Efficacy Assessment in Agriculture

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Overview of presentation on Efficacy Assessment in Agriculture:

- 1. History of regulatory position of efficacy assessment in agriculture
- 2. Current challenges and regulatory developments in efficacy
- 3. Key factors for efficacy testing of biopesticides and biostimulants

1. History of regulatory position of efficacy assessment in agriculture

- In the past Efficacy guidance primarily by EPPO and on national level only
- Efficacy was not a criterion for inclusion or non-inclusion of existing a.s.
- For decades no pressure for EU-wide harmonisation in the efficacy area
- Stimulus for harmonisation in the efficacy area was set with the implementation of the zonal registration system on 14 June 2011.
- Milestones: EPPO conferences Berlin (2011, zonal efficacy data requirement concept) and Sofia (2013, BAD/dRR concept)
- Major regulatory achievement: BAD plus dRR structure of the efficacy section (S3, formerly S7) in order to handle the huge amount of information in the efficacy section

2. Current challenges and regulatory developments in efficacy

- 2.1 Comparative assessments (obligatory for all candidates for substitution)
- 2.2 Dose justification work (in case of GAP changes during renewal of approval of active substances)
- 2.3 Resistance work
- 2.4 Anticipation of future regulatory requirements when planning and designing efficacy trials (Examples: high growing crops, adjuvants)

- 2.1 Comparative assessments (obligatory for all candidates for substitution)
  - According to Art. 24 of Reg. 1107/2009 substances which meet any of the criteria which are listed in Appendix II point 4 candidates for substitution
  - 77 active substances
  - CA on national level since CfS list came into force on 1 August 2015
    - Some countries like NL with later start of binding CAs
    - National formats

- 2.1 Comparative assessments (obligatory for all candidates for substitution)
  - Tiered assessment
    - experience to be gained
    - minor uses
    - Non-chemical alternatives
    - Min. number of modes of action (not harmonised)
    - Comparison of risk mitigations on product labels
  - If these first tiers fail, detailed assessment of agronomic properties (pest spectrum, conditions of use, costs …) in comparison to competitor products
  - Detailed assessment of risk and benefits incl. future pest control (all sections)

- 2.2 Dose justification work (in case of GAP changes during renewal of approval of active substances)

  - If risk assessments (mainly ecotox) do not allow to keep the actually registered dose rate

  - Analysis of available dose justification trial data

    ⇒ evidence of efficacy at reduced rates

  - Setting up of dose justification trial programs

    ⇒ Proof of efficacy at reduced rates

    SCC recommendation: Be proactive. Do not test only the target rate plus one lower rate but a larger range to be prepared for future developments.

2.3 Resistance work (I)

- Update of the resistance dossier is a standard requirement for all product renewal applications according to Art. 43
- Fighting and delaying the process of resistance development is of key importance for the whole plant protection industry.
  - The reasons for resistance development have often been described (e.g. lack of new mode of actions, repeated exposure of pests to one MOA)
  - Reduced field performance to failure of certain products, e.g. ALS inhibitors, Pyrethroids,...
  - Intensified research on mechanisms of resistance development
  - Development of resistance management tools (mixtures, application schemes, …)
  - FRAC, IRAC and HRAC

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➢ 2.3 Resistance work (II)

- ➢ Chemical research and lead follow-up synthesis to identify new modes of action
- ➢ Biological research to identify natural antagonists and other mechanisms
- ➢ Integration different kinds of pest control tools (IPM)
- ➢ Industry initiative (SMART program, chaired by ECPA) to make the public aware of the increasing risk to food safety caused by spreading resistance

- 2.4 Anticipation of future regulatory requirements when planning and designing efficacy trials

  - Example 1: Dose expression: EPPO Workshop on harmonized dose expression for the zonal evaluation of plant protection products in high growing crops

  - Example 2: New Standard EPPO PP 1/291 Evaluation of the influence of tank mix adjuvants on the efficacy of plant protection products

Dose expression: EPPO Workshop on harmonized dose expression for the zonal evaluation of plant protection products in high growing crops (I)

- Example 1: The problem of dose expression
- In the EU-GAP: always kg or L/ha
- No problem in 2-dimensional field crops
- But problematic in high growing (3-D) crops

Dose expression: EPPO Workshop on harmonized dose expression for the zonal evaluation of plant protection products in high growing crops (II)

