

EPPO Workshop on Comparative Assessment in the framework of substitution Brussels, 2009-05-06/07

A SUMMARY OF THE WORKSHOP CONCLUSIONS & RECOMMENDATIONS

Introduction

This Workshop was convened by EPPO in order to consider the subject of Comparative Assessment (CA) which will become an obligatory criterion under Article 50 of the new EU Regulation for the placing of plant protection products (PPPs) on the market:

“Member States shall not authorise or shall restrict the use of a PPP containing a candidate for substitution for use on a given crop where the comparative assessment weighing up the risks and benefits, as set out in Annex IV, demonstrates that:

- ...an authorised PPP, or a non-chemical control or prevention method, already exists which is significantly safer for human or animal health or the environment; and
- the substitution by PPPs or non-chemical control or prevention methods referred to does not present significant economic or practical disadvantages; and
- the chemical diversity of the active substances, where relevant, or methods, and practices of crop management and pest prevention are adequate to minimise the occurrence of resistance in the target organism; and
- the consequences for minor use authorisation are taken into account.”

Essentially, whenever a product containing an active substance that has been proposed as a candidate for substitution (the list of which is yet to be defined) is assessed or reviewed for registration, a Comparative Assessment exercise will be triggered.

The 61 participants of the Workshop considered the technical issues and guidance that will need to be addressed in the context of CA in the proposed new Regulation. For a full outline of each of the technical points that were covered by the discussion groups in the Workshop, see appendix document 09/15196.

1. General aspects of Comparative Assessment

Participants were of the opinion that it was important to have a general agreement amongst Member States on the general principles of CA. However, it was added that the principles defining how to carry out CA should be kept simple and not overly prescriptive. Both expert judgement and supporting data will need to be applied pragmatically in the process, as it was acknowledged that particularly in terms of non-chemical control methods, full datasets will not be available.

Work sharing should be employed where possible in order to gather the necessary information for the CA decision making process. This should include the provision of supporting information from the applicant/industry, and the exchange of dossiers between Member States. However, it was also

acknowledged that final decisions will be country specific, since they will need to consider local conditions and agronomic practices such as local IPM strategies.

1.1 Structure

As a general structure, it was agreed that CA should be addressed using a tiered approach, along the lines of that originally defined by the Swedish Chemicals Agency:

Tier 1. Identify Candidate Product(s) and possible alternatives

- a. Identify chemical and non-chemical alternatives
- b. Efficacy
- c. Resistance

Tier 2. Estimation of practical or economic disadvantages

Tier 3. Compare the human and environmental health profiles.

(Note that human and environmental health aspects were not considered by this Workshop).

Tier 4. Final socio-agro-economic decision.

1.2 Serious danger to plant health

Another key aspect of the new Regulation that was discussed by the Workshop participants was the derogation under Article 4.7:

“By way of derogation..... an active substance is necessary to control *a serious danger to plant health which cannot be contained by other available means including non-chemical control methods*, such active substances may be approved for a limited period necessary to control that serious danger but not exceeding 5 years even if does not satisfy the points 3.6.3, 3.6.4, 3.6.5 or 3.8.2 of Annex II (hazard criteria).”

Participants considered that the key principles for the application of the derogation needed to be clearly defined; in particular, the necessary criteria that need to be met to constitute a ‘serious danger to plant health’ (e.g. crop viability, quarantine pests, emergency cases). In terms of practicalities, the derogation will be implemented by an application process which is appraised by a Commission Standing Committee. Any derogation that is granted will only be applicable to the agreed ‘serious danger’ situation, but will be open for use by other Member States that encounter the same problem. Participants added that the production of a list of essential uses for plant health purposes may be a useful practical reference for conducting CA.

1.3 Integration with other Regulations and Directives

Participants acknowledged that a number of other Regulations are currently in the process of implementation, and will collectively have substantial impact on the availability of PPPs and the possibilities to control pests and diseases. These should be borne in mind when conducting CA which should ensure that the need to maintain effective control options in the future is safeguarded. Other Regulations include: the new EU Regulation on PPP; the Directive for the sustainable use of pesticides; and the new Water Framework Directive.

