Evaluation biologique des produits phytosanitaires
Efficacy evaluation of plant protection products

PP 1/306 (1) General principles for the development of co-formulated mixtures of plant protection products

Specific scope

For the purpose of this Standard, a co-formulated mixture[1] is defined as a plant protection product which contains more than one active substance (including mixtures of different product types, e.g. fungicides plus insecticides or fungicides plus plant growth regulators). In certain cases, manufacturers may provide the individual active substances in separate containers in a common product package; these are usually referred to as 'twin packs' or 'combi-packs'. Such products are outside the scope of this Standard (although some of the same considerations apply for practical farm use).

This Standard provides guidance for the justification for using mixtures from the point of view of efficacy, their potential advantages and disadvantages, plus an examination of the appropriateness of such mixtures in terms of managing resistance. Based on these issues, a series of principles have been drawn up to form the regulatory framework for the decision-making process when considering the approval of such mixtures. These principles should also act as a guide for trial design and the type of data required. Appendices provide additional information for specific product types and situations. The Standard PP 1/277 *Insecticide co-formulated mixtures* will be withdrawn and replaced by this new Standard.

Specific approval and amendment

First approved in 2018-09.

Introduction

Mixtures may be developed for a variety of reasons, including improved effectiveness against one pest[2] or a range of pests, better plant growth regulation, resistance management, a broader spectrum of pest control and other desirable properties such as flexibility of application or improved crop quality.

It is therefore essential that the rationale for, and the specific benefits of, a proposed mixture product are fully explained and demonstrated in the applicant's submission (and in the member state (MS) Registration Report). Depending upon the rationale behind the mixture the evidence needed to support its authorization will also vary.

These benefits should also be balanced against potential compromises in effectiveness; for example when targeting multiple pests there may be conflicts regarding resistance management, optimal timing of application for combinations of plant growth regulators or for the control of individual species, and threshold levels. Particular consideration should be given to explain what benefits the mixture may deliver compared with a solo product (products containing single active substances) to ensure that there is no unnecessary overuse of any active substance.

Under Regulation EC No. 1107/2009 (EC, 2009) authorization for plant protection products may be sought on a zonal level across a range of European Union (EU) Member States. The relevance and appropriateness of a mixture product across a regulatory zone should therefore be demonstrated but may be more difficult to establish than for a solo product, due to differences in pest occurrence, pressure and/or sensitivity.

Different doses may be more appropriate in different regions. If applicants seek authorization for a whole zone this should be fully justified.

Plant protection products may be applied in different situations, for example when appropriate decision support criteria are met or pest densities are reached, where there is a high risk of crop lodging or where crops are being

[1]Hereafter referred to as 'mixture' in this Standard.
[2]In this Standard 'pest' refers to any species, strain or biotype of plant, animal or pathogenic agent that is injurious to plants or plant products (FAO Glossary of Phytosanitary Terms).

grown for particular markets. This will be dependent on favourable conditions for the pest during the growing period or where there is a history and/or likelihood of detrimental effects on marketable yield. Even for species considered as major pests or where there is a history of crop lodging there may be no need to use control measures every season. Thus it is important that the control provided by the co-formulated product is justified as being necessary and of proven benefit. It is considered that in most cases justification should be based on major pests or crops. Exceptionally it may be useful to demonstrate some worthwhile benefit for minor pests or crops, for example in cases where there are no alternatives or in high-value crops where marketability depends on low levels of damage or specific quality traits.

For the reasons summarized above mixtures need careful consideration, both in terms of identifying justified uses and their integration into resistance management strategies and complex crop protection programmes. This Standard explores these issues in greater depth and provides a series of principles. These principles provide a decision-making framework, both for applicants in identifying appropriate uses and generating an appropriate data package and for regulatory authorities in the evaluation process. Details for each product type are given in the Appendices.

This Standard does not specifically address mixtures with safeners or synergists, but the principles may be relevant to them.

The potential disadvantages of mixtures (e.g. human health and environmental concerns) are outside the scope of this Standard but should be addressed in accordance with any relevant scheme of pesticide regulation.

