North American International Harmonization Efforts for Pesticides:

an update on current status and activities

48th Codex Committee on Pesticide Residues (CCPR48)
Radisson Blu Hotel
Chongqing, China
25 - 30 April, 2016

Health Canada Santé Canada

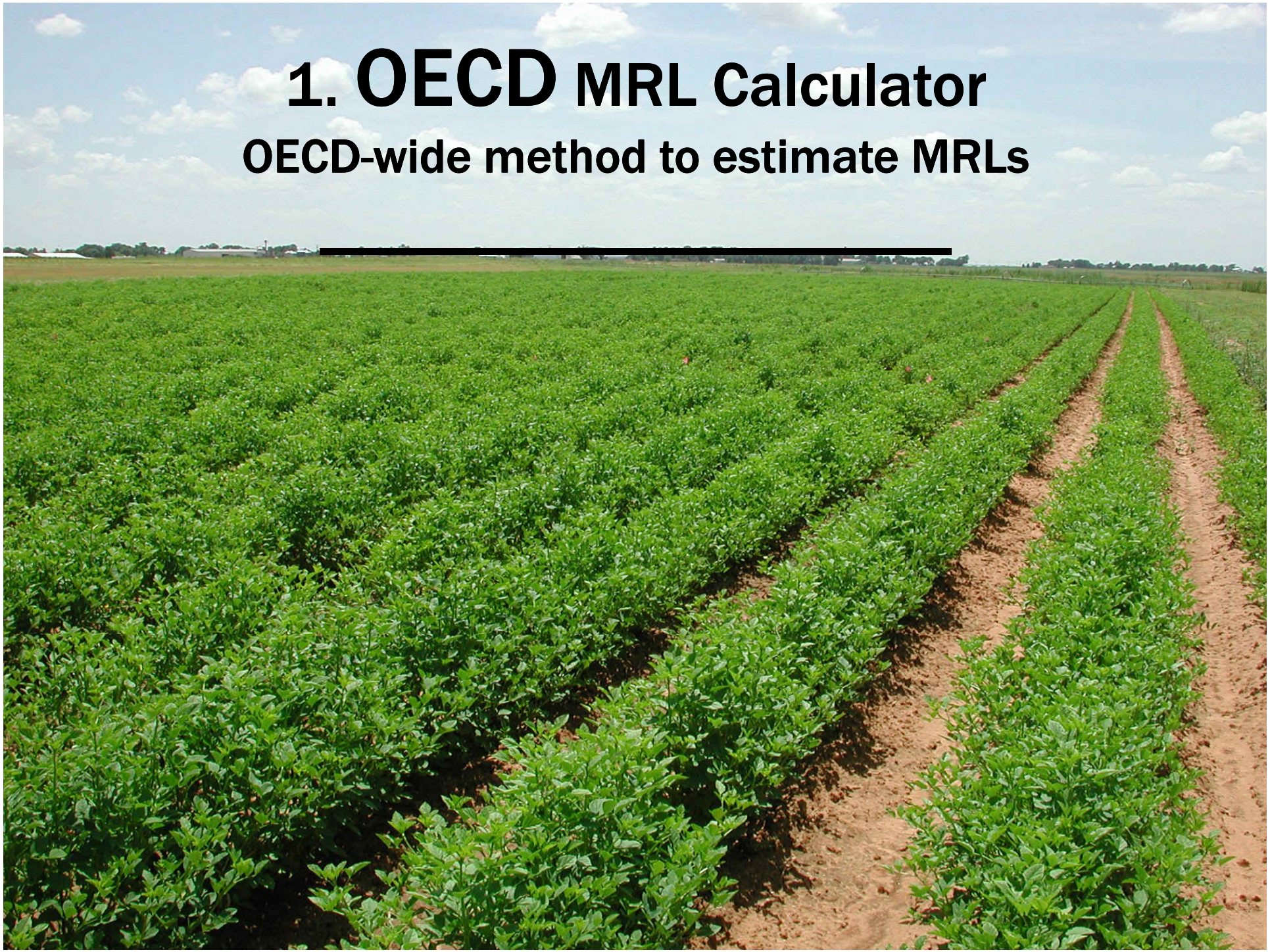
David J. Miller
Office of Pesticide Programs
U.S. Environmental Protection Agency

Update Topics

- OECD MRL calculator
- Global zoning project
- Crop Grouping
- Global MRL database (GlobalMRL.com)

1. OECD MRL Calculator

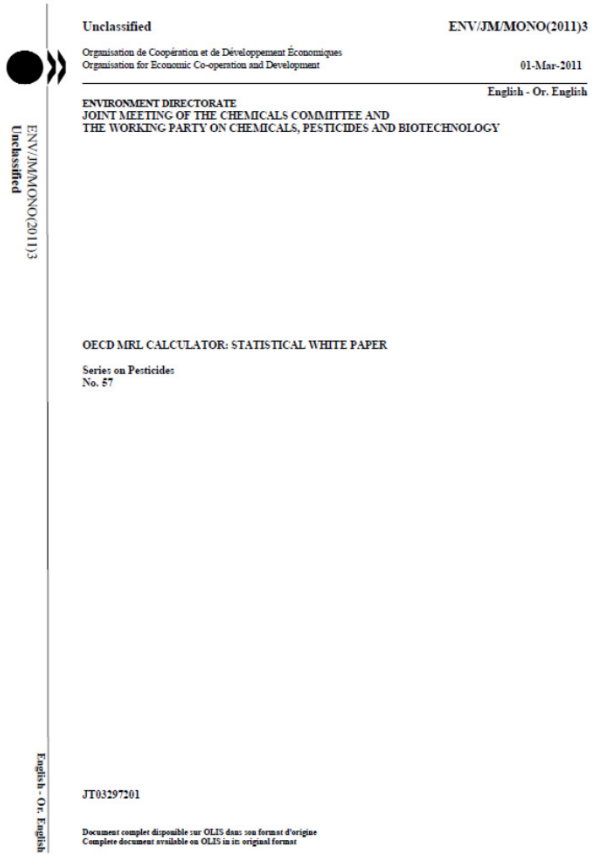
OECD-wide method to estimate MRLs



OECD MRL Calculator

- NAFTA calculator (US, Canada, CA)
- OECD Workgroup formed in 2008 with the goal of harmonizing the calculation of MRLs across the OECD
  - Practical implementation of sound statistical methods
  - Simple to use
  - Clear and unambiguous MRL proposal
  - Harmonize EU and NAFTA procedures to extent possible
- Working Group on Pesticides approved draft OECD MRL calculator in 2010
- Links to OECD User Guide, White paper, and draft calculator available at

http://www.epa.gov/pesticide-tolerances/oecd-maximum-residue-limit-calculator



Unclassified ENV/JM/MONO(2011)3

Organisation de Coopération et de Développement Économiques
Organisation for Economic Co-operation and Development 01-Mar-2011

English - Or. English

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THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

ENV/JM/MONO(2011)3
Unclassified

OECD MRL CALCULATOR: STATISTICAL WHITE PAPER

Series on Pesticides
No. 57

English - Or. English

JT03297201

Document complet disponible sur OLIS dans son format d'origine
Complete document available on OLIS in its original format

OECD MRL Calculator

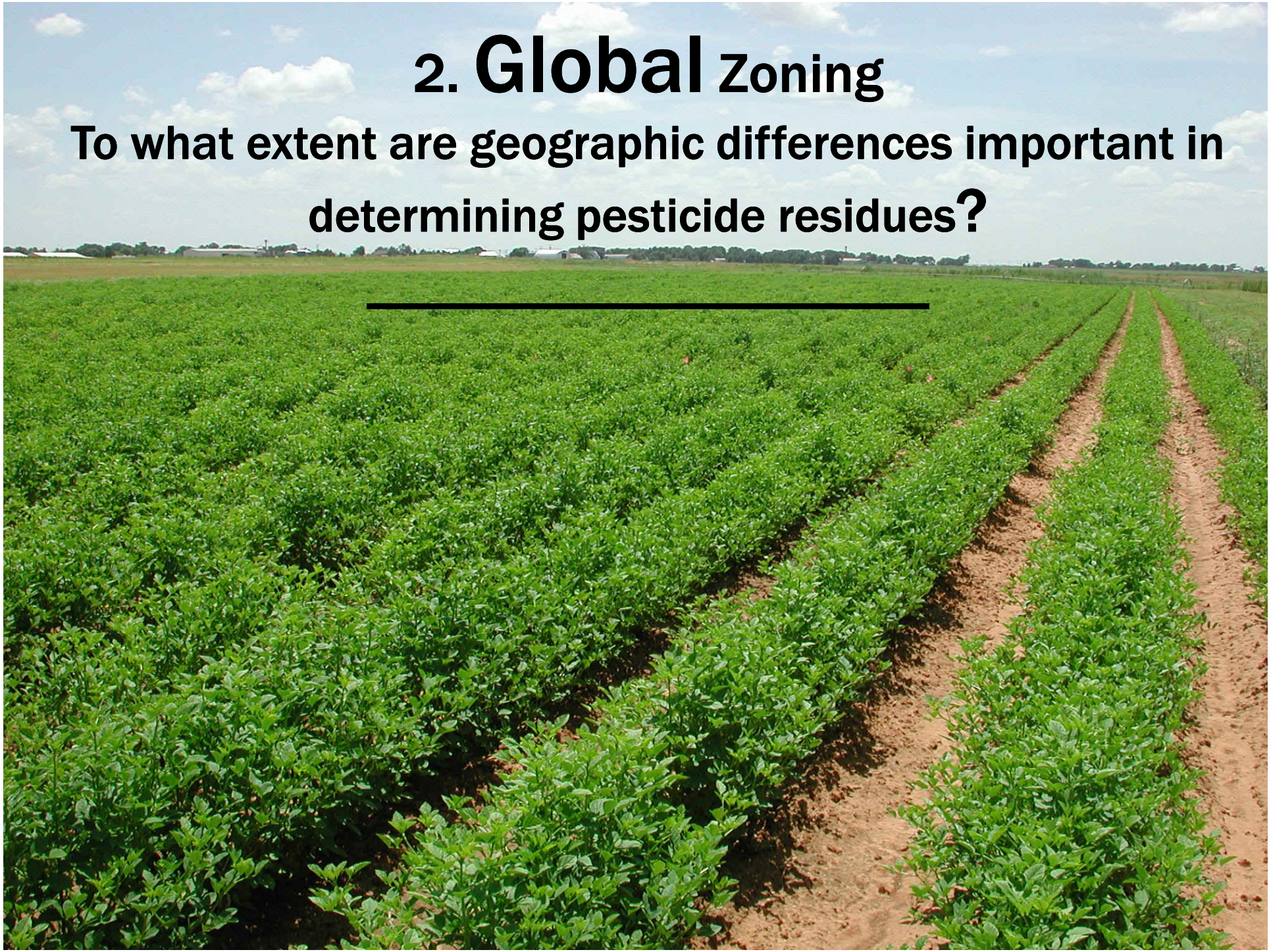
- EPA and PMRA use OECD MRL calculator as standard practice
- If Codex MRL exists, law requires EPA to harmonize with Codex, if feasible/practical as per OECD MRL calculator result
  - Section 408(b)(4) of Federal Food, Drug, and Cosmetic Act (FFDCA)
  - Otherwise, reviewers need to describe reasons for non-harmonized tolerance