2. Identification of candidate product(s) and possible alternatives (Tier 1)

When reviewing a product that contains an active substance that has been identified for substitution, the first task will be to identify suitable chemical and non-chemical alternatives. Within the first Tier of the exercise, efficacy and resistance issues are considered, and the participants were able to provide technical guidance and direction on these specific principles.

2.1 Efficacy

2.1.1 General approach

The Workshop acknowledged that a robust set of criteria should be met to ensure that before substitution (of a candidate for substitution), there are alternatives that: are sufficiently effective; meet growers expectations under a range of appropriate conditions; have acceptable crop safety; do not lead to unnecessary additional applications; have an appropriate control spectrum; and do not create secondary pest problems due to lack of control or adverse effects on beneficials.

With regard to reviewing and comparing efficacy, the participants acknowledged that the approach would need to be different than normal efficacy evaluation for the registration of PPPs. In order to adequately compare the efficacy of chemical and non-chemical control, the assessment should take a more holistic, agricultural systems approach: multi-seasonal information should be sought and compatibility in IPM strategies considered. Guidance on how such an assessment should be carried in order to deliver consistent results is much needed. The Workshop was also of the opinion that environmental aspects of alternatives for candidates for substitution should be considered, including the estimation of carbon footprint.

2.1.2 Specific considerations

Also important at this Tier 1 stage should be a review and comparison of the relative persistence and reliability (contact, systemic, curative) of PPPs, and the method of application/control of substitution candidates in order to facilitate the selection of the most suitable control method. Crop strengtheners and resistant varieties may also be considered at this stage if relevant, and a review of the product formulations may be prudent in order to promote general formulation improvement.

It may be possible to avoid substitution by lowering application rates. However, care needs to be taken as this has implications on reliability, spectrum and resistance. This is already considered in some countries as ‘dose justification’ for PPP authorization.

An important final dynamic is the consideration that the relevance of control methods change over time i.e. efficacy profiles of actives will also change in time and resistance issues will need to be regularly revisited. It will be important therefore to schedule regular reviews of authorized control systems.

2.1.2 Resistance

The Workshop considered resistance in some detail. Of key importance in this area is the need to clearly define what constitutes sufficient plant protection methods in order to make critical decisions with regard to resistance in the context of CA. When addressing this subjective issue, participants considered that asking the question, ‘what constitutes insufficient plant protection methods to render a risk of resistance development’ could be a more useful approach in each specific situation. In order to

facilitate this development, a number of important technical areas regarding resistance were highlighted, which should be incorporated into guidance for addressing resistance risk decisions.

The basis for resistance evaluation should include an information gathering phase to characterize the basic attributes of the relevant actives and an estimation of the resistance risk (associated with the target and active chemistry). This should be detailed (see resistance section of appendix document 09/15196) and include both biological information on resistance mechanisms, and up-to-date information from Resistance Action Groups. It will also be necessary at this point to include information on the resistance susceptibility of associated minor uses (see section 3.1) at this stage. That is, while a major crop-pest combination may not be at risk of resistance development, a minor crop for which the use is relevant, may present resistance issues as a result of substitution.

With regard to addressing the above points relevant to identifying sufficient phytosanitary measures, the Workshop concluded that EPPO Standard PP 1/213(2) *Resistance risk analysis* should be adapted to include guidance specific to CA.

3. Estimation of practical or economic disadvantages (Tier 2)

3.1 Minor uses

The Workshop participants felt that the issue of minor uses was another key component which deserved careful consideration during a CA exercise. It will be important during the assessment to review the minor uses associated with a product: this includes both on-label minor uses (supported by the product approval holder), or extensions of use (off-label uses; supported by organizations other than the product approval holder). If a substitution is likely to cause a serious problem for one or several minor uses the participants were of the opinion that the exercise CA may need to be discontinued. However, participants also expressed that the support of minor uses (on-label or off-label) should not be abused in order to block substitution. The associated minor uses should be justified (by industry or growers organizations) when they are reviewed in CA.