Potential advantages and disadvantages of mixtures with respect to effectiveness

Potential advantages (compared with solo products)

- There may be advantages in combining active substances with different properties. For example, combining contact and systemic action, residual and foliar activity, contact and vapour action or preventative and curative action.
- Such mixtures may also assist control of different development stages of the same pest, particularly when the pest is less accessible due to either pest behaviour or crop structure. It may also be used to control different pests present in the crop at different times, for example a seed treatment mixture with more than one active substance where one active substance targets seed-borne or soil pests and the other provides subsequent control of foliar pests. Such mixtures may also target different metabolic pathways in the case of plant growth regulators.
- The mixture may enhance the overall spectrum of pests covered, allowing control of a range of pests when they are present in the crop at the same time or enhancing control of particular pest species. This may be more advantageous when there is a little or no overlap in activity of the individual active substances against pest species, for example herbicides with activity against grass or broad-leaved weeds. For herbicides this includes the control of weeds in the seed bank, where mixtures can increase the extent and duration of control.
- Using two (or more) active substances in a mixture may provide more effective control than if they are applied singly in sequence. For example, the mixture may provide both rapid action and more residual effects. This may be beneficial, especially where rapid control is required or where control is required of both emerged and pre-emergent weeds for example. Longer-lasting residual activity may also require fewer applications of a mixture compared with solo products
- When the maximum authorized dose of a product has been reduced, for example due to concerns about ecotoxicology or human health, the use of co-formulated mixtures combining lower doses may be relevant. When using active substances in combination, whether against a single pest or a pest complex, lower rates may sometimes be used compared with when using solo products.
- The mixture may provide higher and/or more consistent levels of control against the same species. This could be through additive, synergistic effects or complementary effects via two or more active substances targeting different development stages of the same pest, or acting on different pathways within the plant in the case of plant growth regulators. This could also allow for greater flexibility in treatment timing.
- Other general advantages for the mixture when compared with the solo product could include less packaging and reducing the number of operations for operators.

Potential disadvantages (compared with solo products)

- Two or more pests at levels requiring control by different active substances of a mixture may be present together. However, in some cases it is possible that one active substance will be applied when its target either does not require treatment or indeed may not be present in the crop or the seed bank. Either situation would constitute an overuse or unnecessary use of plant protection products and not be considered as good agricultural practice.
- For some targets the timing of application is critical for achieving an effective treatment, and additionally there may be a relatively short window within which treatments should be applied. If the mixture has more than one target, the timing may not be optimal for all, resulting in reduced effectiveness.
- In some cases, products containing one active substance have different doses recommended for different targets. In this situation, when the mixture is targeting a wide range of pests there will be less flexibility in being able to differentiate doses for individual species. A compromise regarding the dose of each active substance when

combined in the mixture may be needed in order to prevent the following: overuse against some targets; unnecessary use (if the relevant pests for one active substance are not present); less than optimal doses being applied to other targets.
- Mixtures of two or more active substances may result in lower effectiveness of one of them (antagonism).
- Applications of co-formulated mixtures may result in the higher levels of crop damage or other adverse impacts, for example on succeeding or adjacent crops.

Use of mixtures in strategies for management of the risk of resistance

- The use of mixtures is recognized as a potential modifier in a resistance management strategy for any plant protection product. However, their usefulness as a resistance management strategy is dependent on certain criteria. EPPO Standard PP 1/213 *Resistance risk analysis* states that the active substances within the mixture should have different modes of action (MOAs) to claim resistance management benefits. It is recognized that the use of a mixture, particularly where active substances act synergistically, may allow reduced doses to be used. However, for resistance management purposes the relative contribution to overall control from each active substance should be carefully considered (see the Appendices).
- The status of resistance to any of the components of the mixture should be taken into consideration when judging the value for resistance management (see specific sections in Appendices 1–3). It is noted that the resistance status of a MOA and pest scenario is dynamic. The latest available information should be used to assess the resistance risk (e.g. the various resistance action committees, national/regional resistance action groups, the International Weed Resistance Survey and the EPPO Database on Resistance Cases under development in 2018 provide a useful source of information).
- Mixtures can result in a conflict in resistance management for one or more potential target pest species (e.g. where resistance is already present to one of the active substances in the mixture).

