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European and Mediterranean Plant Protection Organization
Organisation Européenne et Méditerranéenne pour la Protection des Plantes PP 1/307(2)

Efficacy Evaluation

PP 1/307(2) Efficacy considerations and data generation when making changes to the chemical composition or formulation type of plant protection products

Specific approval and amendment

First approved in 2018-09.
First revision approved in 2020-09.

Specific scope

This Standard considers the possible impacts of biologically significant changes in the chemical composition of plant protection products and the requirements to support such changes.[1] A change in chemical composition is defined within this Standard as a change in the chemical composition but where the content of active substance remains unchanged and the formulation type remains unchanged.[2] The Standard also covers the circumstances in which a change in formulation type (automatically defined as a new product) may be supported by a more limited data package. Also discussed within the Standard is the development of a new product which is to be based on the principle of comparing with, and 'bridging' to, an existing formulation. The existing authorized formulation should have a full underlying supporting data package.[3]

Introduction

Part I of this Standard describes general considerations when a change in chemical composition within a formulation type is proposed. It provides detailed criteria relevant to efficacy of the key components and the types of changes which may have an impact on efficacy (both effectiveness and crop safety). Whether a change is considered biologically significant or not will determine the requirements for support, through reasoned cases and/or further data, as described in the second part of this Standard. Finally, a section on new products also covers changes in formulation type; the steps and principles that should be followed in considering the possible impact of changes in chemical composition are applicable.

Part II of this Standard describes the type of supporting data required where proposed changes are considered biologically significant. The objective is to generate a limited amount of data in challenging conditions to demonstrate comparable effectiveness and crop safety properties with the existing formulation. It may be sufficient in many circumstances to conduct this testing using glasshouse studies. However, if there are significant differences relative to the

[1]Other areas of the risk assessment will have different criteria and requirements, which are outside the scope of this Standard. For example, a change in technical material resulting in differences in impurities may be of toxicological significance but would not require efficacy consideration or supporting data.

[2]Definition is broadly in accordance with EU Guidance document SANCO/12638/2011 Guidance document on significant and non-significant changes of the chemical composition of authorised plant protection products under Regulation (EC) No 1107/2009 (EC, 2012). However minor changes in the content of active substance and changes of formulation type are also considered within this EPPO Standard. Details on agreed definitions of formulation types can be found in Manual on development and use of FAO and WHO specifications for pesticides (FAO and WHO, 2016).

[3]In this circumstance, the guidance provided within this Standard is based on the premise that there is appropriate data access to the existing formulation. Any consideration of the regulatory basis and procedures in individual member countries concerning data protection and access to unprotected data is outside its scope. Within the European Union, for zonal authorizations involving more than one Member State, the zonal rapporteur Member State will assess the relevance of the data and whether comparability to an authorized product has been demonstrated. However, only individual concerned Member States can determine the data protection status and data access to that authorized product and are able to make a detailed comparison of the relevant formulation details.

existing formulation, further extensive testing is likely to be required.

Active substances

Consideration should always be given to the impact on biological efficacy from changes in active substance(s) content. Generally, these changes are associated with other significant changes to the formulation chemical composition and should therefore be supported by relevant efficacy data.

Some EPPO member countries provide specific guidance describing threshold levels in the individual content of active substance(s), up to which it may be possible to support changes by an appropriate reasoned case.[4] These thresholds are based on extensive national experience and historical data. Guidance should always be sought from the relevant regulatory authority.

Part I: General factors to be considered and information required when a change in chemical composition is proposed

It is essential to have information regarding the nature and the magnitude of the proposed change. This should include information on the chemical nature of the co-formulant(s) being changed (in content, added or removed) and, if relevant, an explanation of their chemical similarity. When considering the potential impact of any change, information on the function of formulation components is most important, together with the reasons for making any changes. This applies particularly to the surfactant system. For example, the function may be to improve formulation stability in the spray tank or improve plant coverage and uptake of active substance in the plant.

It is also helpful to understand the use of the product and how the active substance is delivered to the target. For formulations that are diluted and sprayed on the crop and/or weed this may be via uniform distribution on the leaf surface. Therefore, effectiveness may be modified by changes in distribution and absorption on the leaf surface or by changing the rate of release of the active substance. Crop safety may be a key consideration, whether for a particular active substance or for sensitive plants (often horticultural) which are more susceptible to developing phytotoxic symptoms.