Participants discussed that the approach for assessing minor uses should be similar to the approach with major use, i.e. considering the whole crop cycle, resistance issues, economic considerations etc. However, the key difference is likely to rest in the more limited data and information that is available for the CA assessment, since minor use registrations are often based on reduced datasets (some Member States do not require efficacy data) and extrapolation of the risk assessment from a comparable major use (risk envelope approach). This being the case, the Workshop stressed the importance here of applying principles such as mutual recognition (MR) and extrapolation to support the information requirements of the CA exercise. The application of MR using the newly defined EU zones will be of importance here, as will the application of principles of extrapolation to define the efficacy of products on minor uses (EPPO Standard PP1/257 *Efficacy and crop safety extrapolations for minor uses*). On the latter point, the participants stressed the importance of the continuing work by EPPO on the development of extrapolation tables to support efficacy data requirements on minor crops.

Participants also considered the proposed fund to support minor uses in the new Regulation, and how it may be used in the context of CA. Participants felt that there was a need for information technology resources to facilitate regulatory procedures such as MR and CA. These could include a central database of minor uses (for locating supporting data and dossiers), which should be available to all Member States. An information support platform/exchange amongst Member States to facilitate work-sharing would also be a useful development to identify efficacy and resistance data, plus information

on ongoing trials, in order to avoid work duplication. Participants felt that permanent staff would be required to support the above initiatives.

3.2 Practical and economic considerations

Participants considered the practical and economic points were deemed to be of key importance when considering candidates for substitution. The key point will be to derive a conclusion as to whether substitution would present a major disadvantage on the grounds of economics, or time/labour investment. If this is likely to be the case then the substitution candidate should not be pursued further.

In terms of economics, this should be considered over the long term i.e. in terms of the whole agricultural system. The substitution should not pose increased costs so that crop viability is compromised either: directly; due to increased product costs, or indirectly; through increased labour, machinery or input requirements. The CA process should pay attention to the potential impact on market processes e.g. creation of monopoly situations or rendering a company economically non-viable.

Other practical factors that are relevant when addressing this tier of CA include: the number of applications necessary; environmental factors such as soil compaction and carbon footprint; the cost of data to support alternatives including who will provide it; and the possibility that substitution could result in an increased risk of illegal product use.

With regard to this section of the CA, Workshop participants agreed that new guidance would be necessary to address these points more concisely, since economics and practical aspects are generally not currently addressed in registration processes.

4 Final recommendations

Following a final plenary discussion and distilling the information presented by the Working Groups, the Workshop acknowledged that there were numerous areas outlined that would need to be addressed in order to clarify how the new EU Regulation for the placing of plant protection products on the market would work in practice. In terms of Comparative Assessment, human health, environmental, and economic issues would need to be addressed at Member State level, while three guidance tasks were identified to be addressed by EPPO:

- 1. To support minor use issues, the relevant EPPO Panels should continue their work on minor use extrapolation tables as a priority.**
- 2. Guidance on resistance issues with respect to Comparative Assessment will be provided through a revision of the existing EPPO Standard PP1/213(2), *Resistance risk analysis*.**
- 3. To facilitate the harmonization of procedures, EPPO will produce a general Standard, based on a tiered approach (scheme), to broadly define the general procedures of Comparative Assessment.**

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**APPENDIX OF TECHNICAL POINTS & RECOMMENDATIONS AS
DISCUSSED BY THE WORKSHOP DISCUSSION GROUPS**

The workshop addressed a number of issues in plenary sessions and then divided into a series of separate working groups to discuss issues relevant to the Comparative Assessment (CA) process. This appendix is a compilation of the output of the rapporteurs from each working group summarizing the discussion points, technical issues, questions, and recommendations.