    <u>EPA Exceptions:</u>

    - Harmonization with key trading partners (e.g., Canada)
    - Specific peculiarities/oddities in field trial data

OECD MRL Calculator

- Field trial issues may result in non-harmonized OECD Calculator results among different reviewers
  - For example, how to handle:
    - replicate samples or non-independent field trials
    - LOD or LOQ values
      - Statistical techniques for handling censored data
    - specific peculiarities/oddities in field trial data or conditions
    - Outliers
- EPA and PMRA working to develop common practices with respect to use of and input to the OECD calculator



2. Global Zoning

To what extent are geographic differences important in determining pesticide residues?

Global Zoning & Exchangeability of Field Trial Residues between Zones

- Joint project between US EPA, PMRA, IR-4 and Crop Life America to investigate the question:

"How Important are Geographic Zones in Determining MRLs?"

Global Zoning & Exchangeability of Field Trial Residues between Zones

- Currently, crop field trials are required to be conducted in a variety of (specified) zones
  - Zones are specific to each country/region

BUT:

Climatic (zonal?) differences may not have as much of an impact on residues as might be commonly or traditionally believed

-AND-

There may be a big advantage to MRL setting process in being able to combine field trials from across a larger (global) database

- save field trial review resources
- a more robust MRL can be estimated
- same data set = better harmonization

Early History: Global Zones/Regions

- OECD has supported a zoning committee to study whether world-wide climatic zones could be established for food crop residue trials.

  - Purpose: "to develop the concept of a global zoning scheme to define areas in the world where pesticide trial data could be considered comparable, and therefore where such trials could be used within each zone for MRL–setting purposes, irrespective of national boundaries" -- Report of the OECD/FAO Zoning Project, 29 August 2002

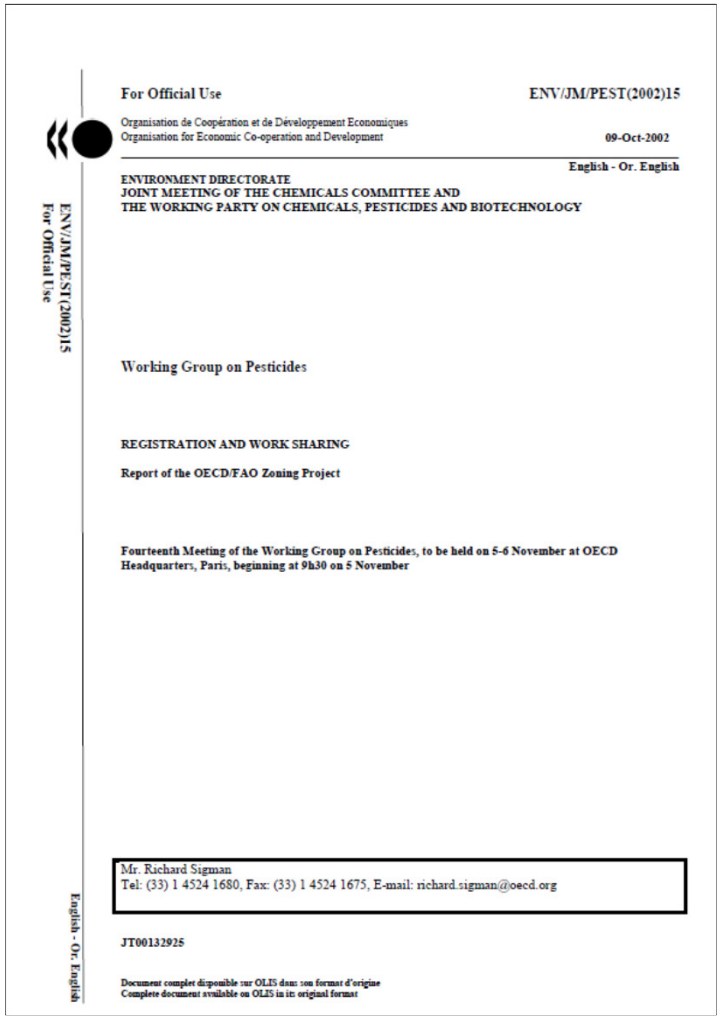
  - Goal: "to provide a technical position to support establishment of a finite number of worldwide zones to conduct food residue studies as part of the Codex process to establish MRLs globally."

-- Report of the OECD/FAO Zoning Project, 29 August 2002

Early History: Global Zones/Regions

- OECD group recommended (2002) that:

"JMPR and residue assessors… be encouraged to review the extent to which they use climatic differences to determine the acceptability of comparable residue trials data from other localities when establishing MRLs, taking into account the relatively small impact that pre-harvest climatic conditions appear to have on residue variability and recognizing the potential advantage of being able to accept residue trials from a larger global database of comparable trials"



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Working Group on Pesticides

REGISTRATION AND WORK SHARING

Report of the OECD/FAO Zoning Project

Fourteenth Meeting of the Working Group on Pesticides, to be held on 5-6 November at OECD Headquarters, Paris, beginning at 9h30 on 5 November

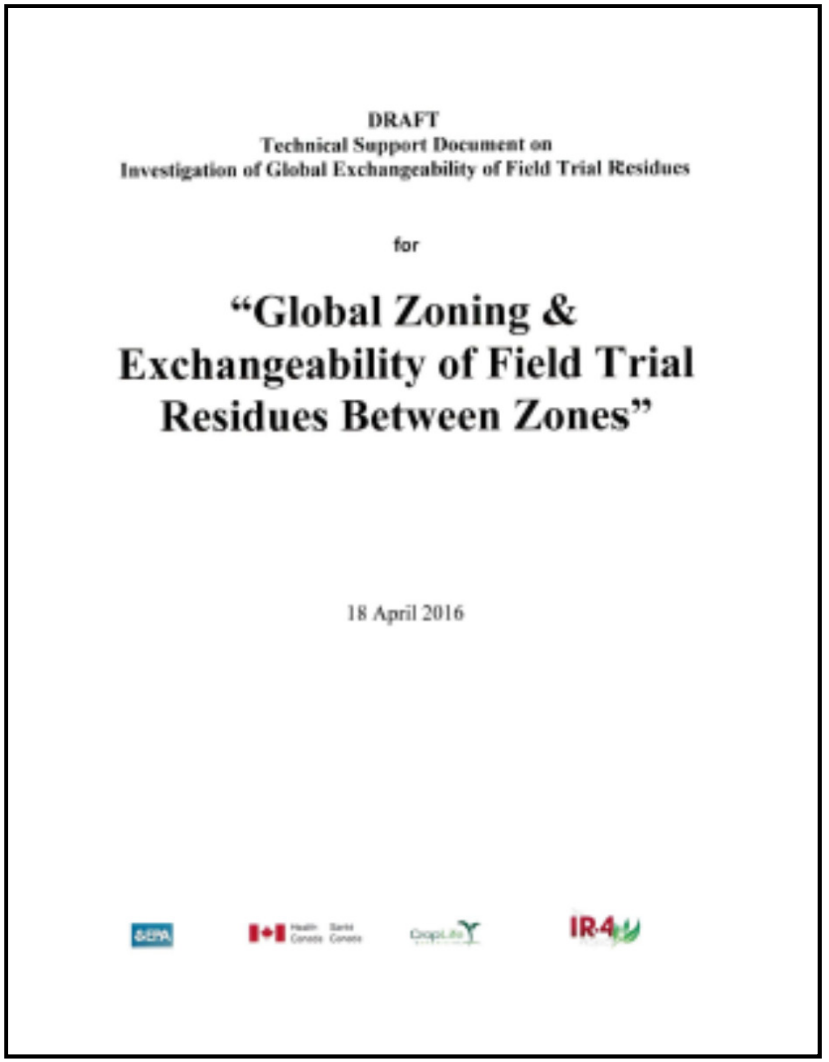
Mr. Richard Sigman
Tel: (33) 1 4524 1680, Fax: (33) 1 4524 1675, E-mail: richard.sigman@oecd.org

JT00132925

English - Or. English

Document complet disponible sur OLIS dans son format d'origine
Complete document available on OLIS in its original format

- US EPA, PMRA, IR-4, and CLA have recently collaborated to investigate further the overall conclusions of the 2002 OECD report, using statistical methods that are now more commonly used to evaluate this kind of data
- A draft version of report is publically available on Codex website (see agenda item 0.81)



DRAFT
Technical Support Document on
Investigation of Global Exchangeability of Field Trial Residues

for

"Global Zoning & Exchangeability of Field Trial Residues Between Zones"

18 April 2016

How Important are Geographic Zones in Determining MRLs?

QUESTION: Are there systematic differences in pesticide residue concentrations between zones?

