Resistance risk analysis and use of resistance management strategies

Purpose of this guideline

This guideline is primarily intended to provide an overview of the most important factors that may need to be taken into account by efficacy evaluators when considering the resistance risk analysis and resistance management strategy sections of dossiers. The guideline is not intended to exhaustively cover all aspects of resistance or provide detailed background information on the subject. It provides guidance on the factors to be considered and the weighting that might be put on those factors when formulating a regulatory decision. It does not, except in the most straight forward of cases, seek to provide the answers. Evaluators should use the guidance to help produce their draft evaluation before discussing it with senior specialists.

The guideline will be made available externally so that the process of evaluation is transparent to applicants and to assist applicants in putting together those sections of the dossier.

Background

Resistance is an inheritable change in a population that reduces the effectiveness of a pesticide. It may build up gradually over time, initially having no significant effect on the performance of a product in the field, or appear suddenly at a very high level. Any pest population may contain a small proportion of individuals resistant to a specific pesticide. Repeated use of this pesticide, or others with the same mode of action, removes susceptible individuals allowing the resistant forms to survive and multiply. This may result in control failures although detection of resistance does not always lead to major problems. Some forms remain uncommon and never become significant problems.

Historically, some targets have developed resistance to products almost as soon as they are introduced, in other cases resistance has only developed after many years of use but resistance can also be present before a pesticide is introduced. Although there are many cases where resistance is not known it is never safe to assume it will not occur. Resistance has been found to virtually all major chemical types, even such unlikely groups as the organomercuries.

When considering resistance the first step is to carry out an assessment of the risk of resistance developing for a particular use. The risk of resistance developing will depend on a number of factors relating to the pesticide (examples in Table 2), the target (examples in Table 3), and how the pesticide is used. Resistance risk analysis is a difficult area that is poorly understood. What we know comes more from experience of how and when resistance has developed in the field than from predictive scientific studies. There are no hard rules, only general guidance.

Figures one and two illustrate the major steps to consider when assessing the inherent risk or resistance developing for different chemistries and organisms. Where there is uncertainty assessments should lean towards assuming a higher risk.

Use the assessment of risk outlined in figure 1 and 2 for both the chemical and organism to come up with an overall risk as shown below.

Table 1: Overall risk of resistance developing

		Risk associate with the chemistry		
		Low Risk	**Moderate Risk**	**High Risk**
Biological risk	**Minimal Risk**	Low	Low	Moderate
	Some Risk	Low	Moderate	High
	Serious risk	Moderate	High	High

Table 2: Examples of risk associated with different chemicals – note these may change with time.

	Insecticide	**Herbicide**	**Fungicide †**
Low risk	Fatty acids	Propyzamide	Coppers Dithiocarbamates Chlorothalonil
Moderate Risk	Neo-nicotonoids METI acaricides	Ureas Dinitroanilines	DMIs Quinoxyfen
High Risk	Pyrethroids OPs	ALS ACCase inhibitors	QoIs Phenylamines

† The FRAC website http://www.frac.info/ provides their assessment of the risk associated with all fungicides.

Table 3: Examples of risk associated with a range of common target organisms

	Pests	**Weeds**	**Diseases**
Minimal risk	Cabbage white butterfly	Most broad leaf weeds	Seed and soil borne diseases Cereal rusts
Some Risk	Pollen beetle Cabbage root fly	Poa Wild Oats Chickweed Poppy	*Rhynchosporium* *Septoria*
Serious Risk	*Myzus persicae* Glasshouse whitefly *Phorodon humuli* *Aphis gossypii*	Black Grass Rye Grass	Cereal powdery mildew Potato late blight Botrytis

The final risk assessment (Table 1) must take account of the potential scale and impact of resistance in the target organism and the use pattern of the product. The **unmodified risk** is the risk assessed assuming that no resistance management action is taken and the product is used at all applicable timings with no restrictions on the number of applications made or alternative methods of control being used. Note that the achievement of higher levels of control from the use of a single product is also often considered to impose a higher resistance risk, although this has been the subject of considerable debate and may depend on the specific resistance mechanism.

