statistically not different residue population provides more accurate estimation of the selected percentile of residue population than a small data set derived from trials representing the critical GAP.

16. In order to make the data assessment process transparent and facilitate its consistent application in various situations, the 2013 JMPR considered and evaluated past experience and decided on the following basic principles in estimation of residue levels for commodity groups.

- Group maximum residue levels are only estimated if the pesticide is registered for a group or sub-group of commodities, also allowing for the differences in Codex and national commodity group classifications.

- Residue datasets reflecting cGAP will be compiled. Once the data sets have been established for individual commodities, the recommendations for residue levels for commodity groups would be considered according to the following principles.

    - The establishment of a commodity group residue level will generally be considered if the median residues of the commodities are within the five times range;

        i. Where the residues in individual commodities in the commodity group are statistically not different (Mann-Whitney or Kruskal-Wallis tests) the residue data can be combined for the estimation of group residue levels;

        ii. Where the residue datasets in individual commodities are statistically different then the dataset leading to the highest maximum residue level would be used for the group, provided that sufficient residue data points are available;

        iii. If the dataset identified under (ii) does not contain sufficient data points (preferably ≥ 8) required to estimate a group maximum residue level, the commodity should be considered as an exception.

    - If the median of residues in an individual commodity dataset differs more than 5 times than those of other commodities, that commodity would not be included in the group and indicated as an exception.

    - If the medians of residues in more than one commodity of the group differ larger than five times, then recommending group residue levels may not be appropriate and would require decision based on all information available

A spreadsheet for the Kruskal-Wallis test has been developed by US-EPA.

17. In view of the large diversity of residue data dependant on the pesticide and other factors, the case-by-case evaluation of the available residue data is considered necessary. Where the Meeting deviates from the above principles, the rational for the divergence will be provided in the report.

18. The 2014 JMPR Meeting concluded that for estimating a group maximum residue level, it is necessary to have data for those representative commodities of the subgroups likely to have the highest and the lowest residues. If there are sufficient data for a subgroup according to the new Codex classification, the Meeting agreed to estimate maximum residue levels for the subgroup only. For each crop group (or sub-group) critical commodities need to be identified.

Wider Extrapolations

19. The term 'wider extrapolations' (also referred to as 'cross group extrapolations') is used in this context for extrapolations that go beyond the bounds of a group or subgroup. Such extrapolations may be possible in special circumstances, on the basis of residue data. Consideration on a case-by-case basis may be given to commodities with very similar shapes, volumes, and weights. For example in Australia, apple, peach, and nectarine may be extrapolated to persimmon.

20. Wider extrapolations may also be considered, on a case-by-case basis, for:

- Situations where residues are expected to be <LOQ (e. g. pre-emergence herbicide uses, pre-flower treatments);

- Situations where the active substance is used early in the growing season (last application before consumable parts of the crop have started to form). (This kind of extrapolation should be used with caution since for some crops the edible part of the crop is always present either as a food or a feed item.);

- Seed treatments, if data from treatment of several different 'representative' seed types all report no detectable residues in the commodities from crops grown from the treated seed;

- Post harvest treatments for non-systemic pesticides to commodities of similar size and morphology on the basis of the same treatment regimes; and

- Soil treatments with granules (depending on extent of residue uptake and distribution in the plant as evidenced by data from different crop types including a root crop).

ANNEX 3
Background information to chapter 3. Proportionality

Background

1. his Annex 3 describes the background as provided by OECD member countries before September 2014 to illustrate where the discussion started and to make transparent why certain conclusions and recommendations were given in the OECD Guidance Document on Crop Field Trials. Especially the different statistical evaluations done to show the acceptability of the proportionality is described hereafter.

2. Proportionality means that when increasing or decreasing the application rate the residue level increases or decreases in the same ratio. In an ideal situation it means that doubling the application rate results in doubling the residue. Proportionality implies that the relationship between application rates and residues is linear.

3. In a publication by MacLachlan and Hamilton (2010) a proposal was made to use day zero data and residue decline studies to estimate median and highest anticipated residues in foliar-treated crops. In this model the residue levels were "normalised" for application rates, which assumes proportionality between application rates and residues. This and other tools may be developed in the future to assist MRL estimation.

Model and criteria for assessing the applicability of corrections based on proportionality

4. A proportional relation between application rate R and residue concentration C is described by the equation $C = k \times R$, or, equivalently, $\ln(C) = a + \ln(R)$, where $a = \ln(k)$. Based on proportionality, a residue level C_2 from a trial at application rate R_2 can be corrected to $C_1 = C_2 \times R_1/R_2$, where R_1 is the critical GAP application rate.

5. A more general model, including non-proportional relations, is given by the equation $C = k \times R^b$, or, equivalently, $\ln(C) = a + b \times \ln(R)$. Note that $b=1$ represents the proportionality assumption, and $b \neq 1$ corresponds to deviations from proportionality.

6. The proportionality assumption can be statistically tested by fitting a linear mixed effects model to available {ln(C), ln(R)} data pairs of side-by-side trials conducted at different application rates, and testing the null hypothesis $b=1$. An alternative approach is the calculation of ratios $(C_2/C_1)/(R_2/R_1)$ as has been done by MacLachlan and Hamilton (2011). Under the general model this ratio is equal to $(R_2/R_1)^{b-1}$, and therefore would equal 1 if $b=1$.

7. Statistical significance of non-proportionality does not imply that corrected C values based on the proportionality assumption ($C_1 = C_2 \times R_1/R_2$) are wrong to a large degree. Small deviations are acceptable in view of larger errors that are expected to arise in practice. Deviations within a range of ±25% of the nominal application rate are considered acceptable without a need for correction of the residue values. A true linear relationship between dose rate and concentration, would allow for a corresponding acceptable deviation in concentration of ±25%. In this guidance the maximum degree of acceptable non-

proportionality will be such that the deviation in the corrected value C_1 from the true value will be restricted within the limits of concern of ±25%.

8. The remainder of this chapter is organised as follows. Paragraphs 9-14 and Appendix 1 describe comparison of side-by-side trails that differed only by application rate. Paragraphs 15-17 and Appendix 2 describe simulations to investigate the significance of deviations from proportionality. Paragraphs 18-21and Appendix 3 describe the approach using the linear mixed effects model. Paragraphs 22-23 and Appendix 4 describe additional simulations to investigate impact on MRL estimates when there are varying degrees of non-proportionality.

Data Evaluation

9. In their publication about the impact of the application rate of pesticides on the residue levels in treated commodities (2011) MacLachlan and Hamilton identified a total of 1146 sets of side-by-side residue trials which were issued in JMPR reports between 2000 and 2009 and differed only by the application rate. The authors analysed this database with respect to a variety of factors including application rate, spray concentration, application type, formulation type, crop, and pesticide and concluded that residues generally scale proportionally with application rate (proportionality principle). They proposed to make use of this principle in regulatory evaluations of pesticides and for MRL calculations.

10. Although the data reviewed by MacLachlan and Hamilton covered a large range of pesticides, formulation types, application methods and crops, some specific pesticides and uses were less well represented. It was especially deemed necessary to review more side-by-side data for herbicides, soil applications, seed treatments, and post-harvest applications in order to determine whether the proportionality principle can be applied to these situations.

11. To this end, industry and regulatory authorities provided residue data from further side-by-side residue data conducted at different rates which had not been reviewed previously by MacLachlan and Hamilton (i.e. that were not included in the JMPR evaluations issued between 2000 and 2009). Data were provided (as Excel spreadsheets) by the governments of China and Japan, as well as by BASF, Bayer CropScience, Dow AgroSciences, DuPont, and Syngenta. The data were distinct from (i.e., supplemental to) that used by MacLachlan and Hamilton (2011). The data structure is given in the following table.

Data structure	Quantity
Trial	**926**
Crop	**92**
Active Ingredient	**80**
Formulation Type	**14**
Application Type	**6**
Country	**36**
PHIs per trial	**1 to 7**
Replicates per PHI	**1 to 4**

12. The new data allow further evaluation of the applicability of the proportionality principle to herbicides, plant growth regulators, soil applications, and seed treatments. Multiple statistical analyses were performed with the dataset using the MacLachlan/Hamilton approach and other statistical methods. For details see Appendix 1.

13. Since the new dataset includes a number of post-harvest trials, it was initially hoped that the dataset would allow further evaluation of the applicability of the proportionality concept to post-harvest treatments. It finally turned out that more data are needed for post-harvest uses.

14. Part of the MacLachlan/Hamilton approach involves comparing the ratio of residue values (C_2/C_1) with the ratio of the respective application rates (R_2/R_1), where R_1 is the lower application rate. If the residues are proportional to application rate, then $C_2/C_1 = R_2/R_1$. The second dataset was analysed in terms of $(C_2/C_1)/(R_2/R_1)$, which should equal 1 if residues are proportional to rate. The mean, RSD, and median of the $(C_2/C_1)/(R_2/R_1)$ ratio were calculated for different formulation types, application types, concentration ranges, pre-harvest intervals, crops, active substances and active substance types. Overall, the results of the second review are consistent with those of the original review, although the medians of the (C2/C1)/(R2/R1) ratios for different application types are somewhat lower, in the range of 0.80 - 0.93 (Appendix 1, table 4b) against 0.86-1.10 in the original review (table 4a).

15. Simulations (Appendix 2) were conducted to determine in which range the median of the $(C_2/C_1)/(R_2/R_1)$ is expected to vary assuming strict proportionality between residues and application rates. The residue distribution was considered to be lognormal with a CV of 0.7, 1.0 or 1.3. Besides the ratio between the application rates R_2/R_1 and the number of individual $(C_2/C_1)/(R_2/R_1)$ ratios (i.e. the number of pairs of side-by-side trials), a key parameter of the simulation was the intra-class correlation ICC, which was defined as:

$$\mathbf{ICC} = \frac{between\ trials\ variance}{between\ trials\ variance + within\ trial\ variance}$$

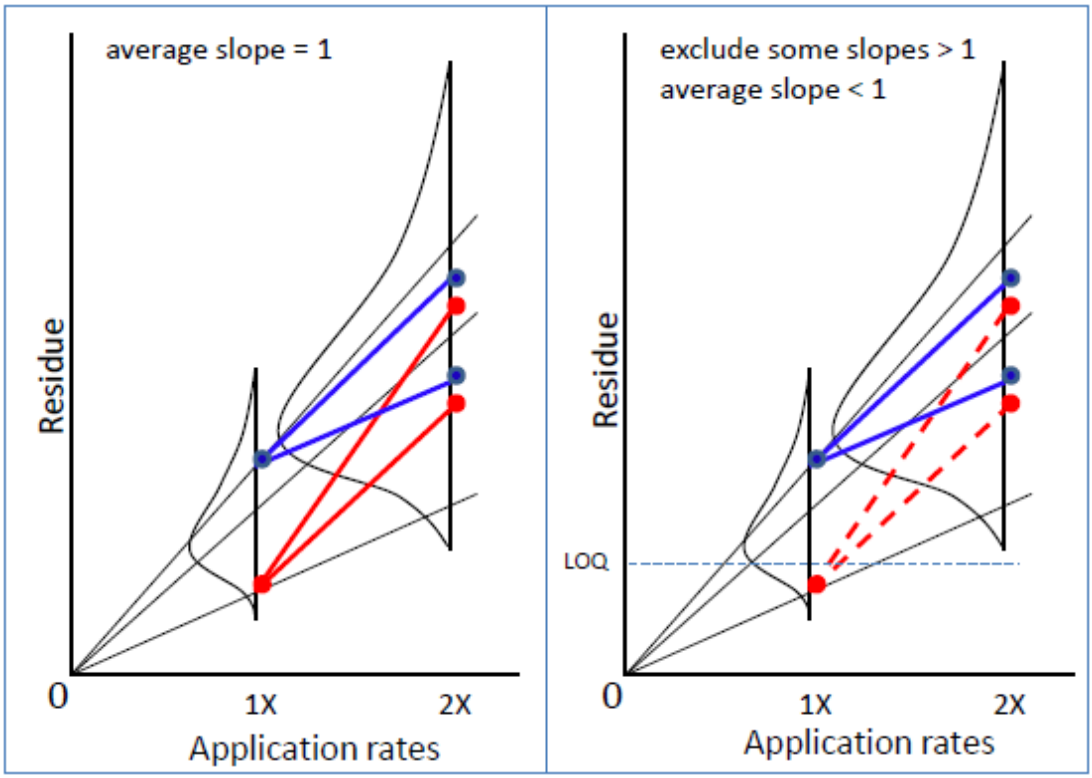
The simulations were conducted for ICCs of 0.5, 0.7 and 0.9. The expected range for the median $(C_2/C_1)/(R_2/R_1)$ ratios narrows as the ICC increases. Based on the simulation results it was concluded that most of the median $(C_2/C_1)/(R_2/R_1)$ ratios for the second review fall outside the range expected in case of strict proportionality. Comparison of the observed ratios from appendix 1 with the limit values obtained by the simulations in appendix 2, confirms that the relationship between application rates and residues is not strictly proportional and often shows a bias in one direction (systematic deviation).

16. It is important to note that the relationship between residue and application rate can only be calculated if residues are greater than or equal to the limit of quantification. Pairs of side-by-side trials where either C_1 or C_2 or both C_1 and C_2 are below the LOQ were not considered. However, this introduces a bias. Logically, if the residue levels are near the LOQ less residue levels are > LOQ on the plot treated at the lower rate (R_1) than on the plot treated at the higher rate (R_2). Only the pairs of trials with comparatively high residues on the plot treated at the lower rate are selected. These comparatively high residues result from the trial parameters (crop variety, weather conditions, …) and also from the sampling uncertainty. For the lower rate the selected data tend to be from trials where, due to sample uncertainty, the measured residues were greater than the mean residues on the plot. This is less true for the higher rate.

17. Figure 1 below visually illustrates why excluding trials with residues < LOQ would result an estimated slope lower than 1, assuming that the relationship between residues vs. application rates is proportional and thus the slope is indeed truly 1. The left portion of the figure presents the proportional relationship between residues vs. application rates. The blue and red segments represent some random residues of field trials at 1X and 2X, respectively. As we see with blue trials, if a residue of a field trial at 1X is a high percentile, there is high probability it has a lower percentile at 2X; and the slopes from these field trials are more likely less than 1. Conversely for the red trials, if a residue of a field trial at 1X is a low percentile, there is high probability it has a higher percentile at 2X; and the slopes of these field trials are more likely greater than 1. The average slope will be 1. The right figure presents the scenario when all

field trials that have residues < LOQ are excluded. The field trials that have residues at low percentiles at 1X would be systematically excluded as shown in red dashed segments; and it is more likely that the field trials excluded in this way would have slopes greater than 1. Therefore, the average slope (estimated slope) will be biased and less than 1.

Figure 1:



18. The proportionality concept was investigated further to determine its potential utility in adjusting residues from higher to lower (or vice versa) application rates. Thus the relationship between residues and application rates was examined by performing a linear mixed effects model analysis (Appendix 53). For each set of side-by-side trials conducted at different application rates and each PHI the logarithm of residues (C) was expressed as a linear function of the logarithm of application rates (R) : $\ln(C) = a + b \times \ln(R)$, which is equivalent to : $C = e^a \times R^b$. Hence the relationship between residues and application rates is proportional if the slope b is equal to 1. The slopes and their confidence intervals were calculated for different application types and crops.

19. As the application rate increases, the resulting residue increases. Foliar applications to rice had an exact linear proportional relationship between application rate and residue (100% increases in application rate would increase 100% in residue), while other crops with foliar application still had a significant relationship with slopes between 0.8 and 0.88 (the estimated residues from 2X to 1X are under-estimated about 10% if using the proportionality principle). Similarly, soil applications and seed treatments also had a slope of 0.88 and 0.79, respectively. The linear effects model analysis (appendix 3) confirms the bias noted in the simulations (appendix 2) and in the second review of residue data (appendix 3). The number of results for postharvest uses (including dipping and direct treatment) is too small to give reliable evidence that the proportionality approach can be used in that case for the moment.

20. When applying the current 25% rule in one parameter like the dose rate, it is accepted to combine residues from trials that have application rates within the range 0.75-1.25 of the cGAP. When assuming a true linear relationship between dose rate and concentration, this would allow for a corresponding acceptable deviation in concentration of ±25%. However, with a slope b = 0.8, the actual deviations of residue at application rates of 0.75 and 1.25 compared to normal (1x) rate are (0.75 EXP 0.8) - 1 = -21% and (1.25 EXP 0.8) - 1 = +20%. So maximum deviations in residues due to the 25% rule are slightly smaller than assumed. In this guidance the maximum degree of acceptable non-proportionality will be such that a ±25% deviation between estimated and actual concentrations is considered acceptable, so slightly larger than the deviations obtained with the current 25% rule.

21. Calculations below show that with a slope of 0.8 (found in the logarithmic approach in the linear mixed effects model) and accepting an error of +/- 25% in residues the proportionality principle allows support of a given GAP based on trials conducted at application rates between 0.33 - 4.2 X the cGAP rate.

The true residue C_1 at application rate R_1, given the slope *b* and residue C_2 at the application rate R_2 is $C_2 = C_1 \left(\frac{R2}{R1}\right)^b$ $C_1 = C_2 (R_1/R_2)^b$. Assuming proportionality where b=1, the estimated residue C_1 at application rate R_1 (using proportionality principle), given the residue C_2 at the application rate R_2 is $C_1 = C_2 (R_1/R_2)$

Correction based on proportionality will result in a bias of $100 \cdot [(R_1/R_2)^{1-b} - 1]$ %.

Downward correction based on proportionality will lead to a negative bias if b<1. For the case b = 0.8, equating the maximum acceptable negative bias of –25% to the above expression leads to R1/R2 = $(0.75)^{1/0.2} = 0.24$, or R2/R1 = 4.2.

Upward correction based on proportionality will lead to a positive bias if b<1. For the case b = 0.8, equating the maximum acceptable positive bias of 25% to the above expression leads to R1/R2 = $(1.25)^{1/0.2}$ = 3.05 (rounded 3.1), or R2/R1 = 0.33.

In other words, if we scale a residue at application rate range within 1x-4.2x down to 1x cGAP or scale a residue at application rate range within 0.33x-1x cGAP up to 1x cGAP, the amount of over/underestimation in the scaled residue will not exceed +25%/-25%. In other words, up-scaling of residues is possible up to a (residue multiplication) factor of 3.1 and down scaling up to a (residue dividing) factor of 4.2. The wordings are equivalent. The acceptable range in R2/R1 application rates will be broader for slopes being nearer to one.

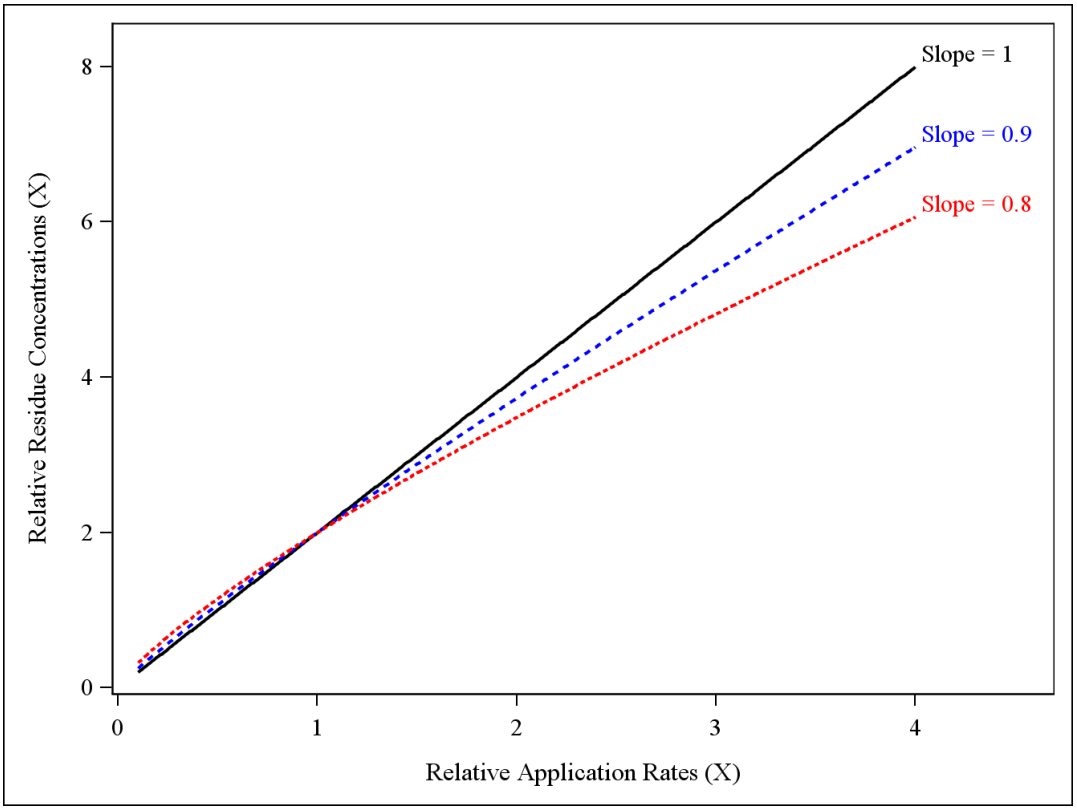


Figure 2A: graphical representation of the relative residues concentration vs. relative application rates (using 1X as reference) for different values of b. "Slope = 1" is the curve of estimated residues. "Slope= 0.9" and "Slope = 0.8" are the curves of actual residues. When scaling up (0.33X-1X up to 1X), the estimated residue is over-estimated. When scaling down (1X-4.2X down to 1X), the estimated residue is under-estimated.

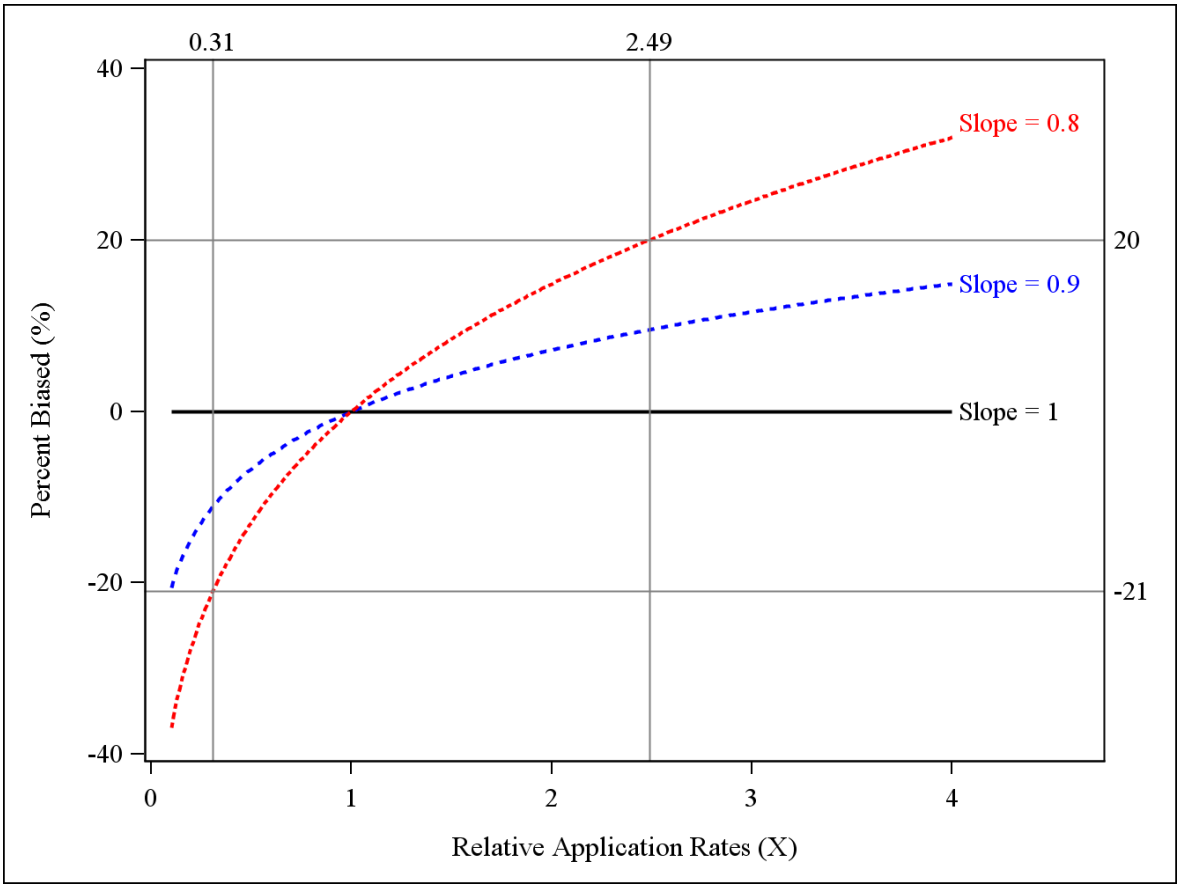


Figure 2B: graphical representation of percent biased when applying the proportionality principle to scale residues at application rate = 1X to other application rates ≠ 1X. When scaling up (0.33X-1X up to 1X), the estimated residue is over-estimated. When scaling down (1X-4.2X down to 1X), the estimated residue is under-estimated.

22. On this basis the proportionality principle as adopted by the Codex Alimentarius Commission is accepted by the OECD: The proportionality concept can be applied to data from field trials conducted within a rate range of between 0.3x and 4x the GAP rate." A further simulation was conducted in order to assess the impact on MRLs from applying the proportionality principle when the relationship "residue vs. application rate" is not perfectly proportional. As discussed in previous paragraphs, with a slope b = 0.8 and adjusting the application rate down up to a (dividing) factor of 3.2 or adjusting the application rate up to a (multiplication) factor of 2.4, the amount of over/under-estimation of the scaled residues would be less than 25% from the true value. MRLs were evaluated by calculating the MRLs from the scaled residues (which are under/over-estimated compared to the residues of GAP trials at application 1X). For calculation of MRLs the OECD Calculator was used.

- Scenario 1: calculation based on **4** random residues from the critical GAP rate field trials
- Scenario 2: calculation based on **8** random residues from the critical GAP rate field trials
- Scenario 3: calculation based on **16** random residues from the critical GAP rate field trials
- Scenario 4: calculation based on **4** random residues from the critical GAP rate field trials and **4** scaled residues from non-critical GAP field trials
- Scenario 5: calculation based on **8** random residues from the critical GAP rate field trials and **8** scaled residues from non-critical GAP field trials

- Scenario 6: calculation based on **8** scaled residues from non-critical GAP field trials

Note: In the simulation, the set-ups were only for extreme but simple scenarios, i. e. all the scaled residues causing either negative biased or positive biased. Scenarios of mixed scaled residues were not evaluated.

23. 23. The simulation was performed using lognormal residue distribution. For each scenario, different CVs (0.7, 1.0, or 1.3) and different under/over estimation factors (-25%, -20%, -15%, -10%, +10%, +15%, +20%, or +25%) were used. The primary criterion to evaluate and compare the MRLs between scenarios is the proportion of MRLs ≥ the true 95th percentile (typically, the aim is to have 95% of the estimated MRLs ≥ the 95th percentile). The secondary criterion is the how close (or "tight") the distribution of MRLs is to the true 95th percentile. As expected, adding more scaled residues (to increase sample size) generally results in better MRL estimates (scenario 4 *vs.* scenario 1, and scenario 5 *vs.* scenario 2); as the proportion of scaled residues increases, the MRL estimates become slightly worse (scenario 4 *vs.* scenario 2, and scenario 5 vs. scenario 3) but the MRL estimates are NOT substantially worse if the entire dataset consists of scaled residues, except the extreme scenario in which the entire dataset were all scaled residues and were 25% under- or over-estimated. However, this extreme scenario as done in the simulation with all scaled residues being under- or over-estimated by 25% does not apply if proportionality is limited to application rates between 4.2× to 0.33× label rate, respectively. With this range, the percent biased in the scaled residue will be within ±25%. The 25% biased case gave acceptable results in the simulation, so using a full adjusted set of data (100%) is acceptable between 4.2x to 0.33x label rate.

24. Another important factor worth mentioning is that the estimated slope from the linear mixed-effects model analysis was underestimated as discussed in paragraph 16. For that reason, the actual amount of under/over-estimation in the scaled residues may be less than the values that were used in the simulation, and the MRL estimates calculated from using scaled residues may be better than what we see in the simulation results.

25. It might be reminded that the adopted proportionality principles by the Codex Alimentarius Commission stated that the concept "may be used where the dataset is otherwise insufficient to make an MRL recommendation. This is where the concept provides the greatest benefit". Currently Codex and JMPR only use the proportionality principle in case an insufficient number of trials has been conducted at cGAP and an MRL cannot be derived based on this insufficient number (see general items in JMPR 2013 report). Proportionality is generally not used to increase the dataset when the number of trials at cGAP is sufficient to derive an MRL, although it could be used to develop a more comprehensive data set for international efforts (MRL harmonization). For harmonisation purposes, it is interesting to note that increasing sample size at 1X by applying the proportionality principle and scaling residue data from trials conducted at application rates in the range from 0.33X to 4.2X, would result in better MRL estimates, even if estimated slopes were as low as 0.8.

26. The above analysis was conducted with the use of the OECD Calculator. It results in MRL estimates that are not different to the use of the current ±25% rule and residue values from trials conducted at rates ±25%.

APPENDIX 1

Relationship between Application Rates of Pesticides and their Residue Levels in Treated Commodities: Further Investigation of the Proportionality Principle

[Frank Laporte, Jane Stewart, 21 November 2012, includes a statistical evaluation for the combined datasets of 2011 and 2012]

MacLachlan and Hamilton recently investigated the impact of the application rate of pesticides on their residue levels in treated commodities (2011). A total of 1146 sets of side-by-side residue trials that differed only by the application rate were identified in the JMPR reports issued between 2000 and 2009 and used for this analysis. Based on these data the authors concluded that there is a proportional relationship between pesticide application rates and resulting residues in treated commodities and they proposed to make use of this principle in regulatory evaluations of pesticides and for MRL calculations.

Although the data reviewed by MacLachlan and Hamilton covered a large range of pesticides, formulation types, application methods and crops, some specific pesticides and uses were less well represented. It was especially deemed necessary to review more side-by-side data for herbicides, soil applications, seed treatments, and post-harvest applications in order to determine whether the proportionality principle can be applied to these situations.

To this end, industry and regulatory authorities were asked to provide residue data from further side-by-side residue data conducted at different rates which had not been reviewed previously by MacLachlan and Hamilton (i.e. that were not included in the JMPR evaluations issued between 2000 and 2009). Data were provided (as Excel spreadsheets) by the governments of China and Japan, as well as by BASF, Bayer CropScience, Dow AgroSciences, DuPont, and Syngenta. They were evaluated using the same approach as in the publication by MacLachlan and Hamilton (see below). In order to facilitate comparison, the results of this review are presented in the same format as those of the original review. The figures and tables framed in orange are excerpts from the publication of MacLachlan and Hamilton while the figures and tables framed in blue correspond to the supplementary dataset and the figures and tables framed in green correspond to the two combined datasets [important note: due to slight differences in the approaches used to evaluate the data, some apparent inconsistencies may be noticed when comparing the three tables; however, these inconsistencies are not expected to significantly impact the outcome of the evaluation].

Overall, the results of the second review are consistent with those of the original review. The new data allow to better evaluate the applicability of the proportionality principle to herbicides, plant growth regulators, soil applications, seed treatments, and post-harvest applications.