General principles to be considered for the justification of mixtures

Within the regulatory framework and requirements for justified, sustainable pesticide use, efficacy evaluation will consider the appropriateness of any mixture in terms of: potentially increasing the effectiveness of treatment; increasing the overall use of plant protection products; and the impact that increased exposure may have on selection pressure for resistance. As such there should be a benefit in using mixtures compared with (available) solo products. Mixtures where there is no benefit over the use of solo products would not be justified. The evaluation of a mixture should consider the justification for use alongside resistance implications, encompassing the positive and negative aspects of both.

The following key principles draw together the various issues discussed above. These considerations will vary depending on the properties and proposed uses/targets of the individual active substances. Applicants should consider these factors when developing mixtures and subsequently designing their efficacy field trials and other studies to support a mixture.
- Mixtures targeting the same pest species could potentially constitute an overuse of product unless there are demonstrable benefits compared with the use of solo products or unless dose is reduced compared with the solo products. Demonstrable benefits might include increases in the levels of effective control. This would particularly apply to pests that are difficult to control, or those which cause significant economic damage. Applicants should be able to provide data and information to justify the 'benefit' of the mixture compared with the use of solo products.
- Mixtures used to control a range of targets, especially where there is no overlap in the spectrum of activity, may be appropriate. There should be a consideration of, for example, targets controlled by the different active substances being present in the crop, and at appropriate (threshold) levels justifying the need for control. The timing of application should also be appropriate to all targets, without compromising effective control. In particular, label wording may be appropriate to indicate the circumstances under which the product should be used (i.e. the factors discussed relating to relevant targets present in the crop at appropriate threshold levels, distribution and timings).
- EPPO Standard PP 1/225 *Minimum effective dose* states that some justification for the ratio of active substances within the mixture should be provided.[3] Where there is no overlap in activity against the target pests a case based on the rates of the solo products may be sufficient. Where some overlap of activity against the target pests exists then the contribution of each component in the ratio should be demonstrated (preliminary data may be sufficient).
- Where it is already known that the dose for one or more of the active substances varies for the same pest between Member States then this would provide a strong indication that the mixture may not be suitable across a regulatory zone.

  It is assumed that the applied dose of each individual active substance in a mixture would not be greater than the corresponding dose of the same active substance in a solo product. Where the dose of an individual active substance in the mixture is increased compared with the solo product then

[3]This is also referred to in the EU efficacy data requirements, section 6.1 'Preliminary tests' of EU regulation 284/2013 (EC, 2013)

the benefit must be clearly identified and the impact on resistance management considered.

General principles to be considered for the justification of mixtures for resistance management

- Where the primary justification for the mixture is resistance management this should be fully supported. Over the period of product authorization sensitivities could be expected to change, therefore the robustness of the effectiveness should be fully explained.
- The potential implications of the use of a mixture on resistance management (positive or negative) should be considered. If the duration of control for the individual active substances within the mixture is similar, this avoids leaving one active substance more exposed to selection pressure, and the duration of control should therefore be taken into account. For resistance management each active substance should have a similar and preferably high level of activity against the target in its own right. Mixtures having the same MOA whilst potentially offering improved effectiveness would not be considered as an anti-resistance strategy and would normally be treated as a solo product for resistance management.
- Where one of the active substances already has a history of resistance in the target pest(s) resulting in control failure this may reduce the potential benefit of a mixture as a resistance management strategy. This is particularly relevant where the incidence of resistance is widespread, i.e. the frequency of resistant genes to one of the active substances within the population is high. Justification should be provided for a mixture where resistance is already present in one of the main pests.
- Where there is a significant risk of resistance for a key pest mixtures can be an important resistance management tool. The components providing resistance management in a mixture should have an activity against the field populations of the pest when used alone and provide a robust contribution to the overall control of the pest(s) considered at risk of developing resistance. The mixture should provide control of the pest when applied at the recommended dose. Further information on assessment of resistance risk and risk management is available in EPPO Standard PP 1/213 *Resistance Risk Analysis*.