Need for harmonisation (Presentation Ingrid Langer, AGES, Vienna 2016)

	Area of application in m²/ ha ground	%
Min	10.000	
Max	10.000	
Diff	0	
Mean	10.000	
SD	0	0

Venturia inaequalis in apples, applied for the Maritime EPPO Zone

n = 67	Area of application in m²/ ha ground	%
Min	10.000	100
Max	22.000	
Diff	12.000	120
Mean	15.715	
SD	3.244	21

Dose expression: EPPO Workshop on harmonized dose expression for the zonal evaluation of plant protection products in high growing crops (III)

- EPPO Workshop on harmonized dose expression for the zonal evaluation of plant protection products in high growing crops
  - 18 to 20 October 2016, AGES, Vienna
    - 86 participants from 18 EPPO countries
    - 35 participants from national Authorities, Research Institutes and Universities,
    - 29 participants from Industry
    - 20 participants from CROs and consulting companies

Dose expression: EPPO Workshop on harmonized dose expression for the zonal evaluation of plant protection products in high growing crops (IV)

- Need for harmonized dose expression in all EPPO countries for all crops was already expressed in an ad hoc Meeting on Expression of dose rate held in 2001 (EPPO document 01/8780).

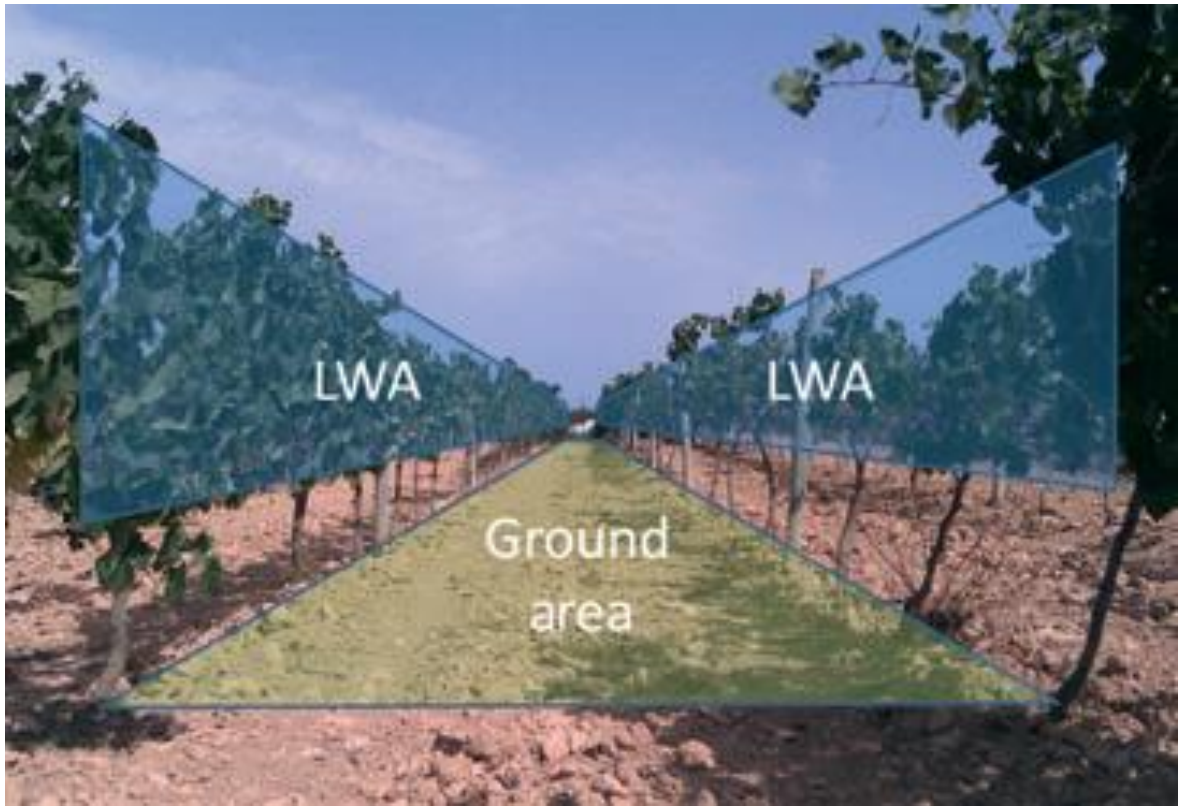
- EPPO Standard PP 1/239 Dose expression for plant protection products was first published in 2005, and revised in 2012 (Leaf wall area and conversion factors)

- Meeting on 'Tree fruits dose expression and adjustment discussion group' held in Wageningen in 2009

- ECPA poposal: treated leaf-wall area (tLWA) as a common dose expression unit in efficacy trials and Biological Assessment Dossiers for most high growing crops for new active ingredients and for new projects.

