Comparative assessment & substitution for plant protection products

Peter Chapman of JSC International looks at the ongoing challenge of examining agrochemical actives for substitution

Regulation 1107/2009 introduced comparative assessment (CA) and substitution to the regulatory process for plant protection products for the first time, making it mandatory for those active substances identified as candidates for substitution. The Regulation required the European Commission (EC) to establish a list of candidates for substitution by 14 December 2013. A draft list (http://ec.europa.eu/food/plant/pesticides/approval_active_substances/docs/draft_list_cfs_en.pdf) of 77 candidates was finally published on the EC website on 27 January 2015.

The criteria for identifying actives as candidates for substitution are set out in Annex II, Paragraph 4 of Regulation 1107/2009. This establishes that an active shall be approved as a candidate for substitution pursuant to Article 24 where any of the following conditions are met:

- Its acceptable daily intake, acute reference dose or acceptable operator exposure level is significantly lower than those of the majority of the approved actives within groups of substances/use categories
- It meets two of the criteria to be considered as a persistent, bioaccumulative and toxic substance
- There are reasons for concern linked to the nature of the critical effects (such as developmental neurotoxic or immunotoxic effects) which, in combination with the use or exposure patterns, amount to situations of use that could still cause concern, for example, high potential of risk to groundwater; even with very restrictive risk management measures (such as extensive personal protective equipment or very large buffer zones)
- It contains a significant proportion of non-active isomers
- It is or is to be classified, in accordance with the provisions of Regulation 1272/2008, as carcinogen category 1A or 1B, if the substance has not been excluded in accordance with the criteria laid down in point 3.6.3 or 3.6.4
- If, on the basis of the assessment of EU or internationally agreed test guidelines or other available data and information, reviewed by the European Food Safety Authority, it is considered to have endocrine disrupting properties that may cause adverse effects in humans, if the substance has not been excluded in accordance with the criteria laid down in point 3.6.5.
One particular concern held by industry is that the list is very likely to be subject to misinterpretation. These actives have already been subject to full EU review and have been approved for use in pesticide products in accordance with their conditions of approval. The EC has included a question and answer document (http://ec.europa.eu/food/plant/pesticides/approval_active_substances/docs/qaa_candidates_substitution_en.pedf) on its website to accompany the list and provide an explanation of substitution and comparative assessment.

Comparative assessment

The concept of CA and substitution in Regulation 1107/2009 was introduced with the aim of reducing risks. Article 50(1) requires that Member States (MSs) shall perform a CA “when evaluating an application for authorisation for a plant protection product containing an active approved as a candidate for substitution”. A draft guidance document on how to conduct the CA when evaluating an application for authorisation of a plant protection product was published in 2014.

The stated overall aim of CA is to reduce risks by gradually replacing products containing candidates for substitution by methods and products of lesser concern in order to benefit the protection of human or animal health, while minimising the economic and practical disadvantages for agriculture.

Article 50(4) of the Regulation requires MSs to perform CA “regularly and at the latest at renewal or amendment of the authorisation”. CA is to be performed at the level of use and will only be applied for additional uses, not for all currently authorised uses. In addition, only the application for an additional use of the product will be considered for substitution, not all other existing authorisations for products containing the same candidate for substitution.

CA is to be done at a national level. The guidance document refers to the standard system as ‘mandatory CA’, with exceptions in cases where it is necessary to acquire experience of use of a product, for example for new actives, new combinations of active with a crop or pest or significant advance in formulations.

The Regulation also allows for CA to be applied in the case of application for the authorisation of a plant protection product not containing a candidate for substitution. The condition for this is that a non-chemical control or prevention method must exist for the same use and is in general use in that MS. The guidance refers to this as ‘optional CA’.

The conditions for substitution are described in Article 50 (2) and Annex IV of the Regulation. They include:

- Significantly lower risk to health or the environment, while ensuring similar effect of the alternative on a target organism
- Sufficient methods or chemical diversity to minimise the occurrence of resistance
- Lack of significant economic and practical disadvantages
In addition, the consequences of substitution on minor use authorisations must be taken into account. The guidance document provides a template for assisting MSs in making an assessment on substitution, suggesting that applicants should provide the information requested in the template.