- If not, residue data of a same crop-pesticide combination from various zones conducted under similar application/harvest scenarios and appropriate growing conditions could be combined to develop (international?) MRLs (possibly after adjusting for application rate)

Global Zoning & Exchangeability of Field Trial Residues between Zones

- Statistical Methods
  - Rank-Sum Test for Clustered Data
    - *non-parametric, analog to Kruskal-Wallis*
  - Mixed-effects model
    - *parametric, assumes residues within each crop-pesticide combination are lognormal*

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What did we find?

Rank-Sum Test for Clustered Data:

- Field trial residues are NOT significantly different between geographic zones (p=0.69)

Mixed-effects models to analyze log(residue)

- Field trial residues do not significantly differ between geographic zones (within ca. +/- 25%)

Global Zoning
Analyses and Results

- **Global Zoning** (North America, Europe, South America, Australia-New Zealand)

Methods	Comparison	Ratio (95% CI)	p-value	ANOVA p-value	# crop-pesticide combos, both zones
Rank Sum Test			0.686		
Mixed-effects model	AU-NZ vs.EU	0.724 (0.507, 1.033)	0.074	0.285	19
	AU-NZ vs.NA	0.874 (0.613, 1.246)	0.449		19
	AU-NZ vs.SA	0.862 (0.496, 1.499)	0.593		5
	EU vs.NA	1.207 (0.919, 1.585)	0.172		32
	EU vs.SA	1.191 (0.713, 1.991)	0.498		7
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CLA database (700 FTs, 36 crop-pesticide combinations, most are insecticides and fungicides) + IR-4 data

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Zones differ by no more than ca +/- 25%

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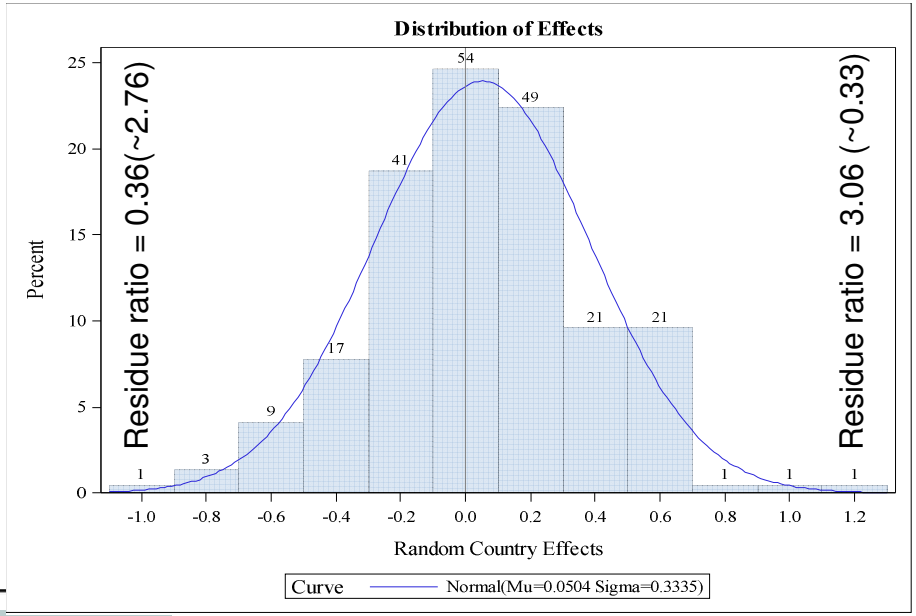
Estimates differ by no more than 2-fold

Canada vs. United States Results

219 crop-pesticide combinations		
Pest Type	N field trials	
	Canada	United States
F	562	1331
I	297	622
H	27	56

Covariance Parameter Estimates		
Cov Parm	Subject	Estimate
Intercept	Crop_Chem	2.1426
Country	Crop_Chem	0.1150
Trials (Crop_Chem)		0.4754
Residual		0.0613

	Mixed-effects model		Rank-Sum test for clustered data
Comparison	Ratio (95% CI)	p-value	p-value
Canada vs. United States	1.052 (0.959, 1.153)	0.281	0.268



What does it mean?

Rank-Sum Test for Clustered Data:

- Field trial residues are NOT significantly different between Canada and the United States

Mixed-effects models to analyze log(residue)

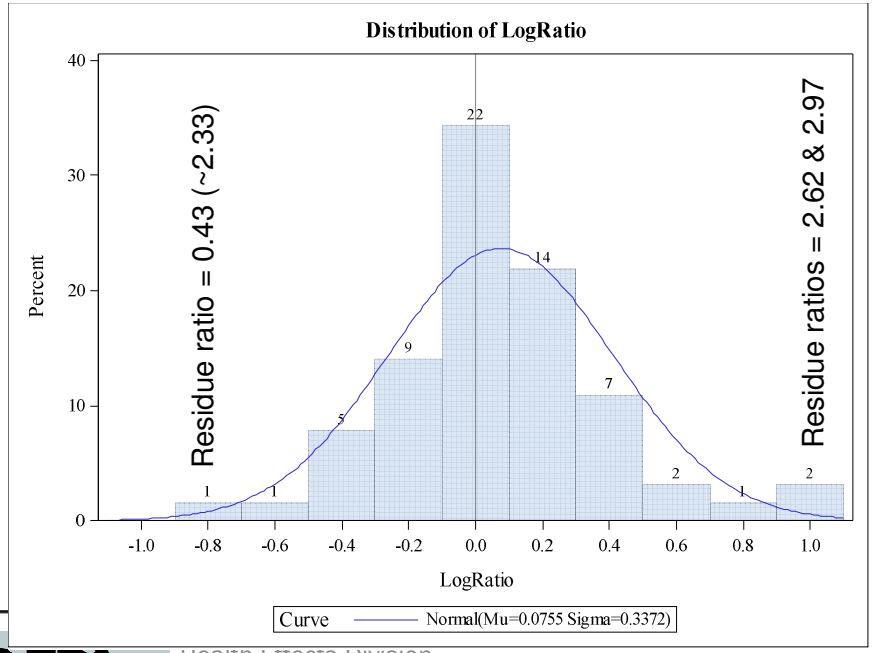
- Field trial residues in Canada are about 5% higher than the United States, but NOT significantly different

Northern Europe vs. Southern Europe Results

64 crop-pesticide combinations		
Pest Type	N field trials	
	EU-N	EU-S
F	91	104
H	8	8
I	234	257

Covariance Parameter Estimates		
Cov Parm	Subject	Estimate
Intercept	CropPest	2.9975
Zone	CropPest	0.1210
Trials (CropPest)		0.5528
Residual		0.0968

	Mixed-effects model		Rank-Sum test for clustered data
Comparison	Ratio (95% CI)	p-value	p-value
EU-N vs.EU-S	1.078 (0.902, 1.290)	0.403	0.876



What does it mean?

Rank-Sum Test for Clustered Data:

- Field trial residues are NOT significantly different between Northern and Southern Europe

Mixed-effects models to analyze log(residue)

- Field trial residues in Northern Europe are about 8% higher than Southern Europe, but NOT significantly different

Steps in Current EPA-PMRA-IR4-CLA Initiative

☑ *STEP 1 : Review past attempts and methods to evaluate Global Zoning*

☑ *STEP 2: Develop Statistical Methods appropriate for use in evaluating the Global Zoning concept*

☑ *STEP 3: Evaluate the selected statistical methods using synthetic residue data*

☑ *STEP 4: Evaluate the "exchangeability" of residues between US and Canada as a test case using a real residue database provided by PMRA*

☑ *STEP 5: Extend the method to a global basis based on datasets collected from around the world*

- ☒ *EU-North vs. EU- South*
- ☒ *Global* (North America, Europe, South America, Australia-New Zealand)

☐ *STEP 6: Internal/External Review*

☐ *STEP 7: Policy, Policy, Policy!*

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Results/Findings for **Global**, **US vs. Canada**, and **EU-N vs. EU-S** are detailed in associated issue paper available on Codex agenda page website

DRAFT
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18 April 2016

3. Crop Grouping

Statistical Techniques to Evaluate Crop Grouping Schemes

Crop Grouping Background

- Crop Grouping is a well-accepted approach that facilitates the establishment of pesticide tolerances for major and minor crops
  - allows field trials supporting MRLs in certain defined "representative crops" to be used to support MRLs in similar crops in that group
  - Used to determine if representative crops can support a crop group

- Several regulatory procedures have been used to establish parameters regarding when a single MRL among crops within a group can be established

  - US EPA / Canada PMRA: rule of 5X maximum values ("Rule of 5X Max")
    - The MRL for each representative crop is calculated separately

      $\Rightarrow$ if within 5-fold, can be grouped into a crop group, with crop group MRL determined by residues in highest representative crop

  - JMPR: rule of 5X median values ("Rule of 5X Med")
    - ratios of median residue values of representative crops

  - The established statistical Kruskal-Wallis or Wilcoxon-Mann-Whitney test

Crop Grouping Background

- **Why are there concerns?**
  - Differing criteria and methods used for setting crop group MRLs may lead to non-harmonized crop-group MRLs across countries for the same pesticide-commodity combination
    - This, despite use of (common) OECD MRL calculator
- Our current (preliminary) analyses focus on *simulations* to:
  - Illustrate how different two lognormal distributions with median values that differ by 5 fold (or 2-, 3-, or 4- fold) can be.
  - Compare the ***power*** of various methods to detect ***target differences*** between the residues of representative crops (e.g., 2-, 3-, 4-, or 5- fold)
  - Explore what resulting MRLs might be depending on what is -- and what is not -- combined.
- Currently, investigation is *exploratory* using *synthetic data* and is a work in progress

Three Issues:

- Question 1: How can we visualize the differences between residue distributions?

- Question 2: "How reliably can we detect "x-fold" differences?
  - Corollary: …and with what statistical methods?