This section details the criteria that determine the categorization of the proposed changes in chemical composition. It also provides a summary indication of the type of data required to support the change, which is discussed in more detail in Part II of this Standard.

Appendix 1 describes more specialized types of products (or situations of use) where different factors are more relevant. For example, for seed treatments the key issue is retention of active substance on the seed, and this may be addressed by reference to physical/chemical data; for baits, addressing any potential changes in palatability may be the main issue.

Changes in co-formulants which are not biologically significant

For these changes, no efficacy data are required. However, an explanation of the biological nonsignificance of any changed co-formulants should be provided, making reference to relevant parts of Table 1. This should be an integral part of a justification to explain why the proposed change is deemed unlikely to impair efficacy.

Note that, as a general rule, it is the amount of active substance and co-formulants applied to the target that is important and not the content of the formulation itself, i.e. the in-use diluted formulation.

It should be remembered that the impact of a series of individually nonsignificant changes may be cumulative. Any comparison of a proposed change in formulation should always be made with the originally authorized formulation. It is not appropriate to make a series of minor changes, each without supporting data, with the final result being a substantively significant change. If the overall changes (compared with the originally authorized and tested formulation) are beyond those considered as nonsignificant, then some data will be required to confirm that efficacy is not adversely affected.

Changes that are nonsignificant for efficacy, where no supporting data are required, are given below. The applicant should notify and provide an appropriate explanation of the nature of the change. For example, it is noted that co-formulants with different Chemical Abstracts Service (CAS) numbers may be chemically equivalent. Equally, for compounds with identical CAS numbers, the degree of ethoxylation can be significantly different. It is up to the applicant to explain and justify function, properties and why they are equivalent, and reference should also be made to the chemistry assessment. Please also note that other criteria are relevant for more specialized formulation types and certain situations of use (see Appendix 1).

Changes in co-formulants which are biologically significant

Significant changes in chemical composition are those regarded as potentially having some biological impact, requiring assessment and supporting data. Where the change is considered significant, data are required to confirm that the performance and crop safety of the proposed change are comparable relative to the current formulation composition.

For most formulations, and particularly foliar applied sprays, the two key components that may affect efficacy are:

- A change in the solvent system, i.e. moving from one solvent to a chemically different solvent or significantly changing the content of individual solvent(s). This may

[4]For example, ranges up to ±10% are commonly specified. Where changes are being made simultaneously to more than one active substance, the cumulative changes should also be taken into account and reference made to the original authorized product.

Table 1. Biologically nonsignificant changes in chemical composition of the formulated product

Proposed change
Exchanging co-formulants for the same amount of chemically equivalent* co-formulants
Alternative source of same co-formulant
Adding (or changes to) a marker co-formulant (e.g. dye)
Changes in co-formulants added to preserve the formulation in the container or in the tank (e.g. preservatives, antifreeze and antifoaming agents)
Changes to the fertilizer component of granular herbicide fertilizer-based granules. The nature of the manufacturing process means that often several different forms of nitrogen, phosphorus, potassium or other elements may be included. Variations in fertilizer base are considered unlikely to affect product performance[†]
In general, changes of less than ±10% in the amount of any co-formulant applied[‡]

*CAS or EINECS/ELINCS number of the co-formulants do not by themselves provide evidence of chemical equivalence (see main text for more explanation).
[†]Formulation details should include the expected concentration range of all the raw materials used in the production of the fertilizer base and the minimum specification of the final formulated product. Details should include the N:P:K ratio, active substance content, particle size, density and dust content.
[‡]Beyond the 10% threshold, supporting data may be required (see Part II for details). Some products contain two or more co-formulants with the same function (e.g. wetters). Provided they are chemically similar, it may be acceptable to change the quantities of individual surfactants by more than 10% provided the overall content is not changed by more than 10%. A case to justify the similarity of the co-formulants concerned should be provided.

