Potential Revision of the IESTI Equation – an Industry Perspective

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- Introduction
- Proposed changes in the IESTI equation – positions and recommendations for further work
- Tiered approach for acute exposure assessment
- Conclusion

→ **Industry position based on information provided in the WHO / RIVM Background document**

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Regulatory Background: WHO / FAO guidance

World Health Organization

Food and Agriculture Organization of the United Nations

- Evaluation of one-day exposures to acutely toxic chemicals in food based on 97.5 th percentile intake. (“large portion” consumption)
- Exposure estimate based on:
  - Commodity unit weights and food portion weights
  - Body weight of consumers
  - High or median residue levels in food items consumed (estimated from measurements in composite samples)
  - Variability factors
- Definition of 4 cases (depending on unit weight and variability case) **2a /2b cases**
- **Final step:** Comparison of exposure with Acute Reference Dose (ARfD) **1/3 cases**

➔ **WHO / FAO guidance implemented in PRIMo Revision 2**
➔ **JMPR: Use of a default variability factor of 3 (for all 2a / 2b cases)**

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Regulatory Background: EU MRL Regulation 396/2005

- MRLs have to be set in accordance with the use directions (critical GAP), but “as low as reasonably achievable” to minimize exposure to residues (“ALARA” principle)
- MRLs are trading standards not safety limits
- MRLs are set for the commodity in trade (e.g. unpeeled banana / orange fruits, wheat grain, soybean seeds)
- MRLs have to be set in such a way that there are **no concerns for public health**, especially with regard to vulnerable subpopulation groups (e.g. children and the unborn)

➔ **For acute assessment: High efforts in risk communication did not prevent NGO actions and the establishment of secondary standards**

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General point – Purpose of the assessment?

- ***In principle, two options:***
  - Evaluation of the dietary risk related to a specific use
  - Evaluation of the dietary risk related to a specific MRL (independent from the probability that residues exceed the MRL level)
- ***Primary purpose has considerable impact on the***
  - Level of conservatism desired
  - Way that assessments will be done
  - What refinement options are available to obtain a better view on realistic consumer exposure

➔ **Purpose needs to be discussed first and harmonized**
➔ **ECPA Position: Safety assessment of uses (as performed by US EPA)**

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Proposed changes – points addressed in the Background Document

Background Document

- Use of the MRL for all three cases?
- How to use variability factors, conversion factors and processing factors?
- How to address differences in consumption behaviour (large portions)?
- How to handle residues below LOQ and residues in food of animal origin?
- Impact of options on the desired “level of protection”?

ECPA Position Paper

LOQ = limit of quantification

➔ Presentation will focus on regulatory aspects (approval of uses, MRL setting)
➔ Position on other points are included in an ECPA position paper

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Proposed changes – use of the MRL for all 3 cases?

- Differentiation by food and by case needed

Food of plant origin

Case	Recommendation
Case 1	Use of MRL acceptable as a starting point for screening To avoid unnecessary high MRL values: • Use of global data sets • Broader extrapolation rules • Principle of proportionality
Case 2	Use of MRL acceptable for screening Keep separation between case 2a and case 2b
Case 3	Keep use of the STMR For PRIMo: Consider harmonization with WHO / GEMS (where by far more commodities are case 3)

➔ **Proposed changes to be considered together with already established changes**
➔ **Use of the OECD MRL calculator , "MRL classes"**

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Proposed changes – use of the MRL for all 3 cases?

- Differentiation by food and by case needed

Food of animal origin

Case	Recommendation
Case 1	No case 1 for food of animal origin anymore, all food commodities of animal origin to be evaluated according to case 3: • MRLs derived from livestock feeding studies • Dose levels in feeding studies are based on multiple worst case assumptions • Generally no detectable residues found in any monitoring programme
Case 3	Keep use of the median residues from the dose level corresponding to “realistic“ feed burden.

➔ **For all cases and commodities: Use of MRL / STMR considered as first tier assessment (Tier 0)**

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Proposed changes – use of variability factors?

- One default variability factor for all compound / commodity combinations is supported by data evaluated by JMPR (2005)
  - Consistent use of **var = 3** if cases 2a and 2b are kept separately
  - If there is <u>one</u> case 2 (option 3): Further theoretical work needed for commodities where the number of units in large portions exceeds 10 (e. g. plums, figs, apricots)

➔ **Depending on outcome: Different factor for "smaller" crops more appropriate**

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Proposed changes – use of processing factors?