Evidence required to support the authorization of a mixture

- A minimum requirement for the mixture is to demonstrate the absence of antagonism in the control of the key targets and to demonstrate crop safety.
- Where one or more of the active substances is approved but not yet authorized in a product the contribution of each active substance to the effectiveness against target pests should be clearly demonstrated. This may be from preliminary data and/or field trials.
- Field trials or any other supporting evidence should primarily focus on the justification for the mixture. The amount of data required for the mixture will depend upon the doses of the mixture compared with existing solo products, the potential overlap in activity of the component active substances and whether a claim is new to both active substances. It will also depend upon the extent of the claims being made across the regulatory zones and whether the pests are considered sufficiently important to justify the use of the mixture. Where required, trials should be designed in accordance with the principles outlined in EPPO Standard PP 1/152 *Design and analysis of efficacy evaluation trials.*
- Where the proposed dose of the mixture applies the same amount of active substance as the solo products and the active substances do not have an overlapping activity, a reduced package of effectiveness data may be sufficient, provided no additional claims are made. In such cases existing data may be used to confirm the minimum effective dose against the key pests provided both actives substances are authorized in accordance with the uniform principles of assessment for the same use(s) in a relevant Member State. In such cases it may be sufficient to provide a limited data set demonstrating the absence of antagonistic effects against some of the major pests and the absence of a significant increase in phytotoxicity. Where there are major differences in the composition of formulation between the solo products and the mixture it would be expected that data confirming the activity of the mixture across a range of the key target pests is provided. Data would be required to support any claims for new pests or synergistic effects.
- Where the new mixture represents significantly reduced doses of one or more of the component actives substances then a full data package would normally be required to demonstrate the effectiveness of the product, and the potential impact on resistance management should be addressed.
- Where there is an overlap in the activity of the constituent active substances field trials would normally be required to justify the need for both the active substances and would be expected to include a comparison of the proposed new mixture product with each active substance alone. The need to include each of the active substances in trials will depend on the spectrum of activity of the individual active substances. For justification of the mixture ratio each active substance in the mixture needs to be included as a solo product. Where it can be demonstrated by laboratory/glasshouse studies that one of the active substances has limited effectiveness against one or more of the target pests when applied at the same dose then it would not be necessary to include the solo active substance in the field trials for these pests. Field trials to demonstrate the

effectiveness of such new mixture products should contain some lower doses to justify the dose rate for the product.

- Where a new pest claim (not authorized for either solo product) is made for the mixture product and no extrapolation is possible from the solo authorized products a full data package would be required for that use in accordance with the principles outlined in EPPO PP 1/226 *Number of efficacy trials*.
- A bridging approach (a reduced data package) may be possible, particularly where there is no overlap in the activity of the active substances and the applied doses in the mixtures are comparable with those of the solo products. Further information on the number of bridging trials is provided in EPPO PP 1/226.
- Where field trials are required for the mixture these should be located in regions relevant to the Member States in which authorization is intended to be sought and should demonstrate effectiveness against the relevant targets for each active component.
- Reference products should be selected according to EPPO PP 1/214 *Principles of acceptable efficacy*. For regulatory purposes it is not necessary to include the corresponding tank mix treatment but applicants may decide to do so for other reasons, such as marketing.

References

EC (2009) Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directive 79/117/EEC and 91/414/EEC. *Official Journal of the European Union L* **309**, 1–50.

EC (2013) Commission Regulation (EU) No 284/2013 of 1 March 2013 setting out the data requirements for plant protection products, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of Council concerning the placing of plant protection products on the market. *Official Journal of the European Union, L* **93/85**.

EC (2009) Directive 2009/128/EC of the European Parliament and of the Council of 21 October 2009 establishing a framework for Community action to achieve the sustainable use of pesticides. *Official Journal of the European Union L* **309**, 71–86.

