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A herbicide resistance risk matrix

Stephen Moss[a,*], Lena Ulber[b], Ingrid den Hoed[c]

[a] Stephen Moss Consulting, 7, Alzey Gardens, Harpenden, Herts AL5 5SZ, UK
[b] Julius Kühn-Institut, Institute for Plant Protection in Field Crops and Grassland, Messeweg 11-12, 38104, Braunschweig, Germany
[c] Health and Safety Executive (HSE), Chemicals Regulation Division, Mallard House, Kings Pool, York, YO1 7PX, UK

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ABSTRACT

Herbicide resistance is of increasing concern, especially as there is a lack of new modes of action. An assessment of resistance risk has been a key part of the pesticide authorisation process in most European countries since the early 2000's. However, little guidance is provided on how to quantify these risks. The risk matrix described here presents a quantitative approach to the evaluation of the resistance risk posed by the use of herbicides. The inherent, 'unmodified' risk is first assessed by ranking herbicides and major target weed species on a scale from low to high resistance risk, based largely on published information. In practice, agronomic management practices ('modifiers') will reduce the risk and these are factored into the matrix. Modifiers can include management strategies relating to herbicide use as well as non-chemical methods of weed control. By assigning defined impact factors to possible agronomic modifiers, the overall resistance risk of a herbicide under defined use conditions can be quantified. The approach, although simple, appears robust and produces realistic assessments of the resistance risks associated with four contrasting test scenarios. The aim is to achieve a better harmonisation of herbicide resistance risk assessment across Europe. Although the matrix has a European legislative focus, the approach and principles are relevant in other parts of the world where the extensive use of herbicides is a relatively recent development, and where there is currently limited knowledge and expertise on herbicide resistance and the evaluation of resistance risks.

1. Introduction

Weeds are a major constraint to agricultural production, causing significant agronomic and economic damage. In conventional cropping systems weed populations are most commonly managed with herbicides, although non-chemical methods are also an essential component of Integrated Weed Management (IWM) strategies. Repeated applications of herbicides with similar modes of action exert a strong selection pressure on target weed populations with the consequence that numerous cases of herbicide resistance have evolved worldwide (Powles and Yu, 2010). By August 2018, resistance had been confirmed in 255 weed species in 92 different crop types in 70 countries, affecting the efficacy of 163 different herbicides from 23 of the 26 known herbicide sites of action (Heap, 2018).

The increasing number of resistant weed biotypes is a major concern for agriculture, horticulture and amenity situations, especially as no new herbicide mode of action has been marketed for over 30 years (Duke, 2012; Westwood et al., 2018). Similar scenarios also occur for other plant protection product groups such as insecticides and, to a lesser extent, fungicides. To reduce the risk of resistance development, and thereby to prolong the period of effective use of plant protection products for the benefit of both producer and end-user, resistance risk has been assessed during the authorisation process in most European countries since the early 2000's. The basis for resistance risk assessment is the EPPO Standard, 'PP 1/213 (4) Resistance risk analysis' (EPPO, 2015). EPPO (European and Mediterranean Plant Protection Organisation) is an intergovernmental organisation responsible for cooperation and harmonisation in plant protection and has 52-member countries in the European and Mediterranean region (EPPO, 2018).

The resistance risk assessment of plant protection products during the authorisation process, as specified for herbicides in the EPPO Standard PP 1/213, includes an evaluation of both the *inherent* and the *agronomic* risk of a herbicide. The *inherent* risk is first assessed using the characteristics of both the herbicide active ingredient(s) and the target weed species. For a herbicide, this includes both the intrinsic mode of action of the active ingredient(s), the known cases of resistance and the mechanisms of resistance and cross-resistance. For the target weeds, consideration is given to both the biological characteristics that may predispose a weed species to evolve resistance (such as length of life cycle; seed production, distribution and longevity; genetic plasticity),

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* Corresponding author.
E-mail address: alopecurus@aol.com (S. Moss).

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and to what extent resistance has already been found in that species. The evaluation of the *inherent* resistance risk of both herbicide active ingredient(s) and target weed species results in an assessment of the resistance risk under unrestricted (unmodified) use conditions.

However, the cropping system where the herbicide will be applied and the herbicide use pattern will also impact on the selection pressure imposed on the target weed populations. Hence the *agronomic risk* in the field may well differ from the unmodified resistance risk, especially if specific cultural and agronomic management practices ('modifiers') are applied to minimize the resistance risk. If the unmodified risk is high, the impact of these modifiers is evaluated in order to reduce the risks associated with an unrestricted use. Modifiers can include management strategies relating to herbicide use as well as non-chemical methods of weed control.