Approach used to evaluate the supplementary data (adapted from MacLachlan and Hamilton)

Figure 1b, Table 1b

To test for proportionality, residue data were obtained from pairs of trials that had been conducted at the same site and same time and where the application rate of one trial was 2.0 times that of the other. The logarithm (natural logarithm, ln or $\log_e$) of the residue at the 2x rate was plotted as a function of the logarithm of the residue at the 1x rate. For proportionality, the slope should be 1 and the intercept should be the logarithm of 2 (i.e. 0.693). Pairs of trials where

one rate was 1.3x,1.5x, 2x, 3x or 4x the other rate were similarly analysed, but there were far fewer trials than for the 2x case.

Tables 3b to 9b

To compare application rates further, the data were analysed as the ratio of residue values (C2/C1) compared with the ratio of the respective application rates (R2/R1), where R1 is the lower application rate. If the residues are proportional to application rate, then C2/C1 = R2/R1. Data were analysed in terms of (C2/C1)/(R2/R1), which should equal 1 if residues are proportional to rate. The mean, RSD, and median of the (C2/C1)/(R2/R1) ratio were calculated for different formulation types (Table 3b), application types (Table 4b), concentration ranges (Table 5b), pre-harvest intervals (Table 6b), crops (Table 7b), active substances (Table 8b) and active substance types (Table 9b).

It is important to note that the ratio $(C_2/C_1)/(R_2/R_1)$ can only be calculated if both C_1 and C_2 are greater than or equal to the limit of quantification. Pairs of side-by-side trials where either C_1 or C_2 or both C_1 and C_2 are below the LOQ were not considered. However, this introduces a bias. Logically, if the residue levels are about the LOQ less residue levels are > LOQ on the plot treated at the lower rate (R_1) than on the plot treated at the higher rate (R_2). Only the pairs of trials with comparatively high residues on the plot treated at the lower rate are selected. These comparatively high residues result from the trial parameters (crop variety, weather conditions, …) and also from the sampling uncertainty. For the lower rate the selected data tend to be from trials where, due to sample uncertainty, the measured residues were greater than the mean residues on the plot. This is less true for the higher rate. As a matter of consequence the ratios $(C_2/C_1)/(R_2/R_1)$ tend to be lower than one. This can partly explain why the median ratio is frequently in the range of 0.8 to 1.0.

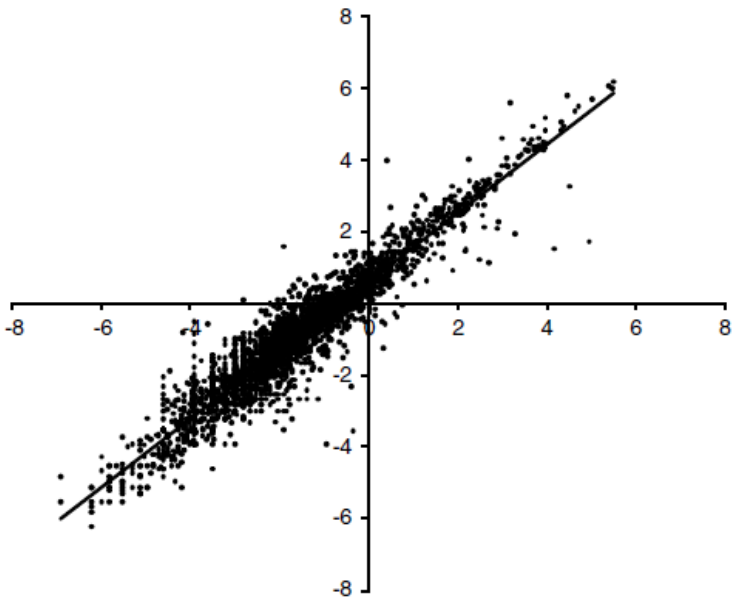


Figure 1a*. Data were available from 2792 datasets where residues were compared for a 1x and a 2x application rate (or spray concentration) at the same time and at the same site. The logarithm of the residue from the 2x application is plotted as a function of the logarithm of the residue from the 1x application. For proportionality, the slope should be one and the intercept should be the logarithm of two (i.e. 0.693). $\ln(C_2) = 0.956 \times \ln(C_1) + 0.610$, $r^2 = 0.91$.

* According to MacLachlan and Hamilton [*Pest Manag Sci* 2011; 67: 609-615].

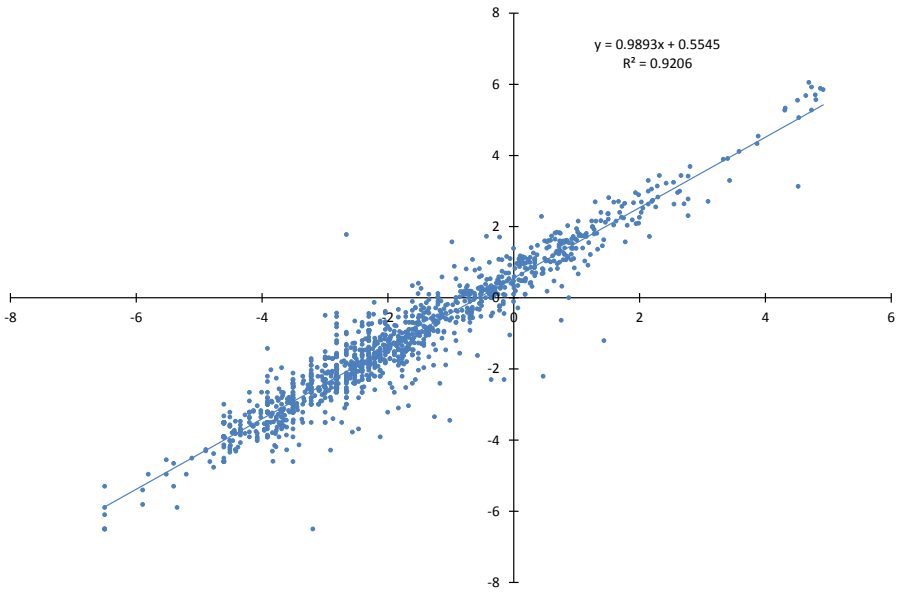


Figure 1b*. Data were available from 1297 datasets where residues were compared for a 1x and a 2x application rate (or spray concentration) at the same time and at the same site. The logarithm of the residue from the 2x application is plotted as a function of the logarithm of the residue from the 1x application. For proportionality, the slope should be one and the intercept should be the logarithm of two (i.e. 0.693).
$\ln(C_2) = 0.989 \times \ln(C_1) + 0.555$, $r^2 = 0.92$.

* Evaluation of the supplementary dataset compiled in 2012.

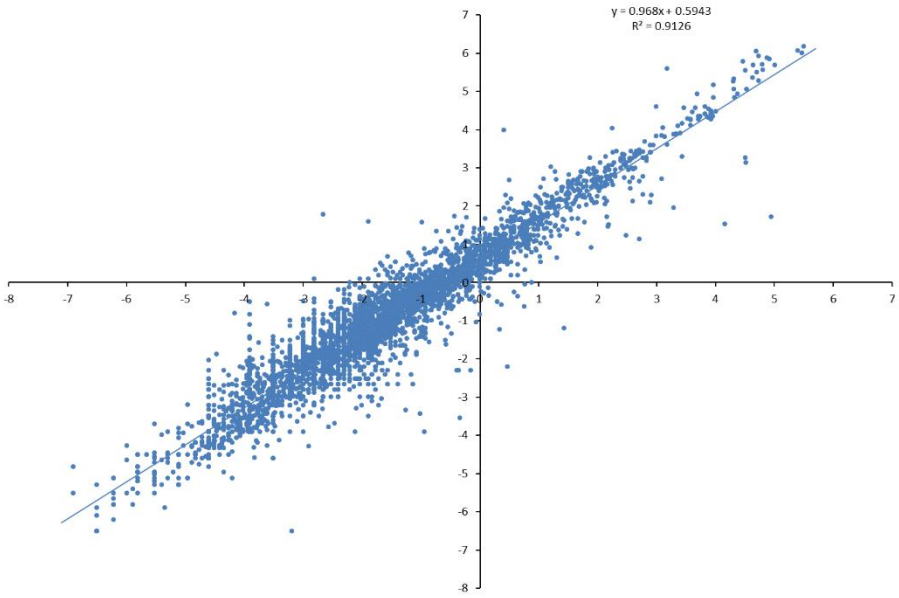


Figure 1c*. Data were available from 4090 datasets where residues were compared for a 1x and a 2x application rate (or spray concentration) at the same time and at the same site. The logarithm of the residue from the 2x application is plotted as a function of the logarithm of the residue from the 1x application. For proportionality, the slope should be one and the intercept should be the logarithm of two (i.e. 0.693). $\ln(C_2) = 0.968 \times \ln(C_1) + 0.594$, $r^2 = 0.91$.

* Combined datasets (2011 and 2012).

Table 1a*. The results of $\log_e$ – $\log_e$ plots of residue data, residues from the higher application rate as a function of residues at the lower rate

R_2/R_1	Slope	Intercept	C_2/C_1 calculated from intercept	n	r^2
1.5	0.957	0.356	1.43	365	0.93
2.0	0.956	0.610	1.84	2792	0.91
4.0	1.016	1.286	3.62	203	0.89
6.0	0.899	1.683	5.38	45	0.79
8.0 – 8.18	1.107	2.025	7.58	65	0.87

* According to MacLachlan and Hamilton [*Pest Manag Sci* 2011; 67: 609-615].

Table 1b*. The results of $\log_e$ – $\log_e$ plots of residue data, residues from the higher application rate as a function of residues at the lower rate

R_2/R_1	Slope	Intercept	C_2/C_1 calculated from intercept	n	r^2
1.3	0.933	0.273	1.31	133	0.94
1.5	0.953	0.351	1.42	700	0.88
2.0	0.989	0.555	1.74	1297	0.92
3.0	0.866	0.842	2.32	69	0.88
4.0	0.977	1.057	2.88	107	0.78

* Evaluation of the supplementary dataset compiled in 2012.

Table 1c*. The results of $\log_e$ – $\log_e$ plots of residue data, residues from the higher application rate as a function of residues at the lower rate

R_2/R_1	Slope	Intercept	C_2/C_1 calculated from intercept	n	r^2
1.3	0.964	0.299	1.35	283	0.95
1.5	0.955	0.353	1.42	1065	0.90
2.0	0.968	0.594	1.81	4090	0.91
3.0	0.878	0.889	2.43	228	0.90
4.0	1.005	1.208	3.35	311	0.87
6.0	0.899	1.683	5.38	45	0.79
8.0	1.128	1.837	6.28	46	0.90

* Combined datasets (2011 and 2012).

Table 2a*. Descriptive statistics of C_2/C_1 values for different ratios of application rates

Rate ratio R_2/R_1	*n*	Mean residue ratio C_2/C_1	CV residue ratio C_2/C_1	Mean of residue ratios ÷ rate ratios	Median residue ratio C_2/C_1	Median of residue ratios ÷ rate ratios
1.3 (1.15 – 1.45)	158	1.30	0.46	1.00	1.18	0.91
1.5 (1.35 – 1.65)	397	1.73	0.49	1.16	1.56	1.04
2 (1.8 – 2.2)	3052	2.33	0.78	1.17	2.00	1.00
3 (2.7 – 3.3)	190	4.06	0.80	1.35	3.57	1.19
4 (3.6 – 4.4)	351	5.00	1.00	1.25	3.95	0.99
5 (4.5 – 5.5)	64	6.91	1.31	1.38	5.30	1.06
6 (5.4 – 6.6)	57	10.56	0.98	1.76	7.63	1.27
8 (7.2 – 8.8)	65	7.20	0.86	0.90	5.64	0.70
10 (9 – 11)	23	10.62	0.70	1.06	10.40	1.04

* According to MacLachlan and Hamilton [*Pest Manag Sci* 2011; 67: 609-615].

Table 2b*. Descriptive statistics of C_2/C_1 values for different ratios of application rates

Rate ratio R_2/R_1	*n*	Mean residue ratio C_2/C_1	CV residue ratio C_2/C_1	Mean of residue ratios ÷ rate ratios	Median residue ratio C_2/C_1	Median of residue ratios ÷ rate ratios
1.3 (1.15 – 1.45)	191	1.52	0.67	1.14	1.29	0.97
1.5 (1.35 – 1.65)	747	1.91	1.23	1.28	1.50	1.00
2 (1.8 – 2.2)	1442	2.08	1.19	1.04	1.80	0.91
3 (2.7 – 3.3)	80	3.46	0.76	1.14	2.69	0.90
4 (3.6 – 4.4)	116	3.81	0.73	0.95	3.22	0.81

* Evaluation of the supplementary dataset compiled in 2012.

Table 2c*. Descriptive statistics of C_2/C_1 values for different ratios of application rates

Rate ratio R_2/R_1	*n*	Mean residue ratio C_2/C_1	CV residue ratio C_2/C_1	Mean of residue ratios ÷ rate ratios	Median residue ratio C_2/C_1	Median of residue ratios ÷ rate ratios
1.3 (1.15 – 1.45)	351	1.52	0.57	1.14	1.33	1.00
1.5 (1.35 – 1.65)	1139	1.85	1.06	1.24	1.53	1.02
2 (1.8 – 2.2)	4485	2.25	0.91	1.13	1.93	0.96
3 (2.7 – 3.3)	259	3.88	0.81	1.29	3.28	1.09
4 (3.6 – 4.4)	468	4.70	0.97	1.17	3.79	0.95
5 (4.5 – 5.5)	83	6.18	1.31	1.23	4.96	0.99
6 (5.4 – 6.6)	45	10.56	0.98	1.76	7.63	1.27
8 (7.2 – 8.8)	68	6.99	0.88	0.87	5.39	0.68
10 (9 – 11)	30	16.87	2.26	1.69	9.40	0.94

* Combined datasets (2011 and 2012).

Note : A slight inconsistency between the three tables is observed for rate ratios about 1.3 (first line) which might be due to the fact that two additional results for the original dataset were taken into account (n = 160, the median for $(C_2/C_1)/(R_2/R_1)$ was found to be 1.03).

Table 3a*. Descriptive statistics of $(C_2/C_1)/(R_2/R_1)$ values for different formulation types

	$(C_2/C_1)/(R_2/R_1)$			
Formulation type	*n*	Mean	RSD	Median
Not specified	216	0.98	0.58	0.88
CS (capsule suspension)	10	1.17	0.26	1.15
EC (emulsifiable concentrate)	549	1.15	0.78	1.00
EO (emulsion, water in oil)	34	0.96	0.31	0.97
EW (emulsion, oil in water)	12	0.87	0.39	0.83
FS (flowable concentrate for seed treatment)	33	0.85	0.39	0.86
GR (granule)	11	1.01	0.56	0.81
SC (suspension concentrate)	622	1.20	0.75	1.00
SE (suspo-emulsion)	37	1.56	1.08	1.17
SL (soluble concentrate)	319	1.23	0.96	1.00
SP (water-soluble powder)	147	1.16	0.62	0.97
UL (ultralow-volume liquid)	84	1.16	1.05	0.83
WG (water-dispersible granule)	431	1.09	0.61	0.92
WP (wettable powder)	293	1.37	0.63	1.16
WS (water-dispersible powder for slurry seed treatment)	10	1.26	0.70	0.92

* According to MacLachlan and Hamilton [*Pest Manag Sci* 2011; 67: 609-615].

Table 3b*. Descriptive statistics of $(C_2/C_1)/(R_2/R_1)$ values for different formulation types

		$(C_2/C_1)/(R_2/R_1)$		
Formulation type	*n*	Mean	RSD	Median
Not specified or several types	13	0.84	0.20	0.83
DF (dry flowable formulation)	5	0.76	0.28	0.78
DP (dispersible powder)	6	1.02	0.76	0.77
EC (emulsifiable concentrate)	813	1.05	0.71	0.93
EW (emulsion, oil in water)	137	1.29	1.12	1.03
FC (flowable concentrate)	59	1.63	0.81	1.33
FS (flowable concentrate for seed treatment)	184	0.91	0.59	0.81
GR (granule)	11	0.83	0.39	0.83
ME (micro-emulsion)	24	0.93	0.30	0.89
OD (oil dispersion)	9	1.86	0.60	1.85
SC (suspension concentrate)	514	1.07	1.12	0.90
SL (soluble concentrate)	508	1.16	1.68	0.94
WG (water-dispersible granule)	154	1.00	0.52	0.93
WP (wettable powder)	294	1.23	1.25	0.99
WS (water-dispersible powder for slurry seed treatment)	11	0.96	0.28	1.00

* Evaluation of the supplementary dataset compiled in 2012.

Table 3c*. Descriptive statistics of $(C_2/C_1)/(R_2/R_1)$ values for different formulation types

		$(C_2/C_1)/(R_2/R_1)$		
Formulation type	*n*	Mean	RSD	Median
Not specified or several types	229	0.97	0.57	0.87
CS (capsule suspension)	11	1.13	0.28	1.13
DF (dry flowable formulation)	8	0.77	0.22	0.79
DP (dispersible powder)	6	1.02	0.76	0.77
EC (emulsifiable concentrate)	1431	1.09	0.74	0.96
EO (emulsion, water in oil)	34	0.96	0.31	0.97
EW (emulsion, oil in water)	149	1.26	1.11	1.00
FC (flowable concentrate)	59	1.63	0.81	1.33
FS (flowable concentrate for seed treatment)	257	0.91	0.57	0.81
GR (granule)	34	0.93	0.47	0.83
ME (micro-emulsion)	24	0.93	0.30	0.89
OD (oil dispersion)	9	1.86	0.60	1.85
SC (suspension concentrate)	1585	1.19	0.96	1.00
SE (suspo-emulsion)	37	1.56	1.08	1.17
SL (soluble concentrate)	1276	1.22	1.33	1.00
SP (water-soluble powder)	173	1.21	0.60	1.01
UL (ultralow-volume liquid)	267	1.25	0.72	1.07
WG (water-dispersible granule)	835	1.01	0.60	0.89
WP (wettable powder)	687	1.30	0.91	1.07
WS (water-dispersible powder for slurry seed treatment)	21	1.10	0.58	0.93

* Combined datasets (2011 and 2012).

Table 4a*. Descriptive statistics of $(C_2/C_1)/(R_2/R_1)$ values for different application types

		$(C_2/C_1)/(R_2/R_1)$		
Application type	*n*	Mean	RSD	Median
Foliar per hectare basis (kg AI ha^{-1})	3441	1.19	0.90	1.00
Foliar spray concentration basis (kg AI hL^{-1})	869	1.20	0.51	1.06
Seed treatment	78	0.91	0.51	0.86
Soil treatment	13	1.06	0.53	1.10

* According to MacLachlan and Hamilton [*Pest Manag Sci* 2011; 67: 609-615].

Table 4b*. Descriptive statistics of $(C_2/C_1)/(R_2/R_1)$ values for different application types

		$(C_2/C_1)/(R_2/R_1)$		
Application type	*n*	Mean	RSD	Median
Foliar**	2120	1.15	1.21	0.96
Soil treatment	266	1.04	0.60	0.90
Post-harvest	147	0.79	0.51	0.80
Seed treatment	200	0.91	0.56	0.83

* Evaluation of the supplementary dataset compiled in 2012.
** Corrected (in the previous versions of the report the so-called broadcast foliar and post-emergence treatments were erroneously omitted).

Table 4c*. Descriptive statistics of $(C_2/C_1)/(R_2/R_1)$ values for different application types

		$(C_2/C_1)/(R_2/R_1)$		
Application type	*n*	Mean	RSD	Median
Foliar per hectare basis (kg AI ha^{-1})	5021	1.16	1.01	0.97
Foliar spray concentration basis (kg AI hL^{-1})	911	1.19	0.52	1.06
Foliar not specfied	497	1.37	1.14	1.08
Soil treatment	281	1.04	0.60	0.90
Post-harvest	147	0.79	0.51	0.80
Seed treatment	277	0.91	0.55	0.83

* Combined datasets (2011 and 2012).

Table 5a*. Descriptive statistics of $(C_2/C_1)/(R_2/R_1)$ values for different residue concentration ranges for C_1

		$(C_2/C_1)/(R_2/R_1)$		
Residue range for C_1	*n*	Mean	RSD	Median
<0.05 mg kg^{-1}	625	1.36	1.84	1.05
0.05 to <0.1 mg kg^{-1}	462	1.21	0.62	1.03
0.1 to <0.2 mg kg^{-1}	500	1.15	0.82	0.97
0.2 to <0.5 mg kg^{-1}	468	1.10	0.54	1.00
0.5 to <1 mg kg^{-1}	257	1.03	0.53	0.93
1 to <2 mg kg^{-1}	211	1.08	1.19	0.91
2 to <10 mg kg^{-1}	225	1.01	0.42	0.96
10+ mg kg^{-1}	60	1.00	0.53	0.97

* According to MacLachlan and Hamilton [*Pest Manag Sci* 2011; 67: 609-615].

Table 5b*. Descriptive statistics of $(C_2/C_1)/(R_2/R_1)$ values for different residue concentration ranges for C_1

		$(C_2/C_1)/(R_2/R_1)$		
Residue range for C_1	*n*	Mean	RSD	Median
<0.05 mg kg^{-1}	707	1.20	1.26	0.95
0.05 to <0.1 mg kg^{-1}	551	1.22	1.57	0.95
0.1 to <0.2 mg kg^{-1}	456	1.08	0.85	0.94
0.2 to <0.5 mg kg^{-1}	360	1.01	0.60	0.90
0.5 to <1 mg kg^{-1}	215	0.93	0.53	0.88
1 to <2 mg kg^{-1}	165	1.03	0.54	0.92

2 to <10 mg kg^{-1}	195	0.95	0.54	0.88
10+ mg kg^{-1}	95	0.94	0.36	0.89

* Evaluation of the supplementary dataset compiled in 2012.

Table 5c*. Descriptive statistics of $(C_2/C_1)/(R_2/R_1)$ values for different residue concentration ranges for C_1

		$(C_2/C_1)/(R_2/R_1)$		
Residue range for C_1	*n*	Mean	RSD	Median
<0.05 mg kg^{-1}	1915	1.30	1.04	1.00
0.05 to <0.1 mg kg^{-1}	1230	1.22	1.15	1.00
0.1 to <0.2 mg kg^{-1}	1171	1.13	0.79	0.97
0.2 to <0.5 mg kg^{-1}	1027	1.06	0.55	0.96
0.5 to <1 mg kg^{-1}	582	0.99	0.52	0.91
1 to <2 mg kg^{-1}	445	1.12	1.30	0.93
2 to <10 mg kg^{-1}	512	1.03	0.69	0.96
10+ mg kg^{-1}	263	0.97	0.54	0.95

* Combined datasets (2011 and 2012).

Table 6a*. Descriptive statistics of $(C_2/C_1)/(R_2/R_1)$ values for different preharvest intervals

		$(C_2/C_1)/(R_2/R_1)$		
Preharvest intervals	*n*	Mean	RSD	Median
Day 0	702	1.08	0.72	0.99
Day 1	389	1.24	1.28	0.97
Day 2	96	1.12	0.76	0.87
Day 3	475	1.18	0.73	1.00
Day 4	98	1.31	0.61	1.08
Day 5	71	1.49	1.27	1.09
Day 7	701	1.19	1.87	1.01
Day 10	48	1.05	0.52	0.88
Day 14	554	1.24	0.76	1.06
Day 21	228	1.20	0.74	1.04
Day 28	245	1.22	0.79	1.00
Days 33 to 37	40	1.33	1.05	1.00
Days 38 to 46	62	0.92	0.55	0.86
Days 47 to 52	17	1.22	0.64	0.98
Days 52 to 294	341	1.11	0.54	1.00

* According to MacLachlan and Hamilton [*Pest Manag Sci* 2011; 67: 609-615].

Table 6b*. Descriptive statistics of $(C_2/C_1)/(R_2/R_1)$ values for different preharvest intervals

		$(C_2/C_1)/(R_2/R_1)$		
Preharvest intervals	*n*	Mean	RSD	Median
Day 0	279	0.98	0.38	0.94
Day 1	61	0.98	0.44	0.93
Day 2	15	1.02	0.62	0.88
Day 3	110	1.03	0.55	0.93
Day 4	15	0.95	0.40	1.06
Day 5	54	1.01	0.66	0.84
Day 6	26	1.03	0.56	1.07
Day 7	371	1.10	1.08	0.90
Days 8-14	445	1.10	1.31	0.86
Days 15-21	320	1.34	1.93	1.00

Days 22-28	149	1.04	0.74	0.89
Days 29-35	187	1.18	0.59	1.00
Days 36-50	202	1.06	0.84	0.90
Days 51-100	323	1.15	0.72	0.93
Days 101-150	73	1.07	0.56	1.00
Days 151-200	51	0.88	0.45	0.84
Days 201-400	24	1.13	0.56	1.03

* Evaluation of the supplementary dataset compiled in 2012.

Table 6c*. Descriptive statistics of $(C_2/C_1)/(R_2/R_1)$ values for different preharvest intervals

		$(C_2/C_1)/(R_2/R_1)$		
Preharvest intervals	*n*	Mean	RSD	Median
Day 0	981	1.05	0.65	0.97
Day 1	451	1.20	1.24	0.96
Day 2	111	1.11	0.74	0.87
Day 3	557	1.15	0.71	0.99
Day 4	113	1.26	0.60	1.07
Day 5	125	1.28	1.18	0.92
Day 6	43	1.14	0.61	1.10
Day 7	1072	1.16	0.94	0.98
Days 8-14	1131	1.18	0.98	1.00
Days 15-21	642	1.28	1.51	1.00
Days 22-28	513	1.20	0.81	0.97
Days 29-35	261	1.22	0.69	1.00
Days 36-50	284	1.03	0.78	0.88
Days 51-100	589	1.14	0.66	0.98
Days 101-150	144	1.04	0.50	0.95
Days 151-200	59	0.94	0.49	0.85
Days 201-400	30	1.09	0.53	1.02

* Combined datasets (2011 and 2012).

Table 7a*. Descriptive statistics of $(C_2/C_1)/(R_2/R_1)$ values for different crops

		$(C_2/C_1)/(R_2/R_1)$		
Commodity	*n*	Mean	RSD	Median
Alfalfa	65	1.01	0.38	0.96
Apple	568	1.14	0.53	1.00
Apricot	68	1.40	0.49	1.22
Asparagus	17	1.36	1.10	1.04
Avocado	13	1.32	0.40	1.14
Barley forage	63	0.94	0.30	0.94
Barley grain	8	0.87	0.21	0.90
Barley straw	17	1.03	0.30	0.95
Bean pulse	43	1.11	0.41	1.10
Bean forage	12	1.26	0.59	0.98
Broccoli	135	0.95	0.63	0.82
Brussels sprouts	37	1.22	0.61	1.00
Cabbage	149	0.91	0.56	0.85
Carrot	8	1.40	0.46	1.31
Cauliflower	115	0.87	0.71	0.69
Celery	30	0.92	0.46	0.85
Cherry	80	1.30	0.48	1.18
Chickpea forage	30	1.00	0.27	1.00
Chilli pepper	11	0.84	0.27	0.97
Chinese cabbage	7	0.85	0.48	0.77
Coffee bean	17	1.14	0.54	1.00
Cotton trash	34	0.99	0.38	0.94

Table 7a*. Descriptive statistics of $(C_2/C_1)/(R_2/R_1)$ values for different crops

		$(C_2/C_1)/(R_2/R_1)$		
Commodity	*n*	Mean	RSD	Median
Cotton seed	160	1.31	0.82	1.10
Cranberry	30	1.03	0.44	0.98
Cucumber	83	1.02	0.37	0.97
Custard apple	11	1.08	0.43	0.97
Eggplant	8	0.83	0.47	0.76
Grape	233	1.28	0.48	1.14
Grapefruit	12	0.67	0.33	0.68
Grass	442	1.46	1.41	1.05
Kiwifruit	60	0.95	0.47	0.93
Leaf lettuce	27	0.99	0.70	0.88
Leafy brassica	7	1.01	0.43	1.13
Lemon	37	1.25	0.57	1.21
Lettuce	14	1.43	0.83	1.14
Lima beans	5	1.38	0.45	1.16
Litchi	4	0.77	0.43	0.66
Maize	4	1.06	0.40	1.04
Mandarin	34	1.47	1.85	0.89
Mango	46	1.03	0.52	0.84
Melon	40	0.93	0.55	0.77
Mushroom	6	0.68	0.11	0.69
Nectarine	38	1.10	0.76	0.94
Oat forage	36	1.07	0.28	0.99
Oat grain	14	1.09	0.22	1.08
Oat straw	9	1.10	0.28	1.13
Onion	5	1.17	0.27	1.25
Orange	129	1.35	0.58	1.20
Papaya	46	1.09	0.36	1.00
Pulses	6	0.81	0.12	0.81
Peach	104	1.20	0.52	1.07
Peanut	5	0.93	0.27	0.86
Peanut forage	23	1.35	0.59	1.08
Peanut hay	7	1.32	0.49	1.20
Peanut shell	6	1.13	0.36	0.98
Pear	134	1.28	0.57	1.13
Peas, green	21	1.61	0.59	1.38
Pepper	115	1.14	0.61	1.01
Pineapple	135	1.58	0.83	1.25
Plum	32	1.24	0.42	1.17
Potato	13	1.07	0.42	1.00
Sorgham	96	1.07	0.54	0.92
Sorgham forage	75	1.42	0.62	1.18
Soyabean	46	1.16	0.59	1.00
Soyabean forage	9	0.98	0.49	0.85
Spinach	49	1.16	0.61	1.00
Summer squash	12	0.74	0.35	0.67
Strawberry	13	1.14	0.27	1.13
Sugarcane	14	1.56	0.59	1.21

Table 7a*. Descriptive statistics of $(C_2/C_1)/(R_2/R_1)$ values for different crops

		$(C_2/C_1)/(R_2/R_1)$		
Commodity	*n*	Mean	RSD	Median
Tea, black	18	0.95	0.07	0.96
Tomato	205	1.19	0.64	1.00
Wheat forage	97	0.98	0.40	0.89
Wheat grain	43	1.37	0.69	1.00
Wheat straw	23	1.05	0.50	0.95
Zucchini	6	0.67	0.98	0.40

* According to MacLachlan and Hamilton [*Pest Manag Sci* 2011; 67: 609-615].