EPPO (2012a) EPPO standard PP 1/225 *Minimum effective dose*. *EPPO Bulletin/Bulletin OEPP* **42**, 403–404.

EPPO (2012b) EPPO Standard PP 1/226 *Number of Efficacy Trials*. *EPPO Bulletin/Bulletin OEPP* **42**, 405–408.

EPPO (2015a) EPPO Standard PP 1/213 *Resistance risk analysis*. *EPPO Bulletin/Bulletin OEPP/(2015)* **45**, 371–387.

EPPO (2015b) EPPO Standard PP 1/214 *Principles of acceptable efficacy*. *EPPO Bulletin/Bulletin OEPP (2017)*, **47**, 293–296.

The resistance section of the EPPO website contains useful information on resistance including links to the RACs and national/regional RAGs. http://www.eppo.int/PPPRODUCTS/resistance/resistance.htm [accessed on 01 Sep 2018]

Checklist of issues to consider when supporting the authorization of a mixture

Principles to consider when justifying the mixture	Key issues to consider
Effectiveness	A clear benefit should be identified and supported by a strong reasoned case or new trials Possible justification may include, but is not restricted to, one or more of the following reasons: (i) improved control of individual targets (ii) control of different life cycle/growth stages (iii) an extended range of targets (that exceed damage thresholds or need treatment at the same time) (iv) greater reliability control (v) greater persistence of control (vi) allows use of lower doses to achieve comparable control (vii) allows flexibility of application (viii) allows longer intervals (fewer applications)
Ratio of active substances in mixture products	The contribution of each active substance to the control of the target pest should be assessed. This may be based on the rates of the solo products (where no overlap in activity against targets exists) or preliminary tests or a small number of trials (where some overlap of activity exists). Any trials conducted should include all solo active substances. Where authorized solo products are not available this may be demonstrated using a test formulation

(continued)

Checklist *(continued)*

Principles to consider when justifying the mixture	Key issues to consider
Resistance	Implications for resistance management should be considered If resistance management is a major part of the justification for the mixture, this should be explained and supported with evidence Mixtures may compromise existing resistance management strategies for either of the active components Consider the resistance management strategy for each active component and implications for the resistance management strategy of the co-formulation Mixing two different MOAs may not always be an acceptable resistance management strategy (See information from Resistance Action Committees, national/regional Resistance Action Groups, and EPPO website and EPPO Standard PP 1/213 *Resistance risk analysis*)
Relevance across the EPPO zone	The claimed benefits of the mixture should apply across all the countries where authorization is proposed Confirm that the main target pests regularly co-appear
Need for effectiveness data with the mixture	As a minimum requirement, data should be provided to demonstrate a lack of antagonism (could be a part of the preliminary data) Minimum effective dose may be extrapolated from solo products in cases where there is no overlap in activity and the dose and formulations of the applied active substance are comparable A full data set is required where the applied doses of the active substances in the mixture are significantly reduced compared with the solo products A full data set is required where new claims (not present for either solo active substance) are proposed A full data set is required to support claims of improved effectiveness relative to the solo products A bridging approach may be possible where the applied doses of the active substances are comparable to the solo products and no claims for improved control are being made
Relevant comparisons	Trials supporting ratio justification should include solo products at the authorized dose where it is available as reference products In addition, where the mixture applies reduced doses of the active substances, those solo active substances should also be included at the same dose to justify the mixture An additional reference product should be included if additional claims are made (not on the label for any solo product)
Potential disadvantages	Unless the mixture is designed exclusively for resistance management, in the absence of a clear benefit in resistance relative to the solo product the mixture may result in an unnecessary use of pesticides. In such cases the dose and timings for all targets should be considered Depending on the use, antagonism against specific targets should be addressed by appropriate warnings/advice, or where antagonism is significant such a product may not be authorized
Need for crop safety data with the mixture product	Data should be provided to demonstrate crop safety
Taint/transformation succeeding/adjacent crops	Consider whether extrapolation can be based on the similarity of formulation types of the mixture and solo products and the relative doses of the active substances