Table 2. Biologically significant changes in chemical composition of the formulated product*

Formulation component	Type of change and required supporting evidence
Solvent content not chemically equivalent	Where such changes in content are >10% (increase or decrease): functional equivalence in effectiveness and selectivity shown on test crops in glasshouse/pot tests
Surfactant content not chemically equivalent	Where such changes in content are >10% (increase or decrease): functional equivalence in effectiveness and selectivity shown on test crops in glasshouse/pot tests
pH adjuster	Changes of >10% (increase or decrease): functional equivalence in effectiveness and selectivity shown on test crops in glasshouse/pot tests

*Please see Table 1 for further explanation on determining comparability of co-formulant.
Calculating change in content is based on the individual content of the relevant co-formulant components, i.e. a change from 10 to 15 g/L is a 50% increase (not a 5% increase). Where changes are being made simultaneously to more than one solvent or more than one surfactant, the cumulative changes in content should be taken into account.

change penetration and distribution. The emphasis of any testing is likely to be more focused on phytotoxicity in these situations.

- Changes in surfactant systems: These are widely regarded as having potentially the greatest impact on effectiveness in most situations. They may change the wetting, spreading and sticking properties of the formulation. Such changes could include changing the contents of individual existing surfactant(s), i.e. adding to them or replacing them with chemically different surfactant(s). The emphasis on biological testing is likely to be more on effectiveness.

Table 2 gives further details on the significance of the change and the nature of any supporting evidence required. Please also note that other criteria are relevant for more specialized formulation types and certain situations of use (see Appendix 1).

Test crops and key targets

Selection of the test crop for crop safety trials should be based on the most sensitive crop(s) covered by the authorized uses. This would be considered the more challenging and representative situation, particularly in laboratory or protected[5] studies where young plant foliage may be more sensitive to damage. The use should be within the authorized uses and include a representative range of growth stages. For effectiveness it is necessary to consider whether the most sensitive crop is also an appropriate test for the key targets. Key targets should be among the most difficult to control where effectiveness is the key concern. It may also be useful to consider crop morphology to include, for example, waxy crops.

It may also be useful to consult, where available, the EPPO extrapolation tables for further guidance on key major crop–pest combinations considered relevant for the whole crop–pest grouping.

[5]In the previous version of this Standard this was called 'glasshouse', but it has been changed to 'protected' as it includes other conditions.

Broader situations and prior knowledge

Experience may have been gained from other products where similar changes in chemical composition have been made and data demonstrate comparable effectiveness and crop safety. In these circumstances, it may be possible to make a reasoned case based on this data to justify comparability in performance.

Similarly, if the intended change in formulation is similar to a change which has already taken place with that active substance, then a case may be used to justify the change and specific comparability testing may not be required.

New products

The criteria outlined for biologically significant changes are equally applicable when developing a new product based on a 'bridging' approach to an existing authorized formulation (and underlying full data package). A demonstration of comparability (whether by a relevant reasoned case or an appropriate data package) allows, in effect, extrapolation to the complete associated claims/uses for the authorized product and the underlying supporting data.

If the new product is a different formulation type to the existing formulation, it is anticipated that data should be generated via field trials (unless the proposed authorized uses are only for protected situations).

Part II: Type and extent of data required for biologically significant changes in formulation

General comments on trials design

The objective of protected or field trials work is to demonstrate that the proposed change in chemical composition does not have adverse impacts on the effectiveness and crop safety properties of the existing formulation or, when developing a new product based on a 'bridging' approach, to demonstrate that these properties are comparable to an existing authorized product. This enables the efficacy data supporting the authorized existing formulation and all relevant uses to be directly applicable to the new product (and avoids the requirement to generate a full data set, provided data access is available).

The extent of the data depends first on how similar the new product formulation is in composition to the existing authorized product. This will determine whether protected or field trials are required. The second determining factor is the range of existing target/crops and, for zonal authorizations, the extent of the range of conditions within the various countries. The extent of the 'bridging' data required on the selected key pest/crop uses will depend on a number of factors: the complexity of the intended uses and national label claims, the diversity of use and the extent of existing knowledge on the active substance and any relevant formulations.