Table 7b*. Descriptive statistics of $(C_2/C_1)/(R_2/R_1)$ values for different crops

		$(C_2/C_1)/(R_2/R_1)$		
Commodity	*n*	Mean	RSD	Median
Alfalfa (forage, hay, seed)	5	1.29	0.66	0.92
Apple fruit	38	0.87	0.34	0.89
Apple leaf	12	0.90	0.57	0.71
Asparagus	3	1.34	0.51	1.14
Avocado	4	1.25	0.06	1.24
Banana (peel, pulp)	149	0.79	0.52	0.80
Barley (forage)	35	1.26	0.54	1.04
Barley (straw)	35	1.04	0.61	0.92
Barley (grain)	32	2.29	3.18	1.00
Bean (forage, hay, straw)	34	1.22	0.87	1.00
Bean (with and without pod)	84	0.91	0.47	0.86
Beetroot	5	0.70	0.56	0.83
Blackberry	6	0.84	0.41	0.81
Broccoli	2	0.75	0.02	0.75
Brussels sprouts	2	0.43	0.68	0.43
Cabbage	69	1.00	0.80	0.83
Cacao	2	1.13	0.16	1.13
Carrot	3	1.06	0.38	1.00
Cauliflower	31	0.91	0.64	0.81
Celery	4	0.72	0.67	0.57
Cherry	2	0.84	0.57	0.84
Chickpea (forage, straw)	26	0.80	0.36	0.79
Chicory	7	0.88	0.41	0.67
Clover	10	1.11	0.34	1.17
Coffee bean (green, dry)	30	0.72	0.80	0.63
Corn/maize (forage, silage, fodder, stover)	208	1.08	0.48	1.00
Corn/maize (cob, grain, kernel)	11	1.17	0.34	1.00
Cotton (seed)	30	0.92	0.52	0.84
Cotton (lint, trash)	11	1.69	0.98	1.19
Cucumber	41	0.87	0.44	0.84
Currant	6	1.07	0.31	1.01
Egg plant	3	1.48	0.34	1.45
Fig	6	0.78	0.20	0.81
Flax (seed)	3	1.14	0.59	1.23
Gooseberry	6	0.92	0.24	0.82

Table 7b*. Descriptive statistics of $(C_2/C_1)/(R_2/R_1)$ values for different crops

		$(C_2/C_1)/(R_2/R_1)$		
Commodity	*n*	Mean	RSD	Median
Grape	64	1.35	0.72	1.08
Grass (forage, hay)	81	1.02	0.43	0.97
Guava	3	1.58	0.09	1.50
Hops	6	1.37	0.35	1.47
Leek	3	0.88	0.64	0.73
Lentil	3	1.08	0.21	1.07
Lettuce	59	1.10	0.60	0.90
Lucerne	4	0.74	0.50	0.84
Lupin (forage, straw)	46	0.81	0.30	0.82
Mandarin	13	0.77	0.34	0.66
Melon	33	0.83	0.32	0.80
Mushroom	3	1.53	0.87	1.20
Mustard	2	1.13	0.86	1.13
Oat (forage)	18	1.09	0.67	0.92
Oat (straw)	2	0.90	0.16	0.90
Oat (grain)	2	0.83	0.28	0.83
Oilseed rape (seed)	14	0.97	0.34	0.90
Olive	7	0.51	0.92	0.23
Orange (fruit, peel)	24	0.89	0.73	0.77
Pea (forage)	38	1.08	0.97	0.72
Pea (with and without pod)	7	0.89	0.59	0.74
Peach	4	1.40	0.18	1.43
Pineapple	10	1.17	0.45	1.04
Potato	36	1.26	0.85	1.00
Raspberry	3	1.07	0.02	1.08
Rice (forage, straw)	155	1.39	0.81	1.04
Rice (grain)	585	1.29	1.31	1.00
Rice (bran, hulls)	56	1.26	0.63	1.02
Rye (straw)	2	0.95	0.27	0.95
Rye (grain)	2	1.81	0.03	1.81
Sorghum (forage)	17	1.05	0.32	1.01
Sorghum (grain, panicle)	32	1.17	0.61	0.93
Soybean (forage, hay)	35	0.79	0.37	0.81
Soybean (seed, seed with pods, hulls)	29	1.02	0.44	0.89
Spinach	10	1.42	0.31	1.34
Strawberry	36	0.98	0.29	0.95
Sugarbeet (tops)	10	1.28	0.24	1.34
Sugarbeet (root)	2	1.01	0.14	1.01
Sugarcane	3	0.67	0.53	0.70
Sunflower (seed)	9	0.94	0.45	1.00
Swede (tops)	2	0.62	0.63	0.62
Swede (root)	2	0.84	0.27	0.84
Sweet pepper	54	0.84	0.39	0.75
Tea (dried leaves)	7	0.98	0.59	0.81
Tobacco (green, dried, and cured leaves)	20	1.11	0.46	0.96
Tomato (incl. cherry tomato)	96	0.93	0.48	0.83
Turnip (leaf)	4	0.95	0.41	0.92

Table 7b*. Descriptive statistics of $(C_2/C_1)/(R_2/R_1)$ values for different crops

		$(C_2/C_1)/(R_2/R_1)$		
Commodity	*n*	Mean	RSD	Median
Turnip (root)	2	0.94	0.06	0.94
Wheat (forage)	53	0.95	0.60	0.76
Wheat (straw)	15	0.91	0.36	0.90
Wheat (ear, grain)	15	1.22	0.67	0.97
Wheat (processed)	8	1.02	0.09	1.05
Zucchini / Summer squash	5	0.94	0.66	0.70

* Evaluation of the supplementary dataset compiled in 2012.

Table 7c*. Descriptive statistics of $(C_2/C_1)/(R_2/R_1)$ values for different crops

		$(C_2/C_1)/(R_2/R_1)$		
Commodity	*n*	Mean	RSD	Median
Alfalfa (forage, hay, seed)	62	1.06	0.41	0.96
Almond hulls	3	1.20	0.88	0.67
Apple fruit	490	1.11	0.53	0.95
Apple leaf	12	0.90	0.57	0.71
Apricot	68	1.40	0.49	1.22
Artichoke globe	4	3.69	1.04	2.68
Asparagus	20	1.36	1.02	1.04
Avocado	17	1.31	0.35	1.17
Banana (peel, pulp)	149	0.79	0.52	0.80
Barley (forage)	98	1.06	0.47	0.99
Barley (straw)	54	1.04	0.52	0.94
Barley (grain)	40	2.01	3.25	0.95
Bean (forage, hay, straw)	52	1.48	1.45	1.00
Bean (with and without pod)	144	1.00	0.44	0.93
Beet leaves	5	0.87	0.51	0.75
Beetroot	5	0.70	0.56	0.83
Blackberry	9	1.21	0.86	1.03
Blueberry	2	1.05	0.24	1.05
Broccoli	137	0.95	0.63	0.82
Brussels sprouts	39	1.18	0.63	0.96
Cabbage	200	0.97	0.64	0.86
Cacao	2	1.13	0.16	1.13
Carrot	11	1.31	0.45	1.07
Cauliflower	164	0.85	0.70	0.69
Celery	34	0.90	0.47	0.81
Cherry	82	1.29	0.48	1.18
Chickpea	4	1.96	1.30	0.79
Chickpea (forage, straw)	58	0.92	0.31	0.91
Chicory	7	0.88	0.41	0.67
Chili pepper	11	0.84	0.27	0.97
Chinese cabbage	7	0.85	0.48	0.77
Clover	10	1.11	0.34	1.17
Coffee bean (green, dry)	49	0.89	0.69	0.71
Collards	3	0.83	0.39	0.66
Corn/maize (forage, silage, fodder, stover)	208	1.08	0.48	1.00

Table 7c*. Descriptive statistics of $(C_2/C_1)/(R_2/R_1)$ values for different crops

		$(C_2/C_1)/(R_2/R_1)$		
Commodity	*n*	Mean	RSD	Median
Corn/maize (cob, grain, kernel)	15	1.14	0.34	1.00
Cotton (seed)	190	1.25	0.81	1.00
Cotton (lint, trash)	45	1.16	0.78	1.00
Cranberry	30	1.03	0.44	0.98
Cucumber	124	0.97	0.40	0.91
Currant	6	1.07	0.31	1.01
Custard apple	11	1.08	0.43	0.97
Egg plant	11	1.01	0.49	0.88
Fig	6	0.78	0.20	0.81
Flax (seed)	3	1.14	0.59	1.23
Garlic	2	0.88	0.20	0.88
Gooseberry	6	0.92	0.24	0.82
Grape	297	1.29	0.54	1.14
Grapefruit	12	0.67	0.33	0.68
Grass (forage, hay)	529	1.38	1.38	1.03
Guava	3	1.58	0.09	1.50
Japanese radish	12	0.78	0.33	0.71
Japanese radish leaves	6	1.48	0.40	1.42
Hops	6	1.37	0.35	1.47
Kiwifruit	60	0.95	0.47	0.93
Leafy brassica	7	1.01	0.43	1.13
Leek	3	0.88	0.64	0.73
Lentil	3	1.08	0.21	1.07
Lemon	37	1.25	0.57	1.21
Lettuce	100	1.12	0.69	0.93
Litchi	4	0.77	0.43	0.66
Lucerne	4	0.74	0.50	0.84
Lupin (forage, straw)	46	0.81	0.30	0.82
Mandarin	47	1.28	1.83	0.87
Mango	46	1.03	0.52	0.84
Melon	73	0.89	0.47	0.78
Mushroom	9	0.96	0.82	0.71
Mustard	2	1.13	0.86	1.13
Nectarine	38	1.10	0.76	0.94
Oat (forage)	54	1.08	0.45	0.99
Oat (straw)	11	1.06	0.27	1.00
Oat (grain)	10	1.03	0.25	1.00
Oilseed rape (seed)	20	0.98	0.30	0.93
Oilseed rape (fodder)	4	1.03	0.30	0.96
Oilseed rape (forage)	3	0.42	0.84	0.24
Olive	7	0.51	0.92	0.23
Onion	5	1.17	0.27	1.25
Onion plant	6	1.63	0.63	1.32
Orange (fruit, peel)	153	1.28	0.61	1.10
Papaya	46	1.09	0.36	1.00
Pea (with and without pod)	35	1.31	0.65	0.95
Pea hay	8	1.10	0.24	1.05

Table 7c*. Descriptive statistics of $(C_2/C_1)/(R_2/R_1)$ values for different crops

		$(C_2/C_1)/(R_2/R_1)$		
Commodity	*n*	Mean	RSD	Median
Pea (forage)	44	1.04	0.94	0.75
Peach	110	1.18	0.53	1.07
Peanut	5	0.93	0.27	0.86
Peanut foliage, forage	23	1.35	0.59	1.08
Peanut hay	7	1.32	0.49	1.20
Peanut nutmeat	1	1.13	#DIV/0!	1.13
Peanut shell	6	1.13	0.36	0.98
Peanut straw	3	0.98	0.27	0.88
Pear	134	1.28	0.57	1.13
Pepper	167	1.06	0.58	0.93
Pineapple	145	1.55	0.82	1.22
Plum	32	1.24	0.42	1.17
Potato	49	1.21	0.78	1.00
Raspberry	3	1.07	0.02	1.08
Rhubarb	4	0.92	0.39	0.85
Rice (forage, straw)	157	1.38	0.81	1.04
Rice (grain)	587	1.29	1.31	1.00
Rice (bran, hulls)	56	1.26	0.63	1.02
Rye (straw)	2	0.95	0.27	0.95
Rye (grain)	2	1.81	0.03	1.81
Sorghum (forage)	92	1.35	0.61	1.12
Sorghum (grain, panicle)	130	1.09	0.56	0.92
Sorghum stover	15	1.11	0.27	1.15
Soybean (seed, seed with pods, hulls)	66	1.12	0.56	0.99
Soybean (forage, hay, fodder)	55	0.84	0.40	0.85
Spinach	59	1.20	0.56	1.12
Strawberry	49	1.02	0.29	1.00
Sugarbeet (tops)	10	1.28	0.24	1.34
Sugarbeet (root)	2	1.01	0.14	1.01
Sugarcane	17	1.41	0.65	1.10
Summer squash / zucchini	23	0.76	0.60	0.64
Sunflower (seed)	13	0.96	0.48	1.00
Swede (tops)	2	0.62	0.63	0.62
Swede (root)	2	0.84	0.27	0.84
Sweetcorn forage/fodder	4	1.85	0.88	1.31
Tangerine	2	1.21	0.22	1.21
Tea (dried leaves)	25	0.96	0.31	0.93
Tea, green	5	1.01	0.08	1.00
Tobacco (green, dried, and cured leaves)	20	1.11	0.46	0.96
Tomato (incl. cherry tomato)	301	1.11	0.62	0.95
Triticale forage	2	0.73	0.59	0.73
Turnip (leaf)	4	0.95	0.41	0.92
Turnip (root)	2	0.94	0.06	0.94
Wheat (forage)	150	0.97	0.48	0.87
Wheat (straw)	38	0.99	0.46	0.95
Wheat (ear, grain)	58	1.33	0.68	1.00
Wheat (processed)	8	1.02	0.09	1.05

* Combined datasets (2011 and 2012).

Table 8a*. Descriptive statistics of $(C_2/C_1)/(R_2/R_1)$ values for different pesticides

	$(C_2/C_1)/(R_2/R_1)$			
Pesticide [a]	*n*	Mean	RSD	Median
Acephate I, s	164	1.17	0.73	1.00
alpha-Cypermethrin I	31	0.80	0.39	0.88
Aminopyralid H, s	421	1.21	1.31	1.00
Azoxystrobin F, s	45	1.02	0.38	0.86
Boscalid F, s	7	0.89	0.34	0.79
Buprofezin I	146	1.34	0.57	1.18
Captan F	63	1.14	0.72	0.88
Chlorantraniliprole I	85	1.04	0.34	1.00
Chlorpyrifos I	94	1.40	0.56	1.22
Clofentezine I	79	1.11	0.50	1.00
Cyprodinil F, s	44	1.34	0.44	1.20
Cyromazine I, s	141	0.90	0.57	0.79
Deltamethrin I	5	1.45	0.48	1.05
Difenoconazole F, s	11	1.09	0.21	1.06
Diflubenzuron I	62	1.30	0.71	0.94
Dimethomorph F, s	8	1.63	0.58	1.44
Disulfoton I, s	23	0.98	0.49	0.81
Endosulfan I	131	1.16	1.26	0.92
Fenbuconazole F	27	1.06	0.55	1.00
Fenproparthrin I	23	0.97	0.08	0.96
Fenvalerate I	17	0.94	0.36	0.96
Fipronil I	588	1.19	1.13	0.91
Flusilazole F, s	49	1.28	0.59	1.08
Haloxyfop H, s	180	1.03	0.35	0.98
Imidacloprid I, s	153	1.13	0.62	1.00
Indoxacarb I	377	1.12	0.71	0.96
Iprodione F	26	0.96	0.73	0.77
Kresoxim-methyl F	31	1.27	0.56	1.21
lambda-Cyhalothrin I	10	1.17	0.26	1.15
Methomyl I, s	149	1.35	0.71	1.05
Methoxyfenozide I	24	1.10	0.86	0.83
Oxamyl I, s	300	1.29	0.79	1.02
Parathion I	15	1.30	0.70	1.03
Phosmet I	7	1.23	0.58	1.19
Profenofos I	33	1.42	0.64	1.21
Propiconazole F, s	19	1.29	0.55	1.14
Pyraclostrobin F, s	8	1.04	0.33	1.13
Quinoxyfen F, s	57	1.37	0.35	1.30
Spinetoram I	332	1.23	0.42	1.16
Spinosad I	165	1.27	1.03	1.01
Spirodiclofen I	5	0.87	0.04	0.88
Tebuconazole F, s	46	1.02	0.26	1.00
Tebufenozide I	68	1.32	0.51	1.11

Table 8a*. Descriptive statistics of $(C_2/C_1)/(R_2/R_1)$ values for different pesticides

Pesticide [a]	$(C_2/C_1)/(R_2/R_1)$			
	n	Mean	RSD	Median
Thiodicarb I, s	68	1.22	0.50	1.17
Triadimefon/triadimenol F, s	29	1.03	0.64	0.85
Zoxamide F	28	1.64	0.71	1.25

[a] I = insecticide or acaricide; H = herbicide; F = fungicide; s = systemic, partially systemic compounds or those that are translamellarly transported.

* According to MacLachlan and Hamilton [*Pest Manag Sci* 2011; 67: 609-615].

Table 8b*. Descriptive statistics of $(C_2/C_1)/(R_2/R_1)$ values for different pesticides

Pesticide [a]	$(C_2/C_1)/(R_2/R_1)$			
	n	Mean	RSD	Median
Acetamiprid I, s	35	1.21	0.24	1.23
Acetochlor H, s	29	1.25	0.76	1.00
Azoxystrobin F, s	21	0.79	0.36	0.81
Beta-cyfluthrin I	107	1.05	0.60	0.96
Bitertanol F, s	2	1.19	0.57	1.19
Buprofezin I	2	1.16	0.22	1.16
Chlorimuron ethyl H, s	16	1.25	0.21	1.26
Chlormequat chloride G, s	10	0.90	0.29	0.90
Chlorpyrifos/chlorpyrifos-methyl I	55	1.30	1.49	1.06
Clopyralid H, s	2	1.10	0.65	1.10
CY86 I, s	89	1.34	0.87	1.00
Cyclanilide G	9	0.82	0.28	0.84
Cycloxydim H, s	6	0.82	0.27	0.77
Cyfluthrin I	192	1.17	0.75	0.94
Cyhalofop H, s	29	0.98	0.41	0.94
Cyproconazole F, s	23	0.63	0.61	0.59
Deltamethrin I	18	1.96	0.84	1.31
Diclocymet F, s	8	0.82	0.25	0.82
Difenoconazole F, s	36	1.28	0.24	1.24
Emamectin benzoate I	24	0.93	0.30	0.89
Endosulfan I	4	1.05	0.21	1.03
Epoxiconazole F, s	16	3.01	1.95	1.07
Ethephon G, s	39	1.00	0.55	0.88
Ethiprole I, s	11	0.77	0.17	0.75
Famoxadone F, s	17	0.99	0.37	0.97
Fenamiphos N, s	3	0.52	0.64	0.36
Fenobucarb I	2	2.33	0.52	2.33
Fenoxanil F, s	36	0.96	0.14	0.96
Fenoxaprop-(P)-ethyl H, s	22	1.00	0.74	0.83
Fenpyroximate I	8	1.02	0.44	1.04
Ferimzone F, s	2	1.06	0.34	1.06
Fluazifop H, s	60	1.06	0.71	0.95
Flubendiamide I, s	12	0.95	0.24	0.89
Fluopicolide F, s	24	0.84	0.27	0.75
Flutolanil F, s	2	0.49	0.69	0.49

Table 8b*. Descriptive statistics of $(C_2/C_1)/(R_2/R_1)$ values for different pesticides

		$(C_2/C_1)/(R_2/R_1)$		
Pesticide [a]	*n*	Mean	RSD	Median
Fosetyl-Al F, s	51	0.95	0.42	0.89
Glufosinate-ammonium H, s	295	1.14	0.68	0.99
Gylphosate-trimesium H, s	46	1.78	3.43	0.93
Haloxyfop H, s	30	1.11	0.50	1.01
Hexaconazole F, s	23	1.22	0.43	1.16
Imazamox H, s	7	1.04	0.35	1.11
Imazapyr H, s	4	0.65	0.54	0.71
Imidacloprid I, s	221	0.96	0.61	0.81
Iprodione F	2	0.56	0.11	0.56
Iprovalicarb F, s	3	1.28	0.35	1.51
Isoprocarb I	19	3.86	1.33	1.27
Isoxaflutole H, s	68	1.03	0.57	0.90
Mefenpyr-diethyl S, s	30	0.94	0.44	0.88
Methiocarb I	3	3.01	0.46	3.30
Myclobutanil F	321	0.90	0.47	0.86
Oxadiazon H	20	1.11	0.46	1.06
Oxydemeton-methyl I, s	2	0.79	0.07	0.79
Pencycuron F	2	0.77	0.13	0.77
Pendimethalin H	3	1.57	0.68	1.29
Penflufen F, s	32	0.94	0.67	0.70
Penoxsulam H, s	9	1.86	0.60	1.85
Phthalide F	4	0.82	0.03	0.82
Prochloraz F	18	1.09	0.40	0.99
Profenofos I	15	1.11	0.65	0.71
Propamocarb F, s	31	0.92	0.49	0.80
Propiconazole F, s	37	0.81	0.46	0.67
Propineb F, s	22	0.93	0.47	0.84
Prothioconazole F, s	4	0.88	0.29	1.00
Quinclorac H, s	5	0.76	0.28	0.78
Silafluofen I	2	1.69	0.54	1.69
Spinosad I	30	1.18	0.40	0.97
Spirodiclofen I	5	0.87	0.04	0.88
Spiromesifen I	10	1.05	0.25	1.00
Sulfoxaflor I, s	95	0.90	0.39	0.84
Tebuconazole F, s	78	0.98	0.30	0.96
Teflubenzuron I	7	1.06	0.50	0.90
Tepraloxydim H, s	5	1.12	0.21	1.14
Thiacloprid I, s	26	0.92	0.35	0.87
Thidiazuron G, s	2	0.81	0.17	0.81
Thiodicarb I, s	3	1.08	0.35	1.00
Tolylfluanid F	24	0.84	0.46	0.83
Triadimefon/triadimenol F, s	21	0.89	0.46	0.88
Triazophos I	37	1.58	0.80	1.13
Tribufos G	4	1.00	0.84	0.82
Tricyclazole F, s	61	1.53	0.92	1.13
Trifloxystrobin F, s	17	1.10	0.79	0.85
Triflumuron I	13	1.00	0.65	0.90

Table 8b*. Descriptive statistics of $(C_2/C_1)/(R_2/R_1)$ values for different pesticides

Pesticide [a]	$(C_2/C_1)/(R_2/R_1)$			
	n	Mean	RSD	Median

[a] F = fungicide; G = plant growth regulator; H = herbicide; I = insecticide or acaricide; N = nematicide; S = safener; s = systemic, partially systemic compounds or those that are translamellarly transported (includes also substances with systemic metabolites).

* Evaluation of the supplementary dataset compiled in 2012.

Table 8c*. Descriptive statistics of $(C_2/C_1)/(R_2/R_1)$ values for different pesticides

Pesticide [a]	$(C_2/C_1)/(R_2/R_1)$			
	n	Mean	RSD	Median
Acephate I, s	164	1.17	0.73	1.00
Acetamiprid I, s	35	1.21	0.24	1.23
Acetochlor H, s	29	1.25	0.76	1.00
alpha-Cypermethrin I	31	0.80	0.39	0.88
Aminopyralid H, s	427	1.19	1.33	1.00
Azoxystrobin F, s	67	0.96	0.41	0.84
Beta-cyfluthrin I	107	1.05	0.60	0.96
Bitertanol F, s	2	1.19	0.57	1.19
Boscalid F, s	7	0.90	0.34	0.79
Buprofezin I	148	1.33	0.57	1.18
Captan F	64	1.14	0.72	0.88
Chlorantraniliprole I	85	1.04	0.34	1.00
Chlorimuron ethyl H, s	16	1.25	0.21	1.26
Chlormequat chloride G, s	11	0.85	0.35	0.80
Chlorpyrifos/chlorpyrifos-methyl I	149	1.36	0.97	1.10
Clofentezine I	79	1.11	0.50	1.00
Clopyralid H, s	2	1.10	0.65	1.10
CY86 I, s	89	1.34	0.87	1.00
Cyclanilide G	9	0.82	0.28	0.84
Cycloxydim H, s	6	0.82	0.27	0.77
Cyfluthrin I	192	1.17	0.75	0.94
Cyhalofop H, s	29	0.98	0.41	0.94
Cyproconazole F, s	23	0.63	0.61	0.59
Cyprodinil F, s	44	1.34	0.44	1.20
Cyromazine I, s	141	0.90	0.57	0.79
Deltamethrin I	23	1.85	0.81	1.05
Diclocymet F, s	8	0.82	0.25	0.82
Difenoconazole F, s	47	1.23	0.24	1.20
Diflubenzuron I	62	1.30	0.71	0.94
Dimethomorph F, s	8	1.63	0.58	1.44
Disulfoton I, s	23	0.98	0.49	0.81
Emamectin benzoate I	24	0.93	0.30	0.89
Endosulfan I	135	1.16	1.24	0.92
Epoxiconazole F, s	16	3.01	1.95	1.07
Ethephon G, s	39	1.00	0.55	0.88
Ethiprole I, s	11	0.77	0.17	0.75
Famoxadone F, s	17	0.99	0.37	0.97

Table 8c*. Descriptive statistics of $(C_2/C_1)/(R_2/R_1)$ values for different pesticides

		$(C_2/C_1)/(R_2/R_1)$		
Pesticide [a]	*n*	Mean	RSD	Median
Fenamiphos N, s	3	0.52	0.64	0.36
Fenobucarb I	2	2.33	0.52	2.33
Fenbuconazole F	27	1.06	0.55	1.00
Fenproparthrin I	23	0.97	0.08	0.96
Fenoxanil F, s	36	0.96	0.14	0.96
Fenoxaprop-(P)-ethyl H, s	22	1.00	0.74	0.83
Fenpyroximate I	8	1.02	0.44	1.04
Fenvalerate I	19	0.93	0.34	0.95
Ferimzone F, s	2	1.06	0.34	1.06
Fipronil I	588	1.19	1.13	0.91
Fluazifop H, s	60	1.06	0.71	0.95
Flubendiamide I, s	12	0.95	0.24	0.89
Fluopicolide F, s	24	0.84	0.27	0.75
Flutolanil F, s	2	0.49	0.69	0.49
Flusilazole F, s	49	1.28	0.59	1.08
Fosetyl-Al F, s	51	0.95	0.42	0.89
Glufosinate-ammonium H, s	295	1.14	0.68	0.99
Gylphosate-trimesium H, s	46	1.78	3.43	0.93
Haloxyfop H, s	210	1.04	0.38	0.98
Hexaconazole F, s	23	1.22	0.43	1.16
Imazamox H, s	7	1.04	0.35	1.11
Imazapyr H, s	4	0.65	0.54	0.71
Imidacloprid I, s	377	1.03	0.62	0.88
Indoxacarb I	379	1.11	0.71	0.96
Iprodione F	28	0.93	0.74	0.76
Iprovalicarb F, s	3	1.28	0.35	1.51
Isoprocarb I	19	3.86	1.33	1.27
Isoxaflutole H, s	68	1.03	0.57	0.90
Kresoxim-methyl F	31	1.27	0.56	1.21
lambda-Cyhalothrin I	10	1.17	0.26	1.15
Mefenpyr-diethyl S, s	30	0.94	0.44	0.88
Methiocarb I	3	3.01	0.46	3.30
Methomyl I, s	149	1.35	0.71	1.05
Methoxyfenozide I	24	1.10	0.86	0.83
Myclobutanil F	321	0.90	0.47	0.86
Oxadiazon H	20	1.11	0.46	1.06
Oxamyl I, s	300	1.29	0.79	1.02
Oxydemeton-methyl I, s	2	0.79	0.07	0.79
Parathion I	15	1.30	0.70	1.03
Pencycuron F	2	0.77	0.13	0.77
Pendimethalin H	3	1.57	0.68	1.29
Penflufen F, s	32	0.94	0.67	0.70
Penoxsulam H, s	9	1.86	0.60	1.85
Phosmet I	7	1.23	0.58	1.19
Phthalide F	4	0.82	0.03	0.82
Prochloraz F	18	1.09	0.40	0.99
Profenofos I	48	1.32	0.65	1.10

Table 8c*. Descriptive statistics of $(C_2/C_1)/(R_2/R_1)$ values for different pesticides

		$(C_2/C_1)/(R_2/R_1)$		
Pesticide [a]	*n*	Mean	RSD	Median
Propamocarb F, s	31	0.92	0.49	0.80
Propiconazole F, s	56	0.98	0.57	0.86
Propineb F, s	22	0.93	0.47	0.84
Prothioconazole F, s	4	0.88	0.29	1.00
Pyraclostrobin F, s	8	1.04	0.33	1.13
Quinclorac H, s	5	0.76	0.28	0.78
Quinoxyfen F, s	57	1.37	0.35	1.30
Silafluofen I	2	1.69	0.54	1.69
Spinetoram I	313	1.22	0.43	1.15
Spinosad I	195	1.26	0.97	1.01
Spirodiclofen I	10	0.87	0.04	0.88
Spiromesifen I	10	1.05	0.25	1.00
Sulfoxaflor I, s	95	0.90	0.39	0.84
Tebuconazole F, s	124	0.99	0.29	1.00
Tebufenozide I	68	1.32	0.51	1.11
Teflubenzuron I	7	1.06	0.50	0.90
Tepraloxydim H, s	5	1.12	0.21	1.14
Thiacloprid I, s	28	0.92	0.34	0.87
Thidiazuron G, s	2	0.81	0.17	0.81
Thiodicarb I, s	71	1.21	0.49	1.16
Tolylfluanid F	24	0.84	0.46	0.83
Triadimefon/triadimenol F, s	50	0.97	0.59	0.88
Triazophos I	38	1.62	0.78	1.15
Tribufos G	4	1.00	0.84	0.82
Tricyclazole F, s	61	1.53	0.92	1.13
Trifloxystrobin F, s	17	1.10	0.79	0.85
Triflumuron I	13	1.00	0.65	0.90
Zoxamide F	28	1.64	0.71	1.25

[a] F = fungicide; G = plant growth regulator; H = herbicide; I = insecticide or acaricide; N = nematicide; S = safener; s = systemic, partially systemic compounds or those that are translamellarly transported (includes also substances with systemic metabolites).

* Combined datasets (2011 and 2012).

Table 9a*. Descriptive statistics of $(C_2/C_1)/(R_2/R_1)$ values for different pesticide types

		$(C_2/C_1)/(R_2/R_1)$		
Pesticide type	*n*	Mean	RSD	Median
Fungicides	505	1.21	0.56	1.04
Herbicides	607	1.14	1.17	0.99
Insecticides (incl. acaricides)	3288	1.19	0.80	1.00

* For the dataset evaluated by MacLachlan and Hamilton [*Pest Manag Sci* 2011; 67: 609-615].

Table 9b*. Descriptive statistics of $(C_2/C_1)/(R_2/R_1)$ values for different pesticide types

		$(C_2/C_1)/(R_2/R_1)$		
Pesticide type	*n*	Mean	RSD	Median
Fungicides	938	1.00	0.96	0.89
Growth regulators	64	0.95	0.51	0.86
Herbicides	661	1.16	1.51	0.97
Insecticides (incl. acaricides)	1048	1.17	0.99	0.93
Safeners	30	0.94	0.44	0.88

* Evaluation of the supplementary dataset compiled in 2012.

Table 9c*. Descriptive statistics of $(C_2/C_1)/(R_2/R_1)$ values for different pesticide types

		$(C_2/C_1)/(R_2/R_1)$		
Pesticide type	*n*	Mean	RSD	Median
Fungicides	1443	1.08	0.82	0.95
Growth regulators	65	0.94	0.52	0.85
Herbicides	1268	1.15	1.36	0.98
Insecticides (incl. acaricides)	4336	1.19	0.85	1.00
Safeners	30	0.94	0.44	0.88

* Combined datasets (2011 and 2012).

APPENDIX 2

Background Paper On Simulation
[Prepared by US EPA, Office of Pesticide Programs, 21 November 2012]

Introduction and Background

MacLachlan and Hamilton (2011) obtained side-by-side residue trial data reported by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) to investigate whether or not the resulting residues in harvested commodities are proportional to the pesticide application rate used on the crop. Numerous sets of trials were identified where the only parameter varied was application rate or spray concentration. The authors analyzed this database with respect to a variety of factors including application rate, spray concentration, application type, formulation type, crop, and pesticide and concluded that residues scale proportionally with application rate (proportionality principle). The authors expressed their belief that pesticide risk assessment would be improved by the use of the proportionality principle by regulators and others interested in pesticide residues.