Appendix 1 – Insecticide mixtures

(a) Insect pest control

Currently, application of more than one active substance at the same time is commonly achieved by tank mixing of appropriate products. This has provided flexibility in facilitating optimal timing, for example against different pests, and at (or approaching) treatment thresholds. This is particularly relevant as most insecticides are applied curatively (except for seed treatments); preventative treatments may be more relevant for control of virus vectors, to aid in crop establishment and/or targeting soil pests (as with seed treatments) or in high-value crops where cosmetic damage or infestation of harvested produce has economic impacts. When broadening out the pest spectrum, to control a range of pests the timing of applications should remain appropriate for all and not compromise effective control of individual pests. The wording on national labels (where relevant) should consider relevant advice on timings and thresholds.

Seed (and soil) treatments may be appropriate, for example where targeting a range of pests at establishment and subsequent foliar feeding pests. These treatments tend to be prophylactic in nature, and therefore should target pests which occur regularly, either at the local or regional level. Evidence should therefore be provided on the extent of the pest and its presence in the trials. For sporadic pests it may be appropriate to treat curatively, usually by foliar applications, as the population develops.

Consideration should be given to the use of the mixture in integrated pest management (IPM) programmes, particularly because of the role that natural predators, parasites and parasitoids play in controlling pest species, including resistant or less susceptible individuals. In some cases, a broad-spectrum mixture may also significantly reduce natural predator populations to a point where they are not able to keep pest species below threshold levels. But equally the application of a mixture, particularly where pest populations are high at the start of the season, may over the long term assist natural predators (following any recovery period). One of the arguments for a mixture may be that over the course of the season the amount of applied insecticide is lower than when one has to make multiple applications of solo products. If this is the case, then having comparisons of different overall treatment programmes over the course of the season can be very helpful in demonstrating this.

(b) Resistance management

Resistance management of insecticides has conventionally been approached by the use of sequences of active substances with different modes of action (MOAs) and not via the use of mixtures. There are a number of reasons for this, including the practical issues when targeting more than one pest, described above. It is also the case that advantages are negated where the target(s) have developed resistance to one of the active substances. In practice this has limited the number of potential appropriate combinations of active substances.

Justification of the use of mixtures principally as a resistance management tool is based on the principle of redundant killing, i.e. killing the insect by more than one mechanism (MOA). However, this rationale is dependent on the appropriateness of combining the different MOAs, as discussed in this Standard. It is important that each active substance makes a significant contribution to the control of the target pest(s), with regard to both efficacy and (if relevant) pest spectrum. Where the active substances have different spectra of control, the greatest consideration should be given to the most resistance-prone organisms.

The principle of redundant killing means, by definition, that the applied mixture will contain a higher total quantity of active insecticide substance than is actually required to kill the target pest. Therefore, the choice of active substances must be appropriate to avoid unnecessary overapplication of more active substances than required (particularly as part of IPM programmes). The benefit may be greater where the resistance mechanism is a specific MOA (e.g. the target site) rather than more than one MOA (e.g. enhanced metabolism).

Resistance management strategies should consider not only direct exposure of the target pest(s) but also indirect exposure of other pests present on the crop. This is particularly relevant to the pest species with high resistance risk found on a wide range of host crops. For example, peach potato aphid, *Myzus persicae*, which includes a number of arable and horticultural crops amongst its hosts, has developed resistance to a number of modes of action. In such circumstances it may be relevant to consider introducing a restriction on the total number of applications of an active substance on a particular crop (independent of individual products). In addition, it may be appropriate to consider the potential selection pressure through longer-term exposure to sub-optimal rates (as residues decline).

Using active substances in mixtures may mean, in practice, reducing the ability to alternate different MOAs in sequence. In many crops there are already limited numbers of authorized active substances, or one of the potential active substances may have induced resistance in the target pest(s). This has an impact on resistance management, particularly if alternation is the more effective strategy. When seed/soil treatments are used, followed by foliar treatments, it is important to consider the potential selection pressure on the target species for the seed treatment if it is subsequently exposed to the foliar treatment. When using alternating strategies it is important to remember that seed/soil treatment is the first treatment in the programme.