Dose expression: EPPO Workshop on harmonized dose expression for the zonal evaluation of plant protection products in high growing crops (V)

- Relationship between LWA and Ground Area in pome fruit



Source: Figure 2 from EPPO PP 1/239(2)

Dose expression: EPPO Workshop on harmonized dose expression for the zonal evaluation of plant protection products in high growing crops (VI)

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- Derivation of leaf wall area conversion factors in apple

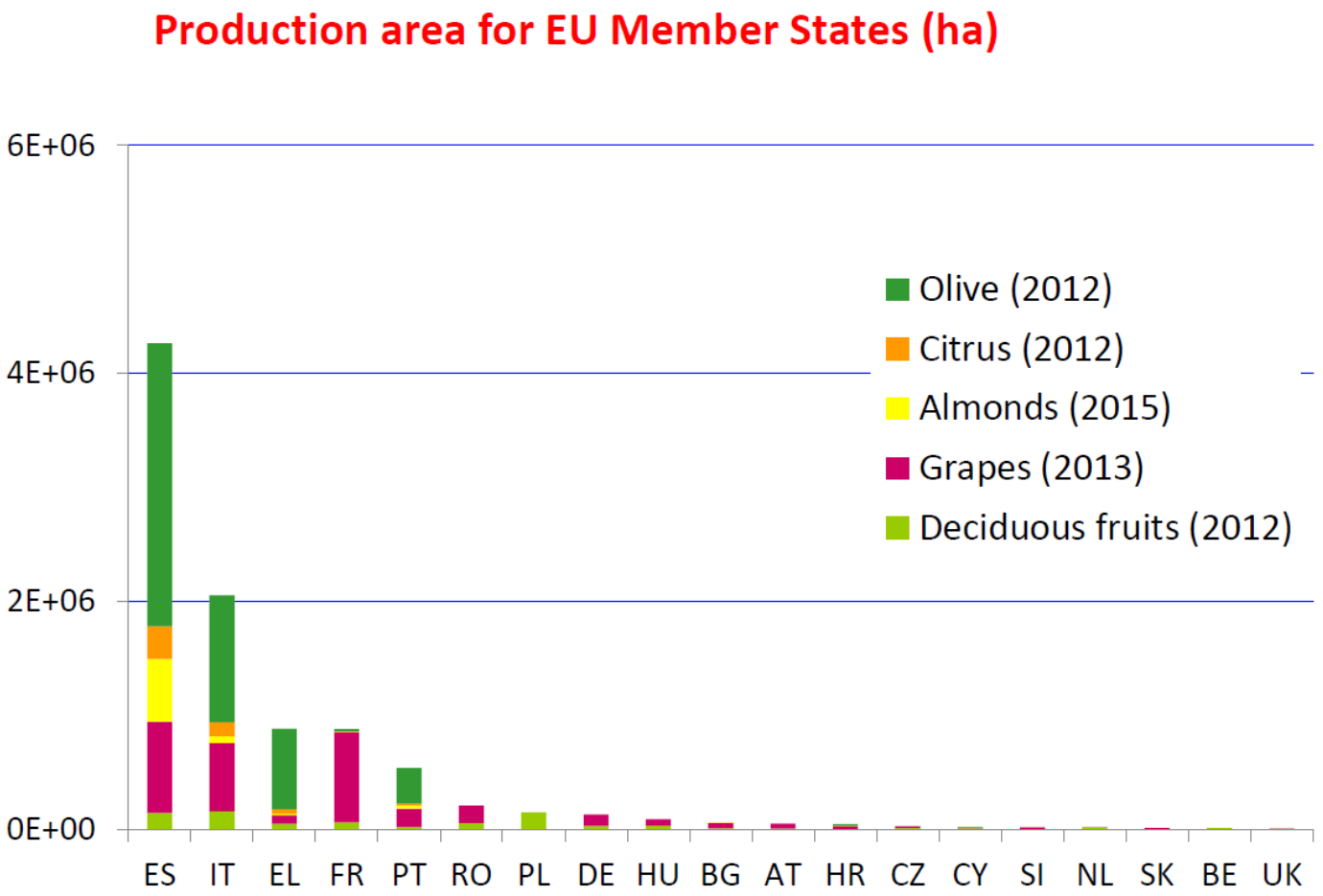
	Canopy or foliage height (m)						
Row distance (m)	1.5	2.0	2.5	3.0	3.5	4.0	4.5
2.5	12 000	16 000	20 000	24 000	n.a.	n.a.	n.a.
3.0	10 000	13 333	16 666	20 000	23 333	n.a.	n.a.
3.5	8 571	11 428	14 286	17 143	20 000	22 857	n.a.
4.0	7 500	10 000	12 500	15 000	17 500	20 000	22 500
4.5	6 666	8 888	11 111	13 333	15 555	17 777	20 000
5.0	6 000	8 000	10 000	12 000	14 000	16 000	18 000