In follow-up work to the MacLachlan and Hamilton paper, Stewart and LaPorte (Relationship between Application Rate of Pesticides and Their Residue Levels in Treated Commodities: Further Investigation of the Proportionality Principle, 2012) recently used additional side-by-side crop residue data sets provided by the Chinese and Japanese governments as well as data provided by BASF, Bayer CropScience, Dow AgroSciences, DuPont, and Syngenta and evaluated the concept of proportionality using the same approach as that described in MacLachlan and Hamilton's paper. The data used by Stewart and LaPorte were distinct from (i.e., supplemental to) that used by MacLachlan and Hamilton and involved a total of 81 different active substances, 14 different formulation types, 4 different application types (foliar, seed treatment, post harvest, soil treatment), and 88 different commodities. Stewart and LaPorte performed multiple analyses using simple linear regression, regressing the natural log residues at a higher application rate vs. 1x application rate using the aforementioned side-by-side trial data. From the available residue data from these side-by-side trials with multiple application rates, Stewart and LaPorte computed the ratio of residue concentrations (C2/C1) and compared this to the ratio of application rates (R2/R1). Theoretically, if the proportionality concept is true, the expected ratio of residue ratio over application rate ratio (C2/C1)/(R2/R1) resulting from these side-by-side trials is equal or close to 1, and the median (C2/C1)/(R2/R1) is expected to be 1.

In a conference call held among US, Dutch, Canadian, French, and Australian participants held in November 2012, further discussion of the Stewart and LaPorte analysis occurred. Specifically, some concern was expressed by call participants that the work by Stewart and LaPorte – while very valuable in extending the work of MacLachlan and Hamilton – did not evaluate the distribution of these ratios using formal statistical tests. Thus, while appropriately estimated ratios would indeed be expected to cluster around 1 if proportionality were true, no formal statistical tests of these resulting ratios were presented to determine if they differed significantly from 1. Specifically, the group from the Netherlands stated that:

> The presented document closely follows the paper of MacLachlan and Hamilton (2011). In this respect all statistical comments below are just as much comments on that original paper. The authors present figures and tables suggesting strongly that proportionality seems to be a valid

assumption on average, and also when stratified for application rates, formulation types, application types, concentration ranges, crops and pesticides. *However, no formal test results are shown*.

In other words: while the Stewart and LaPorte findings did indeed suggest that proportionality was at least approximately (or "on average") correct with the ratios clustering near (and both above and below) 1, the findings did not include an examination of how much these ratios would be expected to deviate from 1 or how much "off" from 1 a specific ratio needed to be in order to suggest that proportionality for that strata or grouping did not hold. Thus, the Stewart and LaPorte data analysis made it difficult to conclude exactly what "close enough" was since no information was provided how much deviation from 1 (aka error) would be expected.

During the conference call, the US agreed to investigate this further by conducting a statistical simulation of what kind (read: amounts) of deviations from the ideal value of 1 would be expected given the nature of the residue distribution and the number of field trials conducted. Specifically, we agreed to develop a short follow-on document that would help to characterize and put into context the Stewart-LaPorte findings and assist in deciding how much of the variation might be to natural (and expected) variability in the ratio and how much might be considered systematic (i.e., truly different from 1 because proportionality did not hold). The following three goals for this exercise were established:

1. To understand the expected range of ratios $(C_2/C_1)/(R_2/R_1)$. For this goal, we set the number of iterations = 10,000 for each simulation (i.e., 10,000 ratios of $(C_2/C_1)/(R_2/R_1)$).

2. To understand the expected range of the median of ratios $(C_2/C_1)/(R_2/R_1)$ for some specific fixed number of trials (number of trials = 10, 20, 30, 50, 100, 200, etc.). These sample sizes can represent for the number of trials per crop, per application type, etc. For this goal, we set the number of medians = 1000 for each simulation (i.e., 1000 sets of 10 trials, 1000 set of 20 trials, etc.)

3. 3. Comparing the residue ratio and ratio of $(C_2/C_1)/(R_2/R_1)$ of the JMPR trials, generated by Stewart-LaPorte with the theoretical distribution of ratios generated from the simulation (see Appendix 3).

Conceptual Approach – Introduction

The conceptual approach that was decided upon was to compute, for multiple application rates, the ratio of residues from the available residue data for the side-by-side trials to the ratio of application rates. Theoretically, if the proportionality concept is true, the expected "ratio of the ratios" – that is the ratio of the residue ratio to application rate ratio $(C_2/C_1)/(R_2/R_1)$ – resulting from these side-by-side trials is equal or close to 1, and the median $(C_2/C_1)/(R_2/R_1)$ is expected to be 1. However, some observed individual ratios in Stewart and LaPorte (as in MacLachlan and Hamilton) of residues C_2/C_1 occasionally are substantially different from the ratio of application rates R_2/R_1 (i.e. $(C_2/C_1)/(R_2/R_1)$ is not close to 1), and the median of residue ratio C_2/C_1 from a number of trials are occasionally not close to the ratio of application rates R_2/R_1 (i.e. $(C_2/C_1)/(R_2/R_1) \neq 1$). The difference causes us to question 1) whether the proportionality principle may be not hold in general (or the proportionality may be not true for some specific strata or scenarios); or 2) whether difference between ratio of residues (or the median of residue ratio) and ratio of application rates is just a result of sampling error (i.e., random noise of residues) given the proportionality concept is valid.

The first question regarding whether proportionality holds in general can be relatively easily addressed by statistically analysing the observed residue data and comparing these observed ratios to ratios

derived from simulations. For the latter question relating the median of the ratios and whether this is equal to 1, it is worthwhile to develop simulations to gain insight into the expected distribution/range of $(C_2/C_1)/(R_2/R_1)$ from side-by-side trials with different application rates R_2 and R_1, given the proportionality is true. This document is the result of efforts to provide the insight of about $(C_2/C_1)/(R_2/R_1)$: what was found by Stewart/LaPorte using the methods of MacLachlan and Hamilton and how this compares to what would be expected if proportionality were to hold.

Method

Assuming that the proportionality concept is valid, we randomly generated using SAS software (see code in Addendum) a large number of residues and compute the ratios $(C_2/C_1)/(R_2/R_1)$, where each pair C_1-C_2 represents residues from a side-by-side trial with different application rate R_1-R_2. For example, C_1 is randomly generated from a distribution of residue at application R_1, and C_2 is randomly generated from a distribution of residue at application R_2, given a stated degree of similarity ICC (intra-class-correlation) after adjustment for application rate between the residue C_1 and residue C_2 since these residues are from a side-by-side trial and are thus correlated. Mathematically, the ICC is calculated as:

$$\text{ICC} = \frac{between\ trials\ variance}{between\ trials\ variance + within\ trial\ variance}$$

where variances are calculated for log-transformed residue values

If the degree of similarity of residues from same trial is strong (compared to residues from different trials *after adjustment for application rate*), the ICC is close to 1. If there is a weak similarity between the residues from the same trials (compared to residues from different trials), the ICC is close to 0. Since the ICC may be different for different crops, different pesticides, different applications, different formulations, different locations, or a combination of these different factors, we set ICC = 0.5, 0.7, 0.9, and 1.0 in our simulation to cover a range of moderate to strong correlation[1]. If the conclusions we reach regarding the $(C_2/C_1)/(R_2/R_1)$ approximating 1 do not meaningfully differ when these different ICCs are used, we can have greater confidence in any conclusions reached (or, more specifically, that any conclusions are not sensitive to a reasonable range of ICCs chosen.

In addition to assuming an ICC (or, more accurately, a set of ICCs), we also needed to make assumptions for this simulation regarding the distributional form (or family) of the residues (e.g., normal, lognormal) as well as its "spread", or variance. It is generally recognized that the distribution of crop residues is right-skewed with an approximate lognormal distribution and that the coefficient of variation

[1] The distribution of estimated ICC values in two different databases provided by Dow AgroSciences and PMRA:

	Dow AgroSciences		PMRA	
ICC	Number of Commodity-Pesticide combinations	PERCENT (%)	Number of Commodity-Pesticide combinations	PERCENT (%)
< 0.5	0	0	22	11
0.5 - 0.6	0	0	7	3
0.6 - 0.7	0	0	15	7
0.7 - 0.8	2	9	23	11
0.8 - 0.9	4	17	44	20
0.9 - 1.0	17	74	108	49

(standard deviation/mean) is about 1[2]. Without loss of generality we assume a geometric mean (GM) residue concentration C1 = 1 at application rate R1 (= 1X critical GAP rate). Further we assume the distribution of residue at application R_1 = 1X is a lognormal distribution with geometric mean = 1 and CV = 1; the distribution of residue at application R_2 =2X is a lognormal distribution with GM = 2 and CV = 1; the distribution of residue at application R_2 =4X is a lognormal distribution with GM = 4 and CV = 1; etc. Similar simulations are also performed with all same assumptions as having been described, except CV=0.7 and then CV=1.3.

Results of Simulation

1. Range of ratio $(C_2/C_1)/(R_2/R_1)$

   Table A and Figure 1 present the ratio $(C_2/C_1)/(R_2/R_1)$ for ICCs of 0.5, 0.7, 0.9 and 1.0. As the correlation approaches 1, it can be seen that the distribution of ratio $(C_2/C_1)/(R_2/R_1)$ becomes narrower and asymptotic to 1, and the ratio $(C_2/C_1)/(R_2/R_1)$ does not depend on the ratio of application rates. For example, when the intra-class correlation = 0.5 (i.e., 50% of the variation of the residue data is from the variation between trials, and 50% of the variation of the residue is from the variation of the residues from same trials), 50% of the ratios $(C_2/C_1)/(R_2/R_1)$ are outside the range of (0.6, 1.7) and 20% of the ratios are outside the range (0.3, 2.9). For a strong correlation with ICC = 0.9, 50% of the ratios $(C_2/C_1)/(R_2/R_1)$ are outside the range of (0.8, 1.3) and 20% are outside the range of (0.6, 1.6)

2. Range of median of ratio $(C_2/C_1)/(R_2/R_1)$

   Tables B, C, and D present the distribution of medians of $(C_2/C_1)/(R_2/R_1)$ when CV = 1.0, 0.7, and 1.3, respectively.
   Figures 2 and 3 visually present the distribution of median of $(C_2/C_1)/(R_2/R_1)$ when CV = 1.
   As the sample size increases, the distribution of median of $(C_2/C_1)/(R_2/R_1)$ becomes narrower and is asymptotic to 1. The same characteristic is applied to the ICC: as the ICC increases and becomes closer to 1, the distribution of the median of $(C_2/C_1)/(R_2/R_1)$ becomes narrower and is asymptotic to 1. The distribution of the median of $(C_2/C_1)/(R_2/R_1)$ is independent from the ratio R_2/R_1. For example, when ICC = 0.5 and sample size = 30 trials, 95% of the medians of $(C_2/C_1)/(R_2/R_1)$ are within (0.67, 1.40). However, for the same ICC = 0.5 but with sample size increasing to 500, 95% of the medians of $(C_2/C_1)/(R_2/R_1)$ are within (0.91, 1.09).

Validate Proportionality Concept

The results of simulations (Tables A and B) can be used as a tool to evaluate whether the proportionality principle is invalid for crop residues in general (i.e., "on average) or invalid for some specific scenarios (for example, seed treatment, soil treatment, etc.). If the median of the ratios observed by Stewart-LaPorte is within the range of the 95% sampling interval of the median in Table B, there is no evidence (at p=0.05) to reject the proportionality concept. However, if the Stewart-LaPorte median of the ratios is outside the range of 95% sampling interval of the median in Table B, there is evidence (again at p

[2] **Descriptive statistics of estimated CV values in two different databases provided by Dow AgroSciences and PMRA:**

Database	Number of Commodity-Pesticide combinations	Values of CV at percentile								
		min	P5	P10	P25	P50	P75	P90	P95	max
Dow AgroSciences	23	0.37	0.54	0.55	0.88	1.14	1.81	2.33	2.44	2.48
PMRA	219	0.05	0.24	0.46	0.50	0.75	1.06	1.44	1.98	5.93

= 0.05) to reject the proportionality principle for that specific scenario (application type, formulation type, etc.).

Stewart and LaPorte have done an excellent job of generating multiple tables of ratios $(C_2/C_1)/(R_2/R_1)$ for a large number of crops, application types, formulation types, etc.; we would use these available ratios and compare them with the theoretical (simulation) distribution of ratio $(C_2/C_1)/(R_2/R_1)$ and we use these here as the observed data. The most appropriate for comparison are the medians of the ratio $(C_2/C_1)/(R_2/R_1)$ in Stewart-LaPorte's tables (3b, 4b, 5b, 6b, 7b, 8b, and 9b) vs. the distribution of median of $(C_2/C_1)/(R_2/R_1)$ in Table B of this current document. For example, for most of the formulation types, the medians of ratio $(C_2/C_1)/(R_2/R_1)$ in Stewart-LaPorte's Table 3b (see below) are within the range 95% sampling intervals of the simulation, assuming the ICC of residues = 0.5. The only few exceptions are FS (flowable concentrate for seed treatment, n=184), FC (flowable concentrate, n=59), and OD (oil dispersion, n = 9). For example, FS: the observed median of $(C_2/C_1)/(R_2/R_1)$ is 0.81, which is equal the 2.5^{th} percentile when sample size = 100, but less than 0.86 (the 2.5^{th} percentile when the sample size = 200). For FC and OD, the observed ratios of 1.33 (n=59) and 1.85 (n=9) are outside the 95% CI of roughly (0.8 , 1.2) and (0.5, 1.8). This suggests the relationship of "double application rate would double residue" does not apply to this specific scenario, but applies to all the remaining. Further investigation should be performed to determine whether proportionality principle does not apply to flowable concentration, seed treatment, or only the combination of these two variables.

Alternatively, if we assume that the ICCs are 0.7, we find that a greater number of formulations "fall outside" the 95% confidence range described in Table B. Specifically, the following formulations fall outside this range: FS (flowable concentrate for seed treatment, n = 184): observed = 0.81 (95% CI = 0.9 to 1.1); FC (flowable concentration, n = 59): observed = 1.33 (95% CI = 0.8 to 1.3); OD (oil dispersion, n = 9): observed= 1.85 (95% CI = 0.6 to 1.6); EC (emulsifiable concentration, n = 813): observed = 0.93 (95% CI = 0.9 to 1.1); and SC (suspension concentration, n = 514): observed = 0.90 (95% CI (0.9 to 1.1). In addition to the mentioned formulations, SL (soluble concentrate, n = 508) would also fall out of the expected range if we assume an ICC of 0.9: observed ratio = 0.94 (95% CI = 0.96 to 1.04). Thus, we might question the extent to which these formulations indeed follow proportionality. While this might suggest further investigation of why the relationship of "double application would double residue" for formulation does not hold *precisely*, it does suggest that the value is usually very close to (but less than) the ideal value of 1. For example, one exception is an OD formulation with an observed ratio of 1.85.

Another interest is related to application type as expressed by the Stewart-LaPorte Table 4b in which four strata were established by application type: foliar; soil treatment; post-harvest; and seed treatment. For foliar application (n=1681), the observed median of $(C_2/C_1)/(R_2/R_1)$ is 0.93 which is outside the 95% CI range of (0.95, 1.05) which would be expected with an ICC of 0.5 and n= 1500 for the simulated median $(C_2/C_1)/(R_2/R_1)$. For ICCs of 0.7 and 0.9 respectively, the corresponding 95% CIs are (0.96, 1.04) and (0.98, 1.02), and the observed median value of 0.93 is similarly outside of these range.

Conclusion

In a conference call held among US, Dutch, Canadian, French, and Australian participants regarding work by Stewart and LaPorte, some concern was expressed that the $(C_2/C_1)/(R_2/R_1)$ ratios they generated to test proportionality were not evaluated using formal statistical tests. That is, while appropriate estimated ratios would indeed be expected to cluster around one if proportionality were true, no formal statistical tests of these resulting ratios were presented to determine if they differed significantly from one.

During the conference call, the US agreed to investigate this further by conducting a statistical simulation and agreed to develop a short follow-on document that would help to characterize and put into context the Stewart-LaPorte findings and assist in deciding how much of the variation might be to natural

(and expected) variability in the ratio and how much might be considered systematic (i.e., truly different from 1 because proportionality did not hold). This analysis was performed using what we believe to be reasonable assumptions regarding the distributional family, the CV, and the ICC. Based on these simulation results, it appears that the Steward-LaPorte results for the $(C_2/C_1)/(R_2/R_1)$ ratio fall outside the expected range of variability for this ratio.

(Excerpt from Stewart-LaPorte document)

Table 3b*. Descriptive statistics of $(C_2/C_1)/(R_2/R_1)$ values for different formulation types

	$(C_2/C_1)/(R_2/R_1)$			
Formulation type	*n*	Mean	RSD	Median
Not specified or several types	13	0.84	0.20	0.83
DF (dry flowable formulation)	5	0.76	0.28	0.78
DP (dispersible powder)	6	1.02	0.76	0.77
EC (emulsifiable concentrate)	813	1.05	0.71	0.93
EW (emulsion, oil in water)	137	1.29	1.12	1.03
FC (flowable concentrate)	59	1.63	0.81	1.33
FS (flowable concentrate for seed treatment)	184	0.91	0.59	0.81
GR (granule)	11	0.83	0.39	0.83
ME (micro-emulsion)	24	0.93	0.30	0.89
OD (oil dispersion)	9	1.86	0.60	1.85
SC (suspension concentrate)	514	1.07	1.12	0.90
SL (soluble concentrate)	508	1.16	1.68	0.94
WG (water-dispersible granule)	154	1.00	0.52	0.93
WP (wettable powder)	294	1.23	1.25	0.99
WS (water-dispersible powder for slurry seed treatment)	11	0.96	0.28	1.00

* Evaluation of the supplementary dataset compiled in 2012.

Table A: Distribution of ratio $(C_1/C_2)/(R_2/R_1)$

Distribution of ratio: $(C_2/C_1)/(R_2/R_1)$						
ICC	R2/R1	10th Pctl	25th Pctl	Median	75th Pctl	90th Pctl
0.5	2	0.3	0.6	1.0	1.7	2.9
	4	0.3	0.6	1.0	1.7	2.9
0.7	2	0.4	0.6	1.0	1.5	2.2
	4	0.4	0.6	1.0	1.6	2.3
0.9	2	0.6	0.8	1.0	1.3	1.6
	4	0.6	0.8	1.0	1.3	1.6

Figure 1: Distribution of ratio $(C_2/C_1)/(R_2/R_1)$

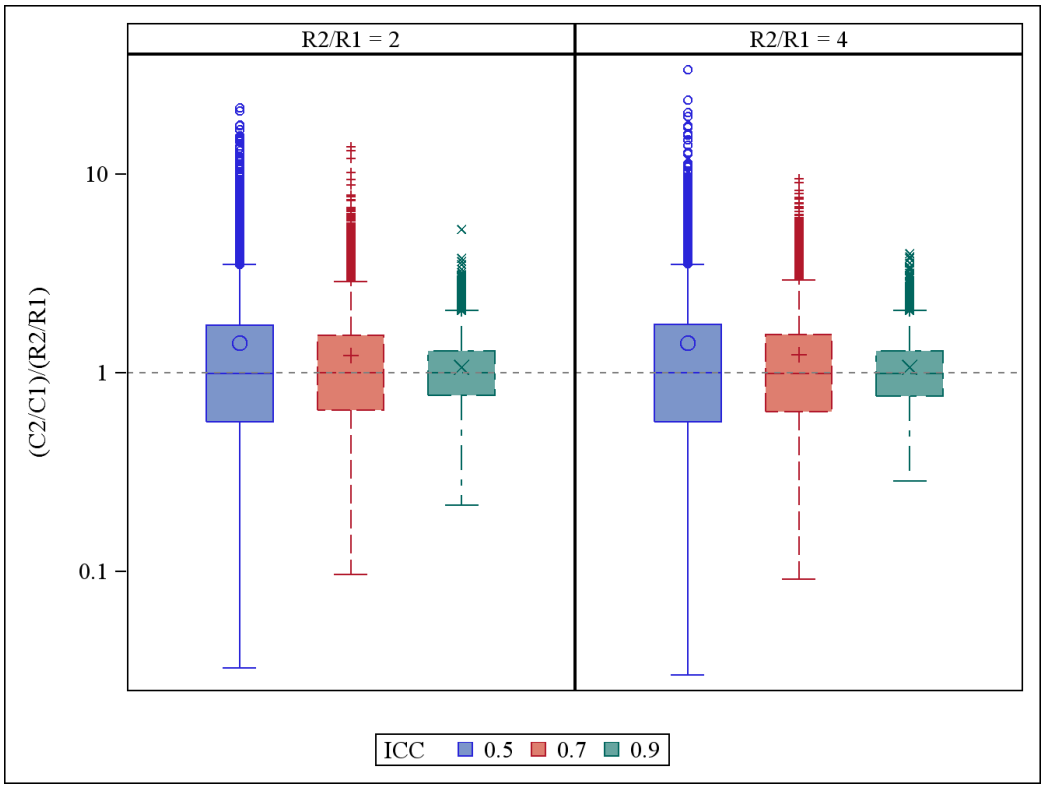


Table B: Distribution of Median of ratio $(C_2/C_1)/(R_2/R_1)$ when CV = 1

Distribution of Median of ratio $(C_2/C_1)/(R_2/R_1)$ when CV = 1											
ICC	R2/R1	Number of Trials	2.5 pctl	5 pctl	10 pctl	25 pctl	50 pctl	75 pctl	90 pctl	95 pctl	97.5 pctl
0.5	2	10	0.54	0.60	0.67	0.81	0.99	1.22	1.49	1.65	1.82
		20	0.63	0.69	0.74	0.87	1.01	1.16	1.33	1.43	1.53
		30	0.67	0.72	0.78	0.88	1.00	1.12	1.26	1.38	1.47
		50	0.75	0.78	0.83	0.90	1.00	1.10	1.20	1.26	1.32
		100	0.81	0.84	0.88	0.94	1.00	1.07	1.13	1.18	1.21
		200	0.86	0.88	0.91	0.95	1.00	1.05	1.10	1.13	1.15
		500	0.91	0.93	0.95	0.97	1.00	1.03	1.06	1.08	1.09
		1000	0.93	0.95	0.96	0.98	1.00	1.02	1.04	1.05	1.06
		1500	0.95	0.96	0.97	0.98	1.00	1.02	1.04	1.05	1.05
0.5	4	10	0.53	0.59	0.68	0.80	1.00	1.25	1.49	1.63	1.79
		20	0.64	0.71	0.76	0.86	1.01	1.17	1.35	1.44	1.57
		30	0.68	0.73	0.79	0.88	1.00	1.13	1.29	1.40	1.48
		50	0.74	0.79	0.83	0.90	1.00	1.10	1.19	1.24	1.32
		100	0.82	0.84	0.87	0.93	1.00	1.07	1.14	1.18	1.22

Distribution of Median of ratio $(C_2/C_1)/(R_2/R_1)$ when CV = 1											
ICC	R2/R1	Number of Trials	2.5 pctl	5 pctl	10 pctl	25 pctl	50 pctl	75 pctl	90 pctl	95 pctl	97.5 pctl
		200	0.87	0.89	0.92	0.96	1.00	1.05	1.10	1.13	1.16
		500	0.91	0.92	0.94	0.97	1.00	1.03	1.07	1.08	1.10
		1000	0.94	0.95	0.96	0.98	1.00	1.02	1.04	1.05	1.06
		1500	0.95	0.96	0.97	0.98	1.00	1.02	1.03	1.05	1.06
		10	0.64	0.68	0.75	0.86	1.01	1.19	1.36	1.47	1.61
		20	0.69	0.74	0.79	0.88	0.99	1.11	1.25	1.35	1.41
		30	0.75	0.78	0.82	0.90	0.99	1.11	1.20	1.26	1.30
		50	0.80	0.83	0.86	0.92	0.99	1.07	1.15	1.20	1.23
0.7	2	100	0.86	0.88	0.91	0.95	1.00	1.06	1.11	1.15	1.17
		200	0.89	0.91	0.93	0.96	1.00	1.04	1.08	1.10	1.12
		500	0.94	0.95	0.96	0.98	1.00	1.03	1.05	1.06	1.08
		1000	0.95	0.96	0.97	0.98	1.00	1.02	1.03	1.04	1.05
		1500	0.96	0.97	0.97	0.99	1.00	1.02	1.03	1.04	1.04
		10	0.63	0.67	0.73	0.85	0.99	1.17	1.36	1.49	1.61
		20	0.71	0.75	0.80	0.89	0.99	1.12	1.25	1.35	1.44
		30	0.75	0.79	0.82	0.91	1.00	1.09	1.19	1.27	1.30
		50	0.80	0.83	0.86	0.93	1.00	1.08	1.16	1.20	1.24
0.7	4	100	0.85	0.87	0.90	0.94	0.99	1.04	1.11	1.14	1.17
		200	0.89	0.91	0.93	0.96	1.00	1.04	1.07	1.10	1.12
		500	0.93	0.94	0.95	0.97	1.00	1.03	1.05	1.06	1.08
		1000	0.95	0.96	0.97	0.98	1.00	1.02	1.03	1.04	1.05
		1500	0.96	0.97	0.97	0.99	1.00	1.01	1.03	1.03	1.04
		10	0.78	0.80	0.84	0.92	1.01	1.10	1.19	1.27	1.33
		20	0.81	0.84	0.88	0.94	1.00	1.07	1.14	1.18	1.22
		30	0.86	0.88	0.90	0.95	1.00	1.06	1.11	1.14	1.17
		50	0.88	0.90	0.92	0.95	1.00	1.04	1.09	1.11	1.13
0.9	2	100	0.91	0.93	0.94	0.97	1.00	1.03	1.06	1.08	1.10
		200	0.94	0.95	0.96	0.98	1.00	1.02	1.04	1.06	1.07
		500	0.96	0.97	0.97	0.99	1.00	1.02	1.03	1.03	1.04
		1000	0.97	0.98	0.98	0.99	1.00	1.01	1.02	1.03	1.03
		1500	0.98	0.98	0.98	0.99	1.00	1.01	1.02	1.02	1.02
		10	0.77	0.80	0.84	0.91	1.01	1.11	1.21	1.27	1.33
		20	0.82	0.84	0.88	0.93	1.00	1.07	1.14	1.19	1.23
		30	0.85	0.88	0.90	0.95	1.01	1.06	1.11	1.14	1.17
0.9	4	50	0.88	0.90	0.92	0.96	1.00	1.05	1.09	1.11	1.14
		100	0.92	0.93	0.94	0.97	1.00	1.03	1.06	1.08	1.10
		200	0.94	0.95	0.96	0.98	1.00	1.02	1.04	1.05	1.06
		500	0.96	0.97	0.97	0.99	1.00	1.01	1.03	1.04	1.04

Distribution of Median of ratio $(C_2/C_1)/(R_2/R_1)$ when CV = 1											
ICC	R2/R1	Number of Trials	2.5 pctl	5 pctl	10 pctl	25 pctl	50 pctl	75 pctl	90 pctl	95 pctl	97.5 pctl
		1000	0.97	0.98	0.98	0.99	1.00	1.01	1.02	1.02	1.03
		1500	0.98	0.98	0.98	0.99	1.00	1.01	1.02	1.02	1.03

Table C: Distribution of Median of ratio $(C_2/C_1)/(R_2/R_1)$ when CV = 0.7

Expected of median of (C2/C1)/(R2/R1) when CV = 0.7											
ICC	R2/R1	Number of Trials	2.5 pctl	5 pctl	10 pctl	25 pctl	50 pctl	75 pctl	90 pctl	95 pctl	97.5 pctl
0.5	2	10	0.63	0.68	0.74	0.85	0.99	1.17	1.35	1.46	1.57
		20	0.70	0.75	0.80	0.90	1.00	1.12	1.24	1.31	1.38
		30	0.74	0.78	0.83	0.91	1.00	1.09	1.19	1.28	1.34
		50	0.80	0.83	0.86	0.92	1.00	1.07	1.15	1.19	1.23
		100	0.85	0.88	0.91	0.95	1.00	1.05	1.10	1.13	1.15
		200	0.89	0.91	0.93	0.96	1.00	1.04	1.08	1.10	1.11
		500	0.93	0.95	0.96	0.98	1.00	1.02	1.05	1.06	1.07
		1000	0.95	0.96	0.97	0.98	1.00	1.02	1.03	1.04	1.05
		1500	0.96	0.97	0.97	0.99	1.00	1.01	1.03	1.04	1.04
0.5	4	10	0.61	0.67	0.75	0.84	1.00	1.18	1.35	1.45	1.55
		20	0.71	0.77	0.81	0.89	1.01	1.12	1.25	1.32	1.41
		30	0.75	0.79	0.83	0.91	1.00	1.10	1.22	1.29	1.35
		50	0.80	0.84	0.87	0.93	1.00	1.08	1.14	1.18	1.24
		100	0.86	0.88	0.90	0.95	1.00	1.05	1.10	1.13	1.17
		200	0.90	0.92	0.94	0.97	1.00	1.04	1.08	1.10	1.12
		500	0.93	0.94	0.96	0.98	1.00	1.02	1.05	1.06	1.07
		1000	0.95	0.96	0.97	0.98	1.00	1.02	1.03	1.04	1.05
		1500	0.96	0.97	0.97	0.99	1.00	1.01	1.02	1.03	1.04
0.7	2	10	0.71	0.74	0.80	0.89	1.01	1.14	1.26	1.34	1.43
		20	0.75	0.79	0.83	0.91	1.00	1.08	1.19	1.25	1.30
		30	0.80	0.83	0.86	0.92	0.99	1.08	1.15	1.19	1.22
		50	0.85	0.87	0.89	0.94	0.99	1.06	1.11	1.15	1.17
		100	0.89	0.91	0.93	0.96	1.00	1.04	1.09	1.11	1.13
		200	0.92	0.93	0.95	0.97	1.00	1.03	1.06	1.07	1.09
		500	0.95	0.96	0.97	0.98	1.00	1.02	1.04	1.05	1.06
		1000	0.96	0.97	0.98	0.99	1.00	1.01	1.02	1.03	1.04
		1500	0.97	0.97	0.98	0.99	1.00	1.01	1.02	1.03	1.03
0.7	4	10	0.70	0.74	0.79	0.89	0.99	1.13	1.26	1.36	1.44
		20	0.77	0.80	0.84	0.91	0.99	1.09	1.18	1.26	1.32
		30	0.80	0.83	0.86	0.93	1.00	1.07	1.14	1.20	1.22

Expected of median of (C2/C1)/(R2/R1) when CV = 0.7											
ICC	R2/R1	Number of Trials	2.5 pctl	5 pctl	10 pctl	25 pctl	50 pctl	75 pctl	90 pctl	95 pctl	97.5 pctl
		50	0.85	0.87	0.89	0.94	1.00	1.06	1.12	1.15	1.18
		100	0.89	0.90	0.92	0.96	0.99	1.03	1.08	1.11	1.13
		200	0.92	0.93	0.95	0.97	1.00	1.03	1.05	1.07	1.09
		500	0.95	0.95	0.96	0.98	1.00	1.02	1.03	1.05	1.06
		1000	0.97	0.97	0.98	0.99	1.00	1.01	1.03	1.03	1.04
		1500	0.97	0.98	0.98	0.99	1.00	1.01	1.02	1.03	1.03
0.9	2	10	0.82	0.84	0.87	0.93	1.01	1.08	1.14	1.20	1.24
		20	0.85	0.87	0.91	0.95	1.00	1.06	1.10	1.13	1.16
		30	0.89	0.90	0.93	0.96	1.00	1.04	1.08	1.10	1.13
		50	0.91	0.92	0.94	0.97	1.00	1.03	1.07	1.08	1.09
		100	0.93	0.94	0.96	0.98	1.00	1.03	1.05	1.06	1.07
		200	0.95	0.96	0.97	0.98	1.00	1.02	1.03	1.04	1.05
		500	0.97	0.97	0.98	0.99	1.00	1.01	1.02	1.03	1.03
		1000	0.98	0.98	0.99	0.99	1.00	1.01	1.02	1.02	1.02
		1500	0.98	0.98	0.99	0.99	1.00	1.01	1.01	1.01	1.02
0.9	4	10	0.82	0.85	0.88	0.93	1.01	1.08	1.16	1.20	1.24
		20	0.86	0.88	0.91	0.95	1.00	1.06	1.11	1.14	1.17
		30	0.89	0.91	0.93	0.96	1.00	1.05	1.08	1.10	1.13
		50	0.91	0.92	0.94	0.97	1.00	1.03	1.07	1.08	1.10
		100	0.94	0.94	0.96	0.98	1.00	1.03	1.05	1.06	1.07
		200	0.95	0.96	0.97	0.98	1.00	1.02	1.03	1.04	1.05
		500	0.97	0.98	0.98	0.99	1.00	1.01	1.02	1.03	1.03
		1000	0.98	0.98	0.99	0.99	1.00	1.01	1.01	1.02	1.02
		1500	0.98	0.98	0.99	0.99	1.00	1.01	1.01	1.02	1.02