Appendix 2 – Fungicide mixtures

The majority of fungicides are available as mixtures. This is because they are commonly used against disease complexes and need to provide both curative and preventative activity. Strategies for resistance management include using fungicides from groups having different MOAs in alternation or recommended formulated mixtures or tank-mixes.

(a) Disease control

Mixtures have historically been used to control some of the most damaging diseases (e.g. *Phytophthora infestans*). The main strategy here is to apply a contact multi-site protectant active substance, for example mancozeb, with a systemic partner. The adoption of such a strategy has played an important part in delaying the occurrence of field resistance for a number of higher-risk active substances to which laboratory resistance can be readily induced.

When the justification for a mixture is a broader disease spectrum it is important to consider whether the diseases are likely to coincide. As an example, a justification based on the combined control of eyespot and *Fusarium* ear blight in cereals would be difficult to accept given the difference in the timing of their occurrence and in the optimum timings for controlling these diseases. Similarly, the importance of a disease in a given location needs to be carefully considered. *Zymoseptoria tritici* is more problematic and more difficult to control in the cooler, wetter EPPO Maritime Zone; thus if this is the primary justification for/of a mixture it is likely to only be of relevance in those countries where it is a significant disease.

It is important to check for potential antagonism: for example, some evidence of reductions in activity of some systemic active substances against powdery mildews and rusts have been reported when co-applied with some surface-acting contact fungicides.

(b) Resistance management

Resistance to fungicides can develop rapidly in plant pathogen populations. A key requirement for any mixture product applied for the purposes of resistance management is that the components of the mixture must not be cross-resistant and the doses of each component used in the mixture should provide sufficient control of sensitive isolates when used alone. The most common mixtures consist of single-site fungicides (with moderate or high resistance risk) and multi-site fungicides (with low resistance risk), either as tank mixes or as co-formulations. However, since more regulatory restrictions are being imposed on multi-site fungicides and highly effective single-site fungicides with different MOAs are available for most crops, mixtures between single-site fungicides are appearing on the market and it is clear that more care with regard to resistance status in pathogen populations needs to be taken when recommending them.

Systemic multi-active fungicide seed treatments (e.g. the succinate dehydrogenase inhibitors) with activity against foliar diseases at the doses used in the seed treatment may impose a selection pressure on those diseases for which foliar applications with the same MOA can subsequently be made. In such cases the implications for the overall resistance management of the MOA should be considered.

The development of resistance can be very dynamic. When considering mixtures of two single-site active substances the situation can change dramatically over time. The rapid development of resistance of G143A to the quinone outside inhibitor (QoI) fungicides in cereal powdery mildew (*Erysiphe graminis*) would therefore raise significant concern that a mixture of a QoI and other moderate-risk active substance would continue to represent a sound resistance management strategy in those areas where QoI resistance is now established. However, such mixtures may provide an effective method of delaying the development of resistance in those regions where resistance is not yet established. When proposing mixtures containing moderate/high-risk active substances a robust consideration of the resistance status must be provided in those regions where the mixtures are intended to be authorized.

Where there is a significant risk of resistance for a key target disease, mixtures are an important resistance management tool. The partners providing resistance management in a mixture should have activity against the field populations of the target pathogen when used alone and provide a robust contribution to the overall control of the target disease(s) considered at risk of developing resistance. The mixture should provide control of the target pest when applied at the recommended dose.

Further details can be found in EPPO Standard PP 1/213 *Resistance risk analysis*.

Appendix 3 – Herbicide mixtures

Herbicides are often available as mixtures. This is because they are often required to control a diverse weed population present at the same time, either as emerged plants or in the weed seed bank. Mixtures are therefore designed to complement the range of activity of individual active substances to control as broad a range of species as possible. The product of choice will depend on individual field situations and reflect the predominant weed species and competitiveness of the crop. Appropriate resistance management for herbicides may be addressed by a range of methods, including using mixtures which combine active substances from different chemical groups with different MOAs, in order to control a specific target species that is at risk of developing resistance.