- Use of processing factors are essential for evaluating dietary exposure
- Processing data are generated by industry (following OECD guideline)
- For use in exposure assessment, availability of appropriate and actual consumption data is a MUST (differentiation of forms)
- Separate IESTI assessments to be conducted for raw and processed food forms (e. g. whole apples – apple juice)

➔ **Current version of EU PRIMo (rev. 2) does not allow differentiation**
➔ **Substantial update or move to WHO / GEMS model needed**

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Proposed changes – use of conversion factors?

- Establishment of residue definitions for MRL setting and risk assessment essential part of the approval process
- To compensate for late changes in residue definitions, use of a conversion factor is essential
- Conversion factor could be derived from metabolism and residue field studies
- Use of highest conversion factor in combination with MRL:

→ **overestimation of risk**

- Higher tier: Generation of appropriate residue data for both definitions

→ **Need for further work and guidance on conversion factors already mentioned in EFSA PPR Panel Opinion "Residue definition for risk assessment"**

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Proposed changes – global large portion data?

- Large portion data should be based on kg per kg bw/day to reflect actual consumer behaviour (correlation between food consumed and body weight)
- An impact assessment can be done using the German model (2009) where both types of calculation are included
- Collection of a global list of large portions (as in WHO / GEMS) important for harmonized assessment approaches, but prior to use considerable harmonization efforts are needed for
  - Residue parameter (e.g. food being consumed, crop grouping, residue definition)
  - Risk assessment methodology (deterministic, probabilistic)
  - Tox endpoints: ARfD setting (whole population or population adjusted)
  - Policy questions

➔ **EU safety assessments should be based on EU consumption behaviour and habits**

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Proposed changes – unit weights and options

- Removal of unit weights not feasible as unit weights are needed for differentiation of cases
- Option 3 will result in a considerable overestimation of risk (assumption for case 2: all commodities consumed within one day will have residues at 3 x MRL level)
- Further work recommended – probabilistic tools
  - Evaluate level of realistic exposure using monitoring data relative to IESTI model changes
  - Compare output with a potential “option 4”: Removal of variability factor for combinations with MRL_{OECD}
    - **Case 1 = Case 2: IESTI = LP_{BW} x MRL_{OECD} x CF x PF**
    - **Case 3: IESTI = median x CF x PF**

Option 1 - 3

➔ Further impact assessment on options needed

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Proposed changes – handling of residues below LOQ?

- Conduct of acute risk assessments (IESTI equation) not needed for cases where no exposure exists
  - ➢ Application of variability, processing and conversion factors not feasible as relevant data might not be available
- Different policies for MRL setting to be considered
  - **JMPR:** CXL for target crops
  - **EU:** Setting of default MRLs for all commodities

➔ **Inclusion of LOQ levels in acute exposure assessment will have major impact in future cumulative assessment**

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Industry proposal for an acute dietary exposure assessment in regulatory context (EU / WHO) – deterministic tiers

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Tier 0
MRL = Unrefined

- **Exposure Estimate**: MRL calculator conservatively sets maximum for statistical limit based on (usually above) field c-GAP MOR field trial data; at 100% crop treated, use of default variability factors of 1 and 3. For first screening: MRL might be also used for case 3 commodities (including food of animal origin)
- **Methodology:** Deterministic

Tier 1
Slightly refined

- **Exposure Estimate**: Use of compound-specific processing factors in combination with MRL, investigate impact of variability factor by using an adjusted ”variability factor” or var = 1 for specific crops
- **Methodology**: Deterministic with fully detailed consumption data

Tier 2
More refined

- **Exposure Estimate**:Use of observed residues from cGAP MOR field trial data: Residue levels (HR, STMR) replaces the MRL (plus use of processing factors and adjusted “variability factors”)
- **Methodology**: Deterministic with fully detailed consumption data

➔ **Today: JMPR assessment according to Tier 2**

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Industry proposal for an acute dietary exposure assessment in regulatory context (EU / WHO) – probabilistic tiers

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- **Exposure Estimate**: Use of the MRL for focal commodity (plus fixed variability factor of 1/3) and monitoring data for other target crops (if not available: consider use of STMRs) in combination with distributions for consumption data
- **Methodology**: Probabilistic according to a "realistic scenario": Exposure is estimated based on all food commodities consumed during a single day.