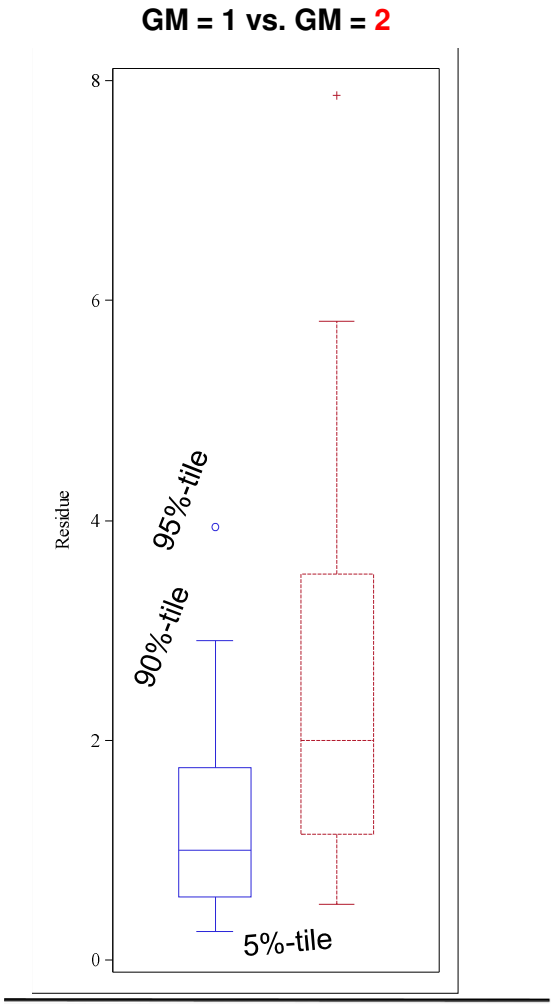
- Question 3: How different will a crop group MRL be when a crop group MRL is established compared to the "would have been" individual representative crop MRLs

Caveat: **All analyses performed here are based on simulated data.. no actual field trial data were used**

Numerical Difference vs. Practical Difference

To what extent are 2-fold-different residues "sufficiently similar"?

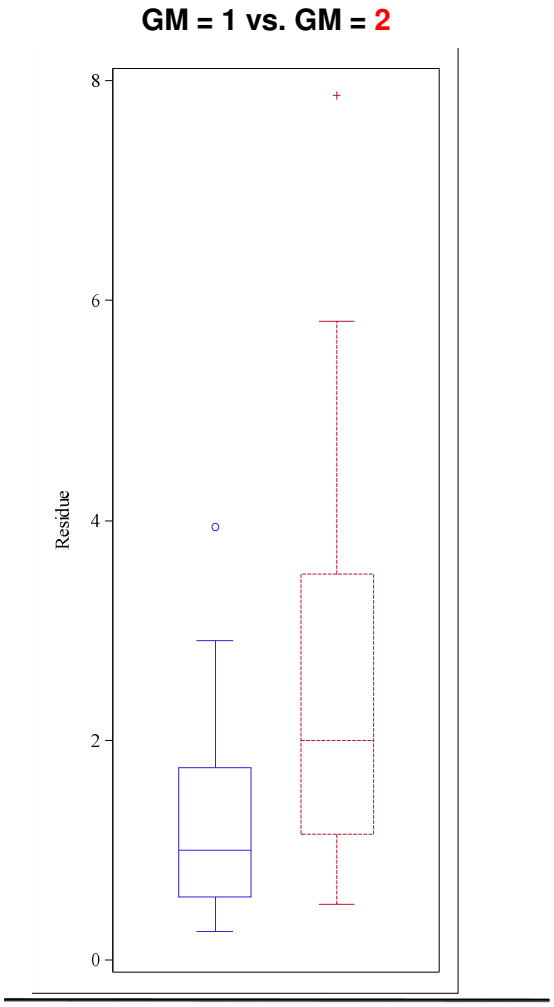
- KEY QUESTION: How different is "different"?



Numerical Difference vs. Practical Difference

How reliably can one detect 2-fold-differences?

- KEY QUESTION: What difference can we detect?



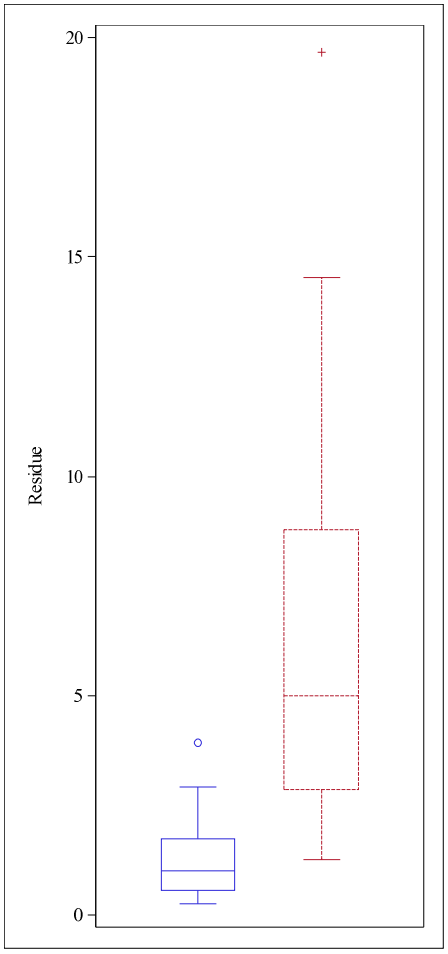
Designed Max Ratio Factor (R)	Number of Groups (rep crops)	N Field Trials per group	Power to detect differences between groups when R=2		
			Kruskal Wallis	Max 5X	Med 5X
2	2	5	**0.22**	0.12	0.07
		7	**0.29**	0.10	0.04
		10	**0.41**	0.09	0.02
	3	5	0.17	**0.22**	0.13
		7	**0.27**	0.19	0.08
		10	**0.39**	0.16	0.03
	4	5	0.18	**0.33**	0.20
		7	**0.29**	0.28	0.14
		10	**0.44**	0.25	0.05
	5	5	0.21	**0.44**	0.27
		7	0.31	**0.37**	0.17
		10	**0.49**	0.33	0.07

Numerical Difference vs. Practical Difference

To what extent are 5-fold-different residues "sufficiently similar"?

- KEY QUESTION: How different is "different"?

GM = 1 vs. GM = 5

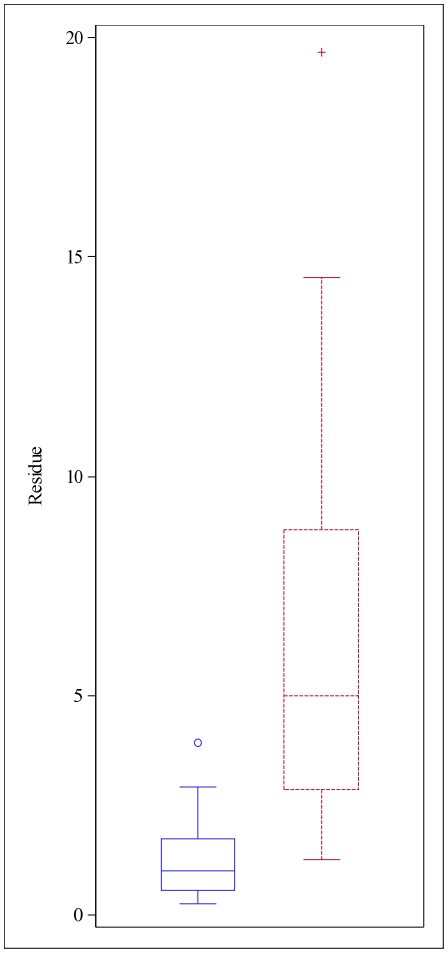


Numerical Difference vs. Practical Difference

How reliably can one detect 5-fold-differences?

- KEY QUESTION: What difference can we detect?

GM = 1 vs. GM = 5



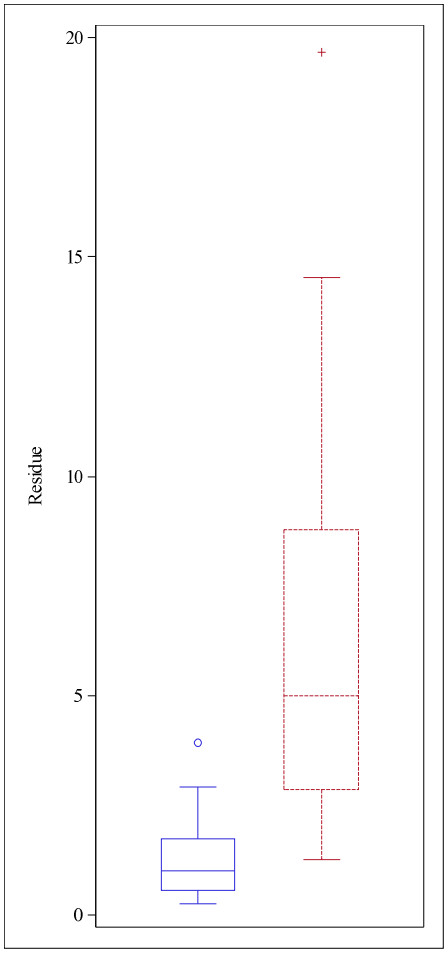
Designed Max Ratio Factor (R)	Number of Groups (rep crops)	N Field Trials per group	Power to detect differences between groups when R=5		
			Kruskal Wallis	Max 5X	Med 5X
5	2	5	**0.75**	0.49	0.50
		7	**0.89**	0.50	0.50
		10	**0.98**	0.49	0.50
	3	5	**0.66**	0.60	0.56
		7	**0.86**	0.61	0.59
		10	**0.97**	0.60	0.58
	4	5	0.65	**0.69**	0.66
		7	**0.85**	0.69	0.66
		10	**0.97**	0.68	0.63
	5	5	0.66	**0.78**	0.73
		7	**0.87**	0.75	0.70
		10	**0.97**	0.74	0.69