Figure 1 – Mandatory CA: Efficacy & related considerations for product containing candidates for substitution, Steps 1-2

1. Does the product contain candidate(s) for substitution?
   - Yes
   - No

Optional CA possible

2.1. Do alternatives exist to the candidate product for controlling the target organism in each target crop?
   - Yes
   - No

STOP CA

2.2. Is the effectiveness of the alternative comparable with the candidate product for that use?
   - Yes
   - No

STOP CA

2.3. Is the crop safety of the alternative comparable with the candidate for that use?
   - Yes
   - No

STOP CA

2.4. Will substitution of the candidate product by the alternative lead to pest problems for which there are no acceptable mitigation possibilities?
   - Yes
   - No

STOP CA

2.5. Will substitution of the candidate product by the alternative lead to disruption of established IPM systems or have a negative impact on beneficials?
   - Yes
   - No

STOP CA

2.6. Does the target pest have a high or medium inherent resistance risk?
   - Yes
   - No

STOP CA

2.7. Is there a product within the same MoA group authorised for use against the target pest?
   - Yes
   - No

STOP CA

2.8. Are there other MoA products authorised for use against the target pest?
   - Yes
   - No

STOP CA

2.9. Does the candidate exhibit negative cross-resistance in the target pest?
   - Yes
   - No

STOP CA

2.10. Is the candidate an important component of the risk management strategy for the target pest and for other pests not subject to CA?
   - Yes
   - No

STOP CA

2.11. Are there practical or other disadvantages resulting from the use of the alternative if the candidate is no longer available?
   - Yes
   - No

STOP CA

2.12. Is the candidate authorised for minor uses (on-label or off-label)?
   - Yes
   - No

STOP CA

2.13. Is substitution of candidate product on a major crop anticipated to lead to unsustainable control of pests on a minor crop?
   - Yes
   - No

STOP CA

2.14. Is gaining pest control with the alternative(s) considerably more expensive than use of the candidate?
   - Yes
   - No

STOP CA

2.15. Are there any wider consequences for maintaining effective crop protection including the security of future pest control that might influence the decision of making substitution?
   - Yes
   - No

STOP CA

Substitution possible

Health and environmental aspects to be assessed: Go to Figure 2

No
In comparing risks, Annex IV states that the alternative must show significantly lower risk to health or the environment. Therefore if an initial comparison of risks posed by different products reveals that there is only marginal difference in risk, then CA can be terminated at this point.

The guidance document advocates a step-wise approach to the conduct of CA. This means that the process can be terminated at any stage. The guidance also recommends that if there is evidence that there may be an issue in a certain area of CA, for example potential development of resistance, then the assessment should be started at this point.

Step 1, identification of candidate for substitution, involves determining whether or not the product contains a substance identified as a candidate for substitution. At this point optional CA may be performed where the product does not contain one.

Step 2, assessment of agronomic aspects, is the mandatory assessment of the agronomic aspects of the uses of the product containing active(s) identified as candidate for substitution. This step encompasses the guidance on CA published in 2011 by the European & Mediterranean Plant Protection Organisation (EPPO).

The EPPO standard states that the first step after the initiation of a CA is to define the uses of the candidate product. When these have been specified, alternatives should be identified against which the CA would be performed. Chemical as well as non-chemical control or prevention methods should be considered.

Decision-making for the CAs for effectiveness, crop safety, and risk for resistance, practicability, economic disadvantages, alternative measures and effects on minor uses as set out in the EPPO standard are all covered (Figure 1). If the conclusion of the assessment is that substitution is not appropriate in view of agronomic considerations, no further assessment is needed.

Step 3, first assessment for health and the environment, is intended to clarify whether the potential for substituting a candidate product actually exists and should be further explored. (Figure 2). An assessment focused on the specific criterion or criteria that resulted in an active being defined as a candidate for substitution should be made.