In all tests/trials, an untreated control should be included along with a reference product, which will usually be the authorized/existing formulation (see comments below for cases where this is no longer commercially available). Comparisons should be made for key target–crop combinations (discussed further below). Provided comparable effectiveness is proven, this is considered to be addressed with reference to the authorized product.

It is recognized that sometimes the original authorized formulation may no longer be commercially available and so direct comparisons in trials are not possible. In such cases, a bridging approach to another authorized product containing the same active substance may still be possible, but the extent of required data is likely to be more than that needed where direct comparisons are available. This approach is dependent on comparisons across a broad and representative range of uses and demonstrating that the proposed formulation performs as expected for such a product type on the basis of existing knowledge on the formulated active substance.

The nature of the required supporting evidence is based on taking a tiered approach using protected or full field trials, depending on the extent of the change. Protected tests may be a useful first step in determining whether a change in formulation affects efficacy. However, it may be more appropriate to proceed directly to field testing.

Protected tests (effectiveness and crop safety). All protected tests in support of formulation changes should be conducted in accordance with the requirements of good experimental practice.

If the main concern is addressing crop safety, then key test crops would be those likely to be the most sensitive to damage and/or those where label warnings already relate to damage (to compare if symptoms are 'worse' or as expected). Varietal trials may be particularly relevant for products authorized in protected conditions and where existing knowledge/authorized labels indicate sensitive crops/ornamentals prone to damage. In this case the purpose is to demonstrate a comparable ('no worse') level of expected damage. For herbicides specifically, a dose higher than that recommended should be included for selectivity trials (see Table 1 in EPPO Standard PP 1/135 *Phytotoxicity assessment*).

At least three different key target species per product should be chosen to confirm effectiveness. Whilst the key decision for effectiveness is to demonstrate comparable performance at the authorized dose, it is recognized that possible differences are more likely to show at a lower dose (e.g. perhaps just test 0.8 times the normal dose). Therefore, the protected study would represent a robust and challenging test in using this approach as an interim first step rather than automatically conducting field trials. In doing so, it compensates for the fact that the natural 'field' environment would normally be considered to influence effectiveness more than the controlled, optimized conditions in a protected study.

Where the proposed formulation is potentially less effective, including, for example, at a lower dose, then further

field trials will be required. These are to examine whether there is a detectable lower performance under the conditions of use of the product (assuming, of course, that field uses are required/authorized).

The demonstration of improved effectiveness of the new formulation relative to the existing authorized product would not be sufficient to support a claim for a higher level of control (for which field trials would normally be required). The aim of the protected studies in this context is to demonstrate the absence of any significant reduction in effectiveness compared with the authorized product.

Number of trials:

- For herbicides and plant growth regulators at least two trials for effectiveness (with fully supportive results) should be conducted on at least three key target species; three trials per crop should be done for selectivity. A rationale for the choice of targets selected is important to establish their relevance.
- For other plant protection products (e.g. insecticides) at least two trials for effectiveness (with fully supportive results) should be conducted on at least three key target species. For crop safety, observations made in these trials may be sufficient. However, if the test crop appropriate for the major target is not the most sensitive/prone to damage (e.g. there are existing label warnings), some additional sensitivity testing on other crops may be appropriate.

Decision-making for both effectiveness and crop safety is based on demonstrating a comparable level of effects to those expected.

Efficacy field trials

Effectiveness trials. The type and extent of bridging data required depends on the range of the crops and the diversity of uses or targets for which the use is intended.

Typically, three to five trials per major target are required. Where several crops are recommended, typically two to four trials per crop per major target are required. These numbers may be reduced for related harmful organisms as the knowledge base increases, for example where there are multiple targets per crop and results show comparability in performance between the two formulations. A larger number of bridging trials may be required if use on a diverse range of crops and pests is sought. It is important that testing covers representatives from the range of crops. Additional trials may be required to confirm comparability of any additional, unusual or niche uses recommended (e.g. a module drench as well as foliar uses on brassicas).[6]

The trials should focus on major targets and crops, and include the most challenging situations (e.g. a difficult to control target, or crops where coverage is particularly important, for example:

- Crops with waxy leaf surfaces (e.g. many brassicas) are considered challenging where the objective is to gain uniform leaf cover. Similarly, onions present a small and challenging leaf where the intention is good leaf cover.
- Examples of challenging targets include pea moth, *Cydia nigricana* (LASPNI) (which spends only a short period on foliage before penetrating the pea pod) and the onion thrips, *Thrips tabaci* (THRITB), which live between leaf sheaths on leeks. Effective distribution of contact-based insecticides on the pods or between the sheaths is vital for control. Changes to surfactant systems may therefore impair performance.
- Similarly, the control of diseases on onions presents a challenging target.
- Control of newly germinated black grass with a foliar acting herbicide.