Any evaluation of the *inherent* and *agronomic* resistance risk is based, not only on published scientific evidence (e.g. The International Survey of Herbicide Resistant Weeds, www.weedscience.org), but also on expert knowledge. Consequently, applicants submitting dossiers for plant protection authorisation purposes, and the evaluators of those dossiers, are attempting to assess future resistance risks based partly on past evidence of resistance, and partly on expert opinion. Applicants and evaluators are likely to have different priorities and, consequently, may reach different conclusions about the resistance risk. In addition, applicants, especially from companies with limited in-house resistance expertise or less familiar with European agronomic conditions, may be uncertain of how much information on resistance risk is required in any dossier.

The risk matrix described in this paper presents a quantitative approach to the evaluation of the resistance risk posed by the use of a herbicide. Herbicide active ingredients and major target weed species are each ranked on a scale from low to high resistance risk, based largely on published information. By assigning defined impact factors to possible agronomic modifiers, the overall resistance risk of a herbicide under defined use conditions can be quantified. The aim is to achieve a better harmonisation of herbicide resistance risk assessment across Europe for the benefit of applicants seeking to register, or re-register herbicides, evaluators and the end-users. Although the matrix has a European legislative focus, the approach and principles are relevant in other parts of the world where the extensive use of herbicides is a relatively recent development, and where there is currently limited knowledge and expertise on herbicide resistance and the evaluation of resistance risks.

2. Materials and methods

2.1. The resistance risk matrix

This risk matrix is based on the assumption that the evolution of herbicide resistance is critically dependent on the interaction of three factors (Moss, 2017a; Vencill et al., 2014).

A. the *inherent* risk of the **herbicide**
B. the *inherent* risk of the **target weed**
C. the **agronomic management practices** (*modifiers*) used in a given field, including the way the herbicide is used as well as alternative non-chemical methods of weed control.

Examples of the individual components contributing to each of these three main risk factors are presented in Fig. 1.

2.1.1. Inherent risk of the herbicide

Most types of herbicides are vulnerable to resistance, although some are more vulnerable than others. The risk posed by a specific herbicide can be estimated from the number of cases of resistance that have evolved to herbicides with the same mode of action (MoA), relative to herbicides with different MoA. In this matrix, the herbicide risk is based on information in the International Survey of Herbicide Resistant Weeds (Heap, 2018). This regularly updated database provides a global overview of cases of herbicide resistant weeds and is supported by government, academic, and industry weed scientists from over 80 countries worldwide. Within the framework of herbicide evaluation by European authorities, it is the major source of information for the assessment of the inherent resistance risk. To classify herbicide active ingredients according to their inherent resistance risk, active ingredients are assigned to their respective herbicide mode of action group (MoA group) as defined by the Herbicide Resistance Action Committee (HRAC). In their classification system, which is used in Europe and most countries worldwide, there are 25 different herbicide mode of action groups (HRAC, 2018). For each HRAC MoA group, the resistance risk is based on the number of resistance cases worldwide (Table 1). HRAC MoA groups are classified as a:

- **high risk** MoA group if the number of species that has evolved resistance to herbicides in that group account for 10% or more of all resistance cases reported.
- **medium risk** MoA group accounts for 5–10% of resistant species.
- **low risk** MoA group accounts for 1–5% of resistant species.
- **very low risk** is assigned to MoA groups with $< 1\%$ of resistant species.

The individual active ingredient(s) of any commercial herbicide mixture should be assessed for their resistance risk. It is unwise to assume that any new herbicide MoA group is automatically 'low' risk simply because it has a novel site of action. It is preferable to consider it as 'high risk' until information is available to better quantify the actual risk. However, if it is closely related to an existing HRAC MoA group, that may be a good indicator of the resistance risk.

2.1.2. Inherent risk of the target weed species

The inherent risk of a weed species evolving herbicide resistance is influenced by the biological and genetic characteristics of that species. For example, annual weed species have evolved resistance much more often and more quickly than biennial or perennial weed species (Holt et al., 2013). Annual species place greater reliance on sexual reproduction and have a shorter generation time, resulting in more genetic variation and more rapid resistance evolution. Cross-pollination appears to be more effective in enabling resistance-endowing gene recombination and accumulation, especially for metabolism-based herbicide resistance, compared to self-pollination which can limit the speed and spread of resistance evolution (Maxwell and Mortimer, 1994). However, self-pollination is certainly no barrier to the evolution of herbicide resistance; *Avena* spp. (wild-oats) are predominantly self-pollinating yet herbicide resistance has evolved in 21 countries worldwide (Heap, 2018). Seed production potential also impacts on resistance evolution and development. A weed species that produces more seeds would, in theory, have a greater chance of developing herbicide resistance due to a greater number of genetic combinations that have the potential to produce an individual with a herbicide-resistance trait (Jasieniuk et al., 1996).