Where the unmodified risk is low, then the proposed use may be acceptable without any modifications or a specific resistance management strategy. Where the unmodified risk is moderate or high, then the second stage of resistance risk analysis is the need to consider a resistance management strategy. The strategy introduces restrictions on use and other measures designed to reduce selection pressures, and should lower the resistance risk to an acceptable level. Further guidance on resistance risk analysis and resistance risk management is provided in the EPPO guideline (‘Resistance Risk Analysis’, PP 1/213).

Figure 1

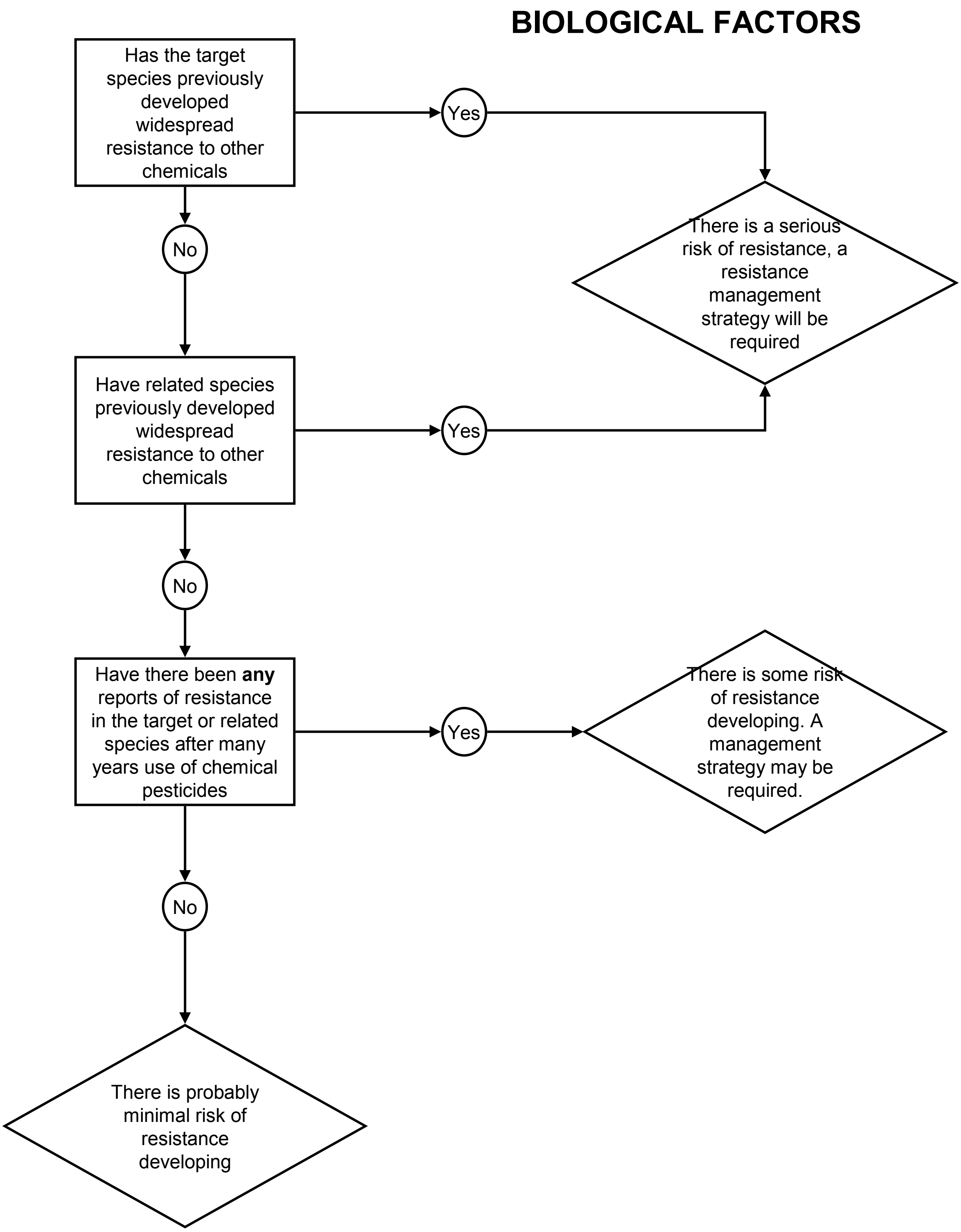
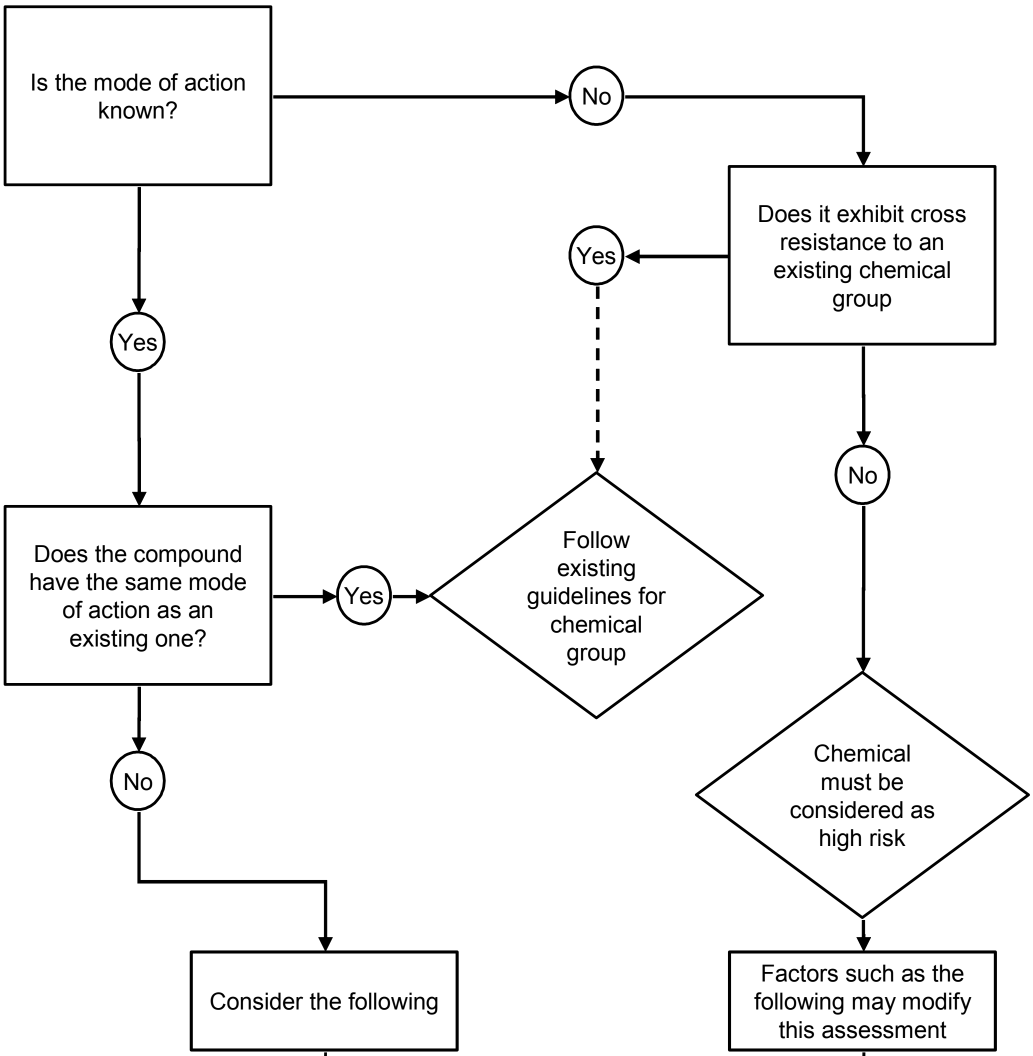