Table D: Distribution of Median of ratio $(C_2/C_1)/(R_2/R_1)$ when CV = 1.3

Expected of median of (C2/C1)/(R2/R1) when CV = 1.3											
ICC	R2/R1	Number of Trials	2.5 pctl	5 pctl	10 pctl	25 pctl	50 pctl	75 pctl	90 pctl	95 pctl	97.5 pctl
0.5	2	10	0.48	0.54	0.62	0.78	0.99	1.28	1.61	1.82	2.04
		20	0.57	0.64	0.70	0.85	1.01	1.20	1.41	1.54	1.67
		30	0.62	0.68	0.74	0.86	1.00	1.15	1.32	1.47	1.58
		50	0.71	0.75	0.80	0.88	1.00	1.11	1.25	1.32	1.39
		100	0.78	0.81	0.86	0.93	1.00	1.08	1.16	1.21	1.25
		200	0.83	0.86	0.89	0.94	1.00	1.06	1.13	1.16	1.18
		500	0.90	0.92	0.93	0.96	1.00	1.04	1.07	1.09	1.11
		1000	0.92	0.94	0.95	0.97	1.00	1.03	1.05	1.06	1.08
		1500	0.94	0.95	0.96	0.98	1.00	1.02	1.04	1.06	1.06
0.5	4	10	0.46	0.53	0.63	0.77	1.01	1.32	1.62	1.80	2.01
		20	0.59	0.67	0.72	0.84	1.02	1.20	1.43	1.54	1.71
		30	0.63	0.69	0.75	0.86	1.00	1.16	1.36	1.49	1.61
		50	0.70	0.76	0.80	0.89	1.00	1.12	1.24	1.30	1.40
		100	0.78	0.81	0.85	0.92	1.00	1.09	1.17	1.22	1.27
		200	0.85	0.87	0.90	0.95	1.00	1.06	1.12	1.16	1.19
		500	0.90	0.91	0.93	0.96	1.00	1.04	1.08	1.10	1.12
		1000	0.93	0.94	0.95	0.97	1.00	1.03	1.05	1.07	1.08
		1500	0.94	0.95	0.96	0.98	1.00	1.02	1.04	1.05	1.07
0.7	2	10	0.58	0.63	0.71	0.84	1.02	1.23	1.45	1.59	1.76
		20	0.64	0.69	0.75	0.86	0.99	1.14	1.31	1.43	1.51
		30	0.70	0.74	0.79	0.88	0.99	1.13	1.24	1.32	1.37
		50	0.77	0.80	0.83	0.91	0.99	1.09	1.18	1.25	1.28
		100	0.83	0.86	0.89	0.94	1.00	1.07	1.14	1.18	1.21
		200	0.87	0.89	0.92	0.95	1.00	1.05	1.09	1.12	1.14
		500	0.92	0.94	0.95	0.97	1.00	1.03	1.06	1.08	1.09
		1000	0.94	0.95	0.96	0.98	1.00	1.02	1.04	1.05	1.06
		1500	0.95	0.96	0.97	0.98	1.00	1.02	1.03	1.04	1.05
0.7	4	10	0.57	0.62	0.69	0.83	1.00	1.21	1.44	1.62	1.77
		20	0.67	0.71	0.76	0.87	0.99	1.14	1.31	1.43	1.54
		30	0.71	0.75	0.79	0.90	1.00	1.11	1.24	1.33	1.37
		50	0.77	0.80	0.84	0.91	1.00	1.10	1.19	1.24	1.29
		100	0.83	0.85	0.88	0.93	0.99	1.05	1.13	1.17	1.21
		200	0.87	0.89	0.92	0.95	1.00	1.05	1.09	1.12	1.14
		500	0.92	0.93	0.94	0.97	1.00	1.03	1.06	1.07	1.09
		1000	0.95	0.95	0.96	0.98	1.00	1.02	1.04	1.05	1.06
		1500	0.95	0.96	0.97	0.98	1.00	1.02	1.03	1.04	1.05

Expected of median of (C2/C1)/(R2/R1) when CV = 1.3											
ICC	R2/R1	Number of Trials	2.5 pctl	5 pctl	10 pctl	25 pctl	50 pctl	75 pctl	90 pctl	95 pctl	97.5 pctl
0.9	2	10	0.74	0.77	0.81	0.90	1.01	1.13	1.23	1.33	1.41
		20	0.78	0.81	0.86	0.92	1.00	1.09	1.17	1.22	1.27
		30	0.83	0.85	0.89	0.94	1.00	1.07	1.13	1.16	1.21
		50	0.86	0.88	0.90	0.95	1.00	1.05	1.11	1.13	1.15
		100	0.90	0.91	0.93	0.96	1.00	1.04	1.07	1.10	1.12
		200	0.93	0.94	0.95	0.98	1.00	1.03	1.05	1.07	1.08
		500	0.95	0.96	0.97	0.98	1.00	1.02	1.03	1.04	1.05
		1000	0.96	0.97	0.98	0.99	1.00	1.01	1.02	1.03	1.04
		1500	0.97	0.98	0.98	0.99	1.00	1.01	1.02	1.02	1.03
0.9	4	10	0.74	0.77	0.81	0.90	1.01	1.13	1.26	1.34	1.41
		20	0.79	0.81	0.86	0.92	1.00	1.09	1.17	1.24	1.28
		30	0.83	0.86	0.89	0.94	1.01	1.07	1.13	1.17	1.21
		50	0.86	0.88	0.90	0.95	1.01	1.06	1.11	1.13	1.16
		100	0.90	0.91	0.93	0.97	1.00	1.04	1.07	1.10	1.12
		200	0.93	0.94	0.95	0.97	1.00	1.02	1.05	1.06	1.07
		500	0.95	0.96	0.97	0.98	1.00	1.02	1.03	1.04	1.05
		1000	0.97	0.97	0.98	0.99	1.00	1.01	1.02	1.03	1.03
		1500	0.97	0.97	0.98	0.99	1.00	1.01	1.02	1.02	1.03

Figures 2 and 3: Distribution of Median of ratio $(C2/C1)/(R_2/R_1)$ when CV = 1

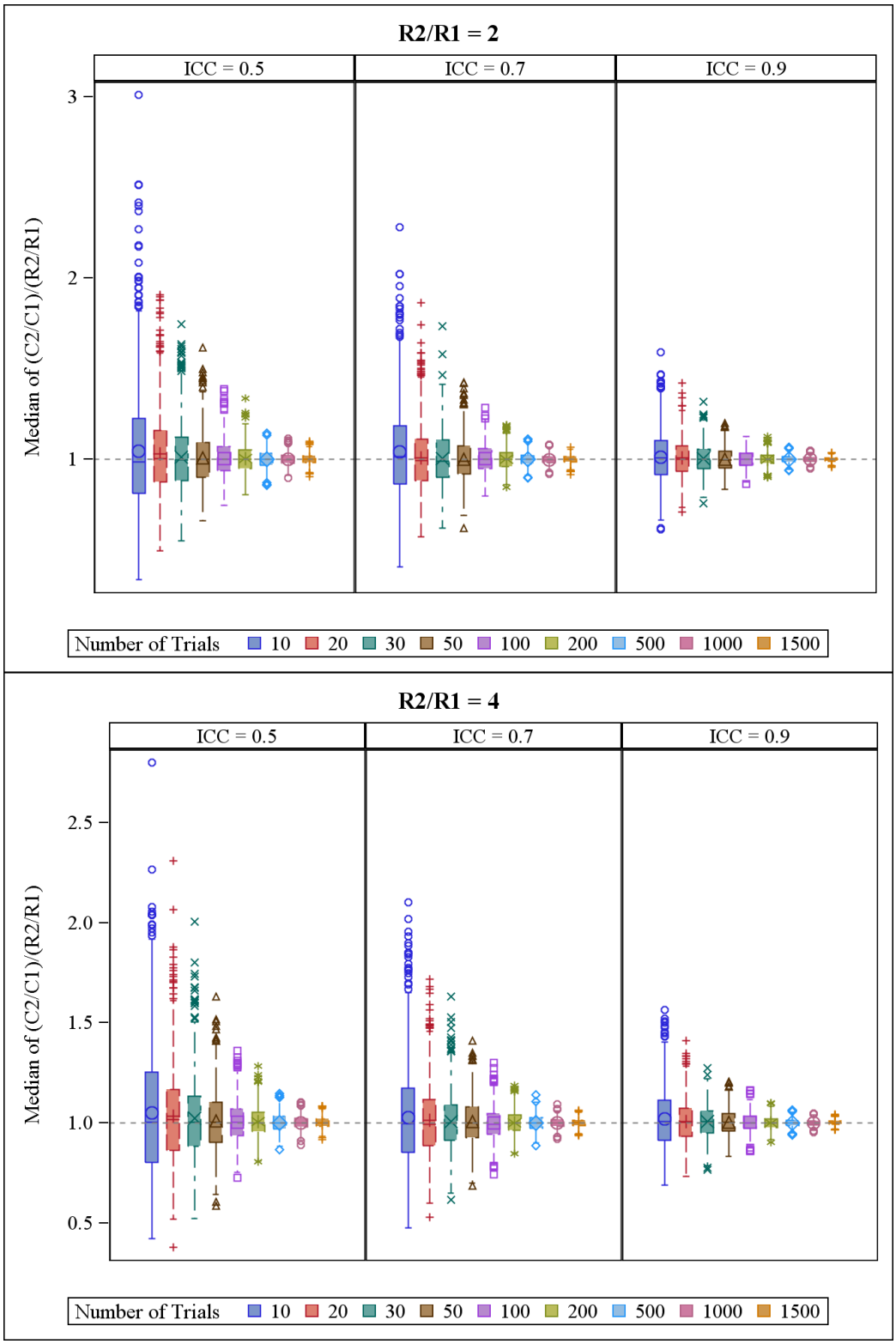
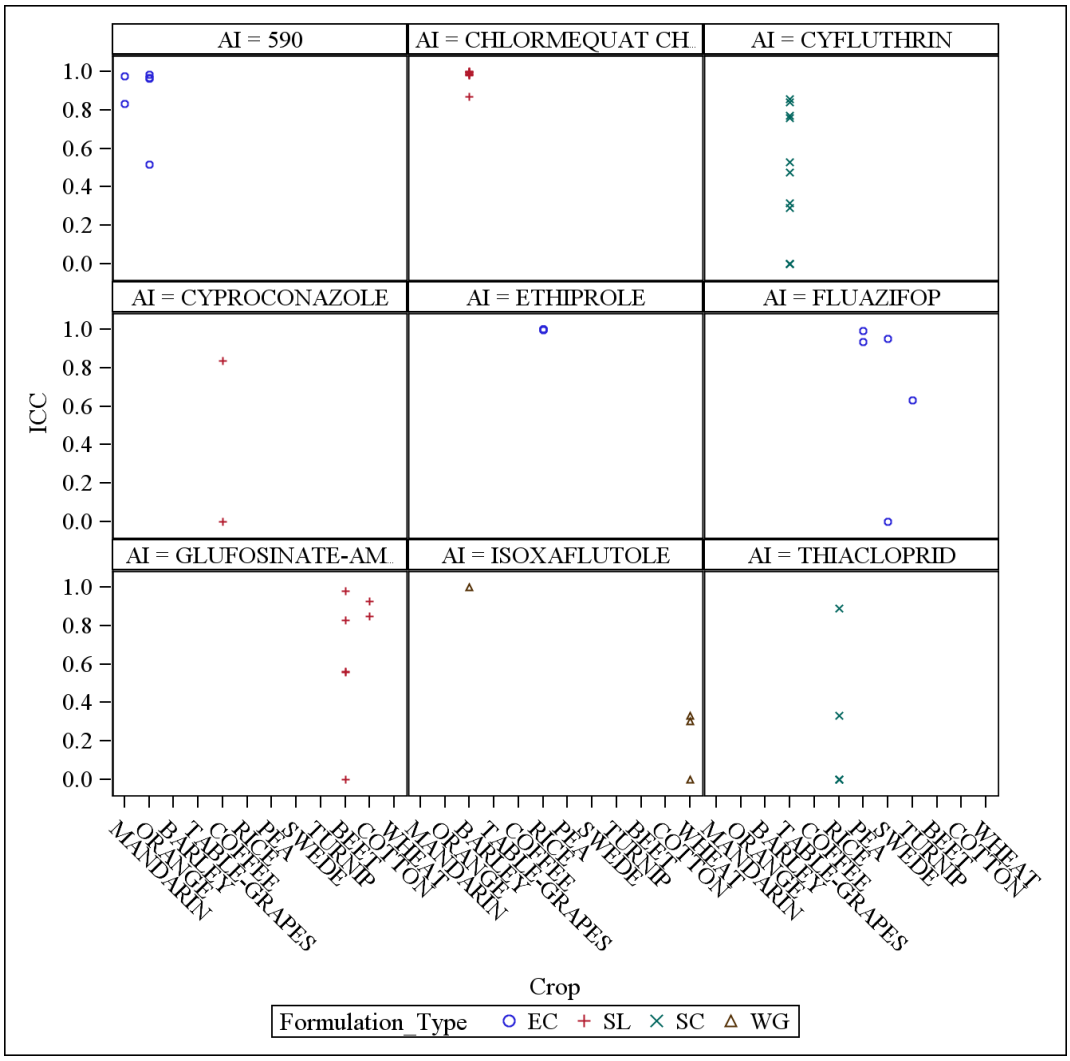


Figure 4: Scatter-plot of ICC estimated from the data that Stewart-LaPorte used in their analysis



ADDENDUM

SAS code

```
%Macro Simulation(NSim=,GM=, CV=, ListICC=, ListAR=, seed=);

* at application rate AR1:
  - mean MY1 = log(&GM)
  - stand. deviation SY = (log(1+&CV**2))**.5
  - stand. deviation b/w trial mean is = (&ICC*log(1+&CV**2))**.5
  - stand. deviation within trial   is = ((1-&ICC)*log(1+&CV**2))**.5;

* at application rate AR2 (the CV is still the same):
  - mean MY2 = log[&AR1/&AR2)*&GM]
  - stand. deviation SY = (log(1+&CV**2))**.5
  - stand. deviation b/w trial mean is = (&ICC*log(1+&CV**2))**.5
  - stand. deviation within trial   is = ((1-&ICC)*log(1+&CV**2))**.5;
%let MY1 = log(&GM);

%let nicc = 1;
%let ICC&nicc = %nrbquote(%scan(&ListICC,&nicc,%str( )));
%Do %while (&&ICC&nicc ^=);
  %let SYB&nicc = (&&ICC&nicc*log(1+&CV**2))**.5;
  %let SYW&nicc = ((1-&&ICC&nicc)*log(1+&CV**2))**.5;
  %let nicc = %eval(&nicc+1);
  %let ICC&nicc = %nrbquote(%scan(&ListICC,&nicc,%str( )));
%end;
%let nicc = %eval(&nicc - 1);

%let nar = 1;
%let AR&nar = %nrbquote(%scan(&ListAR,&nar,%str( )));
%Do %while (&&AR&nar ^=);
  %let nar = %eval(&nar + 1);
  %let AR&nar = %bquote(%scan(&ListAR,&nar,%str( )));
%end;
%let nar = %eval(&nar - 1);

Data Simulation; set _NULL_; run;
Data Simulation;
  Sim = &NSim;
  AR1 = &AR1;
  %do r = 2 %to &nar;
      AR2 = &&AR&r;
      %do i = 1 %to &nicc;
          ICC = &&ICC&i;
          do pair = 1 to &NSim;
            M1 = &MY1 + &&SYB&i*rannor(&seed);
            Rand1 = &&SYW&i*rannor(&seed);
            M2 = log(&&AR&r/&AR1) + M1;
            Rand2 = &&SYW&i*rannor(&seed);
            output;
          end;
```

```
      %end;
  %end;
run;
Data Simulation;
  set Simulation;
  Res1= exp(M1+Rand1);
  Res2= exp(M2+Rand2);
  Ratio=Res2/Res1;
  Ratio1 = Ratio/AR2;
  label AR2 = "R2/R1" Ratio = "C2/C1" Ratio1="(C2/C1)/(R2/R1)";
run;

title;
title1 "Distribution of [residue ratio/a.rate ratio] (Per &NSim simulations)";
Proc means data = Simulation P10 P25 Median P75 P90 maxdec=1 nonobs;
  class ICC AR2;
  var Ratio1;
run;

Proc SGPANEL data = Simulation;
  PANELBY AR2 /columns=%eval(&nar-1);
  VBOX ratio1/group = ICC;
  rowaxis type = log label = "(C2/C1)/(R2/R1)" logbase = 10 logstyle = logexpand;
  refline 1/lineattrs =(pattern = 2)  ;
run;

%Mend;

%Simulation(NSim=10000, GM=1, CV=1, ListICC= 0.5 0.7 0.9, ListAR= 1 2 4, seed=25451);



%Macro Simulation1(NSim=,GM=, CV=, ListICC=, ListAR=, ntrial=, seed=);

* at application rate AR1:
  - mean MY1 = log(&GM)
  - stand. deviation SY = (log(1+&CV**2))**.5
  - stand. deviation b/w trial mean is = (&ICC*log(1+&CV**2))**.5
  - stand. deviation within trial   is = ((1-&ICC)*log(1+&CV**2))**.5;

* at application rate AR2 (the CV is still the same):
  - mean MY2 = log[&AR1/&AR2)*&GM]
  - stand. deviation SY = (log(1+&CV**2))**.5
  - stand. deviation b/w trial mean is = (&ICC*log(1+&CV**2))**.5
  - stand. deviation within trial   is = ((1-&ICC)*log(1+&CV**2))**.5;
%let MY1 = log(&GM);

%let nicc = 1;
%let ICC&nicc = %nrbquote(%scan(&ListICC,&nicc,%str( )));
%Do %while (&&ICC&nicc ^=);
  %let SYB&nicc = (&&ICC&nicc*log(1+&CV**2))**.5;
```

```
  %let SYW&nicc = ((1-&&ICC&nicc)*log(1+&CV**2))**.5;
  %let nicc = %eval(&nicc+1);
  %let ICC&nicc = %nrbquote(%scan(&ListICC,&nicc,%str( )));
%end;
%let nicc = %eval(&nicc - 1);

%let nar = 1;
%let AR&nar = %nrbquote(%scan(&ListAR,&nar,%str( )));
%Do %while (&&AR&nar ^=);
  %let nar = %eval(&nar + 1);
  %let AR&nar = %bquote(%scan(&ListAR,&nar,%str( )));
%end;
%let nar = %eval(&nar - 1);

%let NN = 1;
%let ntrial&NN = %nrbquote(%scan(&ntrial,&NN,%str( )));
%Do %while (&&ntrial&NN ^=);
  %let NN = %eval(&NN + 1);
  %let ntrial&NN = %bquote(%scan(&ntrial,&NN,%str( )));
%end;
%let NN = %eval(&NN - 1);


Data Simulation; set _NULL_; run;
Data Simulation;
  Sim = &NSim;
  AR1 = &AR1;
  %do r = 2 %to &nar;
      AR2 = &&AR&r;
      %do i = 1 %to &nicc;
          ICC = &&ICC&i;
          %do N = 1 %to &NN;
            do Sim = 1 to &NSim;
               NTrial = &&ntrial&N;
               do pair = 1 to &&ntrial&N;
                  M1 = &MY1 + &&SYB&i*rannor(&seed);
                  Rand1 = &&SYW&i*rannor(&seed);
                  M2 = log(&&AR&r/&AR1) + M1;
                  Rand2 = &&SYW&i*rannor(&seed);
                  output;
               end; *pair;
            end; *Sim;
          %end; *N;;
      %end; *i;
  %end; *r;
run;
Data Simulation;
  set Simulation;
  Res1= exp(M1+Rand1);
  Res2= exp(M2+Rand2);
  Ratio=Res2/Res1;
```

```
  Ratio1 = Ratio/AR2;
  label AR2 = "R2/R1" Ratio = "C2/C1" Ratio1="(C2/C1)/(R2/R1)";
run;

Proc means data = Simulation N median;
  class ICC AR2 Sim NTrial;
  var Ratio1;
  ods output Summary=Summary1;
run;
Data Summary1;
  set summary1;
  label Ratio1_Median="Median of (C2/C1)/(R2/R1)" NTrial = "Number of Trials";
run;
Proc Univariate data = Summary1 noprint;
  by ICC;
  class AR2 NTrial;
  var Ratio1_Median;
  output out = Pctls1 pctlpts=2.5 5 10 25 50 75 90 95 97.5 PCTLPRE=median;
run;

title1 "Distribution of [(C2/C1)/(R2/R1)] (Per &NSim simulations)";
Proc Print data = Pctls1 noobs label;
  var ICC AR2 NTrial median2_5 median5 median10 median25 median50 median75 median90
median95 median97_5;
  format median2_5 median5 median10 median25 median50 median75 median90 median95
median97_5 6.2;
  label median2_5= "2.5 pctl" median5= "5 pctl" median10= "10 pctl" median25= "25 pctl"
        median50= "50 pctl" median75= "75 pctl" median90= "90 pctl" median95= "95 pctl"
median97_5= "97.5 pctl";
run;

title;
%do i = 1 %to %eval(&nar-1);
  %let j = %eval(&i+1);
  title "R2/R1 = &&AR&j";
  Proc SGPANEL data = Summary1;
       where AR2 = &&AR&j;
       PANELBY ICC /columns=&nicc;
       VBOX Ratio1_Median/group = NTrial;
       refline 1/lineattrs =(pattern = 2)  ;
  run;
%end;
ods rtf close;
%Mend;

%Simulation1(NSim=1000, GM=1, CV=1, ListICC= 0.5 0.7 0.9,
            ListAR= 1 2 4,
            ntrial= 10 20 30 50 100 200 500 1000 1500 ,
            seed=25451);
```

APPENDIX 3

Linear Mixed Effects Model Analysis – A Statistical Method to Evaluate the Proportionality Principle: Residues vs. Application Rate

[Prepared by US EPA, Office of Pesticide Programs, 20 November 2012]

Contents

Introduction

Maximum residue limits (MRLs) of pesticide residue in food commodity are needed to regulate pesticide use and are calculated using residue data collected from supervised field trials using good agricultural practice (GAP). In order to generate robust MRLs, it is always preferable to have residue data from a larger rather than a smaller number of field trials. A larger number of field trials produce more reliable MRLs that more nearly – and reliably- approximate the high end of the residue distribution. In order to obtain a large number of field trials for use in estimating tolerances, current practice under certain conditions permits using residues from field trials which are ±25% of the target application rate. The residues from the ±25% field trials, however, are not necessarily routinely adjusted upward or downward for the exaggerated application rate, and this necessarily leads to a biased estimate of the MRL. Allowing such deviating application rates without adjustment of the resulting residues typically relies on the fact that actual field practices may have this much uncertainty in the rate.

The desire to appropriately incorporate residues from a wider range of application rates (more than ±25%) in field trials into the MRLs calculation has led to a proposal of the proportionality principle which states that, within limits, residues resulting from field trials conducted at exaggerated rates can be adjusted proportionally to the a 1x application. This proposal has led to the need to evaluate the proportionality principle in order for it to see wider, more acceptable use.

MacLachlan and Hamilton (2011) were one of the first groups to investigate the proportionality concept by regressing $ln(C2) = a + b \times ln(C1)$, where (C1, C2) are residues from side-by-side field trials at application rates (R1, R2) and R2>R1. For their test case, they used the side-by-side residue trial data reported by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR). In order the proportionality concept to be valid as applied here, the slope *b* must be equal 1 and the intercept *a* must be equal to $ln(R_2/R_1)$. MacLachlan and Hamilton also looked into the ratios $(C_2/C_1)/(R_2/R_1)$ which – if the proportionality is valid – would be equal to 1. Stewart and LaPorte later followed MacLachlan and Hamilton's approach using additional side-by-side crop residue data provided by the Chinese and Japanese governments as well as data provided by BASF, Bayer CropScience, Dow AgroSciences, DuPont, and Syngenta to evaluate the concept of proportionality (*Relationship between Application Rate of Pesticides and Their Residue Levels in Treated Commodities: Further Investigation of the Proportionality Principle,* 2012).

The approach used by MacLachlan and Hamilton and later followed by Stewart and LaPorte has been reviewed and received a number of comments. One specific comment is that the authors have not provided any formal statistical testing of the intercept and slope (i.e., the confidence interval for the estimates of intercept *a* and slope *b*); and repeated measures (resulting from multiple application rates) were not addressed, etc. These comments are also applicable to their investigation into the $(C_2/C_1)/(R_2/R_1)$ *ratio*.

While there is nothing intrinsically incorrect in the approach proposed by MacLachlan and Hamilton and later followed by Steward and LaPorte, criticism centered around the inability of the method to produce confidence intervals around their ratio estimates. Recognizing the issue, US EPA/OPP perform what we believed to be a more appropriate statistical analysis, using the same data that Stewart-LaPorte had used in their analysis to examine proportionality. This is presented below. The current analysis will be able to incorporate residues of all application rates and all replicates into a single analysis while correctly and appropriately handling the correlation between these data. Furthermore, we believe that it will be easy to evaluate the proportionality concept by examining only one single statistic, slope *b* (described in next section) and its confidence interval and not require the simultaneous evaluation of a slope and an intercept as in the Maclachlan and Hamilton approach used by Stewart and LaPorte.

Rationale of fundamental statistical model for proportionality principle

Assume residue of a crop follows a lognormal distribution. Let *y* be the residue of a trial with application rate *x*. Below is the linear regression equation of ln(*y*) vs. ln(*x*):

$$\ln(y) = a + b * \ln(x), \qquad (1)$$

where a is the intercept and b is the slope. Exponentiate both sides of equation (1), we have:

$$e^{\ln(y)} = e^{a+b*\ln(x)}$$

$$y = e^{a} e^{b*\ln(x)}$$

$$y = e^{a} * x^{b} \qquad (2)$$

If $b = 1$, equation (2) becomes:

$$y = e^{a} * x \qquad (3)$$

From equation (3), we see that *y* has a proportional relationship with *x*.

Therefore, a proportionality relationship between residues vs. application rate is true if the slope "*b*" = 1 in equation (1), and it does not depend on the intercept "*a*" since that is a constant.

An analysis showing slope *b* in equation (1) is not different from one will lead to a conclusion that the proportionality concept is valid.

Statistical Methods

To examine the relationship between residues and application rate, we only used residue data from side-by-side field trials. The residue data consisted of multiple crops, and each crop might have multiple trials from different countries. Each trial had residues resulting from different application rates, and might have residues at different PHIs as well as multiple replicates (multiple samples from the same trial at the same application rate and PHI). Since different pesticides, different application types, different formulation types, different crops, different trials may have used different application rates, we normalized the application rates of each trials by dividing the application rates (within each trials) by the lowest application rate of the trial. There were many different active ingredients (pesticides), different formulations, and different application types (seed treatment, soil, foliar, etc.) included in the data.

By the nature of random effects, different trials might have different intercepts *a* and different slopes *b*. Furthermore, residues from the same trial are likely correlated. Recognizing these characteristics, it is appropriate to use mixed-effects models to examine the relationship as in equation (1) between residues and application rate. The mixed-effects models allow each trial to have its own intercept and slope and correctly take into account the correlation of the data[3]. The type of pesticide formulation was included into the models as a covariate. Country, Crop, Active Ingredient (AI), and Trial were categorized as a set of

[3] Given the short time available for the analysis, the model that assumes all trials have different intercepts but the same common slope has not been examined. However, the use of a common slope model (which might be suggested if a likelihood ratio test showed no statistically improvement over using a random slope model) does not mean that all trials have the same slope. Regardless of whether the common slope model and random slope model are statistically different, the estimated common slope and the estimated average slope are theoretically equivalent (only the confidence interval of estimated common slope is narrower than that of estimated average slope, which is already narrow due to large number of trials in the analysis).

random effects. Residues at different application rates of the same trial and replicates (residues of the same trial, same application rate, and same PHI) were considered as repeated measures (longitudinal data).

Since we focus on the relationship between residues vs. application rate at the same PHI of side-by-side trials (i.e., the importance of relationship *"residue vs. application rate"* at each PHI for trial with multiple PHIs is the same as for the PHI of trials with single PHI), we treated each PHI from trials with multiple PHIs as a different trial with single PHI[4].

Data handling

To reduce the number of categories of application types that had only small number of records, additional regrouping was done as following:

- Dip Commodity
- Directed Commodity (a directed post-harvest application)
- Seed treatment (including: seed treatment, seed treatment commodity, and seed treatment dry)
- Post harvest (including: foliar and post harvest, post harvest, and post harvest dip)
- Soil (including: soil, broadcast soil, soil (1^{st}):foliar, and soil/foliar)
- Foliar (including: foliar, broadcast foliar, and foliar (post-emergence))

Results

Separate analyses were done for the data of each application type: dip commodity (6 trials), directed commodity (19 trials), postharvest (17 trials), seed treatment (36 trials), soil application (97 trials), and foliar application (751 trials) which included rice (161 trials), maize (56 trials). Based on the distribution of number of trials (i.e., records) per crop, 7 separate analyses were performed for foliar application as follow: 1) rice crop; 2) maize crop; 3) all crops that had more than 10 trials (excluding rice and maze); 4) all crops that had more than 10 trials that used the same spray volume within each trial; 5) all crops that had less than 10 trials; 6) all crops that had less than 10 trials that had same spray volume within each trial; and 7) all foliar trials that used different spray volumes within each trial. The reason behind three of the analyses – 4), 6), and 7) – was that about 11% of the foliar trials used different spray volumes (as opposed on different spray concentrations) to achieve different application rates. These three additional analyses would allow us to examine whether the multiple-spray-volume practice altered the *"residue vs. rate"* relationship (e.g., through foliar run-off)

- Table 1 presents the data structure that was used in the analyses.
- Table 2 summarizes the results of slope analyses of different application types.

[4] One may let the PHIs nest into the trial; however, by doing that, the importance of *"residue vs. rate"* relationship at each PHI from multiple-PHI trials is less than the relationship at the PHI of single PHI trials, which is not what was wanted. Furthermore, by treating PHIs as different trials, we could reduce one nesting level in the model and avoid computational difficulties and to allow us to check whether the relationship held at different PHIs.