The relationship between different plant families and their propensity to evolve resistance is correlated to a large degree with their frequency of occurrence as major weeds (Holt et al., 2013). However, some families (e.g. Poaceae and Brassicaceae) are significantly overrepresented in the list of resistant species, relative to their frequency as weeds in general. Although there is only a weak bias at the plant family level, at the individual genus level there is good evidence that some weeds are more prone to evolve resistance than others. Several weed species from each of the genera, *Lolium*, *Amaranthus*, *Conyza* and *Echinochloa,* are some of the most problematic herbicide-resistant weeds worldwide.

Perhaps surprisingly, given the amount of research conducted on herbicide resistance, it remains unclear why resistance evolves faster in

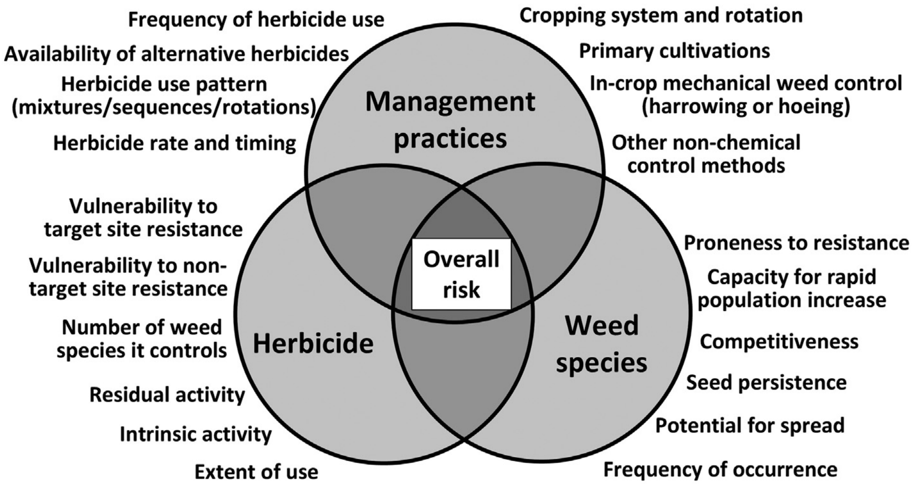


Fig. 1. Components of each of the three main resistance risk factors (Moss, 2017a).

Table 1
Herbicide resistance risk based on HRAC Mode of Action (MoA) groups (Heap, 2018; *Information collated 31 August 2018*).

Resistance Risk	HRAC Herbicide MoA Groups		Example of active ingredient	Number of resistant species worldwide	% of total
High	B	ALS inhibitors	chlorsulfuron	160	32
	C1	PSII inhibitors (triazines)	atrazine	74	15
	A	ACCase inhibitors	cycloxydim	48	10
Medium	G	EPSP synthase inhibitors	glyphosate	42	8
	O	Synthetic auxins	MCPA	38	8
	D	PS I electron diverters	paraquat	32	6
	C2	PSII inhibitors (ureas & amides)	isoproturon	29	6
Low	E	PPO inhibitors	acifluorfen	13	3
	K1	Microtubule inhibitors	pendimethalin	12	2
	N	Lipid inhibitors	tri-allate	10	2
	F3	Carotinoid biosynthesis (unknown target)	amitrole	6	1
	K3	Long chain fatty acid inhibitors	flufenacet	5	1
	C3	PSII inhibitors (nitriles)	bromoxynil	4	1
	F1	Carotinoid biosynthesis inhibitors	diflufenican	4	1
	H	Glutamine synthase inhibitors	glufosinate	4	1
	L	Cellulose inhibitors	dichlobenil	3	1
	Z	Anti-microtubule mitotic disrupter	flamprop-methyl	3	1
Very low	–	Six other MOA	–	8 (1–2/MoA)	2

some weed species than others (Holt et al., 2013). Consequently, it is difficult to classify any individual weed species as *inherently* more or less likely to evolve resistance to a particular herbicide. Currently, the best predictor is the occurrence and severity of resistance in the same, or closely related, species growing in similar agronomic systems and climatic conditions.

In this matrix, the resistance risk posed by an individual weed species is based on the occurrence and severity of resistance using information in the International Survey of Herbicide Resistant Weeds (Heap, 2018) combined with 'expert judgement'. The 13 species or genera listed in Table 2 are all included in the EPPO Standard, 'PP 1/213 (4) Resistance risk analysis' (EPPO, 2015) as examples of weeds in the EPPO region which have developed resistance.

All other weed species are considered to have a low inherent risk of evolving resistance provided they have not yet evolved resistance within Europe. World-wide experience may indicate that some weed species should be classified as 'medium' or 'high risk' even though no cases have been detected in Europe so far. For example, this might apply to species closely related to those where resistance has been confirmed. It is important to recognise that the actual species included within such a risk analysis will differ considerably in other regions of the world and that the categorisation process will change with time as resistance is confirmed in additional species.