BIOLOGICAL FACTORS
Has the target species previously developed widespread resistance to other chemicals
Yes
No
There is a serious risk of resistance, a resistance management strategy will be required
Have related species previously developed widespread resistance to other chemicals
Yes
No
Have there been **any** reports of resistance in the target or related species after many years use of chemical pesticides
Yes
There is some risk of resistance developing. A management strategy may be required.
No
There is probably minimal risk of resistance developing

Figure 2

CHEMICAL FACTORS



High risk factors	**Risk Reducing factors**
➢ Single site mode of action ➢ Wide variation in existing sensitivity ➢ Easy to generate resistant strains in laboratory or glasshouse assays. ➢ Targets or related species have developed resistance to other chemicals	➢ Multi site mode of action ➢ Difficult or impossible to generate resistant strains in laboratory or glasshouse assays ➢ Targets and related species have not previously developed resistance

Low relevance factors
➢ Resistant laboratory or glasshouse strains are unfit or unstable ➢ No change in sensitivity seen in the field during development

Resistance management strategies

Resistance management strategies are designed to prevent or delay the development of resistance in a population. Where resistance does develop they may also delay and restrict its spread throughout the entire population, thus allowing an active substance to continue to be used despite the existence of resistance. Selection pressure for resistance is linked to the exposure of the gene pool to a particular mode of action. Thus, the main ways of reducing the likelihood of resistance developing are reducing the frequency and/or duration of exposure. This may be by limiting the number of applications or restricting the extent of exposure of the gene pool by ensuring that treated populations are exposed to more than one method of control, including different chemical modes of action and non-chemical control methods.

Outlined below are the principle components of a strategy but the list is not exhaustive. Some of these are common to all strategies and representative of good agricultural practice e.g. appropriate use of product, alternating chemicals with different modes of action. Other measures will be appropriate in specific circumstances, or may only be required when the resistance risk is considered to be moderate/high. For a high-risk situation as many components as possible should be included in the strategy. As the risk reduces, it may be possible to have a strategy based either on fewer components or less restrictive ones. At the end of this section, Table 4 summarises the main components depending on resistance risk.

For active substances from chemical groups where resistance is already known to occur there will often be existing guidelines for resistance management. In general UK Resistance Action Group guidelines should be followed where they exist and many of these are available in the 'Advisory Groups' section of PSD's website . Guidelines published by the Resistance Action Committees (RACs) may also be considered as a starting point but may require adapting to UK conditions. In situations where there is no existing guidance there may be similar situations (e.g. related pest species or chemistry considered to pose a similar risk of resistance, etc) that may provide a starting point.

Monitoring pest populations and use of threshold levels

In a resistance management programme using the product against the correct target and only when justified minimises selection pressure. The smaller the population at the time of treatment the lower the selection pressure is likely to be. Monitoring and correct identification of pest species is a basic principle in preventing unnecessary or ineffective sprays. Past history can give a good indication of potential problems, especially for weeds and soil pests and pathogens. Information from sampling and other sources such as weather stations can be used to predict when sprays are necessary. It is also important to consider whether secondary pests are present in the crop, which may be inadvertently exposed and potentially at sub-lethal doses.

Cultural control measures (including ICM, IPM and IWM)

Cultural or other non-chemical control measures have the potential to reduce pest numbers without exerting any selection pressure at all. If there are any obvious non chemical control or prevention methods that can be used instead of chemical controls these should be included and mentioned on the label. In many cases these will relate to good agricultural practice and probably ought to be mentioned anyway. Examples include;

- Crop rotations; can reduce resistant populations over time, allow different pesticides to be used to target populations (particularly weeds), or reduce selection pressures by not having to apply pesticides onto consecutive crops which are common hosts for the main pest species.
- Resistant crop varieties can be used that reduce infestations thus reducing the need for pesticide applications.
- Cultural measures such as adjusting planting dates, providing an environment that encourages beneficial insects or introducing bio-control agents may all help reduce the need for pesticides.
- Cultivation, e.g. ploughing and mechanical weeding to disrupt pests and weeds and bury seeds and pathogens.
- Stale seed beds and delayed drilling can permit the destruction of weeds pre-sowing thus reducing the potential weed population in the crop.
- Good crop hygiene, for example by destroying overwintering hosts and other sources of inoculum, such as potato dumps.

Where it is not possible to cover these in adequate detail on the product label these approaches should be explored in any supporting company information.

Restrictions on number of uses

The main reason for resistance development is the repeated sole use of pesticides with the same mode of action on a particular target species. Restricting the number of applications reduces the exposure of that species to a particular mode of action. For persistent pesticides it also reduces the length of time a target is under resistance pressure. Note that any restriction should apply to all related chemistry. If necessary, this can be made a statutory restriction. It may also be formalised through use of the Annex V label phrase '**To avoid the build up of resistance do not apply this or any other product containing** *(identify active substance or class of substances, as appropriate)* **more than** *(number of applications or time period to be specified)'* or similar phrase or by specific restrictions to this effect. Further guidance on the use of the annex V phrase is given at the end of this guideline.