(a) Weed control

Mixtures have historically been used to control both grasses and broad-leaved weed species at the same time through

the use of combinations of specific graminicides with active substances having broad-leaved weed activity, thus widening the spectrum of control. This can also be the rationale for combining different broad-leaved weed herbicides in the same product, particularly if each has distinct targets for control. When the justification for a mixture is a broader spectrum of weed control it is important to consider whether the active substances have overlapping activity, since this may have implications for the justification of the ratio of the active substances and minimum effective dose.

For weed control there are also situations where herbicides may be mixed because each has a different persistence of activity, for example combining an active substance with foliar activity and one with soil residual activity in order to provide control of both emerged weeds and those yet to emerge.

Active substances may also be co-formulated to achieve control not only of a wider range of species but also potentially weeds at more advanced growth stages.

It is also important to check for potential antagonism between the active substances in the mixtures. For example, there is some evidence of reduction in activity of translocated herbicides when used in combination with contact herbicides and reduction in control of some specific graminicides when co-applied with certain acetolactate synthase-inhibiting herbicides.

(b) Resistance management

Mixtures are used in weed control for resistance management. Where two or more active substances with different MOAs are effective against the same target this can form part of a resistance management strategy. For resistance management the individual components must be capable of giving acceptable control on their own, although complications will arise where the products have different spectra of control. In this situation the greatest consideration should be given to the most resistance-prone weed. The components should ideally exert a similar duration of control, or at least the one more at risk should have a shorter duration of control. Inclusion of an inappropriate partner is likely to be ineffective as a technique for managing resistance. In addition, if resistance mechanisms are present that affect pesticides with different MOAs (e.g. non-target site resistance to herbicides), the benefits of such mixtures in a resistance management strategy may be less than where resistance is present to a specific MOA (e.g. target site resistance).

Appendix 4 – Seed treatments with combined activity against different insect pests and pathogens

Seed treatment products which are mixtures of, for example, fungicides and insecticides may also exert a selection pressure against the respective target organisms. Therefore, the impact on resistance management strategies for the individual active substances should also be addressed for these types of mixtures. This would need to consider the potential impact of subsequent foliar or soil-applied treatments of the same active substance or MOA and may require additional guidance on the use of alternative MOAs and/or on the total number of applications of the active substances per crop/season.

Appendix 5 – Plant growth regulators

Active substances with plant growth regulation properties may be co-formulated typically with other plant growth regulators or with fungicides.

Plant growth regulators may be combined where each active substance works on a different pathway or a slightly different growth stage. This has the potential to widen the application window, which can be critical for plant growth regulators. Equally plant growth regulators may be combined which operate on a similar pathway and this may facilitate a reduction in the dose of each active substance applied.

Furthermore, plant growth regulators may be co-formulated with fungicides to control fungal diseases and modify plant growth, for example to improve winter hardiness or reduce lodging.

In principle, in the case of co-formulated mixtures with plant growth regulators the same justification is required as for mixtures of other plant protection products. However, where plant growth regulators are combined it may be difficult to establish ratio justification, for example, in the field, particularly where the product is seeking to improve quality of yield or reduce lodging since many agronomic and climatic factors will also have an influence on plant growth. In these situations, it may be possible to support the co-formulation through the use of a reasoned case based on the MOA of the active substances.

Where fungicides and plant growth regulators are co-formulated it is important to consider the timing of application as the optimal time to achieve pest control may not be the same as that for growth regulation.

Appendix 6 – Home garden products

Home garden products, intended primarily for use by amateurs, will typically contain active substances authorized for use on a range of widely grown crops/scenarios. In principle the same justification is required for these mixtures as for a professional mixture (see Appendices 1 and 2). In the first instance it would be expected that extrapolation from the established activity of relevant professional products against similar pests could be used to justify the main target pests and doses for a home garden mixture product. Where no extrapolation from professional products can be made then it will be necessary to provide some evidence that the main target pests do co-exist and that the mixture has activity against them. Consideration should be given to appropriate label advice.