Tier 3a
Refined Dietary

- **Exposure Estimate**: Use of compound-specific processing factors in combination with MRL for focal commodity, monitoring data for other target crops (if not available: consider use of STMR(p) values), distributions for consumption data
- **Methodology:** Probabilistic according to a "realistic scenario"

Tier 3b
Refined

➔ **Today: US EPA assessments in accordance with probabilistic tiers**

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Industry proposal for an acute dietary exposure assessment in regulatory context (EU / WHO) – probabilistic tiers

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- **Exposure Estimate**: Use of whole distribution of residue data from supervised field trials / processing data for focal commodity (for other target crops: see above) in combination with distributions for consumption data
- **Methodology**: Probabilistic according to a "realistic scenario" (reference: EFSA PPR Panel GD on probabilistic RA)

Tier 4
Highly Refined

Tier 5

- **Exposure Estimate**: Use of additional refinements as e.g. percent of crop treated (based on market share data from agronomic uses databases
- **Methodology**: Probabilistic (important in context of cumulative exposure assessment)

➔ **Highest tier for estimating actual exposure of consumers**

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Conclusion

- Potential revision of the IESTI equation
  - Considerably increases the conservatism of acute exposure assessment
  - Has different impact on different cases and different types of food (plant, animal origin)
  - Results in an overestimation of exposure especially for option 3
  - Might further increase public concerns on safety of pesticide residues
- Purpose of risk assessment to be clarified / harmonized first
  - Dietary risk related to a specific use?
  - Dietary risk related to the MRL?

➔ **Promote international harmonization between JMPR, Japan, Europe and USA / Canada**

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Conclusion

- Further work on selected input parameters for IESTI equation suggested:
  - Variability factor (if LP > 10 units)
  - Conversion factor between residue definitions
  - Inclusion of relevant consumption data (EU PRIMo 2)
- Continue development of a probabilistic tool for single active substances allowing an impact assessment and a tiered approach:
  - Goal: Evaluate level of actual exposure using monitoring data relative to IESTI model changes by probabilistic tools (e.g. MCRA 8.1)

➔ **Keep current IESTI equation (as applied by JMPR) until full impact is known and further work is completed**

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Acknowledgements:

- ECPA ad-hoc group dietary risk assessment

  - ✓ **Adama**
  - ✓ **Bayer**
  - ✓ **BASF**
  - ✓ **DuPont**
  - ✓ **DOW**
  - ✓ **Monsanto**
  - ✓ **Syngenta**

Thank you for your kind attention!

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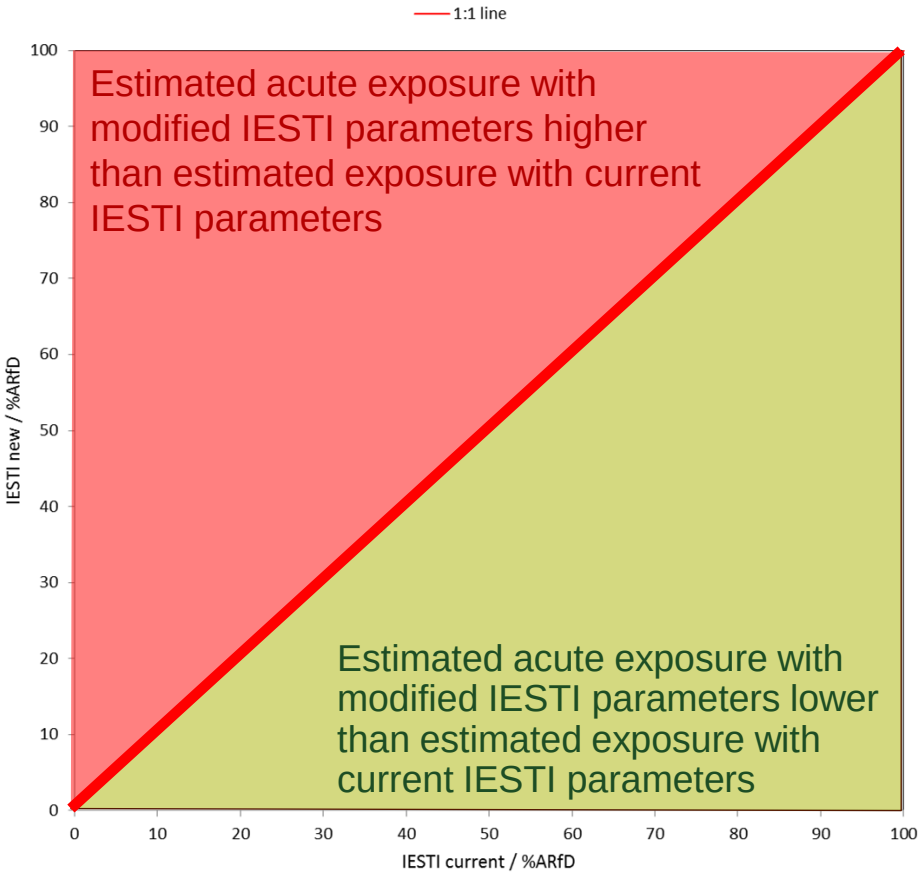
Preliminary impact assessment (for option 1)