Green: the most common typical row distances, foliage heights and LWA.
Yellow: common, but less frequent.
Grey: exceptions.
Source: Bayer CropScience, 2007.
Leaf wall areas expressed in m^2 leaf per ha ground area for the example of apple orchards.
The conversion factor is calculated by dividing the leaf wall area by 10 000. Values may vary for other crops.

Source: Table 2 from EPPO PP 1/239(2)

Dose expression: EPPO Workshop on harmonized dose expression for the zonal evaluation of plant protection products in high growing crops (VII)

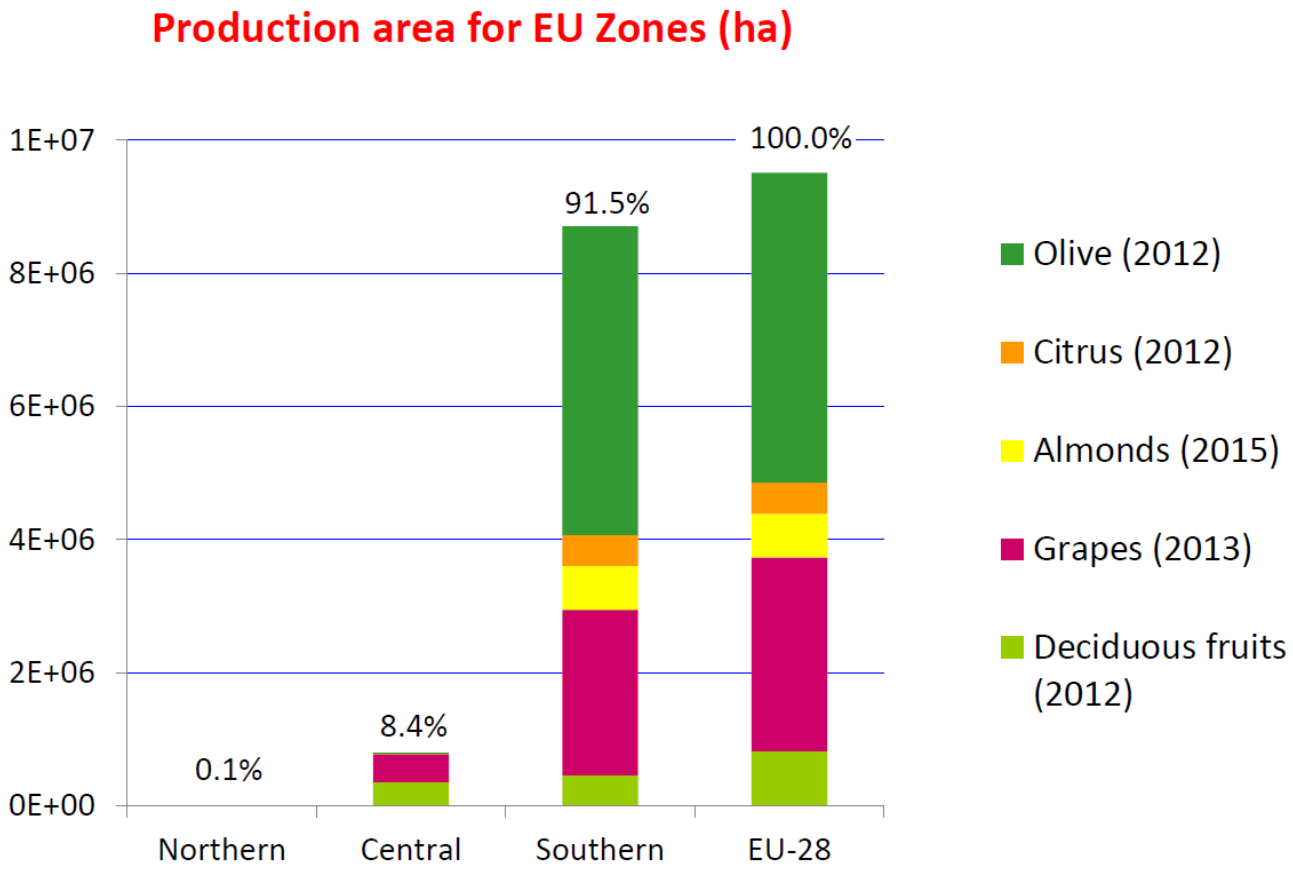
- Distribution of high growing crops in the EU (Eurostat data, 2016)