1. Efficacy

The Workshop considered the following to be key points for addressing issues of equivalence in efficacy:

- An alternative must be of equivalent efficacy before substitution; i.e. must meet grower expectations in challenging and variable conditions, and also market expectations in terms of crop safety and maintaining appropriate control levels.
- CA should be applied at a pest level but must consider the need to have available effective control options for different life stages or different timings needed for the control of target pests.
- CA should take account of effects on the target organisms; control spectrum, modes of action; application methods; persistence and reliability as well as crop safety of the different control methods including.
- Efficacy is currently judged on a seasonal basis, though other control methods may need to be viewed differently, over several seasons (long term).
- Comparison of effectiveness should take account of the whole agricultural system (e.g. rotational effects). Must consider the relevant cropping period including multi-seasonal aspects.
- Suitability for use in IPM systems must be considered as part of CA.
- The alternative to the substitution product must have acceptable crop safety.
- Environmental aspects of non chemical solutions should be taken into account, including carbon footprint.
- CA may compare different formulations of same active: formulation improvement.
- Crop strengtheners may be considered as alternative possibilities in CA exercises.
- It may be possible to avoid substitution by lowering the dose. However, care needs to be taken as this has implications on reliability, spectrum, and resistance. This is already considered in some countries as 'dose justification' for PPP authorization.
- Need to consider the changing relevance of the control methods. A substitution made today might not be relevant in 5 years time. The efficacy profiles of actives will also change in time and resistance issues will need to be revisited.
- Consideration of disease spectrum: pests that are presently controlled effectively by chemical means could once again become prevalent if fewer more selective tools are available. The pest may be fortuitously controlled, i.e. not directly targeted, but indirectly controlled by broad spectrum applications for other uses.

The Workshop identified the following problems/limitations:

- Knowledge of the impacts, effectiveness and safety of alternatives (non chemical) is limited.
- Substitution must not create secondary pest problems due to lack of control or by adverse effects on beneficials.
- Substitution must not lead to unnecessary additional practicalities e.g. several applications/treatments when one was previously sufficient.
- Substitution must not create a gap in season control for the protection of the crop.
- The substitution candidate should not be significantly inferior.
- If the substitution product has narrow spectrum, more products/solutions will be needed to cover the same spectrum of diseases.
- It will be necessary to employ both expert judgment and the evaluation of biological data. Datasets are unlikely to be available for some non-chemical control methods.
- Substitution might have residues consequences which will need to be addressed.
- Varietal resistance should be considered as part of CA.
- Substitution candidates should be considered in the context of being components of pest control programs/IPM strategies, rather than stand-alone alternatives.

The Workshop recommended that guidance/clarification was needed to address the following points:

- What are the specific efficacy data requirements for the comparison of control methods?
- How should similarity in terms of efficacy be defined? The Swedish tiered approach would be a good starting point, and should be kept as broad and simple as possible (not too prescriptive).
- It is difficult to compare products containing multiple active ingredients. Some guidance is needed.
- For chemical control, products are compared to a reference product. Such direct comparisons may not be possible for non-chemical control methods.
- The levels of control used or required by Member States vary. This will need to be addressed to facilitate zonal mutual recognition.

The Workshop considered the following control methods as options that should be considered when reviewing a product containing an active proposed for substitution:

- Other plant protection products with human and environmental profiles that lie within the established hazard criteria (taking into account both active substance and formulation).
- Alternative methods (primarily for weed control): mechanical hand hoeing, steaming, burning, plastic mulching, soil disinfection.
- Cultural practices: sowing density, crop rotations, manipulation of sowing dates.
- Biological control: there is an increasing diversity of options although the experts acknowledged that these were not available for all crop-pest/disease combinations. Potential with respect to weed control is limited.
- Varietal resistance: although limited scope for weed control.