Restrictions should apply to the typical use of the product in most seasons, rather than the stated maximum number of applications which may be higher and rarely required. For example, applicants have proposed limiting the use of a cereal mildewicide to two sprays. However, as it is unusual to spray more than twice against mildew in wheat (and once on barley) this is not a significant restriction.

Such a strategy requires multiple sprays per season to be effective. Although it is possible to advise growers not to spray in two sequential years such a strategy would be difficult to implement and should normally be avoided. In protected glasshouse situations restrictions need to take into account the fact that crops may be grown almost continuously, or different crops which are also host to the same target may be growing in other parts of the same glasshouse. Therefore it may be more appropriate to specify the number of applications within the glasshouse structure per year, rather than by crop or season

As general guidance for multiple **fungicide** spray situations where there is significant risk of resistance developing a solo product should make up no more than 33% of all sprays and a mixture no more than 50%. For multiple application situations you should consider both the total number of applications that can be applied throughout a season and the maximum number that should be used in a block (i.e. sequentially before switching to an alternative mode of action)

In the UK various statutory restrictions on the use and number of applications have been made in what are considered to be high risk situations. Further details are available in the relevant individual product guidelines (see 'Further information').

Pesticide rotation, sequences and mixtures

The continued use of the same pesticide or pesticides having the same mode of action in the same field year after year should be avoided unless it is integrated with other control practices. Pesticide rotation between seasons can be a useful tool. This refers to the use of different modes of action in subsequent crops. For example, non-selective herbicides can be used to control early flushes of weeds (prior to crop emergence) and/or weed escapes. Break crops in the rotation can provide a useful opportunity to extend the choice of pesticide mode of action.

Within a season, sequences and mixtures can be a useful tool in managing or delaying the development of resistance and should be considered as a component of the resistance management strategy for all but the lowest risk cases. For this to be at all effective the mixture and/or sequence must comprise two or more components with different modes of action.

The RACs publish classifications of pesticides by mode of action which are regularly updated. When considering alternating or using sequences it is important to consider any seed treatments and early systemic treatments. In some cases consideration should also be given to the pesticides used on previous crops, and whether the target pest may migrate to the new crop.

Where multiple sprays are permitted consider how many should be applied in a block. If there is a high risk advising against sequential sprays may be sensible. As for the above this should apply to all related chemistry

Mixtures

Mixtures, either as products containing multiple active substances or as recommended tank mixes are commonly used in weed and disease control. Where two or more actives with different modes of action are effective against the same target this can form part of a resistance management strategy. The individual components must be capable of giving good 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 organisms. It is probably not necessary to have a full dose of each of the components in a mixture but guidance on how far doses can be reduced is limited. If a reduced dose is proposed in mixture, evidence should be produced that this rate is still effective if applied alone, this may come from earlier dose justification data. Reference to those data are advised. The components should ideally exert a similar duration of control, or at least the more at risk one should exert a shorter duration.

Including an inappropriate mixture partner is not only ineffective as a resistance management technique but is also a waste of money and contrary to good agricultural practice. In addition, if resistance mechanisms are present that affect pesticides with different modes of action, (e.g. enhanced metabolism resistance to herbicides), the benefits of mixtures or sequences in a resistance management strategy may be less than where resistance is present to a specific mode of action (e.g. target site resistance to herbicides).

Also be aware that the routine use of mixtures may go against government policy of reducing pesticide use.

The use of mixtures can be made statutory by refusing or restricting the approval of solo products.

Timing

Smaller weeds and earlier, juvenile, stages of pests are generally more susceptible to pesticides. For contact insecticides some pests may need to be targeted before the larvae move into sheltered areas. Similarly, for diseases it is generally easier to prevent infection than cure it. Pathogens also appear to be more likely to develop resistance to systemic than preventative fungicides, this may be due to both the larger populations, and therefore gene pool, present in curative situations and the more selective nature of systemic chemicals. Avoiding curative use or use against established disease will therefore reduce resistance risk. Label recommendations may need to be carefully worded to cover this as infection often establishes early on but only develops significantly later (e.g. *Septoria*).

Where the number of applications is restricted it may be useful to advise using a product only in certain situations, such as when there is a high risk of disease or pest attack (again probably in response to forecasting).