- Sets of IESTI calculations were conducted for the commodities relevant to the uses of different active substances (in total: about 10) , each on a variety of crops
- Each set of calculations was performed using PRIMo rev. 2, with the following parameters:
  - For the *"current-method IESTI"* calculation
    - Variability factor = 1 or 5 or 7
    - Residue level = HR or STMR
  - For the *"modified-method IESTI"* calculation
    - Variability factor = 1 or 3
    - Residue level = MRL



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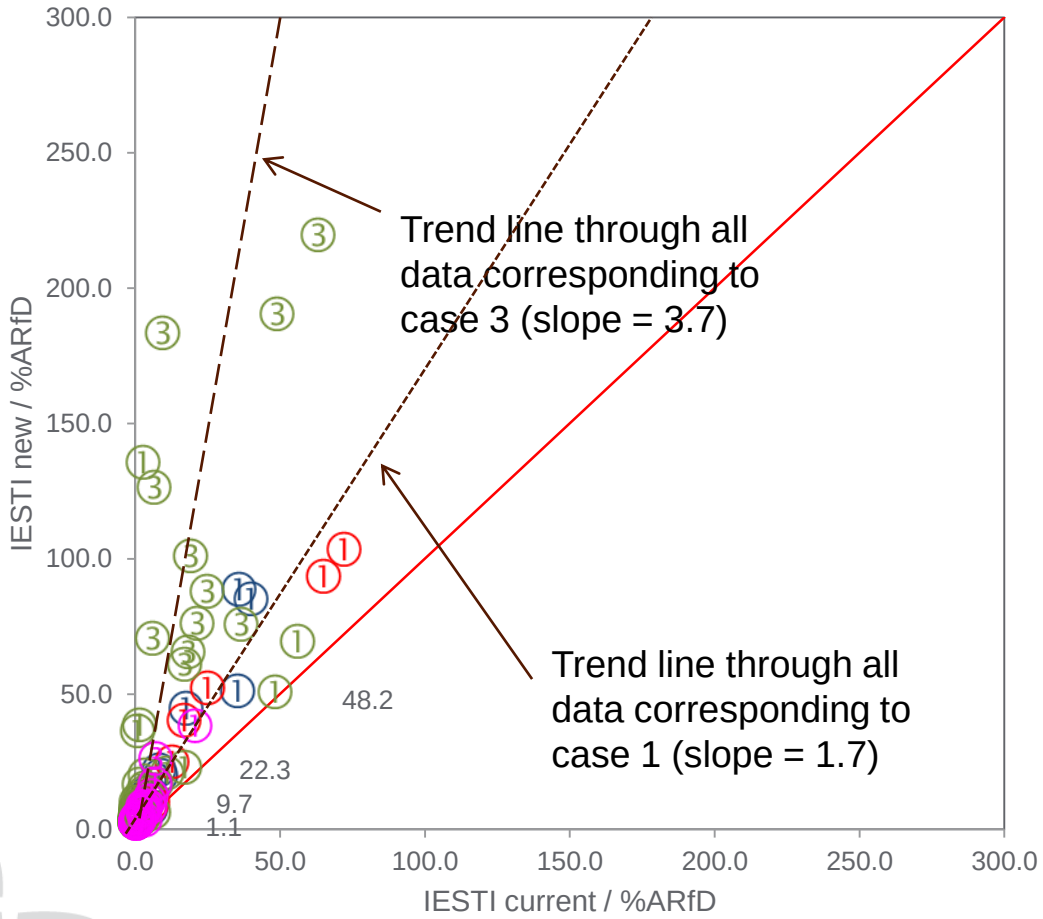
The impact of amending the IESTI equation