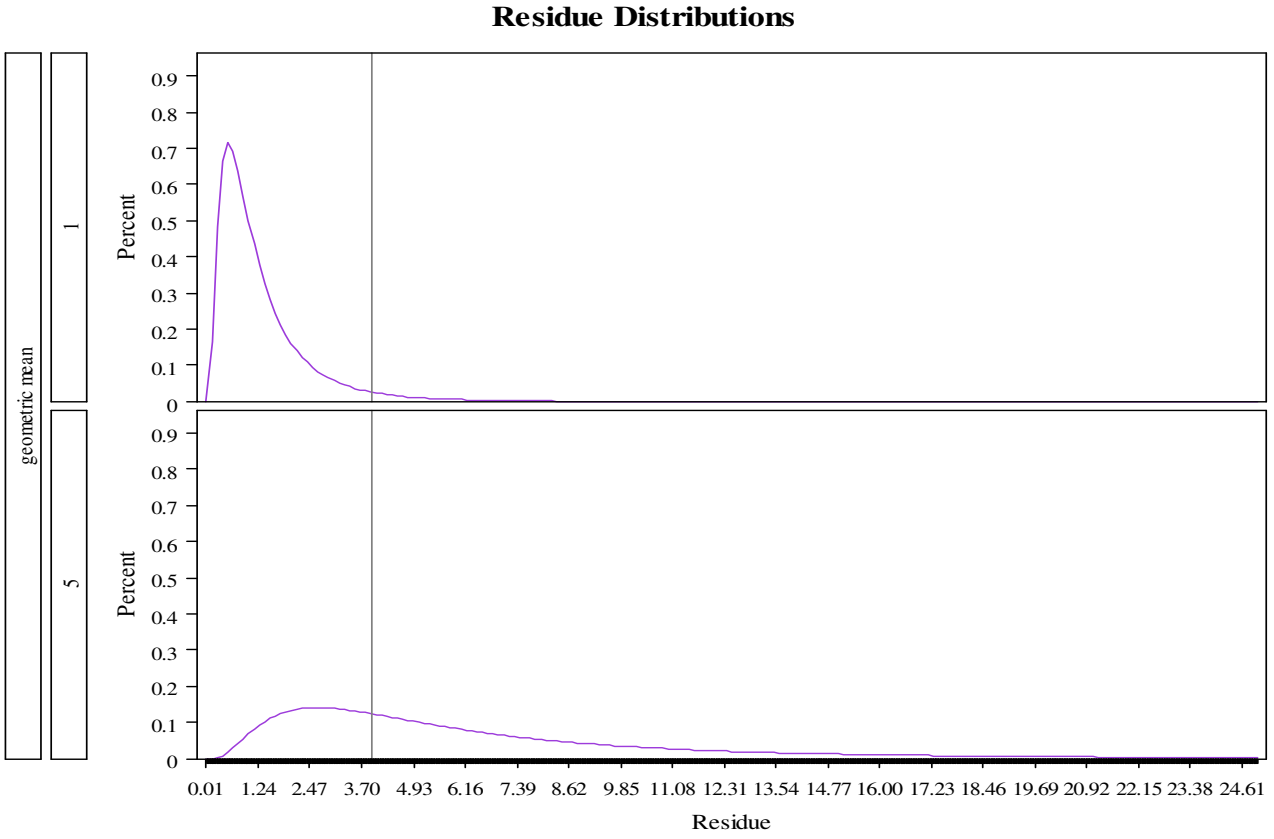
Numerical Difference vs. Practical Difference

How reliably can one detect x-fold-differences?

- KEY QUESTION: What difference can we detect?

GM = 1 vs. GM = 5





CONCLUSION: **Using the KW test, we can reliably (> ca 70%) detect 5-fold differences (re-illustrated here) in residue distributions**

- detecting < 5 fold is less reliable (as low as ~50%

Side-note: Risk of False Rejection

There is also in interest in not rejecting the combining of rep crops when there is indeed no difference in residue distributions

Probabilities here are of incorrectly rejecting the combining of the rep crops (here Max Ratio Factor, R = 1, so distributions are equal)

- NOTE: look for these probabilities to be small

Risk of False Rejection (R=1)

Designed Max Ratio Factor (R)	Number of Groups (rep crops)	N Field Trials per group	Power to detect differences between groups when R=1		
			Kruskal Wallis	Max 5X	Med 5X
1	2	5	0.06	0.05	0.01
		7	0.05	0.03	0.00
		10	0.05	0.02	0.00
	3	5	0.05	0.11	0.03
		7	0.04	0.07	0.01
		10	0.04	0.05	0.00
	4	5	0.04	0.18	0.06
		7	0.04	0.12	0.02
		10	0.04	0.10	0.00
	5	5	0.04	0.24	0.08
		7	0.04	0.18	0.03
		10	0.04	0.13	0.00

Probabilities here are of incorrectly rejecting the combining of the rep crops (recall: here Max Ratio Factor, R = 1, so distributions are equal)

Developing and Evaluating Crop Group MRLs

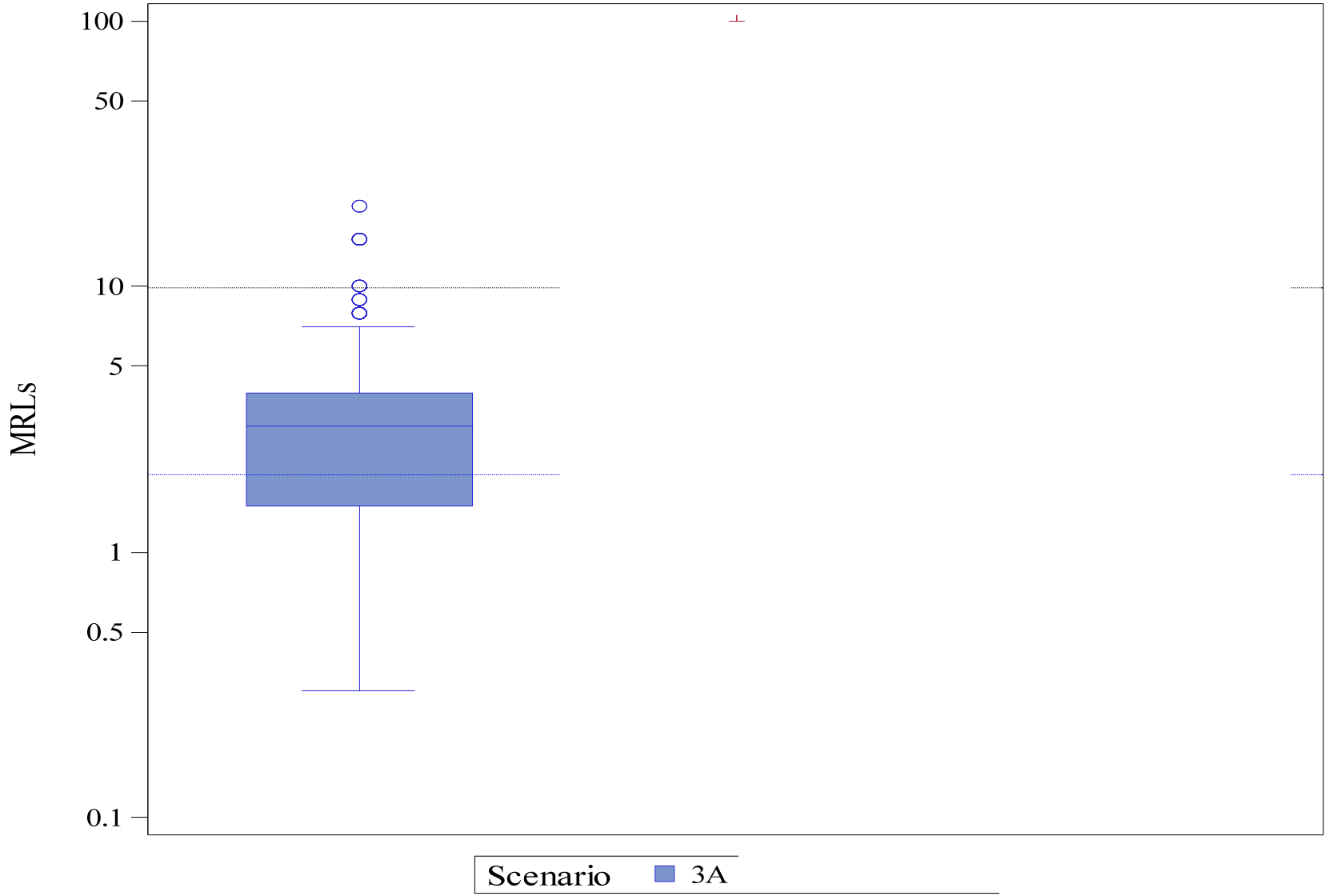
- In addition to:
  1) being able to reliably (e.g., > 70%) determine a difference determined to be of substantive importance (e.g., 5 fold) ; and
  2) not incorrectly rejecting the combining of crops when there is no difference,

  …we want to ensure that the resulting crop group tolerance is not inordinately high or inordinately low