Dose advice

Dosage advice is occasionally proposed as part the label recommendations relating to resistance management. However, such advice has often been controversial. In theory, robust, highly effective doses may help prevent enhanced metabolism resistance to herbicides, which tends to develop as a staged process under conditions of low selection pressure. Conversely however, high doses may select for target site (or disruptive) resistance. This typically occurs in a single step often appearing quite suddenly and resulting in a high level of resistance. This theory is not, however, well supported by field evidence relating resistance development to pesticide dose and the consideration of ‘selection pressure’ is much more relevant than dose.

For fungicides their may be some validity in ensuring that the dose of preventative fungicides is adequate to prevent disease outbreaks, and thus keep inoculum low and reduce the need for curative applications, which may present a higher risk from the resistance viewpoint. Again though, this is a controversial area and any such advice requires careful consideration in relation to the pathogen’s biology.

Consequently although arguments relating to dose should be taken into account they should not form a major part of any management strategy. Where the use of mixtures is advised, recommendations and advice related to ensuring that partners are applied at sufficiently robust doses to give effective control may be useful.

Do not use

This option should normally only be considered once resistance has already developed and is so widespread that there are significant doubts that there is any benefit to the continued use of a product against a given target. Typically, claims would simply be removed from the label, although occasionally, for example if continued use against another target present in the crop at the same time would significantly increase the risk of resistance developing to a related active substance, specific label advice not to use the product in certain circumstances may be warranted.

From a regulatory standpoint it may be valid to refuse approval for a particular product if there is perceived to be a significant risk of resistance occurring in an important target in another crop, or non-target pest, or related chemical. (For example we might refuse approval of a product against tomato late blight if it increased the risk of resistance beyond that already existing for potato blight). In such cases, consideration must also be given to the availability of suitable alternative control options in both crops.

Establishing baseline sensitivity and monitoring population sensitivity

While this will do nothing to reduce the likelihood of resistance developing it will provide a means to detect it if it does. For new active substances establishing the baseline sensitivity is considered good practice. The data become important in any future investigations where poor control has been observed and resistance is suspected. Whenever possible, standard populations should be maintained for potential future use in comparative assays. It is acknowledged that this is easier to achieve with weeds (store seeds of baseline populations) than for most pests and pathogens. Where baseline populations cannot be stored or maintained, it is essential that the assays used for quantifying resistance are shown to be robust and repeatable. Where the resistance risk is determined as high then established baseline sensitivity and undertaking a monitoring programme is considered essential.

To be effective a baseline must be sufficiently extensive and the number of samples will generally be determined by the nature of the target. We should encourage applicants to make baselines available to other researchers and in some cases we may consider requiring monitoring reports to be submitted to PSD on a regular basis. Details of the methodology of measuring sensitivity must also be provided. If resistance already exists, it is important to establish whether existing resistance affects the new active substance.

For high risk situations there should be an undertaking to proactively monitor resistance and to investigate reported control failures. We should take account of the potential cost of monitoring, particularly when considering issues around minor crops and that extensive monitoring may not be financially viable in all cases.

A note about baselines

These need to include tests carried out on samples that are representative of populations from a good geographical range. It may be argued, particularly for established chemistry, that it is no longer possible to establish a baseline as populations may already have adapted to some extent. While this may be semantically correct, it misses the point. The baseline is a mechanism that enables us to test for any future changes in sensitivity. Information on the current sensitivity of a population can still be used to detect further reductions in sensitivities even if some adaptation has taken place. Where there is a possibility of resistance already being present in the field any wide variation in sensitivity, including any outliers in the data set should be examined carefully as it may indicate that resistance is already developing.

Where there is good cross resistance between chemicals, i.e. where resistance to one chemical has been shown to impart a similar level of resistance to another, separate baselines for each individual chemical may not be required and it may be possible to conduct resistance testing using any of the cross resistant active substances. This is the case for the QoI (strobilurin type) fungicides.

Communication

It is important that any strategy is effectively communicated to growers. The strategy must, at the very least, therefore be adequately detailed on the label. For insecticides there is an established set of resistance management statements (Efficacy guideline 601) which should be included for certain actives and target species. For higher risk cases we might expect the applicant to take additional steps to communicate the strategy, for example through their promotional material or training of advisors.