Preliminary impact assessment:

Cases 1 and 3

(based on 4 actives)



Source: Syngenta

➔ **Estimates result in significantly higher calculated exposures (increased conservatism)**

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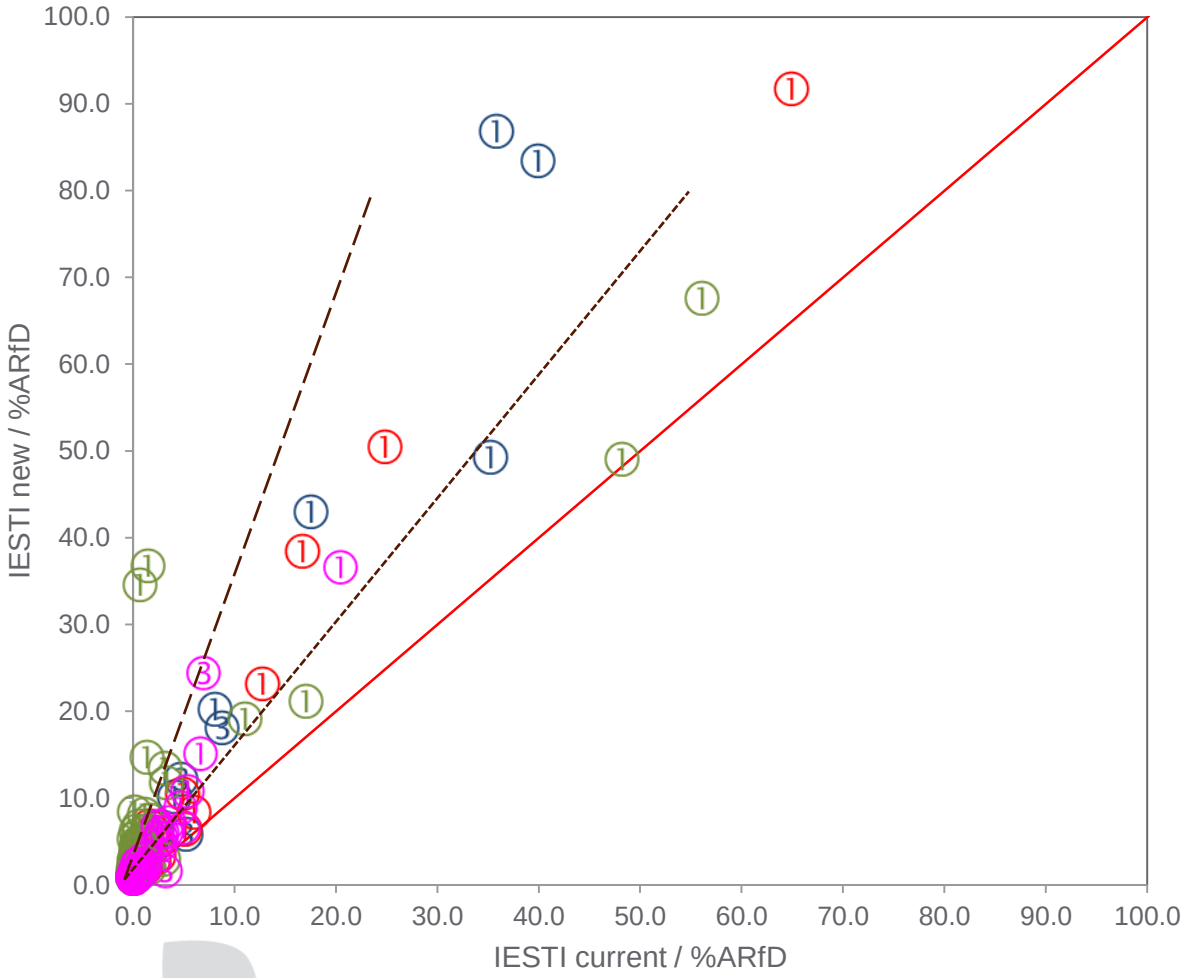
The impact of amending the IESTI equation