Conduct of all trials in a single year may provide sufficient evidence unless results are variable, and then trials over 2 years may be required.

For existing products authorized on a zonal basis, effectiveness and crop safety across all relevant EPPO climatic regions will have been originally established. Therefore, when proposing changes in chemical composition it is not necessary to generate comparability data across all regions. As indicated, the location of trials should reflect challenging conditions based on crop/pest and environment. For example, for a fungicide authorized across Europe the most appropriate locations to demonstrate comparability under challenging conditions would most likely be in the EPPO Maritime Zone, with the UK and Ireland often having the highest disease pressures for those diseases associated with wetter and cooler climates, for example *Zymoseptoria tritici* (SEPTTR) for winter wheat and *Pyrenophora teres* (PYRNTE) or *Rhynchosporium secalis* (RHYNSE) for winter barley. Alternatively, for a number of insect pests the key consideration may be the number of generations per season, with the more challenging pest pressures in regions with prolonged warmer periods.

Testing in different zones may be more likely where the diversity of uses or crops is such that they are insufficiently represented in any one EPPO climate region. For further guidance see EPPO Standard PP 1/278 *Principles of zonal data production and evaluation* (Table 3).

Crop safety trials. Assessments of phytotoxicity should be made in the effectiveness trials but it is important that trials are conducted on a range of proposed crops, including those which are more sensitive. Where these trials indicate that the proposed formulation is significantly less crop safe than the existing formulation, and for herbicides and plant growth regulators, specific crop safety bridging trials should be conducted according to Table 1 of EPPO Standard PP 1/135. Typically, three to five trials per crop are required, although where several crops are authorized, and as the

[6]EPPO Standard PP 1/226 *Number of efficacy trials* will be amended to remove guidance on similar formulations which is now covered in this Standard.

Table 3. Guide to the number of effectiveness trials required for biologically significant changes in chemical composition

Use situation	Number of fully supportive trials on major target*
Single crop, small number of targets	Minimum of five trials where there is one major target: three to five trials per additional major target†
Range of crops or many targets	Two to four trials per crop per major target†, reducing as knowledge and experience from the trials increases

*Trials are not required on 'minor' targets (although may be relevant if they are representative of challenging conditions).
†Additional trials may be required to confirm comparability of any additional unusual or niche uses recommended (e.g. a module drench as well as foliar uses on brassicas).

Table 4. Guide to the number of crop safety trials required for biologically significant changes in chemical composition

Product type	Number of crop safety trials for biologically significant formulation change on major crops and most sensitive minor crops*
Insecticides and fungicides	Not normally required (assessments may be made in protected effectiveness trials). It may be relevant for protected uses, and varietal trials can be useful in these circumstances
Herbicides and plant growth regulators	Minimum of five trials. Three to five trials per crop reducing to two to four trials per crop as knowledge base increases. Testing on closely related crops may not be necessary

*Testing on a 'minor' crop may be relevant if it is representative of crops more prone to damage.

knowledge base increases, this number may be reduced to two to four trials per crop and testing on closely related crops may not be necessary. Specific crop safety bridging trials are generally not required for insecticides or fungicides. Where there is existing knowledge or indication, for example label warnings and restrictions on the authorized product that specific crops or varieties may be susceptible to damage, more extensive testing, including relevant crops, may be required. For products authorized on a zonal basis, testing in different EPPO climatic zones is again only necessary where the diversity of crops susceptible to damage is such that they are insufficiently covered from testing in a single EPPO climatic zone (Table 4).

Results

It is difficult to draw conclusions on comparability between proposed and existing formulations where effectiveness is similar, but the existing formulation has lower levels of control than expected. This may be a function of trial conditions or an indication of resistance but does not necessarily provide evidence that the proposed formulation is inherently as effective. As such, evidence is still needed of appropriate or expected control under suitable trial conditions.