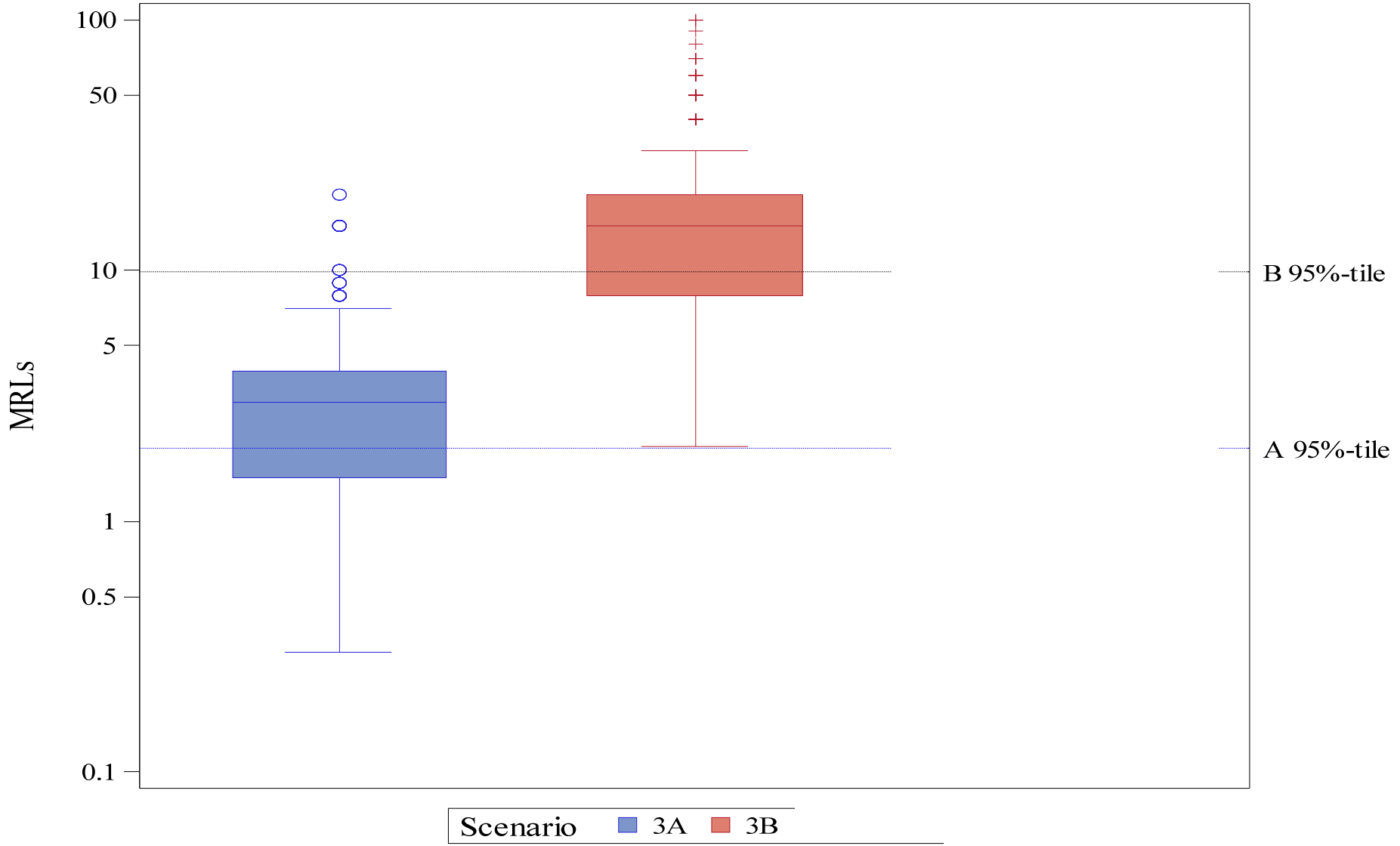
  - Necessarily a judgement call

  - Possible to simulate a crop group MRL and compare it what would have been individual representative crop MRLs had they not been combined
    - How does crop group MRL compare to ("would have been") individual (rep crop) MRLs?

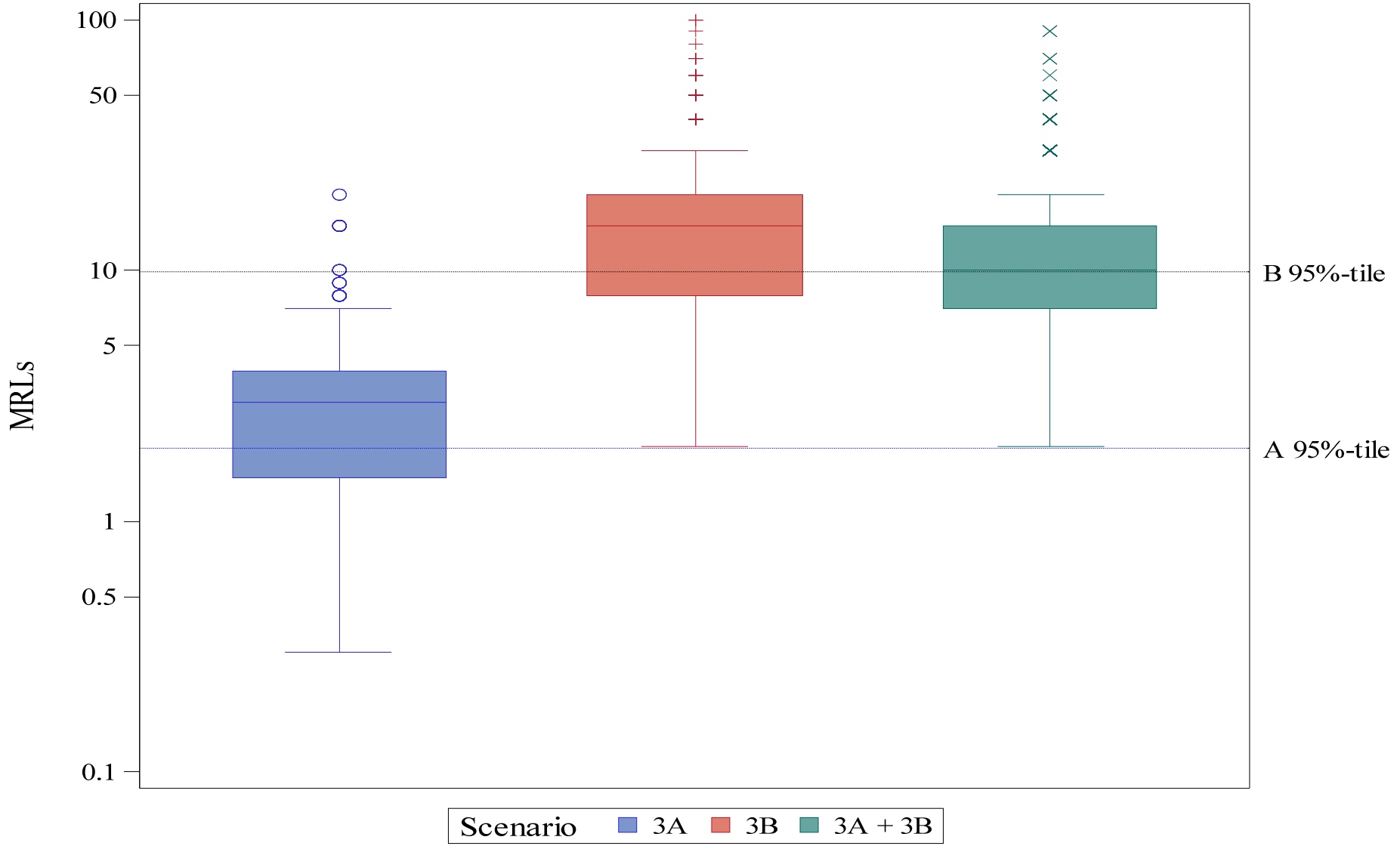
Impact of crop grouping 1X & 5X on MRLs: 3 trials



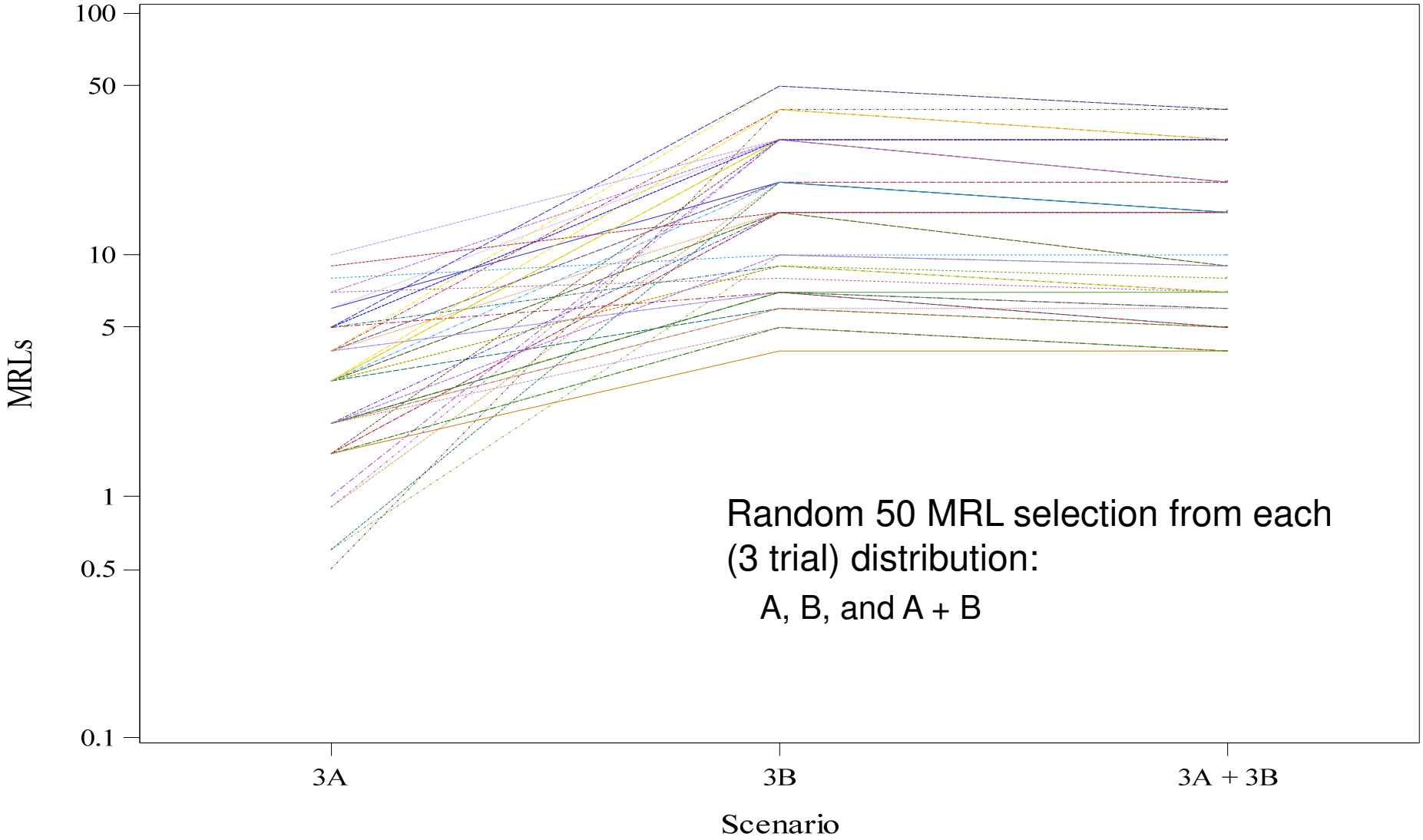
Impact of crop grouping 1X & 5X on MRLs: 3 trials