- Tables 3 – 9, 10a, 10b, 11a, 11b, and 12 present the results of individual analysis by application type.

- Tables 13 – 16 present the frequency of trials by formulation type, country, AI, and crops.

As shown in Table 2, only rice and maize, which were the two major crops in the foliar application trials, had slopes that were not significantly different from 1. The slope for rice was 0.98 (95% CI = 0.89, 1.07); and the slope for maize was 0.80 (95% CI = 0.59, 1.01). Slopes of 1 indicate proportionality: that is, an increase of a given percentage in the application rates results in that same percentage increase in the residue levels (e.g., doubling the application rate would double the residue).

The estimated slopes of other application types and crops (various combinations of crops) were significantly less than 1 (i.e. 95% CIs did not include 1) (see Table 2). For example, the slopes for "dip commodity" (n=6), directed commodity (n=19), postharvest treatment (n=17), and seed treatment (n=36) applications ranged from between 0.6 and 0.8. In other words, if there were a 100% increase in the application rates for these applications (a doubling), it would result only about 50% to 75% increase in the residue (percent increase = $2^b - 1$). One the other hand, the estimated slope for soil application was 0.88 and for foliar application (excluding rice and maize) were between 0.8 and 0.88. This means a 100% increase (i.e., doubling) in the application rate for soil application would result in an increase in the residue of 84% and for foliar treatment (excluding rice and maize) somewhere between 74% and 84%.

In addition to presenting the slopes, Table 2 also presents the impact of applying the proportionality principle to a 1.25x rate, by contrasting this with the residues that would be assumed with no adjustment (current practice) to the residues. By applying the proportionality principle to adjust the residues from 1.25X to 1X for foliar application, the estimated residues are generally under-estimated by less than 5% (i.e., percent over/under estimated = $\frac{x^b - x}{x}$, where x is the factor of application rate). However, without any adjustment, the residues at 1.25X are generally 20-25% higher than the residues at 1X for foliar application. Similarly, the resulted residues are over-estimated by less than 5% if using proportionality principle to convert residues at 0.75X to 1X for foliar application. Without adjustment, the residues at 0.75X are generally about 20-25% less than residues at 1X (not shown in Table 2).

In some case, the exaggerated application rate was achieved by applying a greater volume of liquid, for example, as opposed to the same volume with a higher concentration. To the extent that the extra volume may run-off or otherwise be unavailable to the plant, this may affect the determination of proportionality. Thus, we also investigated the effect of whether spraying a different volume to achieve different application rates (as opposed to the same volume with a higher concentration) would alter the relationship the residue vs. application rate. The analyses were conducted on those trials that modified application amounts by modifying either the volume or concentration vs. those conducted which modified the amount of pesticide applied by only changing the concentration generally produced similar slopes (0.8 vs. 0.8 for crops that had less than 10 trials; and 0.87 vs. 0.88 for crops with more than 50 trials). The estimated slope of trials with different spray volume = 0.82 was in line with that of analysis including all trials. Thus, we conclude that the changing the amount of pesticide applied by either modifying the concentration or modifying the spray volume was not, in these trials, a significant factor.

The analysis here chiefly uses slopes to evaluate the validity of the proportionality assumption, with a slope of 1 indicating that residues scale proportionately to application rate. The paper by MacLachlan and Hamilton (Pest Manag Sci 2011; 67:609-615) – and by extension the work by Stewart and Laporte – use a ratio (or, better described, a ratio of ratios) to describe this relationship, with a ratio of 1 (and an intercept equal to the log of the ration of application rates) indicating proportionality. One can convert the slopes that we estimated in Table 2 into ratios $\frac{C_2/C_1}{R_2/R_1}$ that can be compared to the Stewart/Laporte analyses by

using the following formula $\frac{C_2/C_1}{R_2/R_1} = \frac{(R_2/R_1)^b}{R_2/R_1}$. As we can see, $\frac{C_2/C_1}{R_2/R_1}$ is a function of $\mathbf{R_2/R_1}$, and it is not a constant when b ≠1. In Table 2, we calculated the estimated ratio $\frac{C_2/C_1}{R_2/R_1}$ for $\mathbf{R_2/R_1}$ = 1.5 and 2. Since majority of data in Stewart-Laporte analysis had a ratio $\mathbf{R_2/R_1}$=2, the estimated ratios computed from slope of mixed-effects models for a ratio $\mathbf{R_2/R_1}$=2 compare well with the ratios that calculated by Stewart-LaPorte. For example, the ratios computed from slope vs. Stewart-LaPorte ratios are 0.92 vs. 0.90 for soil treatment; 0.87 vs. 0.83 for seed treatment; and 0.80 vs. 0.80 for post-harvest, and 0.87 to 0.99 vs. 0.93 for foliar. The similarity of these results is encouraging, and suggests that the two methods – the hierarchical (multilevel) mixed model used here and the ratio method used by Stewart/Laporte from the work of MacLachlan and Hamilton produce similar conclusions with respect to the relationship between application rate and resulting residues. Specifically: that while strict proportionality which would be demonstrated by a ratio of 1 is ruled, out, the observed values for the soil and foliar application methods are reasonable close to 1 suggesting that there is reasonable near to a proportionate relationship between application rate and resulting residues. For other application types the deviations from strict proportionality were larger. Regression diagnostics were performed to detect any systematic difference in the relationship between residue and application rate among the formulation types. There was no clear evidence indicating that any of available formulation types would have the relationship different from others. We do not here present the resulting tables from the diagnostics given a short time frame for this work, but it appears that formulation type is not a factor that affects proportionality. We have not checked whether any systematic differences were caused by different PHIs.

Conclusion

Our analysis found a significant relationship between the *residue vs. application rate*. As the application rate increases, the resulting residue increases. Foliar applications to rice had an exact linear proportional relationship between *application rate and residue* (100% increases in application rate would increase 100% in residue), while other crops with foliar application still had a very significant relationship with slopes between 0.8 and 0.88 (the estimated residues from 2X to 1X are under-estimated about 10% if using the proportionality principle). Similarly, soil applications and seed treatments also had a A slope of 0.88 and 0.79, respectively. This linear effects model analysis confirms the bias noted in the simulations (appendix 2) and in the second review of residue data.

There appears to be less evidence for a proportionate relationship between *application rate and residue* for other application types. Although the numbers of trials was comparatively smaller and thus estimates are less precise, a 100% increase in application rate would result in 60% to 80% increase in the residue for dip commodity, directed commodity, and post-harvest applications.

While the slope is not exactly 1, it is reasonable close to 1. Our calculations suggest that by assuming proportionality when it is not precisely true will result in many cases in only minor over-or under-estimations of residues which are typically less than the maximal errors introduced by using the ±25% rule for combining field trials. We suggest that the closeness of the factor to 1 suggests further investigation for its potential utility (best use) in adjusting residues from higher to lower (or vice versa) application rates than the proposed range and its wider adoption for uses currently excluded.

Finally, we note that the estimated ratios calculated from the slope derived from our mixed-model analysis closely agrees with the ratios calculated from the raw data (by Stewart-LaPorte).

Table 1: structure of the data in the analysis

Data structure	Quantity
Row	5355
Trial	926
Crop	92
Active Ingredient	80
Formulation Type	14
Application Type	6
Country	36
PHIs per trial	1 to 7
Replicates per PHI	1 to 4

Table 2: summary results of analyses

Application Type	# Rows	# Trials	Slope (95% CI)	$\frac{C_2/C_1}{R_2/R_1}$ (95% CI)		Stewart - LaPorte $\frac{C_2/C_1}{R_2/R_1}$	% under/over estimated residue (*) using slope = 1		
				R_2/R_1 = 1.5	R_2/R_1 = 2		R_2/R_1 = 1.25 (**) adjusted vs. non-adjusted	R_2/R_1 = 0.5 (***)	R_2/R_1 = 2 (***)
DIP COMMODITY	66	6	0.63 (0.41, 0.86)	0.86 (0.79, 0.94)	0.77 (0.66, 0.91)	NA	-7.9% vs. 15.1%	29.2%	-22.6%
DIRECTED COMMODITY	223	19	0.73 (0.59, 0.87)	0.90 (0.85, 0.95)	0.83 (0.75, 0.92)	NA	-5.8% vs. 17.7%	20.6%	-17.1%
POSTHARVEST	105	17	0.67 (0.47, 0.88)	0.88 (0.81, 0.95)	0.80 (0.69, 0.92)	0.80	-7.1% vs. 16.1%	25.7	-20.4%
SEED TREATMENT	283	36	0.79 (0.66, 0.93)	0.92 (0.87, 0.97)	0.87 (0.79, 0.95)	0.83	-4.6% vs. 19.3%	15.7%	-13.5%
SOIL TREATMENT	618	97	0.88 (0.78, 0.98)	0.95 (0.92, 0.99)	0.92 (0.86, 0.99)	0.90	-2.6% vs. 21%	8.7%	-8%
FOLIAR	4060	751				0.93			
Rice	1286	161	0.98 (0.89, 1.07)	0.99 (0.96, 1.03)	0.99 (0.92, 1.05)		-0.4% vs. 24.4%	1.4%	-1.4%
Maize	360	56	0.80 (0.59, 1.01)	0.92 (0.85, 1.00)	0.87 (0.75, 1.00)		-4.4% vs. 19.5%	14.9%	-12.9%
Crops, 10 < # trials<50	1307	371	0.80 (0.73, 0.86)	0.92 (0.90, 0.94)	0.87 (0.83, 0.91)		-4.4% vs. 19.5%	14.9%	-12.9%
Crops, 10 < # trials<50 (same spray volume)			0.80 (0.73, 0.87)	0.92 (0.90, 0.95)	0.87 (0.83, 0.91)		-4.4% vs. 19.5%	14.9%	-12.9%
Crops, # trials ≤ 10	1107	163	0.87 (0.80, 0.93)	0.95 (0.92, 0.97)	0.91 (0.87, 0.95)		-2.9% vs. 21.4%	9.4%	-8.6%
Crops, # trials ≤ 10 (same spray volume)			0.88 (0.81, 0.94)	0.95 (0.93, 0.98)	0.92 (0.88, 0.96)		-2.6% vs. 21.7%	8.7%	-8.0%
Multi Spray Volume	497	82	0.82 (0.70, 0.94)	0.93 (0.88, 0.98)	0.88 (0.81, 0.96)		-3.9% vs. 20.1%	13.3%	-11.7%

Total	5355	926							

(*): % under/over estimated using slope=1 is $\frac{x^b - x}{x}$.

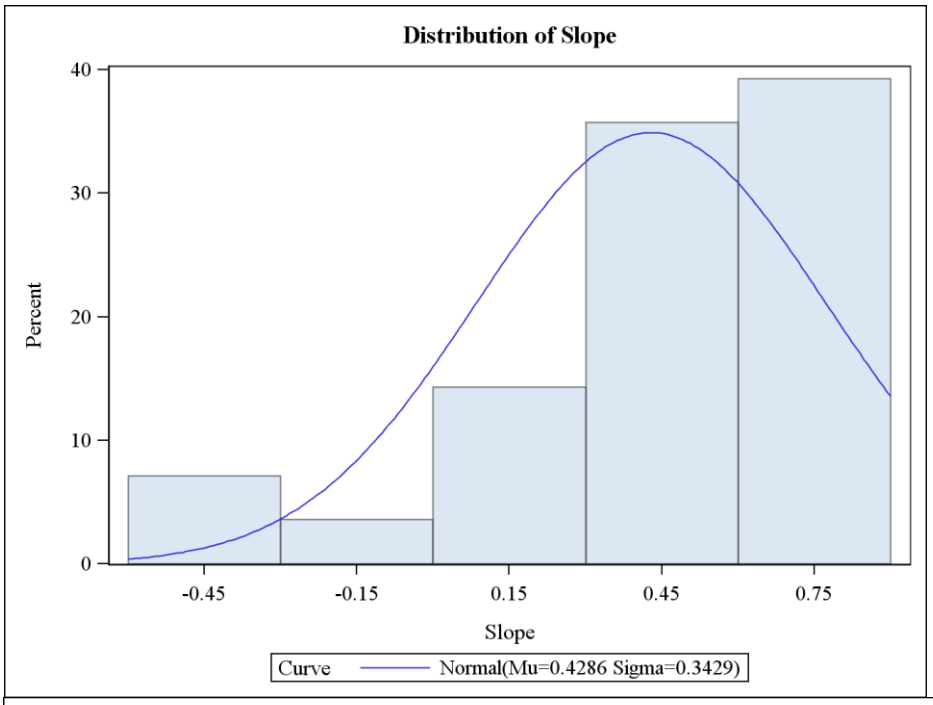
(**): The percent on the left is the percent of under/over-estimated in the residue if proportionality principle is used. The percent on the right is the percent of over/under valued if no adjustment has been made to the residue when lumping a residue at 1.25X back to 1X.

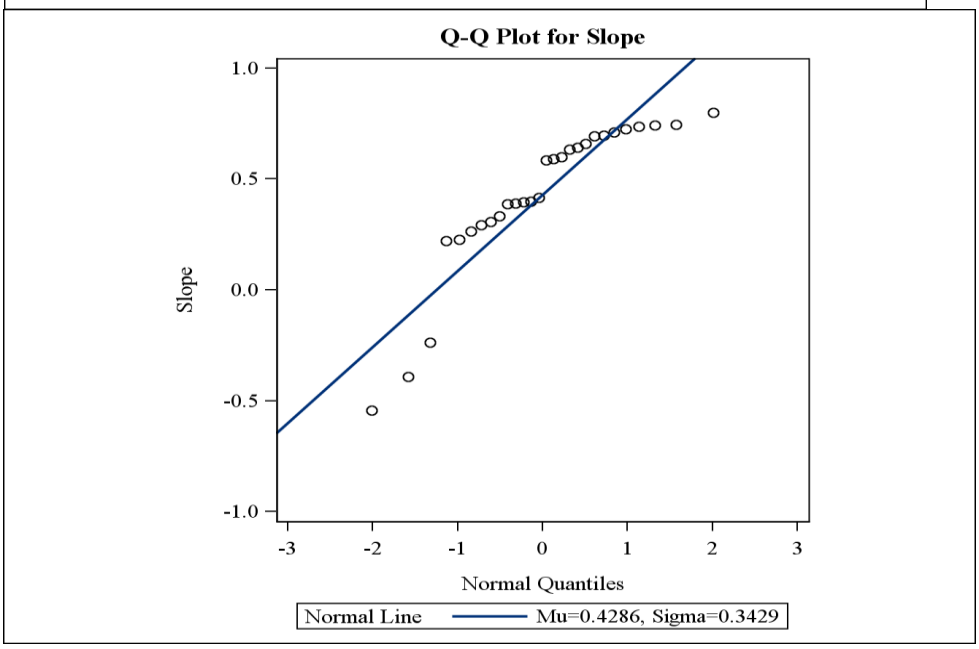
(***): percent of over/under-estimated in the residues when using proportionality principle to adjust residues at 0.5X or 2X to the application rate 1X.

1. Dip Commodity

Table 3: Slope analysis for crops with application type = dip commodity

Solution for Fixed Effects					
Effect	Estimate	Standard Error	Pr > |t|	Lower	Upper
log(rate)	0.6317	0.1095	<.0001	0.4070	0.8565

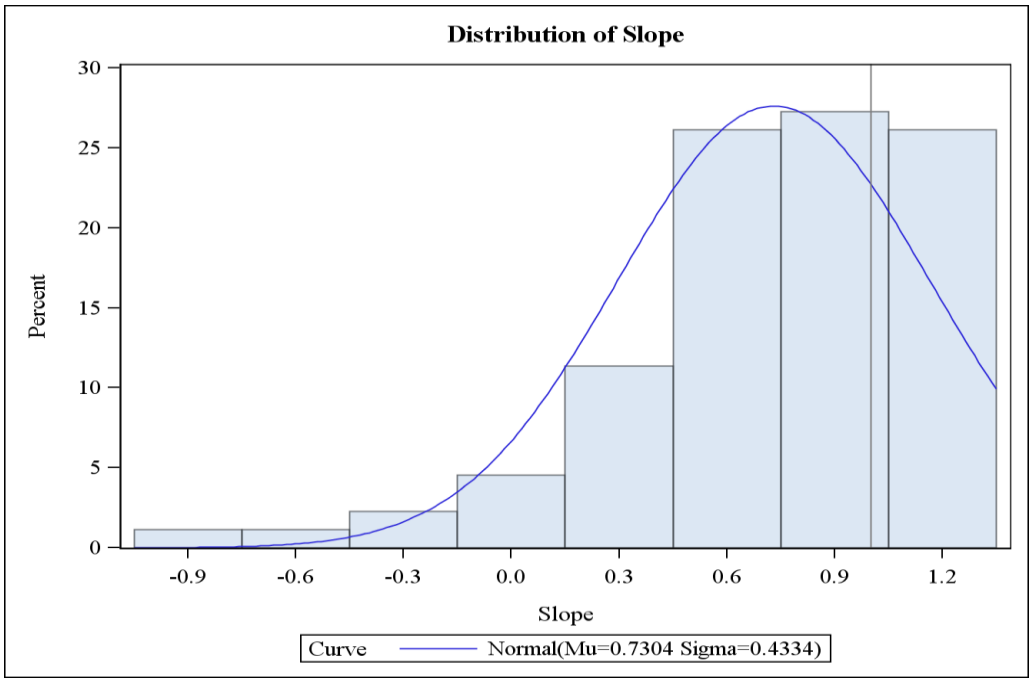


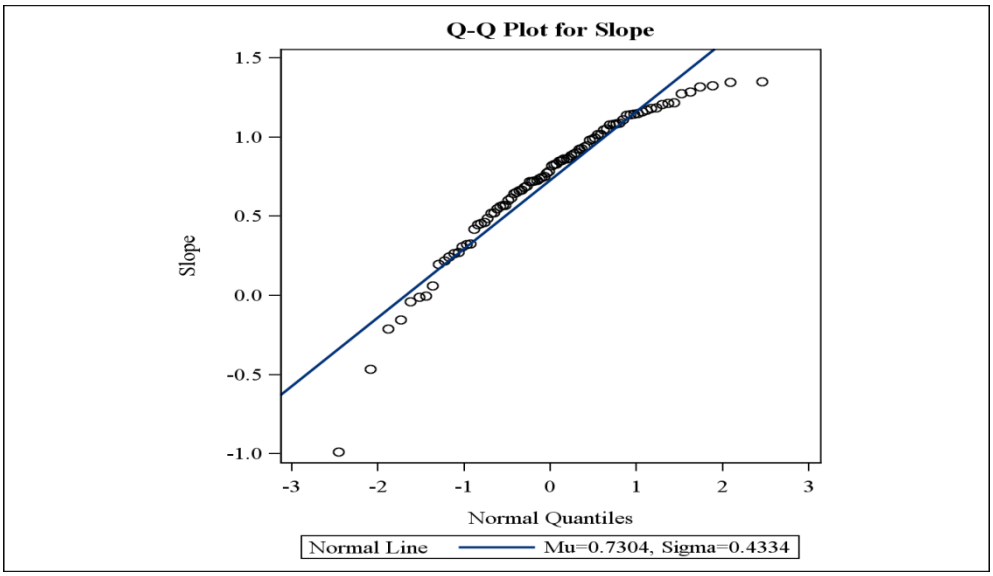


2. Directed Commodity

Table 4: Slope analysis for crops with application type = directed commodity

Solution for Fixed Effects						
Effect	Formulation	Estimate	Standard Error	Pr > |t|	Lower	Upper
Formulation Type	EC	-2.1880	0.2918	<.0001	-2.7751	-1.6009
	WP	-1.3688	0.6441	0.0389	-2.6645	-0.0731
log(rate)		0.7304	0.07149	<.0001	0.5883	0.8725

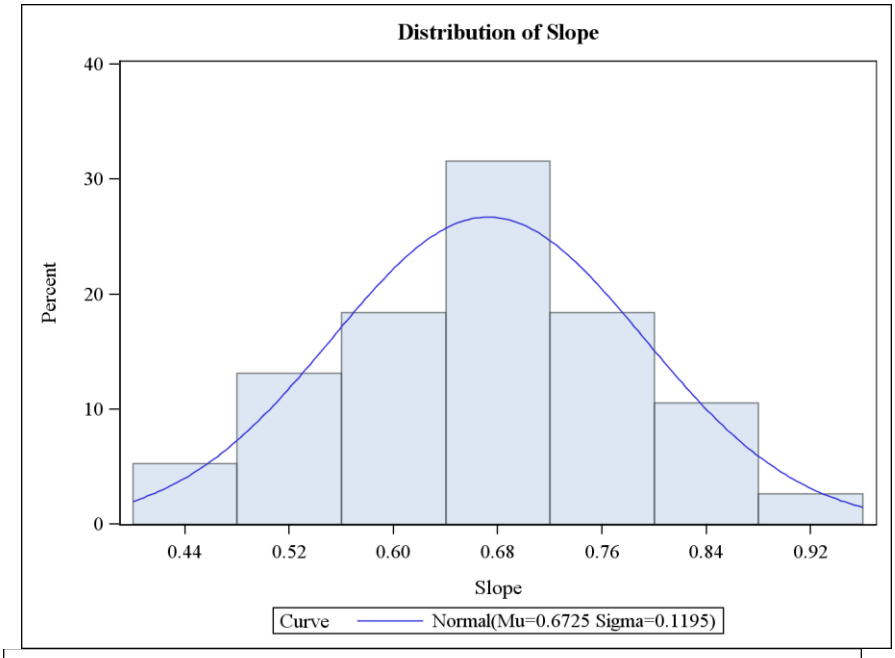


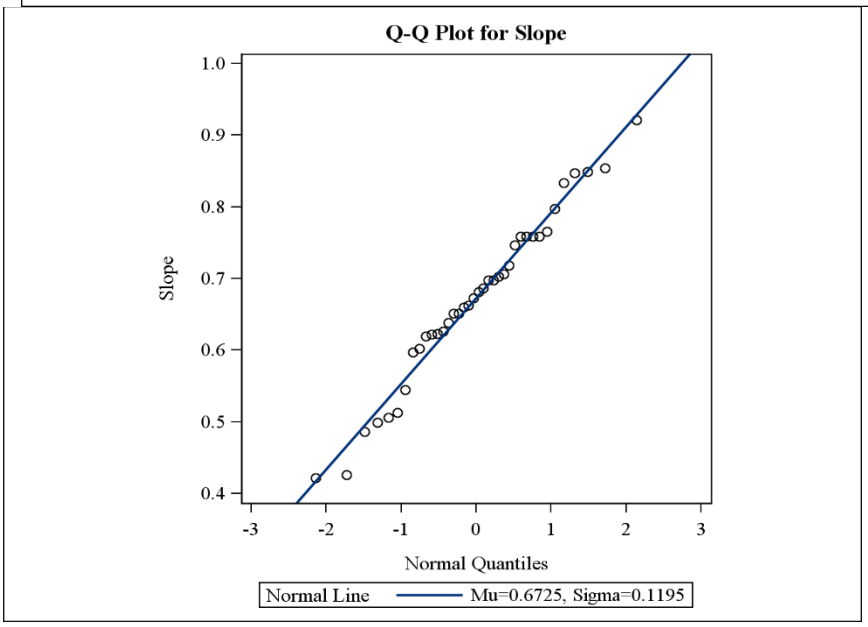


3. Post Harvest

Table 5: Slope analysis for crops with application type = postharvest

Solution for Fixed Effects						
Effect	Formulation	Estimate	Standard Error	Pr > |t|	Lower	Upper
Formulation Type	DP	-2.4260	1.3812	0.0896	-5.2510	0.3989
	EC	0.2556	0.2388	0.2934	-0.2328	0.7440
	SC	-2.0381	0.6934	0.0064	-3.4564	-0.6199
log(rate)		0.6725	0.1000	<.0001	0.4698	0.8751

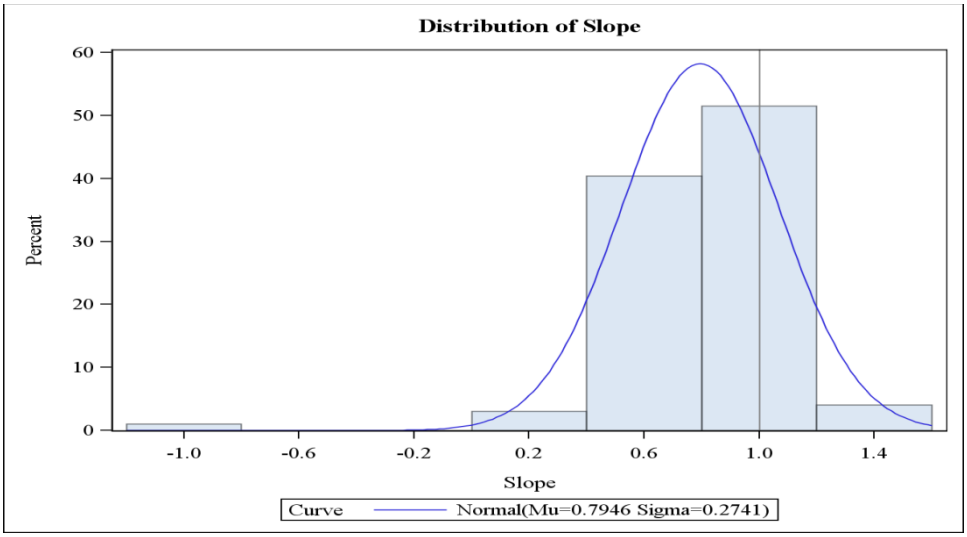


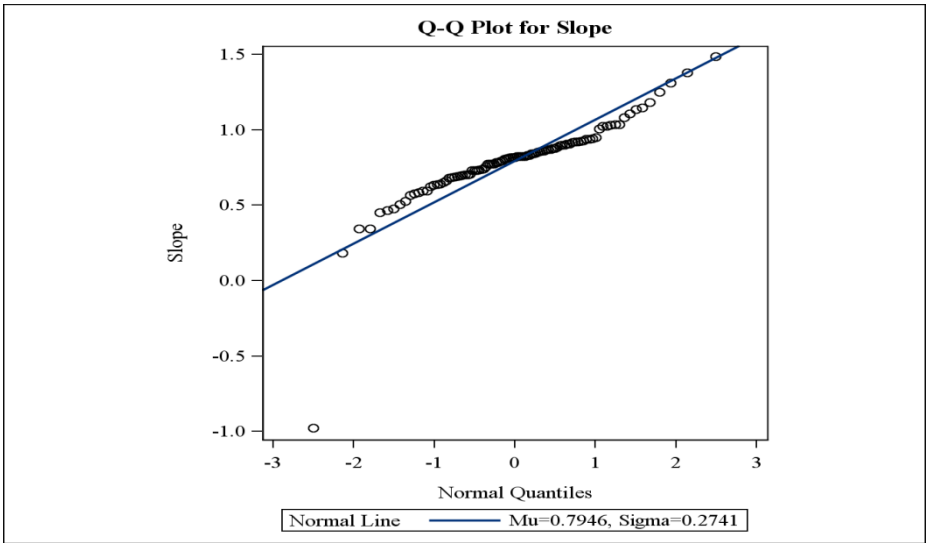


4. Seed Treatment

Table 6: Slope analysis for crops with application type = seed treatment

Solution for Fixed Effects						
Effect	Formulation	Estimate	Standard Error	Pr > |t|	Lower	Upper
Formulation Type	DS	-2.4867	2.1555	0.2519	-6.7723	1.7990
	EC	1.5349	1.6321	0.3496	-1.7101	4.7799
	FS	-1.9071	1.0718	0.0787	-4.0380	0.2239
	SC	-4.1142	1.3922	0.0040	-6.8823	-1.3461
	WP	-2.5199	2.3431	0.2852	-7.1786	2.1389
	WS	-3.2319	1.5762	0.0434	-6.3658	-0.09796
log(rate)		0.7946	0.06937	<.0001	0.6569	0.9323

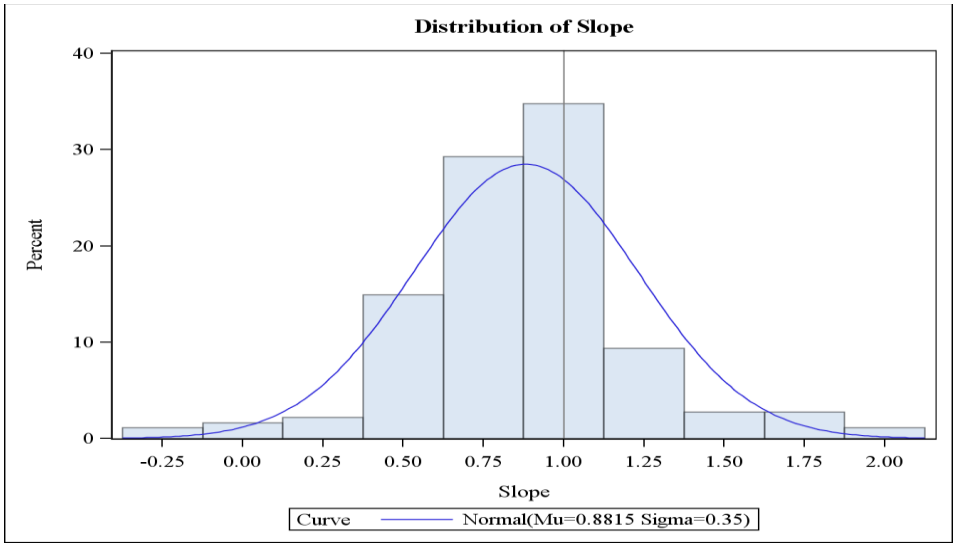


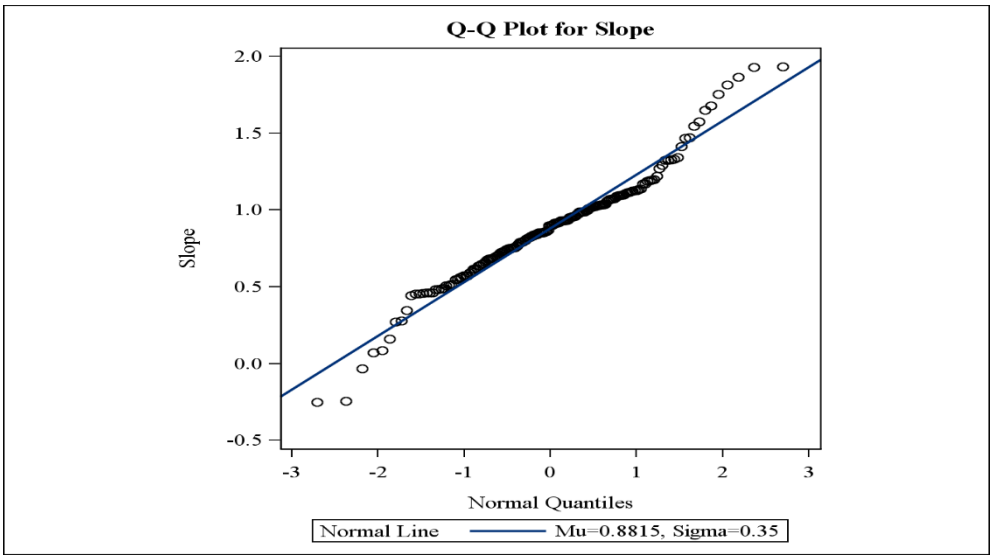


5. Soil

Table 7: Slope analysis for crops with application type = soil

Solution for Fixed Effects						
Effect	Formulation	Estimate	Standard Error	Pr > |t|	Lower	Upper
Formulation Type	EC	-1.4538	0.9603	0.1313	-3.3450	0.4374
	FS	-0.4864	1.1594	0.6752	-2.7697	1.7968
	SC	0.6001	1.1329	0.5968	-1.6309	2.8310
	SL	-1.0099	0.6925	0.1460	-2.3737	0.3538
	WG	-1.0924	0.8285	0.1885	-2.7240	0.5393
	WP	-1.4846	0.7438	0.0470	-2.9495	-0.0198
log(rate)		0.8815	0.05011	<.0001	0.7827	0.9804