2. Practical/economic considerations

The Workshop considered the following to be key practical/economic points to be addressed to ensure that substitution does not present 'significant economic or practical disadvantages':

- The availability, quality and cost of labour to administer the control method.
- Practicalities of non-chemical methods.
- The substitution must not create monopoly situations (e.g. one product/company).
- Methods should respect the local practice.
- Alternatives must not cost significantly more.
- Crop viability/economics should not be affected.
- The availability of substitution replacements should be considered.
- There must be suitable equipment available for application.
- The viability of a new method should be considered (e.g. scaling up use of biologicals for production).
- Consideration of finding appropriate data to support alternatives: cost, efficacy, yield and quality information.
- Consideration of the number of applications/input necessary for alternative substituted method: time implications, soil compaction, carbon footprint, cost, etc.
- Economic comparisons must be made over the long term, using agronomic systems approaches.
- Economic impact for companies which would lose important activities.
- Could the substitution increase the risk of illegal use?
- There needs to be some element of 'future proofing' to ensure that if substitution occurs the long term viability of the alternative is safeguarded

The Workshop recommended that guidance/clarification was needed to address the following points:

- There is no simple, defined guidance for consideration of economic factors.
- How should information be collected?

3. Minor uses

The Workshop considered the following to be key points to be addressed with specific regard to minor uses:

- It will be very important to consider both the major and minor uses associated with a product when applying CA, including the associated rotations.
- If CA leads to a problem for one or several minor uses (some products may support many minor uses), the substitution should either be postponed or stopped.
- Voluntary mutual recognition processes should be considered as part of CA in order to limit as much as possible, the loss of susceptible minor uses.
- CA should be carried out on a case by case basis, addressing each crop-target combination.
- The support of minor uses (on-label or off-label) should not be abused in order to block substitution. The associated minor uses should be justified (by industry or growers organizations) when they are reviewed in CA.
- When considering the applications/control methods, the whole cropping system should be considered e.g. indoor (propagation stage), followed by outdoor.

The Workshop recommended that guidance/clarification was needed to address the following points:

- Guidance is needed for comparing different cropping systems.
- Clarification of criteria for comparing efficacy data between MS, since this may hamper mutual recognition. There should be sufficient flexibility to facilitate MR processes.
- Some general principles are needed for comparison between chemical and non-chemical control methods as data are unlikely to exist for all control alternatives.

The Workshop considered the proposed fund in the new Regulation, to support minor uses and how it may be used in the context of CA:

- It was discussed that there is a need for a central database of minor uses to support MR and CA processes (for locating supporting data and dossiers), which should be available to all MS
- There is a need to make information available on existing efficacy data and resistance data, plus ongoing trials, in order to avoid work duplication, and the restriction of uses.
- There is a need for an information support platform/exchange amongst MS to facilitate work-sharing. It should be EU based, but open to other non-EU members.
- The Workshop felt that permanent staff would be required to support the above initiatives.
- The above systems should be used to facilitate CA and MR activities.

The Workshop came up with the following practical recommendations to support minor uses in the context of CA:

- EPPO to continue the important work on minor use extrapolation tables.
- European Commission to support and give priority to the important issue of Minor Uses.
- CA to be done on the whole of the crop rotation.
- Growers should be involved when gathering decision making information.
- Industry should be encouraged to put minor use on the label.
- MS should be proactive in sharing information.

4. Resistance

The Workshop considered the following to be key points, which should be addressed during Comparative Assessment with specific regard to resistance:

The availability and practicality of alternatives (both chemical and non-chemical):

- EPPO to continue the important work on minor use extrapolation tables.
- Level of chemical diversity (reference: RAC guideline)
- Number of mode of actions
- Pests and crop context

Attributes of active ingredients:

- Systemic
- Foliar

Resistance profile of targets:

- Resistance mechanism
- Inheritance
- Mode of action
- Cross-resistance
- Single vs. multiple site of action
- Type of resistance (metabolic vs. target site)

Resistance mapping target/s:

- Frequency
- Distribution
- Availability of monitoring techniques
- What we know about distribution of resistance mechanisms