Source: EPPO Workshop, Vienna 2016

Dose expression: EPPO Workshop on harmonized dose expression for the zonal evaluation of plant protection products in high growing crops (VIII)

- Distribution of high growing crops the EU registration zones (Eurostat data, 2016)



Source: EPPO Workshop, Vienna 2016

Dose expression: EPPO Workshop on harmonized dose expression for the zonal evaluation of plant protection products in high growing crops (IX)

- Important take aways of the EPPO workshop
  - 90 % of the production area of high crops is located in the Southern zone
  - Southern zone:
    - Some MS reject change in the dose expression, the current models are satisfying.
    - Other SEZ countries had been of the opinion that a change to LWA can be an improvement of the current situation.
    - Three dimensional high crops (olive trees with 3 trunks!) at the very start
  - Northern zone:
    - Only 0.1 percent of high crops in the EU are grown in the Northern zone
    - Leave decision to really affected countries
  - Belgian proposal (Pierre Hucorne):
    - Regulators should establish a listing of “equipment and crop” parameters that must be reported in trials with vertical crops.
    - GEP organisations should note all the “equipment and crop” parameters in the efficacy trial reports
    - Applicants should present a concise table of the “equipment and crop” parameters for each trial in the BAD in order to be prepared for the future.

Dose expression: EPPO Workshop on harmonized dose expression for the zonal evaluation of plant protection products in high growing crops (X)

- "Equipment and crop parameters" for all types of laterally treated crops
  (Proposal Pierre Hucorne, EPPO Vienna 2016)

	Needed today	Needed tomorrow
Application	Actual treated height	
	Actual treated length	
	Actual spray volume	
	Actual spray concentration	
	Nb of treated rows, nb of treated sides	
	+ conversion in kg/ha LWA	
Spray quality	Nozzle type	
	Pressure	
	Description of the vertical boom (nb of nozzles, spacing of the nozzles)	
		Spray of the entire canopy (or not) = spray band, treated height of the canopy
		Airflow profiles
		Speed of travel of sprayer
		Type of sprayer
		Relevance of the sprayer used in the trial (to the practical conditions of use)
		Quality of the spray covering
		Uniformity of the spray covering
Habitus of the crop	BBCH Crop growth stage	
		Crop porosity, leaf canopy density
		Foliar volume
		Positioning of the disease/pest observations
		Leaf Area Index
		Maximum height of the plants, height and mid width of the crown
Crop density in the field	Distance between rows	
	Distance between plants in the row	
		Pruning or training system
		Arrangement in rows (single, double), or as single plants

Dose expression: EPPO Workshop on harmonized dose expression for the zonal evaluation of plant protection products in high growing crops (XI)

- **SCC recommendations:**

- Key information to be recorded in all trials done in high growing crops
  - Actual amount/ha ground, LWA and tLWA
  - Distance between rows in the trial
  - Sprayed height in the trial
  - Describe crop/canopy density and take pictures of typical plots at each assessment
  - Describe shape and growing system of
    - Vines, Hops, Citrus, Olives …
    - and also tomatoes, cucumber … in the greenhouse
  - Select trial sites which are in the "green range" (see above Table 2 from EPPO)
  - Special advice: Consider testing of 3 or even 4 dose rates in large plantations which will allow very flexible interpretation of results