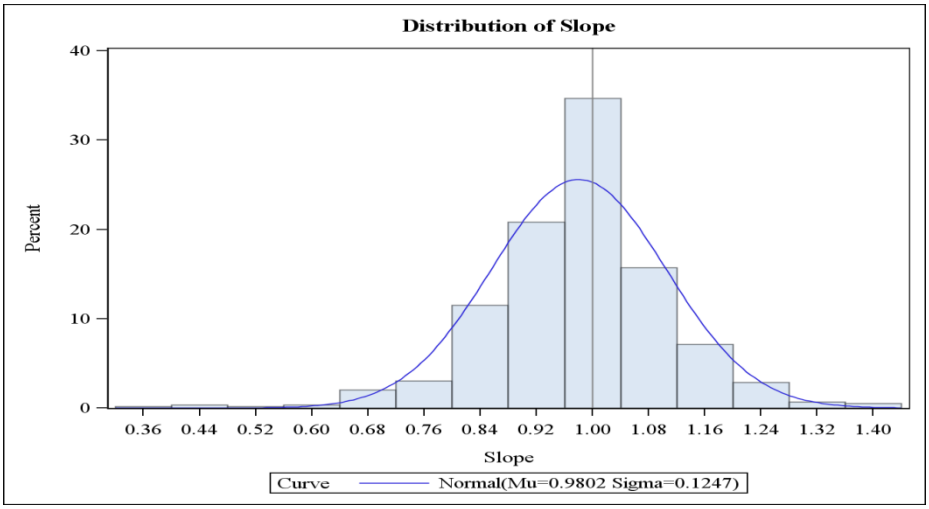


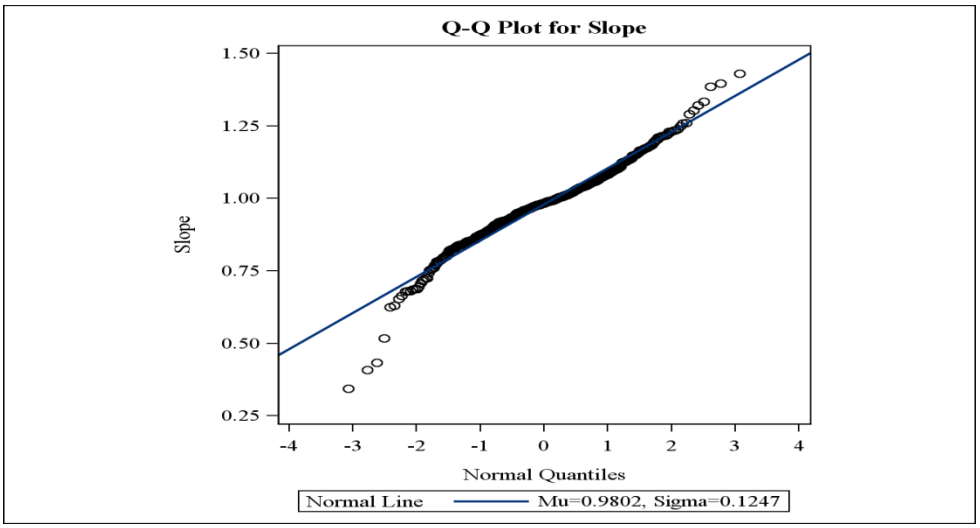


6. Foliar: Crop = Rice

Table 8: Slope analysis for Rice crop with application type = foliar

Solution for Fixed Effects						
Effect	Formulation	Estimate	Standard Error	Pr > |t|	Lower	Upper
Formulation Type	EC	-2.0024	0.5133	0.0002	-3.0204	-0.9844
	EW	-1.5037	0.6855	0.0305	-2.8630	-0.1444
	GR	-2.9458	1.3146	0.0272	-5.5527	-0.3389
	OD	-1.8936	1.0379	0.0710	-3.9517	0.1646
	SC	-2.0488	0.5824	0.0006	-3.2037	-0.8939
	SL	-1.8223	0.8408	0.0325	-3.4897	-0.1550
	WG	-2.7942	0.8614	0.0016	-4.5024	-1.0859
	WP	-1.2738	0.6270	0.0448	-2.5172	-0.03038
log(rate)		0.9802	0.04764	<.0001	0.8867	1.0738

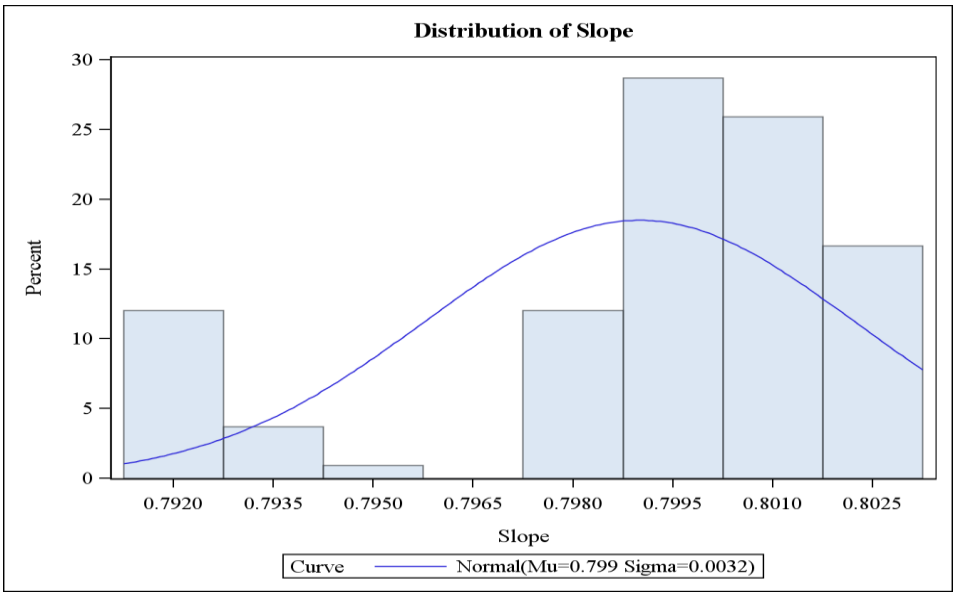


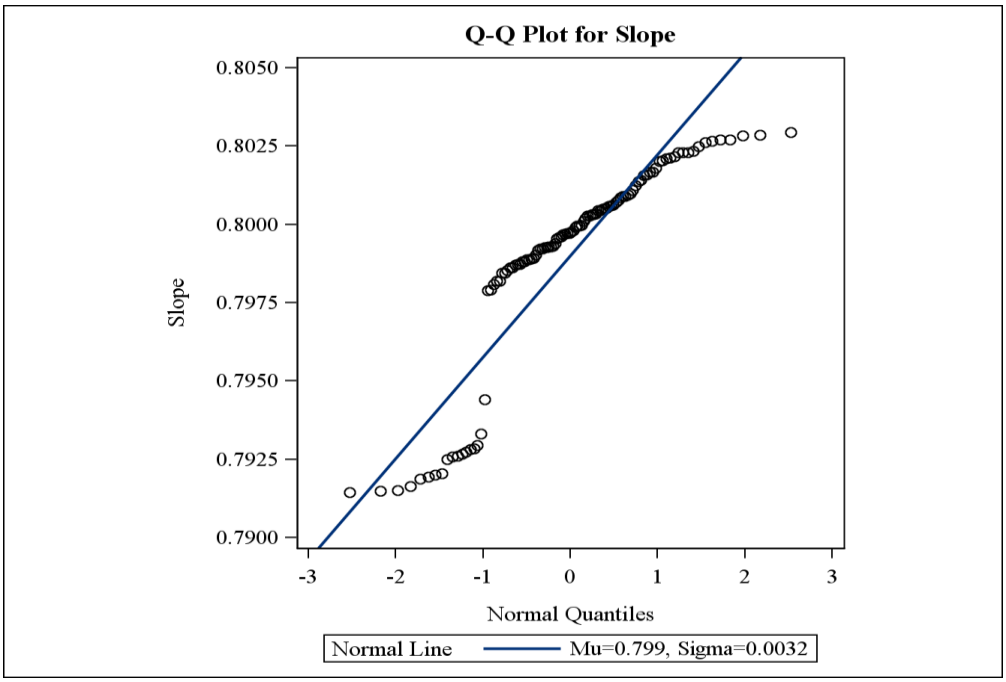


7. Foliar: Crop = Maize

Table 9: Slope analysis for Maize crop with application type = foliar

Solution for Fixed Effects						
Effect	Formulation	Estimate	Standard Error	Pr > |t|	Lower	Upper
Formulation Type	SC	-3.9913	1.0153	0.0001	-5.9980	-1.9845
	SL	-1.0635	0.3127	0.0009	-1.6816	-0.4454
log(rate)		0.7990	0.1049	<.0001	0.5911	1.0069

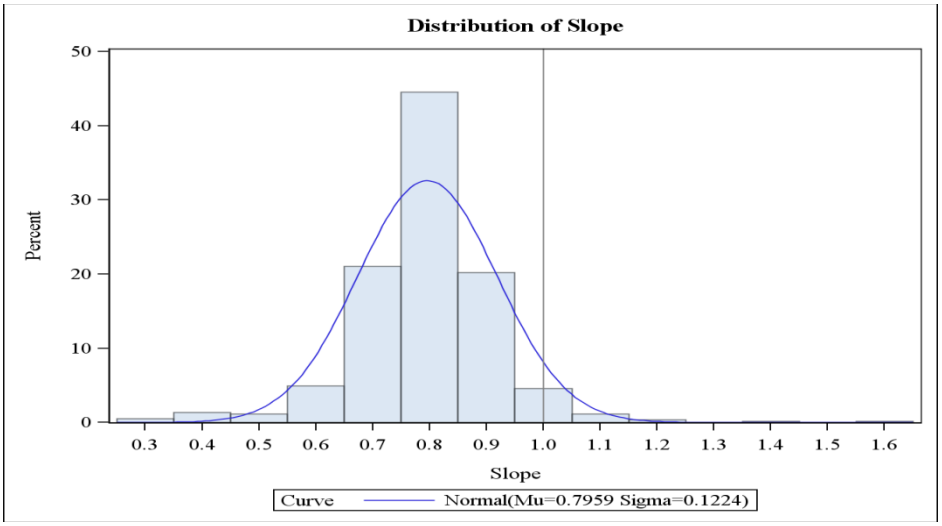


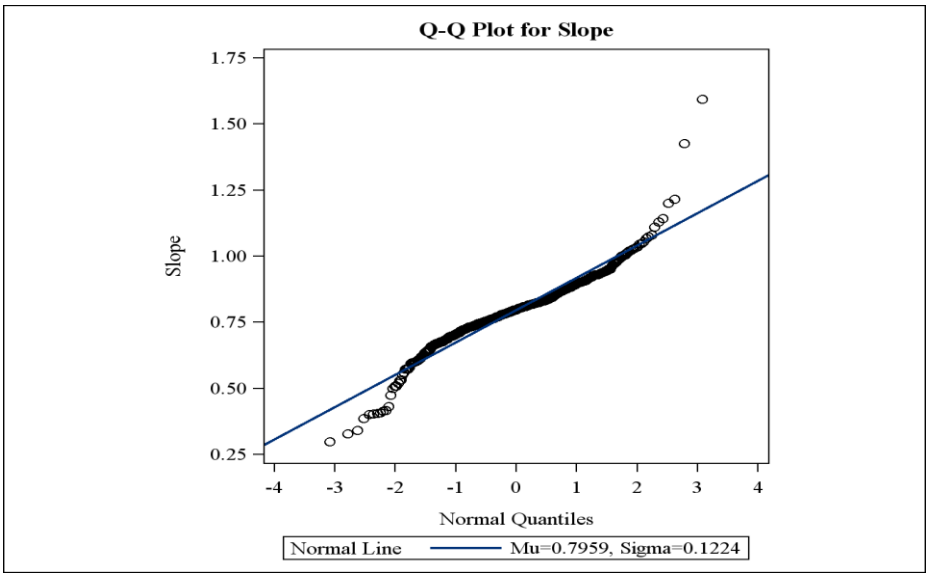


8. Foliar: crops with number of trials greater than 10 and less than 50

Table 10a: Slope analysis for crops with application type = foliar and had more than 10 trials/crop

Solution for Fixed Effects						
Effect	Formulation	Estimate	Standard Error	Pr > |t|	Lower	Upper
Formulation Type	EC	-1.6747	0.3413	<.0001	-2.3527	-0.9966
	EW	-0.9401	0.9226	0.3110	-2.7732	0.8931
	SC	-2.0178	0.3373	<.0001	-2.6880	-1.3476
	SL	-1.8232	0.4068	<.0001	-2.6315	-1.0149
	WG	-2.7703	0.4810	<.0001	-3.7260	-1.8146
	WP	-1.2488	0.3836	0.0016	-2.0111	-0.4865
log(rate)		0.7959	0.03211	<.0001	0.7328	0.8589

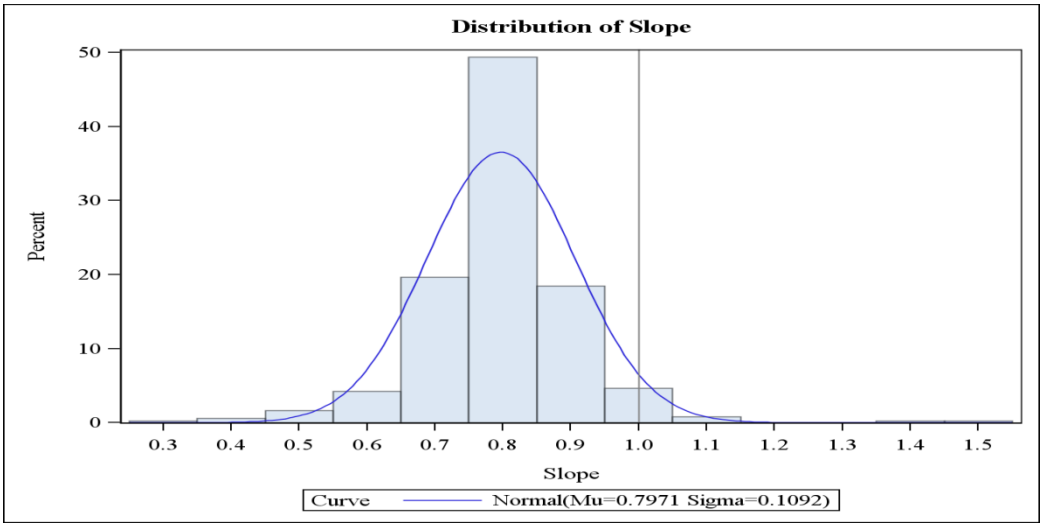


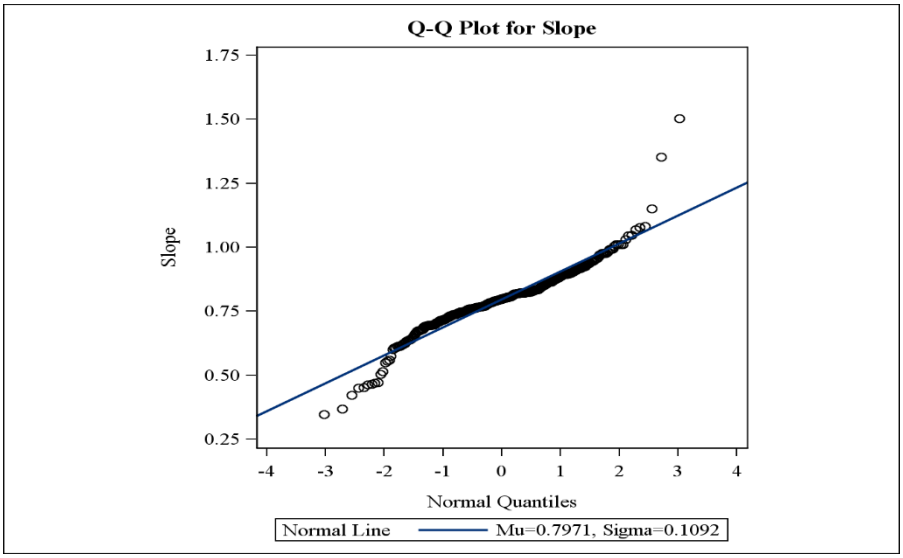


9. Foliar: crops with number of trials greater than 10 and less than 50 (same spray volume)

Table 10b: Slope analysis for crops with application type = foliar and had more than 10 trials/crop (same spray volume)

Solution for Fixed Effects						
Effect	Formulation	Estimate	Standard Error	Pr > |t|	Lower	Upper
Formulation Type	EC	-1.4613	0.4491	0.0016	-2.3544	-0.5681
	EW	-0.7501	0.9443	0.4293	-2.6279	1.1278
	SC	-1.7208	0.4494	0.0002	-2.6144	-0.8271
	SL	-1.6348	0.5039	0.0017	-2.6369	-0.6327
	WG	-2.6059	0.5786	<.0001	-3.7565	-1.4552
	WP	-1.0518	0.4872	0.0337	-2.0206	-0.08288
log(rate)		0.7971	0.03539	<.0001	0.7276	0.8667

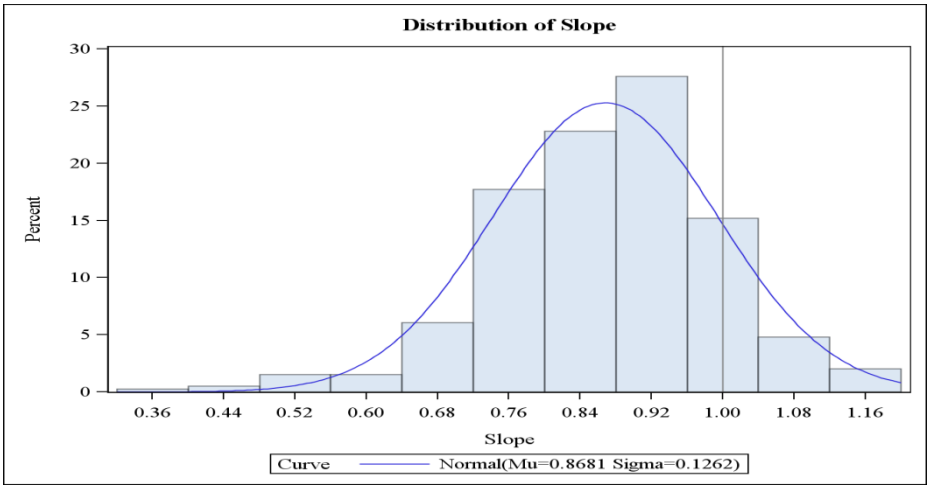


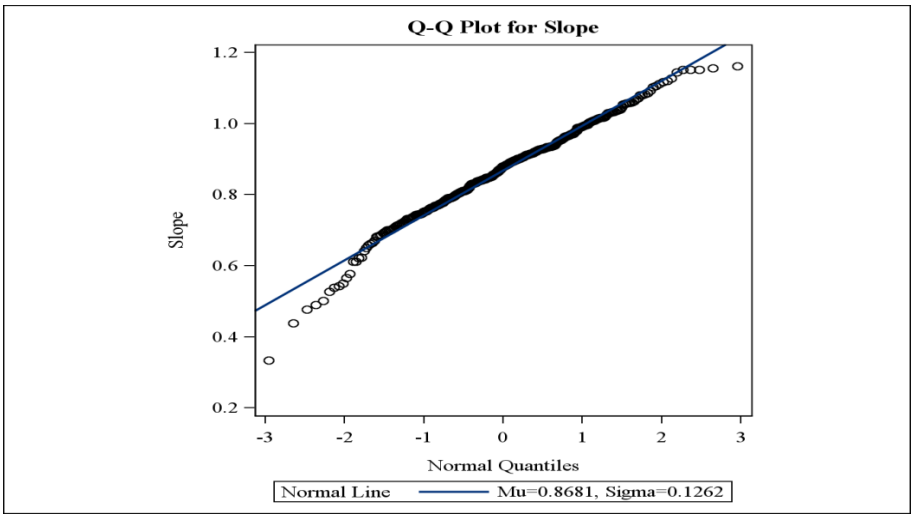


10. Foliar: crops with number of trials less than 10

Table 11a: Slope analysis for crops with application type = foliar and had less than 10 trials/crop

Solution for Fixed Effects						
Effect	Formulation	Estimate	Standard Error	Pr > |t|	Lower	Upper
Formulation Type	CS	-1.2754	1.2457	0.3067	-3.7264	1.1755
	DP	-3.5681	0.9625	0.0002	-5.4618	-1.6743
	EC	-1.8344	0.4299	<.0001	-2.6802	-0.9885
	GR	-6.9224	1.0695	<.0001	-9.0266	-4.8182
	Liquid	-2.2544	0.8615	0.0093	-3.9493	-0.5595
	SC	-1.6561	0.5436	0.0025	-2.7255	-0.5866
	SL	-2.0550	0.5148	<.0001	-3.0678	-1.0422
	WG	-2.4851	0.7413	0.0009	-3.9436	-1.0266
	WP	-0.5941	0.6089	0.3300	-1.7921	0.6039
log(rate)		0.8681	0.03228	<.0001	0.8047	0.9316

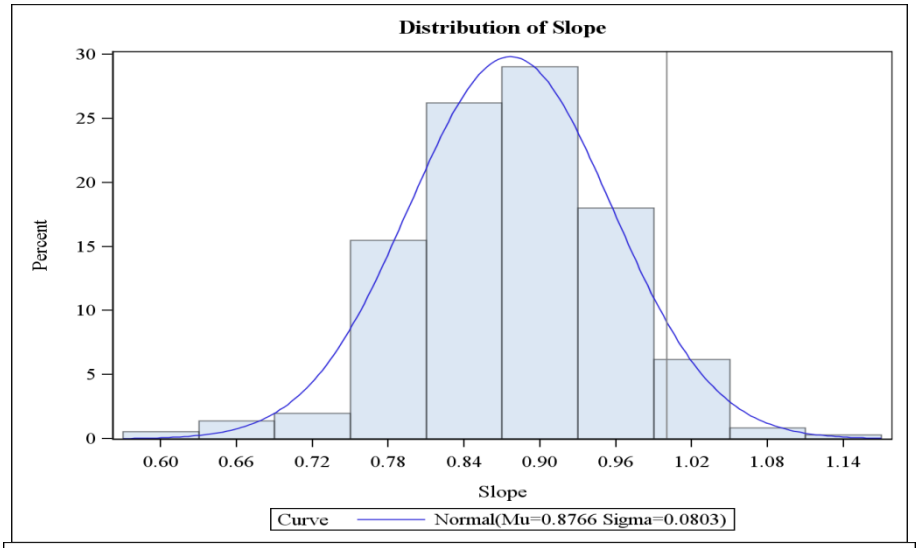


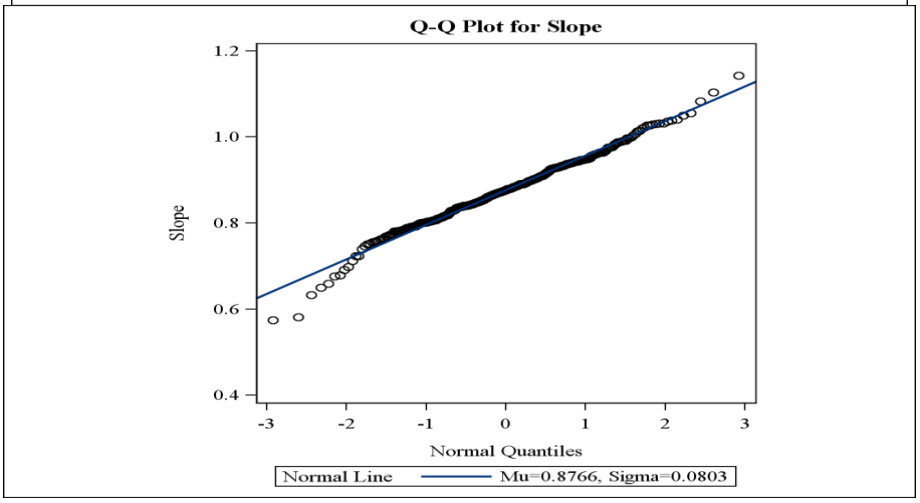


11. Foliar: crops with number of trials less than 10 (same spray volume)

Table 11b: Slope analysis for crops with application type = foliar and had less than 10 trials/crop

Solution for Fixed Effects						
Effect	Formulation	Estimate	Stand. Error	Pr > |t|	Lower	Upper
Formulation Type	CS	-1.1804	0.8597	0.1711	-2.8747	0.5138
	DP	-3.3765	0.9966	0.0008	-5.3406	-1.4124
	EC	-1.7661	0.4437	<.0001	-2.6406	-0.8916
	GR	-6.8789	1.1159	<.0001	-9.0781	-4.6796
	Liquid	-2.1113	0.8912	0.0187	-3.8676	-0.3550
	SC	-1.4421	0.6005	0.0171	-2.6255	-0.2588
	SL	-1.9253	0.5680	0.0008	-3.0447	-0.8059
	WG	-2.3803	0.7688	0.0022	-3.8955	-0.8651
	WP	-0.6040	0.6364	0.3436	-1.8581	0.6502
log(rate)		0.8766	0.03165	<.0001	0.8143	0.9388

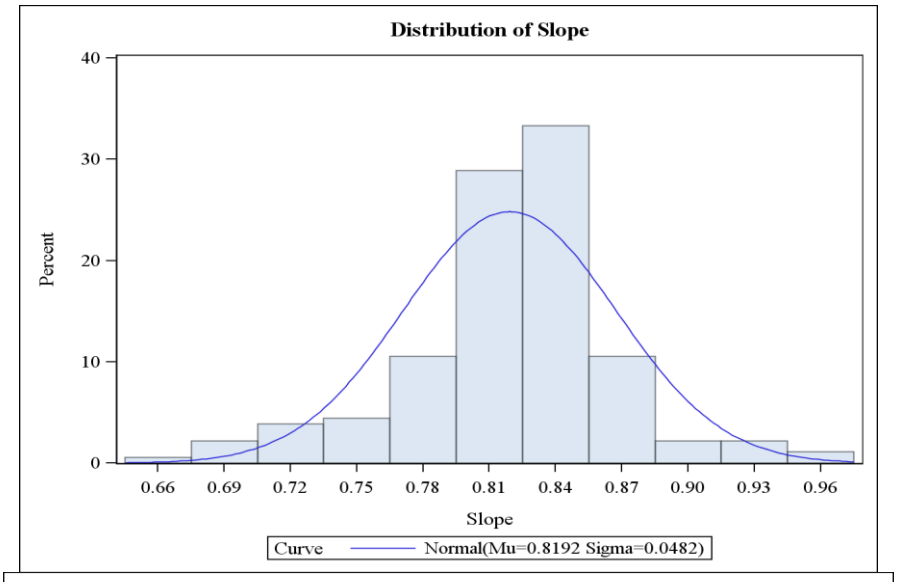




12. Foliar – multiple spray volume

Table 12: Slope analysis for crops with application type = foliar and had less than 10 trials/crop

Solution for Fixed Effects						
Effect	Formulation	Estimate	Standard Error	Pr > |t|	Lower	Upper
Formulation Type	EC	-2.4103	0.5323	<.0001	-3.4628	-1.3578
	OD	-1.5623	0.9245	0.0933	-3.3904	0.2658
	SC	-3.6855	0.5497	<.0001	-4.7726	-2.5984
	SL	-0.8749	0.5225	0.0963	-1.9082	0.1583
	WG	-1.9435	0.7996	0.0164	-3.5246	-0.3623
log(rate)		0.8192	0.06279	<.0001	0.6953	0.9431



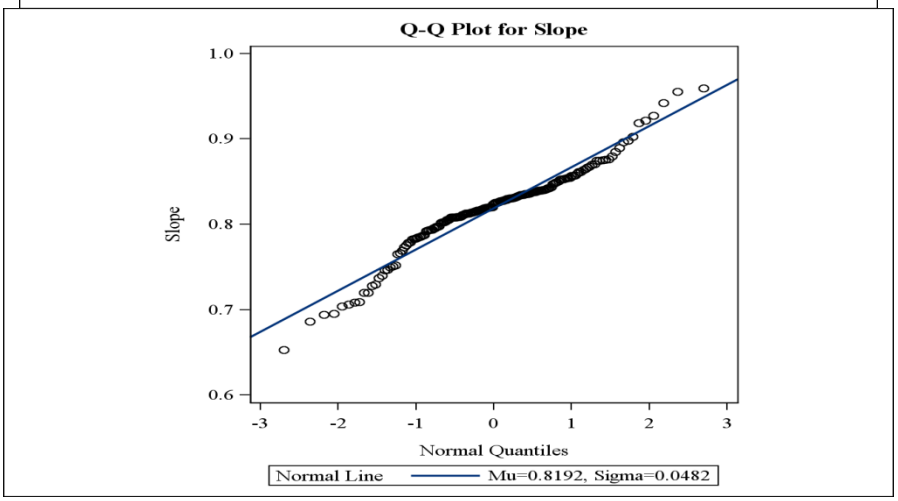


Table 13: Frequency of trials by Formulation Type:

Formulation Type	Frequency
CS	1
DP	2
DS	1
EC	256
EW	52
FS	31
GR	4
Liquid	4
OD	4
SC	213
SL	173
WG	69
WP	114
WS	2

Table 14: Frequency of trials by Country

COUNTRY	Frequency
ARGENTINA	3
AUSTRALIA	122
BELGIUM	5
BRAZIL	291
BULGARIA	2
CANADA	3
CERIALE	1
CHINA	80
COSTA RICA	6
DENMARK	10
DUNS TEW OXFORD	2
FINLAND	1
FRANCE	30
GERMANY	21
GREAT TEW OXFORD	1
GREECE	30
HOLLAND	7
HUNGARY	3
INDONESIA	1
ITALY	31
MALAYSIA	3
MAROCCO	1
MEXICO	2
NETHERLANDS	2
NEW ZEALAND	2
PHILIPPINES	7
POLAND	2

COUNTRY	Frequency
SOUTH AFRICA	22
SPAIN	39
SURINAM	1
SWEDEN	1
SWITZERLAND	1
THESSALONIKI	2
UK	54
USA	136
ZAPPONETA	1

Table 15: Frequency of trials by Active Ingredient

AI	Frequency
517 01	1
517 22	2
590	12
693	2
720	1
ACETAMIPRID	6
AZOXYSTROBIN	6
BETA-CYFLUTHRIN	29
BITERTANOL	2
BYF 14182	12
CHLORIMURON ETHYL	3
CHLORMEQUAT CHLORIDE	5
CHLORPYRIFOS	6
CYCLANILIDE	6
CYFLUTHRIN	28
CYPROCONAZOLE	11
DAS1	1
DAS10	10
DAS11	1
DAS12	6
DAS13	34
DAS14	4
DAS15	2
DAS2	13
DAS3	4
DAS4	1
DAS5	15
DAS7	8
DAS9	87
DELTAMETHRIN	7
DIFENOCONAZOLE	6
ENDOSULFAN	4
EPOXICONAZOLE	4
ETHEPHON	24
ETHIPROLE	1

AI	Frequency
ETHOXYSULFURON	1
FAMOXADONE	23
FENOXANIL	6
FENOXAPROP-ETHYL	2
FENOXAPROP-P-ETHYL	9
FENPYROXIMATE	3
FLUAZIFOP	35
FLUOPICOLIDE	24
FOSETYL	17
FOSETYL-AL	5
GLUFOSINATE-AMMONIUM	89
GYLPHOSATE-TRIMESIUM	15
HEXACONAZOLE	6
IMIDACLOPRID	75
IPRODIONE	1
IPROVALICARB	3
ISOPROCARB	4
ISOXAFLUTOLE	15
MEFENPYR-DIETHYL	25
METHIOCARB	1
NNI-0001	12
OXADIAZON	8
OXYDEMETON-METHYL	2
PENCYCURON	2
PROCHLORAZ	6
PROFENOFOS	4
PROPAMOCARB	6
PROPAMOCARB HYDROCHLORIDE	7
PROPICONAZOLE	9
PROPINEB	23
PROTHIOCONAZOLE	4
RIMSULFURON	3
SPIRODICLOFEN	5
SPIROMESIFEN	10
TEBUCONAZOLE	49
TEFLUBENZURON	1
THIACLOPRID	4
THIDIAZURON	2
THIODICARB	3
TRIADIMENOL	6
TRIAZOPHOS	8
TRIBUFOS	1
TRICYCLAZOLE	3
TRIFLOXYSTROBIN	14
TRIFLUMURON	11

Table 16: Frequency of trials by crop

Crop	COUNT
ALFALFA	1
AVOCADO	1
BROAD BEAN	1
CELERY	1
CITRUS FRUITS	1
CLOVER	1
FIELD PEA	1
FLAX	1
GRASSLAND (PASTURE)	1
KAKI	1
KIDNEY BEAN	1
LENTIL	1
MUSTARD	1
OLIVE	1
ONION	1
PASSION FRUIT	1
PEACH	1
RASPBERRIES, RED, BLACK	1
RUTABAGA	1
SPINACH	1
SUNFLOWER	1
SWEDE	1
TABLE-GRAPES	1
TEA	1
BLACKBERRIES	2
CACAO BEANS	2
CHERRY, SOUR	2
GARDEN PEA	2
GUAVA	2
LUPIN	2
MELONS, EXCEPT WATERMELON	2
OATS	2
RAPE SEED	2
RYE	2
SMALL FRUIT/BERRIES	2
SUGAR CANE	2
SUMMER SQUASH	2
CARROT	3
CAULIFLOWER	3
CHICORY, LEAVES	3
EGG PLANT	3
HOPS	3
LEEK	3
LETTUCE	3
LUCERNE	3

Crop	COUNT
OILSEED RAPE	3
RAPE	3
TURNIP	3
CURRANT, RED	4
MEADOW GRASS	5
CANTELOUPE	6
CORN	6
PINEAPPLE	6
FIG	7
MANDARIN	7
PEA	7
TOBACCO	7
CABBAGE	8
SORGHUM	8
BEET	9
DRY HAY	10
SNAP BEAN (YOUNG PODS)	13
STRAWBERRY	13
APPLE	14
CUCUMBER	15
PEPPERS	15
CHERRY TOMATO	17
COFFEE	17
ORANGE	17
SOYBEAN	18
BEAN	19
WHEAT	19
MELON	21
GRAPES	23
POTATO	23
COTTON	34
TOMATOES	40
BARLEY	43
MAIZE	56
RICE	161

APPENDIX 4

Possible Impact of the Proportionality Approach on MRL Setting

[Frank Laporte, 22 Nov. 2012, as revised by USEPA, April 2013]

As a general rule, MRLs are set based on residue data from supervised trials conducted at the critical GAP rate ± 25%. However, assuming proportionality between application rates and residue levels in treated commodities at harvest, it may be possible to also consider the results of supervised trials conducted at rates below or above +/- 25% of the critical GAP rate, provided the observed residue levels are corrected for the application rate ("scaled") before use for MRL calculation. This could possibly broaden the statistical basis for MRL calculation and hence improve the accuracy of the MRLs.