Preliminary impact assessment:

Cases 1 and 3

(based on 4 actives)

[truncated axes]



Source: Syngenta

Results in line with BASF evaluation (5 actives)

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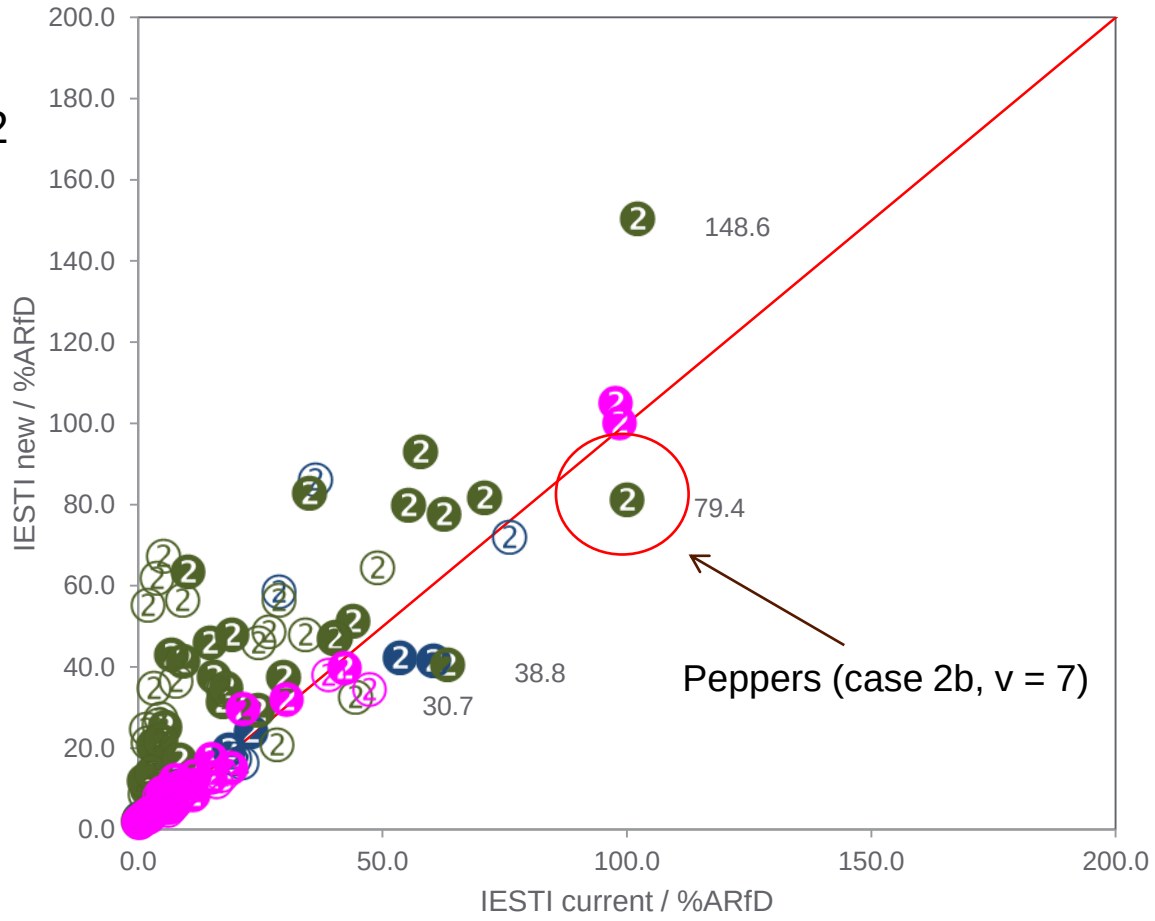
The impact of amending the IESTI equation Preliminary impact assessment:
Cases 2a and 2b
(based on 3 actives) – option 2

Open data markers indicate variability **case 2a**

Filled data markers indicate variability **case 2b**

[truncated axes]