Impact of crop grouping 1X & 5X on MRLs: 3 trials



Impact of crop grouping 1X & 5X on MRLs: 3 trials



4. GlobalMRL.com

Software to improve accessibility of national MRL information

GlobalMRL.com

- US EPA MRLs (aka “tolerances”) published in the electronic Code of Federal Regulations (40 CFR, 180, Subpart C) available at eCFR.gov
- eCFR has limited search capability – mostly textual
  - Good for “forward searches” by chemical
  - Can be difficult to reliably search in other directions
    - e.g., “backward search” by crop or crop group

      => *Strawberry* listed a dozen different ways

GlobalMRL.com

- US EPA and USDA have cooperatively funded Bryant-Christie, Inc. to make GlobalMRL.com available worldwide
  - Launched February 2015
  - Subscription currently “open access” to all for US tolerances (through December 2019)
  - updated version of FAS-Online, MRLdatabase.com
    - Improved user interface (to include Excel downloads)
    - Includes veterinary drug tolerances, processed commodity MRLs, facility use tolerances, and US import tolerances
  - User doesn’t need to know that US MRLs for strawberries listed more than a dozen ways in eCFR
    - GlobalMRL.com “maps” each of these back to “strawberry”

GlobalMRL.com

- Requires users to login and register at http://globalmrl.com
  - *Non-US based users*: access to US MRLs (including import MRLs) only
  - *US-based users*: access to US MRLs and foreign *MRLs for which there are US tolerances*
    - Global perspective with MRLs available for over 800 active ingredients and 700 commodities in more than 100 countries
  - *USEPA and USDA users*: further enhanced access (Enterprise version)
- User selects Commodities, Pesticides, and Markets + additional optional filters
  - User guide and FAQs available to users
  - See example video at https://player.vimeo.com/video/145323858

SUMMARY

- OECD MRL Calculator generally considered a success

  ..and at least puts national regulators on the same page with respect to initiating a discussion on MRL differences

- OECD established a workgroup in the early 2000s to explore establishment of a finite number of worldwide zones to conduct residue studies as part of the Codex process to establish MRLs globally
  - Using earlier OECD work, EPA-PMRA-IR4-CLA sought to advance this using currently available residue data and more current statistical methods. This is actively under investigation and we anticipate bringing this to OECD in the near future.

SUMMARY

- EPA and PMRA are currently conducting exploratory analyses with respect to Crop Grouping Issues and how the OECD MRL calculator might be best used in setting Crop Group MRLs
  - Using the KW test, we can reasonably reliably (> ca 70%) detect 5-fold differences in residue distributions
    - detecting < 5 fold is less reliable (as low as ~50%)
  - Kruskal-Wallis is better technique to compare residue distribution in crop grouping than 5X-Max rule and 5X-Median rule
  - Determination of whether a 5-fold difference is meaningful in the regulatory context of crop grouping and field trials is a judgment call

SUMMARY

- Simulation of a crop group MRL and individual representative crop MRLs can be used to show impact on crop group MRL of using KW test to determine if representative crops can be combined into a single crop group

  …we want the resulting crop group tolerance to be "reasonable" for all crops in established group

  - not inordinately high or inordinately low
  - Necessarily a judgment call

- US EPA and USDA have jointly funded a GlobalMRL.com database that provides international users no-charge access to a database of US tolerances on the internet
  - US users have expanded access

Acknowledgements:

James Nguyen

PMRA

Crop Life America

IR-4


Thank you !

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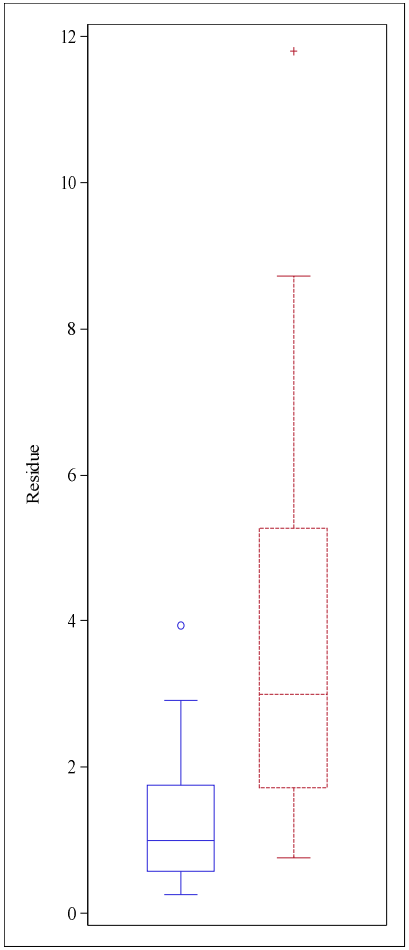
Additional Slides

Numerical Difference vs. Practical Difference

How reliably can one detect 3-fold-differences?

- KEY QUESTION: What difference can we detect?

GM = 1 vs. GM = 3



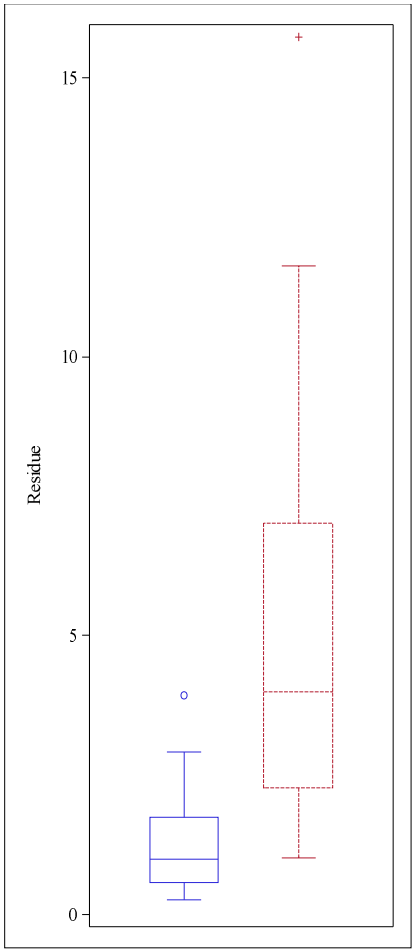
Designed Max Ratio Factor (R)	Number of Groups (rep crops)	N Field Trials per group	Power to detect differences between groups when R=3		
			Kruskal Wallis	Max 5X	Med 5X
3	2	5	**0.46**	0.25	0.20
		7	**0.60**	0.24	0.17
		10	**0.78**	0.23	0.12
	3	5	0.36	**0.37**	0.28
		7	**0.54**	0.34	0.24
		10	**0.74**	0.32	0.17
	4	5	0.35	**0.47**	0.37
		7	**0.55**	0.44	0.31
		10	**0.75**	0.40	0.22
	5	5	0.37	**0.58**	0.45
		7	**0.57**	0.53	0.37
		10	**0.77**	0.50	0.26

Numerical Difference vs. Practical Difference

How reliably can one detect 4-fold-differences?

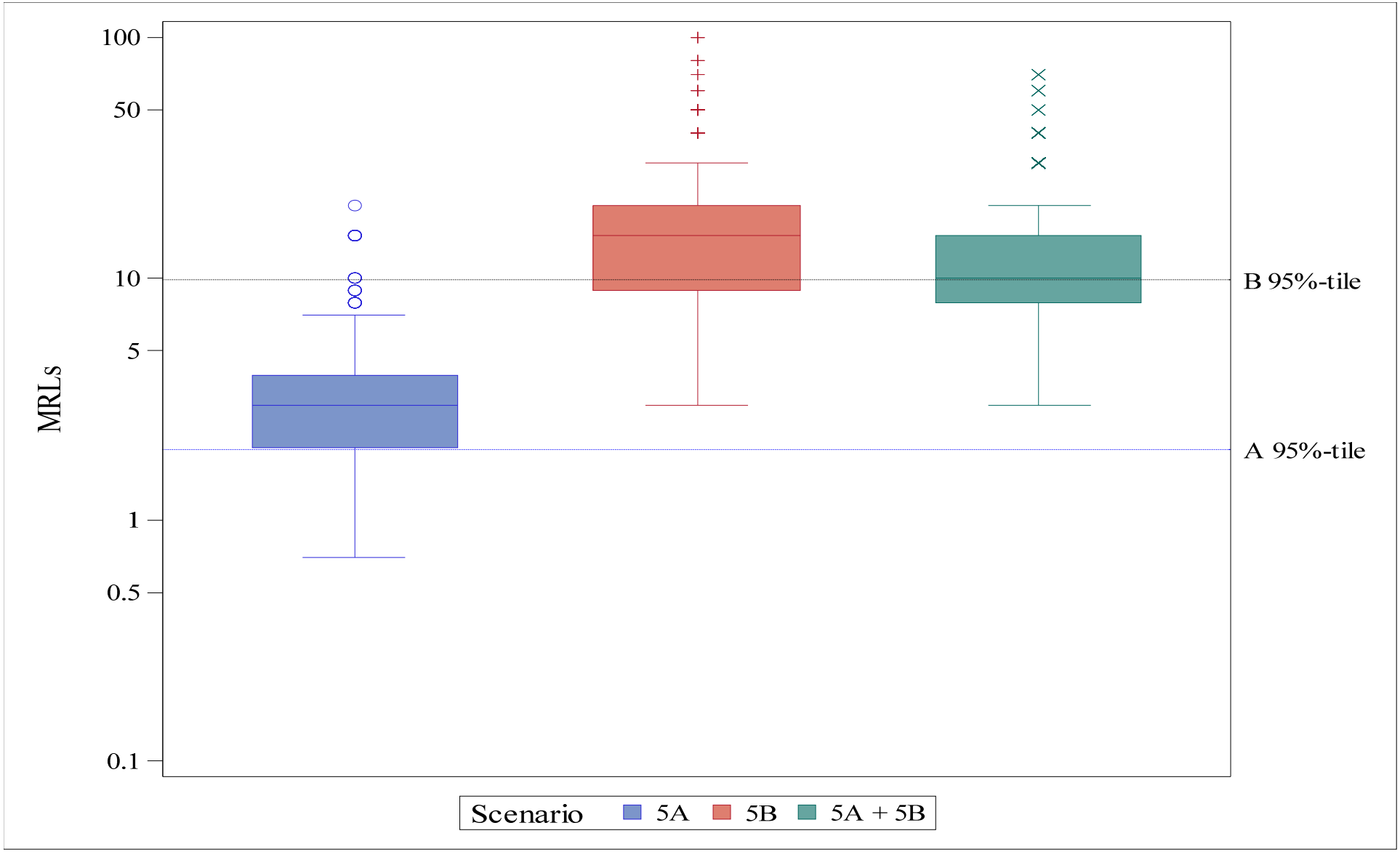
- KEY QUESTION: What difference can we detect?