Pest, weed and disease biology, e.g.:

- Life cycle
- Genetics
- Productivity
- Population characteristics
- Mobility
- Number of crops affected

Resistance Risk (refer to EPPO Standard PP 1/213(2) *Resistance risk analysis*):

- Associated with target
- Associated with type of chemistry

Efficacy of the candidate for substitution compared with:

- Alternative control options and
- Complete agronomic system

Contribution to overall programme:

- Crop protection programme
- Other agronomic practices
- IPM practices
- Pest spectrum
- Potential need for emergency derogations
- Could it increase selection pressure to other modes of action/types of resistance?

Economic impact:

- Cost of alternative products, non-chemical alternatives and or programmes
- Economics of the overall system, within season and taking into account future seasons

“Future proofing”:

- Other candidates for substitution
- New technologies
- Long-term sustainability
- Invasive species
- Climate change

All CAs should be examined on a case-by-case basis. There are likely to be other considerations and expert judgement should always be applied.

The Workshop recommended that guidance/clarification was needed to address the following points:

- There should be a clear definition of what constitutes sufficient phytosanitary measures for dealing with crop protection issues.

The Workshop came up with the following practical recommendations to resistance issues in the context of CA:

EPPO could contribute by adaptation of the existing Standard PP 1/213(2) to:

- Address the context of comparative risk assessment
- Change from the context of one active ingredient, to resistance implications for relevant agronomic systems
- Take account of minor uses
- Taking account of the above listed key technical points

The Workshop felt that this revision of the Standard should be supervised by the EPPO Panel on resistance and it should be completed within the following two and a half years.

5. Wider scope issues

The workshop considered the following to be key wider scope issues that needed to be addressed in terms of Comparative Assessment:

- Responsibility in terms of the legal basis of a CA decision needs to be clearly defined.
- The principles of CA should not be too prescriptive, although it will be highly beneficial to have agreement amongst MS on the general principals (a common understanding) to support decision making. A tiered, harmonised approach will be necessary.
- Definition of what is considered significantly safer? A safe formulation of a candidate for substitution might be preferable to a less safe non candidate for substitution?
- CA should be kept, wherever possible, as simple as possible. Expert judgement as well as supporting data plays an import role in the decision making processes.
- Work sharing:
 - At the time of review/application the applicant/industry should be encouraged to provide supporting information and data.
 - The exchange of dossiers (registration reports etc.) including information on CA would help.
- CA and IPM:
 - Importance for IPM to be considered.
 - IPM strategies are dynamic: suitability changes over time.
 - Should be part of the tiered approach.
 - IPM is the responsibility for the MS.
- Non-EU EPPo countries :
 - List of substitution candidates may be used by retailers (export).
 - Principles of CA can also be used by non-EU members.
- Other regulations. A number of other Regulations are currently in the process of implementation, and will collectively have an impact on the use of PPPs. The should be borne in mind when conducting CA:
 - Regulation on PPP.
 - Directive for the sustainable use of pesticides.
 - Water framework Directive.

The Workshop was of the opinion that the underlying principles of the derogation under Article 4.7 were of major importance in the new Regulation:

- The applicant (producer) applies for approval and documents the serious danger.
- The Commission decides on the approval after consulting the Standing Committee.
- The derogation applies to all MS who encounter the 'serious danger' but can only be used to control that specific 'serious danger'.
- It will be essential to define what constitutes a 'serious danger to plant health'.
- The principles for the deployment of the derogation must be defined e.g. to maintain crop viability/regional competitiveness; quarantine pests; invasive alien species; cases of emergencies; crop losses and quality e.g. mycotoxins.

The Workshop recommended that guidance/clarification was needed to address the following points:

- How can CA procedures be future-proofed against unforeseen issues?
- It will be essential to define what constitutes a ‘serious danger to plant health’ and clarify the principles for the deployment.
- It may be necessary to define a list of essential uses for plant health purposes.