In Steps 3a-e the candidate product is first compared to alternative(s) only with respect to the individual criterion/criteria that was met by the candidate. This approach is considered to be the most straightforward and keeps the workload to a minimum.
3. A comparison is first made only with respect to the criteria in Annex II, point 4 that was met by the candidate product: Go to 3a-3e below, as appropriate.

3a. The candidate product was subject to CA due to low ADI, ARfD, or AOEL:
- Where relevant, consider exposure of different population subgroups, directly or indirectly and compare the risk.
- Where relevant compare the stringency of the imposed restrictions and prescribed PPE.
Significantly lower risk from chemical or non-chemical alternative?

3b. The candidate product was subject to CA since two of the criteria for PBT were met:
- Compare the risk for long-term effects on soil-living organisms and on aquatic organisms using estimated cumulative exposure
- Where relevant, compare the risk for bioconcentration, biomagnification and secondary poisoning of aquatic and terrestrial vertebrates, and
- Where relevant, compare also the potential for indirect exposure of humans.
Significantly lower risk for long term effects, or for bioconcentration, or secondary poisoning, also taking into account the risk mitigation options warranted, or significantly lower risk for indirect exposure of humans from use of chemical or non-chemical alternative?

3c. The candidate product was subject to CA since the critical effect in combination with use exposure patterns could still cause concern, even with very restrictive management measures:
- Compare the risk management measures necessary together with the nature of the critical effect.
Significantly less restrictive measures needed to manage the risk posed by chemical or non-chemical alternative, and/or significantly lower level of concern?

3d. The candidate product was subject to CA due to a significant proportion of non-active isomers:
Is there on the market alternative(s) that contain only the active isomer(s)?

3e. The candidate product was subject to CA since it is to be classified as carcinogen 1A/1B, or as toxic for reproduction category 1A/1B, or it is considered to have endocrine disrupting properties that may have adverse effects in humans; but the substance was not excluded in accordance with criteria in Annex II point 3.6.3, 3.6.4, or 3.6.5, respectively.
Consider the risk for exposure for the candidate product and compare the risk posed to human health, in relation to the properties of the candidate product,
Significantly less restrictive measures needed to manage the risk posed by chemical or non-chemical alternative, and/or significantly lower risk from alternatives?

4. Are there significant risks to health or the environment identified in the risk assessment for the chemical or non-chemical alternative in other aspects than those considered in 3a-3e (as relevant) and/or are extensive risk assessment measures necessary for the chemical or non-chemical alternative?

Yes

No

STOP CA unless available data or knowledge indicate a need for further evaluation in other areas of risk

Mandatory CA completed
Substitution possible

Figure 2 – Mandatory CA: Efficacy & related considerations for product containing candidates for substitution, Steps 3-4
Step 4, second assessment for health and the environment, requires the complete risk profiles of the candidate product and the potential alternative to be taken into account. When the candidate for substitution criteria are applied in the step-wise approach described above, it may be that the alternative was not of concern in relation to specific criteria used in the comparison at Steps 3a-3e, but instead poses a risk that warrants risk mitigation for some other aspect of the assessment for human or animal health and the environment. In such cases the conclusion may be that substitution would not be the best tool for achieving risk reduction.

Implementation

The guidance document will apply for applications for authorisations, renewal or extension of use of a plant protection product containing a candidate for substitution submitted from 1 August 2015. The publication of the list does not affect existing authorisations or trigger an immediate review of them. It is clear that even if CA and substitution is applied in a pragmatic way there will be an additional workload for industry and regulatory authorities. This will lead to increased costs and the possibility of further delays in completing evaluations.

A study has suggested that in Germany the requirement for CA may affect up to 25% of all plant protection products and around 50% of all uses of plant protection products. Taking into account the numbers of candidate products and the number of uses of products, it is estimated that some 18,500 pair-wise comparisons of candidate products with alternatives will have to be done.

Conclusions

CA and substitution becomes a reality for new applications for the authorisation of plant protection products in the EU in 2015. This process puts a further regulatory burden on industry and regulatory authorities at a time when both are struggling to meet existing deadlines and workloads. As CA is conducted at MS level individual country requirements will differ in detail causing additional complications for industry.

Reference:
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