- 2.4 Anticipation of future regulatory requirements when planning and designing efficacy trials
- Example 2: New Standard EPPO PP 1/291 Evaluation of the influence of tank mix adjuvants on the efficacy of plant protection products
  - The use of tank mixture adjuvants is very common in trial programs with various types of pesticides.
  - The design of trial programs with adjuvants is often not very consistent
  - Sometimes only few trials can later be used in BADs as bridging is not possible
  - EPPO PP 1/291 (approved Sept. 2016) provides advice for better design

New Standard EPPO PP 1/291 Evaluation of the influence of tank mix adjuvants on the efficacy of plant protection products (I)

- New Standard EPPO PP 1/291 Evaluation of the influence of tank mix adjuvants on the efficacy of plant protection products

- Guidance on „effectiveness or other pesticidal properties and the phytotoxicity of adjuvants in tank mixtures with a plant protection product.”

- Mandatory (e.g. twin pack) of voluntary mixture?

- Mandatory mixture: Data requirements like for conventional PPP

New Standard EPPO PP 1/291 Evaluation of the influence of tank mix adjuvants on the efficacy of plant protection products (II)

- Voluntary mixture:

1.) Determination of the function of the adjuvant

Modification of the effect of the spray mix on the target:

- improving retention, for example reducing the rebound of the droplets
- improving the spread on the target surface
- preserving/maintaining spray mix properties
- maintaining the viability of microorganisms for biocontrol
- improving wash-off resistance of the spray deposit to rain or irrigation
- improving the speed of penetration or the rate of penetration into the target.

Modification of the physical properties of the spray mix:

- improving the quality of the spray mix, for example antifoam agents, colouring agents, adhesive agents for treated seeds
- improving the quality of application/sprayability, for example by reducing drift

New Standard EPPO PP 1/291 Evaluation of the influence of tank mix adjuvants on the efficacy of plant protection products (III)

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Voluntary mixture:

2.) Determination of the possible plant protection products to be used with adjuvants
3.) Determination of the possible intended crops
4.) Determination of the possible target organism
5.) Determination of the dose

“The mixture of the adjuvant and plant protection product should normally be applied at the dosage specified for the intended use. Doses higher or lower than the intended dose may be tested to determine crop safety and the margin of effectiveness (see EPPO Standard PP 1/225 Minimum effective dose).“

New Standard EPPO PP 1/291 Evaluation of the influence of tank mix adjuvants on the efficacy of plant protection products (IV)

- New Standard EPPO PP 1/291 Evaluation of the influence of tank mix adjuvants on the efficacy of plant protection products

The following treatments should be included in field trials.

	Effectiveness	Selectivity
Untreated	Yes	Yes
Adjuvant alone	Some trials, need not include field trials	Yes some trials, **n**
Plant protection product alone	**N** and lower dose (e.g. 0.8N)	**N** 2**N** for herbicides and PGRs
Plant protection product + adjuvant	**N** and lower dose (e.g. 0.8N) + **n**	**N** + **n** 2**N** + 2**n** for herbicides and PGRs

N, plant protection product at recommended dose; **n**, adjuvant at recommended dose; PGRs, Plant Growth Regulators.

New Standard EPPO PP 1/291 Evaluation of the influence of tank mix adjuvants on the efficacy of plant protection products (V)

- Preliminary testing methods for identifying the function of the adjuvant

Functions	Preliminary testing methods (not exhaustive)
1. Improving retention/adhesion	Measurement of retention/adhesion of the spray mix can be done in several ways: active substance content, co-formulant dosage or visually with the use of a colouring agent (e.g. fluorescein)
2. Improving the spread on the target surface	1. Assessment of target coverage by deposit 2. Measurement of contact angle
3. Preserving/maintaining the properties of the spray mix (to avoid degradation of the PPP)	Evolution of the physico-chemical properties of the spray mix over time (e.g. degradation of the active substance, salt precipitation with pH change, UV protection, pH correction, hardness of the water, etc.)
4. Wash-off resistance	1. Wash-off bank test 2. Residual efficacy assessment (on potatoes, in a vineyard) or other recognized method

- Efficacy testing of biopesticides and biostimulants (I)