Where comparability is not demonstrated further efficacy data may be required. Where the formulations are shown to be not comparable, a full dataset will be required according to EPPO Standard PP 1/226 *Number of efficacy trials*. Depending on the product and use pattern, comparability may be demonstrated on certain crops or for certain uses and not on others. In such cases the applicant should seek to understand the reasoning for the differences between the proposed and authorized formulations.

Reference

European Commission (2012)SANCO/12638/2011 of 20 November2012 rev.2: *Guidance document on significant and non-significant changes of the chemical composition of authorised plant protection products under Regulation (EC) No 1107/2009 of the EU Parliament and Council on placing of plant protection products on the market and repealing Council Directives 79/117/EEC and91/414/EEC*.

Appendix 1: Specialized formulation types and situations of use where additional considerations are relevant

Below are some examples of more specialized formulations and situations of use where other factors and formulation components are important considerations for potential changes in chemical composition.

Simple salts in water

Formulations that are simple salts in water are taken to be comparable to other products containing the same salt of an active substance, provided the amount of active substance applied to the target is comparable. Products containing different salts of the same active substance are taken to be comparable if both salts disassociate equally in water. Examples of active substances which can be formulated in this manner are arylalkanoic acids (the 'hormone' herbicides), dicamba and chlormequat.

Herbicides used pre-emergence

It is generally accepted that once a formulation is present in the soil, then the co-formulants have no significant effect

on performance. This means that for a herbicide applied before emergence of both crop and weed no data are required to establish comparability. For herbicides used before emergence of the crop on emerged weeds then only data on effectiveness are required. If used before weeds emerge on an emerged crop, then only crop safety data are required. A case may be provided to reduce the data required where the herbicide is only active through the roots.

Exceptions to this are granular and capsule suspension formulations or slow-release formulations, for which some data are required. Trials may be conducted in either the glasshouse or field on an appropriate range of soil types, with the applicant providing an appropriate justification.

For a change in granule size or alteration of the material from which release occurs data are required to show that efficacy is not affected. For the latter, this may be based on data on physical properties, such as active substance release rate.

Other types of soil-applied products (insecticides and fungicides)

For soil-applied/compost-incorporated products, a case for a reduced comparability package may be considered, depending on the type of activity and the considerations of release rate and coverage (as above for herbicides).

For granular and capsule suspension formulations generally, laboratory data to demonstrate comparability in release rates of active substances are required unless efficacy trials are conducted and specifically address changes in carrier. These trials could be conducted in the glasshouse. For a change in the size of soil-applied granules, data are required to show that efficacy is not affected as the frequency distribution of the granules in soil will be altered.

Bait formulations (including molluscicides)

For bait formulations, changes in any co-formulant could potentially have impacts on palatability or, where relevant, pellet integrity. Small-scale studies to demonstrate no significant differences in these properties may be necessary (e.g. those described for molluscicides in EPPO Standard PP 1/289 *The design and the use of molluscicide small plot cage (barriered) field trials*).

Seed treatments

For chemical changes in composition it may be possible to submit physical/chemical data showing that the loading of the active substance, and thus its availability, on the treated seed is equivalent rather than carrying out field trials. This would normally be evaluated in the chemistry section of a submission. If the decline in retention of active substance is significantly different it may be necessary to carry out field studies to indicate sufficient effectiveness.

Where new co-formulants are introduced into a seed treatment, or substantive changes to content are made, germination and early crop emergence studies are required to confirm adequate crop safety.

Fumigant products (including hot and cold fogging treatments)

Where the product is a fumigant, then provided that either the gas is evolved from the formulations at a similar rate and total quantity or gas levels are maintained through monitoring and re-dosing the formulation is considered unlikely to affect efficacy. Physical/chemical data to show comparable release rates as well as total quantity of gas released are required to confirm this. A simple laboratory study(s) (under appropriate conditions, e.g. soil moisture content) to demonstrate comparability is sufficient.

Taint

When a plant protection product is applied directly to a stored harvested product for consumption risks of taint should be considered.