However, the evaluation of side-by-side trials conducted at different application rates suggests that the residue levels are not strictly proportional but only nearly proportional to the application rates. A further simulation was conducted in order to assess the impact on MRLs from applying the proportionality principle when the relationship "residue vs. application rate" is not perfectly proportional. As shown in figure 2B, with a slope b = 0.8 obtained from the mixed linear effect model and the application rate of the scaled residue ranging from 0.33X – 4.2X the GAP rate, the relative amount of over-estimated or under-estimation amount in the scaled residues would be less than 25% from the true value. The objective of this simulation is to evaluate the MRLs calculated from scaled residues (which are under/over-estimated) and compare these to the residues of GAP trials at application 1X.

For the residues of GAP field trials (application rate = 1X; thus, no scaling was needed), we randomly generated a distribution of residue values from a log-normal distribution. To obtain scaled residues (resulted from applying proportionality principle to non-GAP field trials, at application rates ≠ 1X), we multiplied under-estimating/over-estimating factors to the residues at 1X. For example, to create a scaled residue with 25% under-estimation, we multiplied 0.75 by a randomly generated residue at 1X.

The impact of applying proportionality on the MRLs was evaluated when the scaled residues are under/over-estimated by 25%, 20%, 15%, and 10%. We used the lognormal distributions with geometric mean = 1 and CV = 0.7, 1.0, and 1.3 to represent the distributions of residues at 1X (using different geometric mean values may slightly have different simulation results due to the OECD rules of rounding MRL values; however, the conclusions would not change). The simulation included 1000 datasets (1000 MRLs) per scenario. Below are the scenarios that MRLs were evaluated:

- Scenario 1: calculation based on **4** random residues from the critical GAP rate field trials
- Scenario 2: calculation based on **8** random residues from the critical GAP rate field trials
- Scenario 3: calculation based on **16** random residues from the critical GAP rate field trials
- Scenario 4: calculation based on **4** random residues from the critical GAP rate field trials and **4** scaled residues from non-critical GAP field trials
- Scenario 5: calculation based on **8** random residues from the critical GAP rate field trials and **8** scaled residues from non-critical GAP field trials
- Scenario 6: calculation based on **8** scaled residues from non-critical GAP field trials

The primary criterion to evaluate and compare the MRLs between scenarios is the proportion of MRLs ≥ the true 95th percentile (typically, we aim to have 95% of the estimated MRLs ≥the 95th percentile). The secondary criterion is the how close (or "tight") the distribution of MRLs is to the true 95th percentile.

Conclusions:

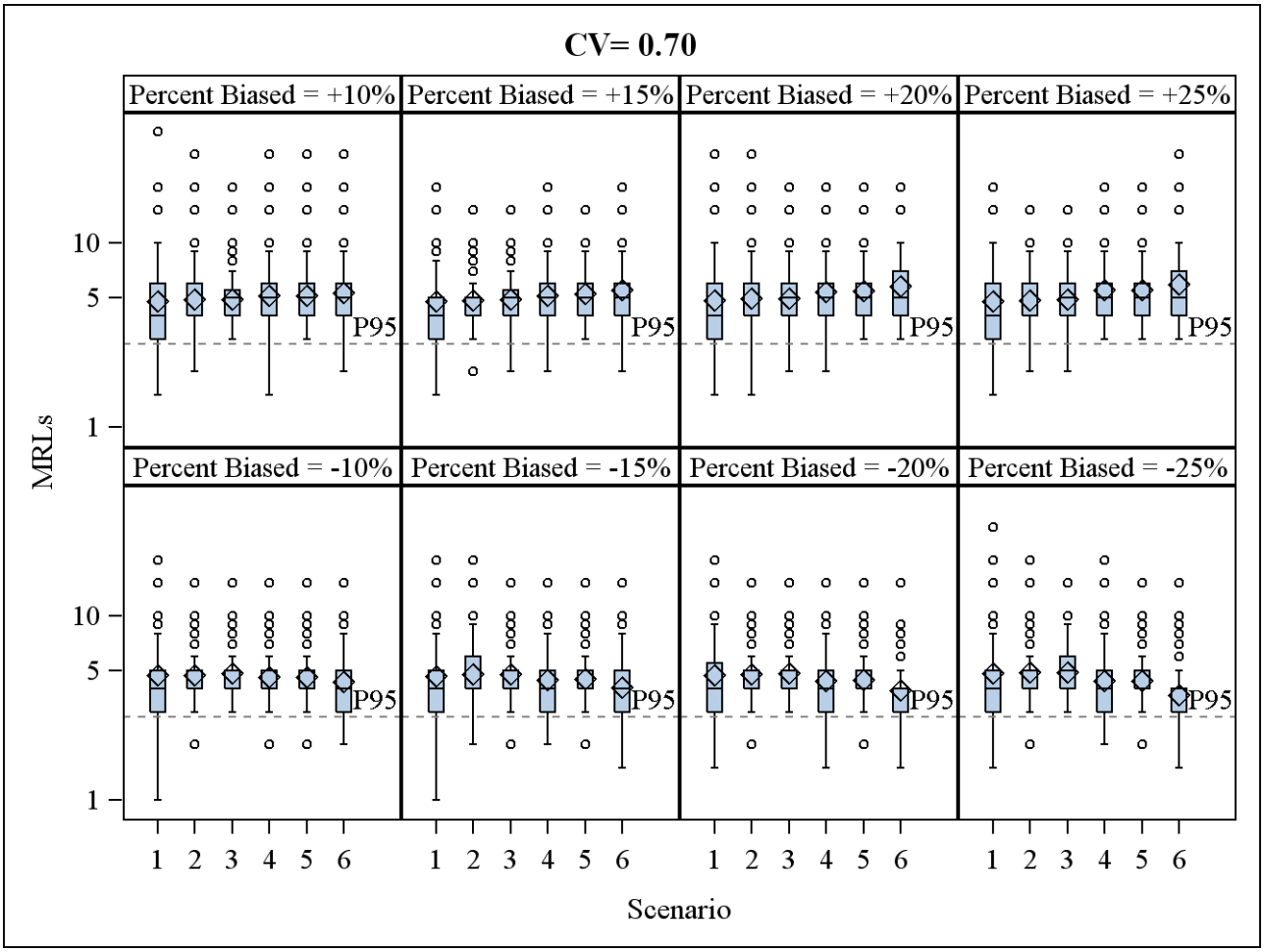
- Adding more scaled residues (to increase sample size) generally results better MRL estimates (scenario 4 vs. scenario 1, and scenario 5 vs. scenario 2).
- As the proportion of scaled residues increases, the MRL estimates become slightly worse (scenario 4 vs. scenario 2, and scenario 5 vs. scenario 3), but the MRL estimates are NOT substantially worse if the entire dataset consists of scaled residues, except in the extreme scenario in which the entire dataset were all scaled residues and were 25% under- or over-estimated (scenario 6 vs. scenario 2). However, this extreme scenario as done in the simulation with all scaled residues being under-or over-estimated by 25% does not apply if proportionality is limited to application rates between 4.2× to 0.33× label rate, respectively. With this range, the percent biased in the scaled residue will be within ±25%. The 25% biased case gave acceptable results in the simulation, so using a full adjusted set of data (100%) is acceptable between 4.2x to 0.33x label rate.
- Another important factor worth mentioning is that the estimated slope from the linear mixed-effects model analysis was underestimated for the same reasons for which the ratio (C2/C1)/(R2/R1) was underestimated (refer to Appendix 1 and paragraph III.16).. For that reason, the actual amount of under/over-estimation in the scaled residues may be <u>less</u> than the values that were used in the simulation, and the MRL estimates calculated from using scaled residues may be <u>better</u> than what we see in the simulation results.

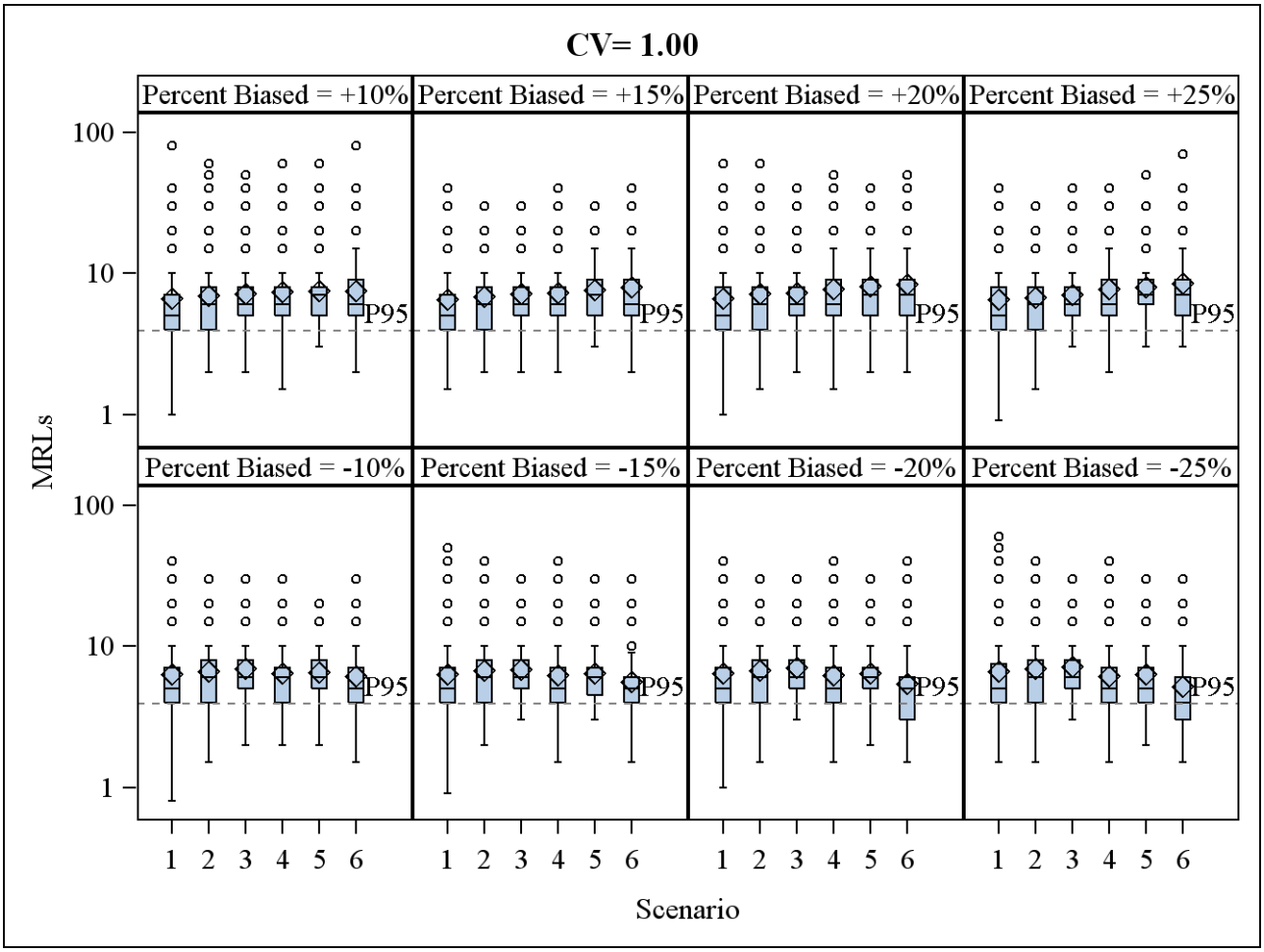
Therefore, increasing sample size by applying the proportionality principle on trials in which the application rate ranges from 0.33X to 4.2X the target rate results in better MRL estimates than would result if only the 1X (target) rate was considered even when the estimated slope is as low as 0.8.

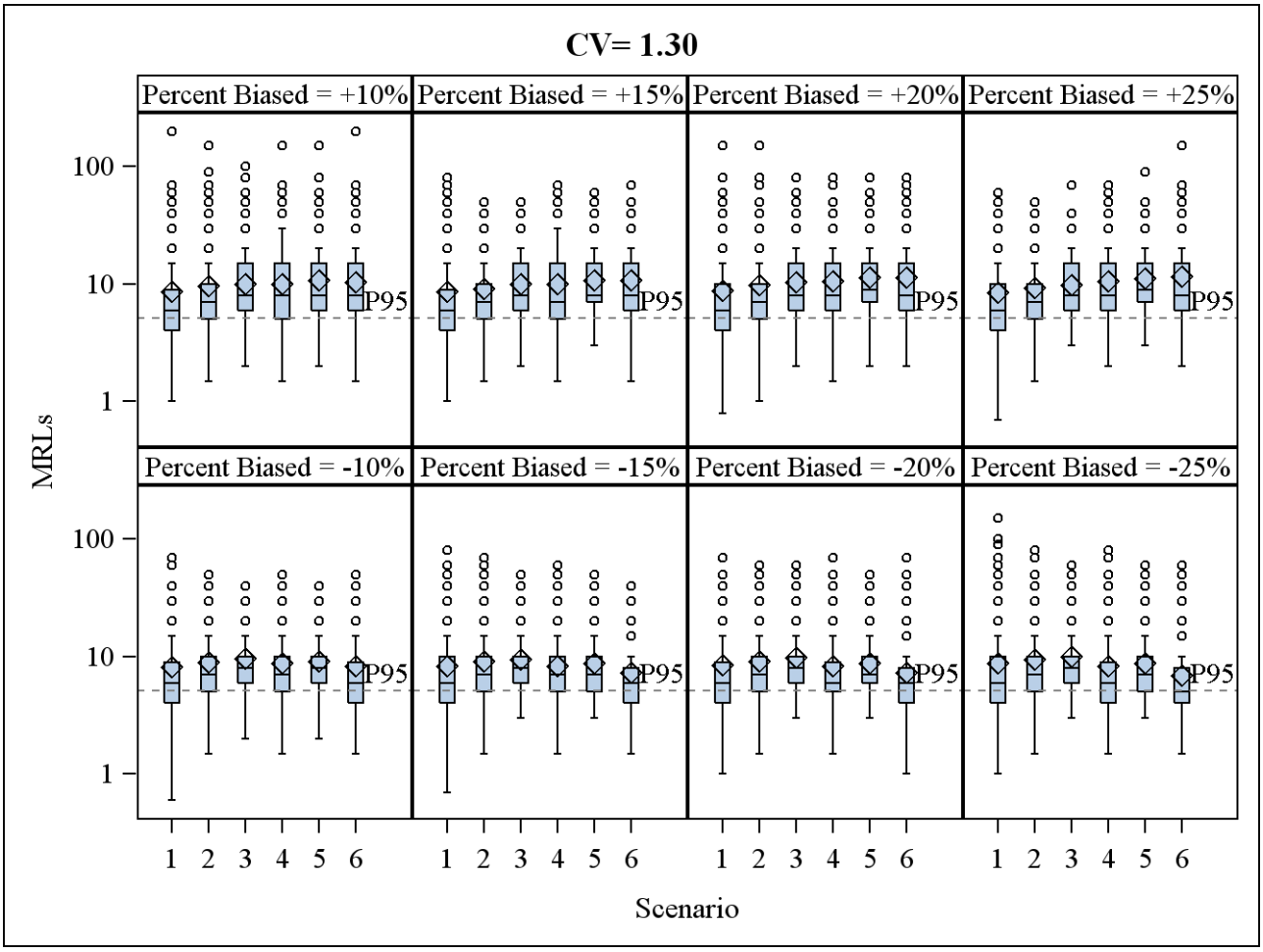
Simulation Results

CV	Percent biased in Scaled Residue	Proportion of MRL ≥ 95th percentile					
		Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5	Scenario 6
		4 GAP residues	8 GAP residues	16 GAP residues	4 GAP residues + 4 scaled residues	8 GAP residues + 8 scaled residues	8 scaled residues
0.7	- 25%	0.954	0.993	1.000	0.972	0.997	0.891
	-20%	0.938	0.987	1.000	0.974	0.996	0.928
	-15%	0.955	0.991	0.999	0.990	0.999	0.950
	- 10%	0.952	0.993	1.000	0.986	0.998	0.977
	10%	0.953	0.991	1.000	0.994	1.000	0.997
	15%	0.947	0.995	0.999	0.998	1.000	0.996
	20%	0.951	0.991	0.998	0.996	1.000	1.000
	25%	0.941	0.993	0.999	1.000	1.000	1.000
1.0	- 25%	0.790	0.902	0.975	0.826	0.940	0.712

CV	Percent biased in Scaled Residue	Proportion of MRL ≥ 95th percentile					
		Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5	Scenario 6
		4 GAP residues	8 GAP residues	16 GAP residues	4 GAP residues + 4 scaled residues	8 GAP residues + 8 scaled residues	8 scaled residues
	-20%	0.765	0.891	0.968	0.828	0.931	0.749
	-15%	0.772	0.887	0.965	0.837	0.946	0.786
	- 10%	0.769	0.880	0.961	0.876	0.947	0.830
	10%	0.789	0.892	0.978	0.926	0.986	0.933
	15%	0.791	0.917	0.978	0.922	0.987	0.930
	20%	0.787	0.899	0.970	0.944	0.987	0.953
	25%	0.771	0.889	0.972	0.949	0.985	0.968
1.3	- 25%	0.544	0.677	0.833	0.591	0.735	0.482
	-20%	0.552	0.688	0.829	0.618	0.756	0.533
	-15%	0.526	0.668	0.798	0.631	0.738	0.546
	- 10%	0.555	0.674	0.832	0.666	0.804	0.613
	10%	0.562	0.682	0.827	0.731	0.862	0.759
	15%	0.567	0.696	0.841	0.724	0.873	0.762
	20%	0.575	0.706	0.821	0.769	0.881	0.780
	25%	0.558	0.690	0.825	0.766	0.893	0.808


CV= 0.70
Percent Biased = +10%
Percent Biased = +15%
Percent Biased = +20%
Percent Biased = +25%
Percent Biased = -10%
Percent Biased = -15%
Percent Biased = -20%
Percent Biased = -25%
P95
MRLs
10
5
1
1 2 3 4 5 6
Scenario


CV= 1.00
Percent Biased = +10%
Percent Biased = +15%
Percent Biased = +20%
Percent Biased = +25%
Percent Biased = -10%
Percent Biased = -15%
Percent Biased = -20%
Percent Biased = -25%
P95
MRLs
100
10
1
1 2 3 4 5 6
Scenario


CV= 1.30
Percent Biased = +10%
Percent Biased = +15%
Percent Biased = +20%
Percent Biased = +25%
Percent Biased = -10%
Percent Biased = -15%
Percent Biased = -20%
Percent Biased = -25%
P95
MRLs
100
10
1
1 2 3 4 5 6
Scenario

SAS code:

```
*============================================================*
* Programmer: James Nguyen                                   *
*                                                            *
* Project: Proportionality                                   *
*                                                            *
* Purpose: Perform Simulation to evaluate the impact on MRLs *
*          when applying proportionality principle in fact   *
*          that the relationship between residue vs.         *
*          application rate is not precisely proportional    *
*                                                            *
* Data Source:                                               *
*    - simulation                                            *
*                                                            *
* Descriptions:                                              *
*      - generate data from lognormal,  given GM (=1) and    *
*        CV (= 0.7, 1.0, and 1.3)                            *
*      - under/over-estimated percent = -25%, -10%, 10%, 25% *
*      - calculate MRL for each dataset of each scenario     *
*      - created box-plot MRL for each scenario              *
*      - caculated proportion of MRL > 95%-tile              *
*                                                            *
* Date Started: 4/09/2013                                    *
*                                                            *
*============================================================*;
Option FormDlim = "=" NoDate NoNumber;
ods noptitle;

Data OECD_RoundRule;
            input actual proposed @@;
            datalines;
            0.000001  0.01  0.0105  0.015  0.0155  0.02  0.021  0.03
            0.031  0.04  0.041  0.05  0.051  0.06  0.061  0.07
            0.071  0.08   0.081  0.09  0.091  0.1  0.105  0.15
            0.155  0.2  0.21  0.3  0.31  0.4  0.41  0.5  0.51  0.6
            0.61  0.7  0.71  0.8  0.81  0.9  0.91  1  1.05  1.5
            1.55  2  2.1  3  3.1  4  4.1  5  5.1  6  6.1  7  7.1  8
            8.1  9  9.1  10  10.5  15  15.5  20  21  30  31  40
            41  50  51  60  61  70  71  80  81  90  91  100  105  150
            155  200  210  300  310  400  410  500  510  600  610  700
            710  800  810  900  910  1000  1050  1500  1550  2000
            2100  3000  3100  4000  4100  5000  5100  6000  6100  7000
            7100  8000  8100  9000  9100  10000  10500  15000
            15500  20000  21000  30000  31000  40000  41000  50000
            51000  60000  61000  70000  71000  80000  81000  90000
            91000  100000
            ;
run;
```

```
Data OECD_RoundRule;
        set OECD_RoundRule end=lastrow;
        call symputx("act"||left(_N_ -1),actual);
        call symputx("pro"||left(_N_),proposed);
        if lastrow then call symput('nround', _N_);
run;

title;
%Macro Simulation(NSim=,GM=, CV=, ListRate =, seed=);

        %let MY = log(&GM);
        %let SY = sqrt(log(1+&CV**2));

        %let nRate = 1;
        %let Rate&nRate = %nrbquote(%scan(&ListRate,&nRate,%str( )));
        %Do %while (&&Rate&nRate ^=);
            %let nRate = %eval(&nRate+1);
            %let Rate&nRate = %nrbquote(%scan(&ListRate,&nRate,%str( )));
        %end;
        %let nRate = %eval(&nRate - 1);


        Data P95;
            P95 = exp(&MY + 1.645*&SY);
            call symput('P95',P95);
        run;

        Data Simmer;
            %do i = 1 %to &nRate;
                Rate = &&Rate&i;
                do Sim = 1 to &NSim;
                  do N = 1 to 16;

                      *==> create set of 16 residues at GAP;
                      res  = exp(&MY + &SY*rannor(&seed));

                      *==> create a new set of residues:
                      - first 8 data points are at GAP (no scaling is made)
                      - last 8 data points are under/over estimated (not GAP)
                      - the amount under/over-estimated = 1 - Rate;
                      ares = res*((N<=8) + (N>8)*Rate);

                      output;
                  end;
                end;
            %end;
        run;

        Proc SQL;
            create table Scenario1 as
                select Rate, Sim, count(*) as N, avg(Res) as MeanV,
```

```
            max(res) as MaxV, std(res) as SD,
            max(calculated MaxV, calculated MeanV*3,
            calculated MeanV + calculated SD*4) as MRL
        from Simmer
        where N <= 4
        group by Rate, Sim;

    create table Scenario2 as
        select Rate, Sim, count(*) as N, avg(Res) as MeanV,
            max(res) as MaxV, std(res) as SD,
            max(calculated MaxV, calculated MeanV*3,
            calculated MeanV + calculated SD*4) as MRL
        from Simmer
        where N <= 8
        group by Rate, Sim;

    create table Scenario3 as
        select Rate, Sim, count(*) as N, avg(res) as MeanV,
            max(res) as MaxV, std(res) as SD,
            max(calculated MaxV, calculated MeanV*3,
            calculated MeanV + calculated SD*4) as MRL
        from Simmer
        group by Rate, Sim;

    create table Scenario4 as
        select Rate, Sim, count(*) as N, avg(aRes) as MeanV,
            max(ares) as MaxV, std(ares) as SD,
            max(calculated MaxV, calculated MeanV*3,
            calculated MeanV + calculated SD*4) as MRL
        from Simmer
        where N <= 4 or N >= 13
        group by Rate, Sim;

    create table Scenario5 as
        select Rate, Sim, count(*) as N, avg(aRes) as MeanV,
            max(ares) as MaxV, std(ares) as SD,
            max(calculated MaxV, calculated MeanV*3,
            calculated MeanV + calculated SD*4) as MRL
        from Simmer
        group by Rate, Sim;

    create table Scenario6 as
        select Rate, Sim, count(*) as N, avg(aRes) as MeanV,
            max(ares) as MaxV, std(ares) as SD,
            max(calculated MaxV, calculated MeanV*3,
            calculated MeanV + calculated SD*4) as MRL
        from Simmer
        where N > 8
        group by Rate, Sim;
quit;
```

```
Data AllScenarios;
    set Scenario1(in=s1) Scenario2(in=s2) Scenario3(in=s3)
        Scenario4(in=s4) Scenario5(in=s5) Scenario6(in=s6);
    P95 = &P95;
    if s1 then Scenario = 1;
    if s2 then Scenario = 2;
    if s3 then Scenario = 3;
    if s4 then Scenario = 4;
    if s5 then Scenario = 5;
    if s6 then Scenario = 6;

    *==> apply OECD rounding rules;
    if MRL > 91000 then MRL = 100000;
    %do i = 1 %to %eval(&nround-1);
        else if MRL < &&act&i then MRL = &&pro&i;
    %end;

    Pass = (P95 <= MRL);
run;

Proc SQL;
    create table PassRate as
    select Rate, Scenario, avg(Pass) as Pass
    from AllScenarios
    group by Rate, Scenario;
quit;

proc transpose data= PassRate prefix= Scenario
    out= PassRate(drop=_name_);
    by Rate;
    ID Scenario;
    var Pass;
run;

Data PassRate;
    set PassRate;
    Rate = Rate-1;
run;

ods listing;
title "CV= &CV";
Proc print data = PassRate noobs;
    format Rate percent6.2;
run;

Data AllScenarios;
    set AllScenarios;
    if Rate = 0.75 then Percent_Biased = "-25%";
    if Rate = 0.80 then Percent_Biased = "-20%";
    if Rate = 0.85 then Percent_Biased = "-15%";
    if Rate = 0.90 then Percent_Biased = "-10%";
```

```
            if Rate = 1.25 then Percent_Biased = "+25%";
            if Rate = 1.20 then Percent_Biased = "+20%";
            if Rate = 1.15 then Percent_Biased = "+15%";
            if Rate = 1.10 then Percent_Biased = "+10%";
            label Percent_Biased = "Percent Biased";
        run;

        ods listing close;
        Proc SGPANEL data = AllScenarios;
            PANELBY  Rate / rows = 2 columns = 4;
            VBOX MRL/category = Scenario;
            rowaxis type= log label= "MRLs" logbase= 10 logstyle= logexpand;
            colaxis offsetmax = .2 label= 'Scenario';
            refline &P95/lineattrs =(pattern = 2) label = ('P95');
        run;
        Proc datasets nolist;
            delete AllScenarios  Scenario: Simmer Summary P95;
        quit;
%Mend;

%let outpath = C:\Documents and Settings\jnguyen\Desktop\SAS Junks;
option orientation = landscape;
ods rtf file = "&outpath\Proportionality Impact.RTF" bodytitle startpage = no;
%Simulation(NSim=1000,GM=1,  CV=0.70,  ListRate  =  0.75  0.8  0.85  0.9  1.10  1.15  1.20  1.25,
seed=16513);
%Simulation(NSim=1000,GM=1,  CV=1.00,  ListRate  =  0.75  0.8  0.85  0.9  1.10  1.15  1.20  1.25,
seed=16513);
%Simulation(NSim=1000,GM=1,  CV=1.30,  ListRate  =  0.75  0.8  0.85  0.9  1.10  1.15  1.20  1.25,
seed=16513);
ods rtf close;
option orientation = portrait;
```