  - In principle the same rules apply as for chemical PPPs
    - General EPPO Standards
    - Specific EPPO Standards for microbials as for chemicals
    - Role of GEP
    - Sequence of testing (Laboratory, greenhouse, field)

  - However, the data requirements are reduced for “Low risk substances”

  - EPPO Workshop: Efficacy Requirements and Evaluation of Plant Protection Products based on Low-Risk Active Substances, Ede (NL), 2016
    - Reduced data requirements for low risk substances (no. of trials, bridging options,…
    - EPPO Standard in progress (publication expected September 2017)

- Efficacy testing of biopesticides and biostimulants (II)

  - SCC Practical experience / recommendations
    - Understand the mode of action of your product
    - Ideal conditions: timing of application(s), protective applications, climatic conditions
    - Make use of literature search to clarify ideal conditions
    - Identify ideal target organism for field tests in pre-tests
    - Careful selection of crop varieties
    - Make use of extrapolation tables
    - Chose experienced CROs (experience with crops and type of biopesticide)
    - Design trials as to show efficacy close to harvest
    - In case of microorganisms take care of viability of strains and units applied
    - Assessments always according to EPPO
    - Record all parameters that could be important for later interpretation of the trial results

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Draft EPPO Standard on Formulation changes

- The draft EPPO standard is being worked on, but still has to be developed through the panels. It does have the types of principles in the draft, trying to take a tiered approach, and is looking at providing more guidance on criteria for significant changes, as well as the type of data required. However, it will take a while to get agreement, so it will not be published this year (2017). (Sue Mattock, pers. commun.)
- "It was put forward that even where the 10% trigger was exceeded for a co-formulant, the resulting changes in effectiveness or crop safety are unlikely to be significant enough to be detectable in a small number of trials, and therefore it was suggested that there may not be justification for asking for comparability data where differences are unlikely to ever be demonstrated. ... There was a general agreement that using some kind of tiered approach, rather than automatically requiring field data, was a sensible approach. For example, comparability could be initially tested in various controlled situations (e.g. the laboratory, glasshouse, or outdoor pot trials), with a requirement for field trials only where necessary in specific circumstances. Requirements for a zonal bridging package were discussed. The general consensus was that field trials should be placed in challenging and representative locations, rather than automatically having to spread across each representative EPPO zone. Targets/crops chosen should principally reflect the major and/or most challenging uses"
- Source: EPPO Workshop Sofia Conclusions Theme 1: Efficacy considerations when making changes to the chemical composition of plant protection products

Recently issued Extrapolation tables (examples)

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Fungicides

Crop group / Disease group	Table type	
Bulb vegetables (*Allium* spp.)	Effectiveness	-
Chenopodiaceous vegetables NEW	Effectiveness	-
Citrus fruit NEW	Effectiveness	-
Cucurbitaceae	Effectiveness	-
Currants and berries	Effectiveness	-
Damping-off, soil and airborne fungal diseases NEW	Effectiveness	-
Flower bulbs and -tubers and bulb- and tuber flower crops -	Effectiveness	-
Fruiting solanaceous crops	Effectiveness	-
Hop	Effectiveness	-
Leafy vegetables	Effectiveness	-
Miscellaneous fruit (edible peel) NEW	Effectiveness	-
Miscellaneous fruit (inedible peel, large) NEW	Effectiveness	-
Miscellaneous fruit (inedible peel, small) NEW	Effectiveness	-
Pome fruit	Effectiveness	Crop safety
Seed borne diseases NEW	Effectiveness	-

Example for extrapolation table

EXTRAPOLATION TABLE for EFFECTIVENESS of HERBICIDES

▶ **WEEDS IN BETA CROPS** e.g. sugarbeet *Beta vulgaris subsp. altissima var. saccharifera* BEAVA, chard beet/ Leaf beet *Beta vulgaris subsp. vulgaris var. cicla* BEAVV, beet root *Beta vulgaris subsp. vulgaris var. conditiva* BEAVD, fodder beet *Beta vulgaris subsp. vulgaris var. crassa* BEAVC

Weed		Crop: within the *Beta* crops		Crop: outside the *Beta* crops	
1	2	3 Indicator crops	4 Extrapolation to other crops	5 Data from these crops can support the indicator crops (reduced data or no data *)	6 Extrapolation to crops (reduced or no data*)
		Any *Beta* species BEASS	Any *Beta* species BEASS		Spinach SPQOL (spring sowing)