Table 4, Summary of Main Components of Resistance Management Strategies

Management factor	Low risk	Moderate risk	High Risk
ICM	Should always be considered		Identify options on label wherever possible
Frequency/Number of Applications	No restriction may be required	If possible should be used as part of a programme including other actives	Use may be restricted (particularly for mobile pests and diseases) consider statutory restrictions.
		Consideration should include both total no. of applications and the maximum number recommended in a block before switching to an alternative mode of action.	
Sequences and Mixtures	Good practice Should always be considered when high numbers (>4) of applications required.	Whenever possible treatment programmes should include other actives.	Where possible products must be applied in appropriate sequences or mixtures
Timing	Follow good practice	Advise use at lowest risk timing/preventative use/against early stages.	
Dose advice		Advice relating to the use of partner products in mixtures may be useful Other advice relating to dose should only be included following consultation with the Senior Specialists.	
Monitoring	Sufficient to follow up reports of control failure.	Baselines required. Some monitoring advisable, need not be every year.	Baselines required (for a major/high risk target species, possibly including those found in minor crops. Routine monitoring must be conducted against the same range of species.
Communication	None may be required (although any relevant standard resistance phrases must always be used)	Label advice required	Label must carry adequate advice. Approval holder should also undertake additional steps to ensure the resistance management strategy is adequately communicated to growers.

Further information

Resistance risk assessment and resistance management are extremely complex areas and the subject of much disagreement among experts. This guideline is intended to build on the EPPO standard on resistance risk analysis by giving basic guidance on the assessment resistance risk assessment cases and proposals for resistance management strategies proposed in applications. The following sources may also provide useful information, and applicants should also be aware that in 2007 EPPO have formed a permanent Resistance panel on plant protection products.

- EPPO standard pp 1/213(2) Resistance Risk analysis
- UK guidance 601: Resistance warnings and restrictions on labels of insecticide and acaricide products
- UK guidance 602: Resistance warnings and restrictions on labels of professional herbicide products
- UK guidance 603: Fungicide resistance label advice and restrictions
- Resistance Action Group Websites; http://webarchive.nationalarchives.gov.uk/20151023155227/http://www.pesticides.gov.uk/guidance/industries/pesticides/advisory-groups/Resistance-Action-Groups (Archive only available)
- Fungicides Resistance Action Committee website: http://www.frac.info/
- Herbicides Resistance Action Committee website: http://www.hracglobal.com/
- Insecticides Resistance Action Committee website: http://www.irac-online.org/

Annex V Labelling phrases: resistance

This section gives guidance on PSD's use of the annex V phrase relating to resistance.

Annexes IV and V - the labelling Annexes of Directive 91/414/EEC, have now been issued with the intention of harmonising product labelling throughout Europe.

One of the 'new' label warnings presented in Annex V is a resistance warning, listed under section 2.3: Safety Precautions related to good agricultural practice:

To avoid the build up of resistance do not apply this or any other product containing *(identify active substance or class of substances, as appropriate)* **more than** *(number of applications or time period to be specified)*.

The attribution criteria for applying this phrase are simply given at 3.4 as: *The phrase shall be assigned when such a restriction appears necessary to limit the risk of development of resistance*.

Implementation

Implementation of the annex V labelling phrases will be at product re-registration following annex 1 listing of the active substance, or for new actives at product authorisation.

Assessment of resistance risk is part of both re-registration and of authorisation of a new active, and thus consideration of appropriate risk mitigation will be made. This assessment will determine the risk of resistance and whether risk mitigation is appropriate.

i) Where the risk is negligible and no risk management is necessary, no resistance phrase is necessary.

ii) If risk mitigation is considered necessary, and appropriate mitigation is via restriction of numbers of applications (for products proposing multiple applications), then the above phrase should be used as the basis of the resistance mitigation measure. Additional guidance such as reference to RAG advice, cultural or other control options should be added appropriately.

iii) It may be that resistance management needs to be by some other method than purely restriction to numbers of applications, or a combination of both. For example, where only a single application is proposed and mixtures are considered essential. In this situation, an appropriate wording will need to be used. Where possible the bold text should be used as the basis of any phraseology with appropriate additional text added.