Source: Syngenta

➔ **Calculated acute exposure generally increases, but also decreases (V_F = 7)**
➔ **For majority of cases: Increase is observed (higher conservatism)**

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The impact of amending the IESTI equation Preliminary impact assessment:
Cases 2a and 2b
(based on 3 actives) – option 2

Open data markers indicate variability **case 2a**

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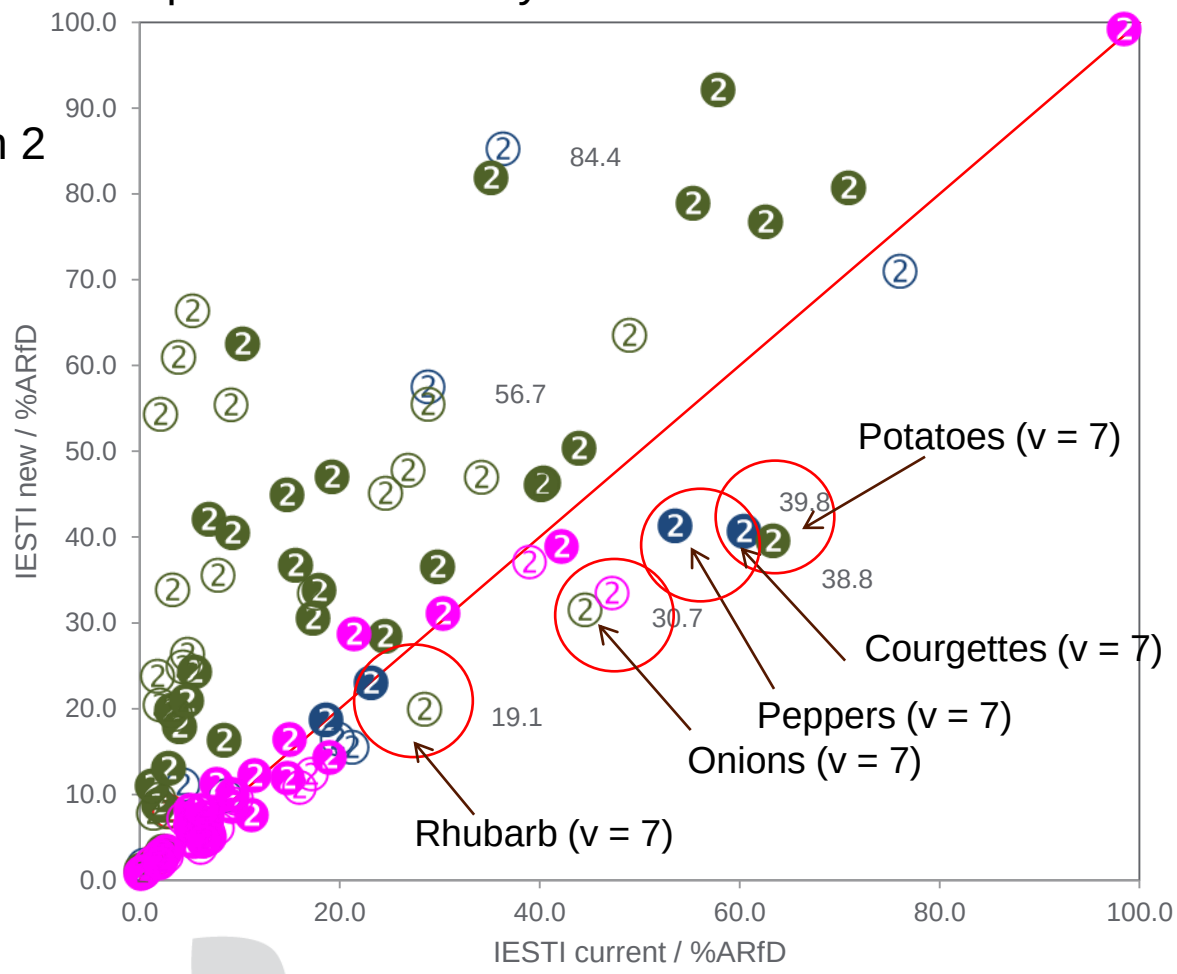
[truncated axes]



Source: Syngenta

→ Results in line with BASF evaluation (9 actives)