GM = 1 vs. GM = 4

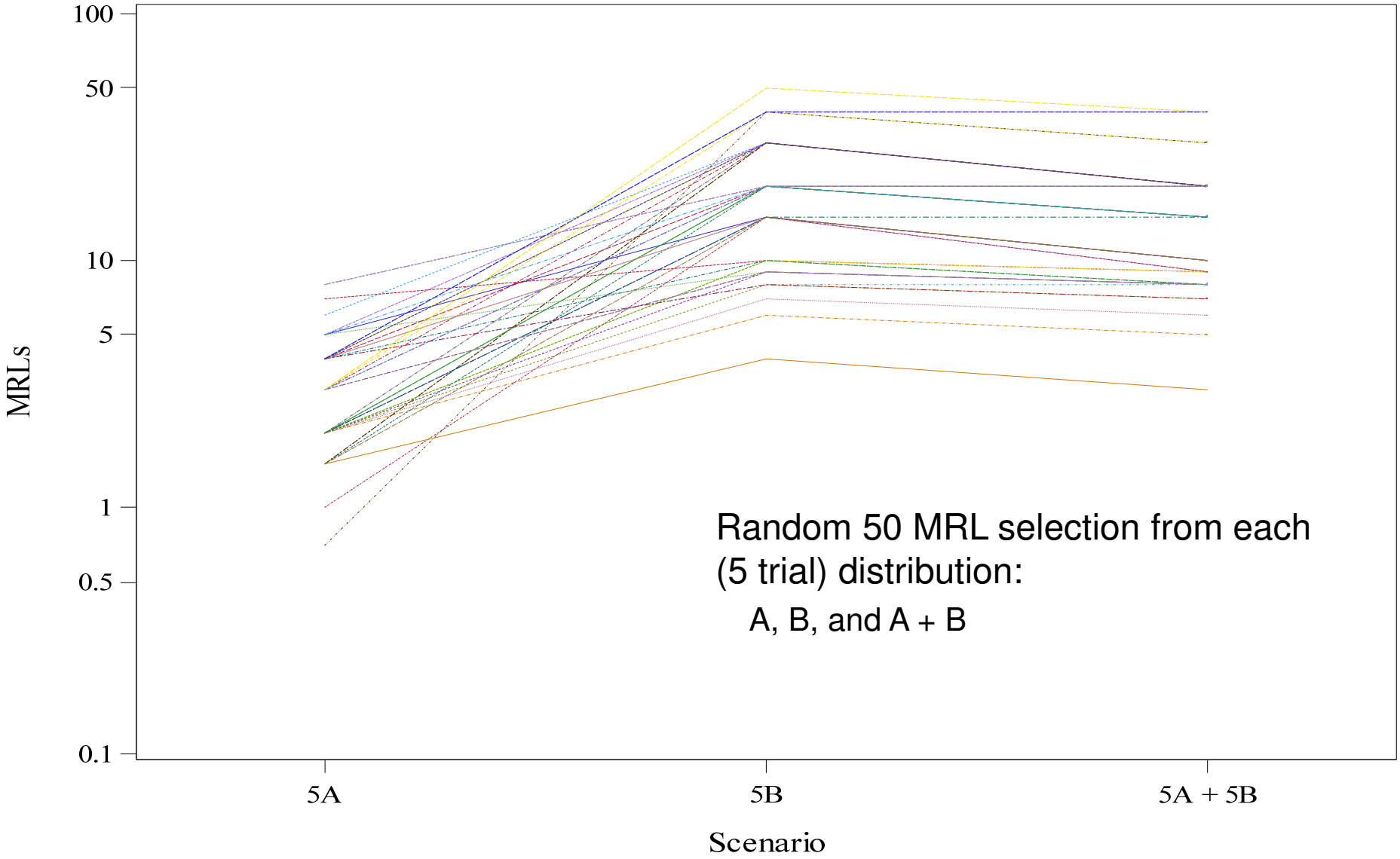


Designed Max Ratio Factor (R)	Number of Groups (rep crops)	N Field Trials per group	Power to detect differences between groups when R=4		
			Kruskal Wallis	Max 5X	Med 5X
4	2	5	0.63	0.38	0.36
		7	0.80	0.38	0.33
		10	0.93	0.36	0.31
	3	5	0.53	0.49	0.43
		7	0.74	0.49	0.42
		10	0.91	0.46	0.38
	4	5	0.51	0.60	0.54
		7	0.74	0.58	0.50
		10	0.91	0.56	0.44
	5	5	0.54	0.69	0.60
		7	0.75	0.65	0.55
		10	0.92	0.64	0.50

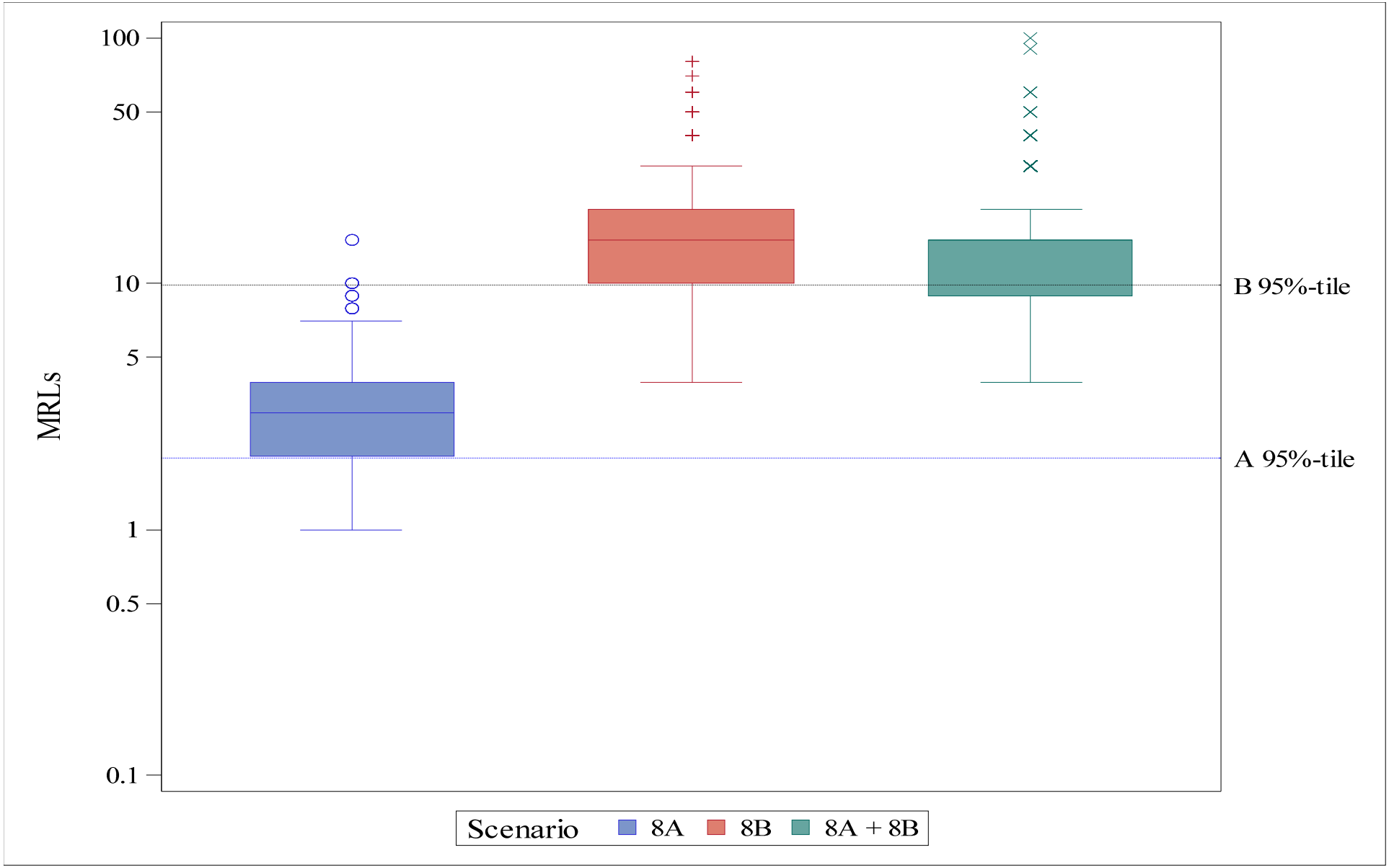
Impact of crop grouping 1X & 5X on MRLs: 5 trials



Impact of crop grouping 1X & 5X on MRLs: 5 trials



Impact of crop grouping 1X & 5X on MRLs: 8 trials



Impact of crop grouping 1X & 5X on MRLs: 8 trials