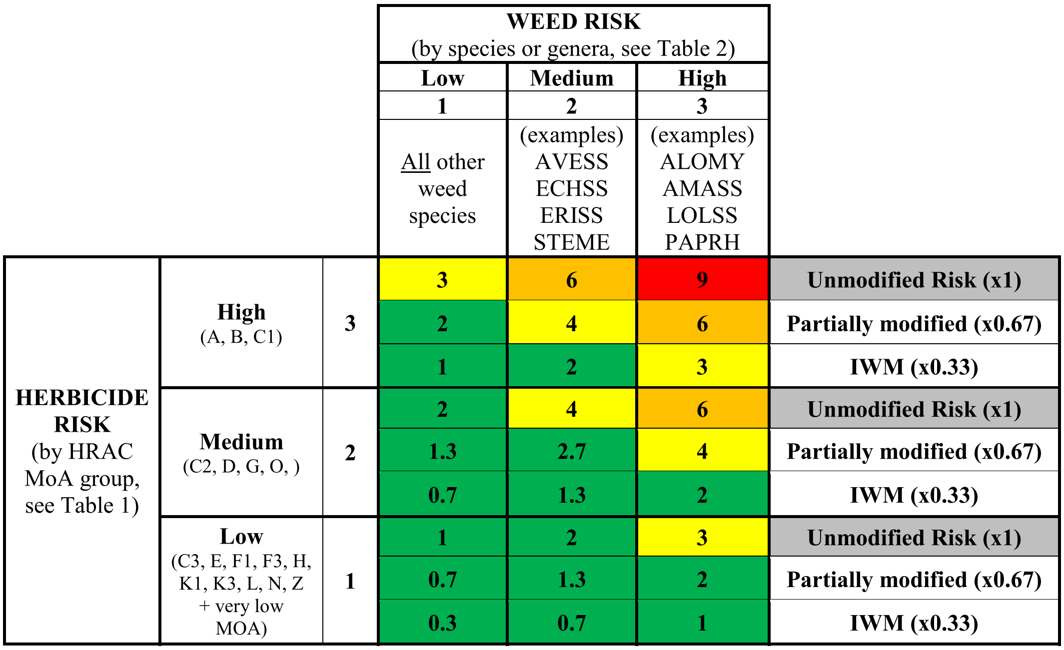
Table 2
Thirteen weed species or genera (with EPPO code) which have evolved resistance in the EPPO region and for which information on the impact of resistance would be expected to be provided as part of the authorisation process for plant protection products (based on EPPO, 2015).

Weed species or genera considered to have a high inherent risk of evolving resistance		Weed species or genera considered to have a medium inherent risk of evolving resistance	
Alopecurus myosuroides	ALOMY	*Avena* spp.	AVESS
Amaranthus spp.	AMASS	*Conyza* spp.	ERISS
Apera spica-venti	APESV	*Echinochloa* spp.	ECHSS
Chenopodium spp.	CHESS	*Matricaria* spp.	MATSS
Lolium spp.	LOLSS	*Phalaris* spp.	PHASS
Papaver rhoeas	PAPRH	*Senecio vulgaris*	SENVU
		Stellaria media	STEME

3. Results

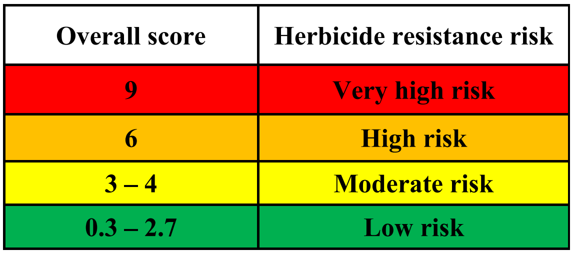
3.1. Using the resistance risk matrix

This matrix is adapted from previous risk assessments for pesticide resistance (Brent and Hollomon, 2007; Vencill et al., 2014) but updated and revised to make the procedure more applicable for use in countries within the EPPO region (Fig. 2). HRAC MoA groups were ranked on a



			WEED RISK (by species or genera, see Table 2)			
			Low	**Medium**	**High**	
			1	**2**	**3**	
			All other weed species	(examples) AVESS ECHSS ERISS STEME	(examples) ALOMY AMASS LOLSS PAPRH	
HERBICIDE RISK (by HRAC MoA group, see Table 1)	**High** (A, B, C1)	3	3	6	9	**Unmodified Risk (x1)**
			2	4	6	**Partially modified (x0.67)**
			1	2	3	**IWM (x0.33)**
	Medium (C2, D, G, O,)	2	2	4	6	**Unmodified Risk (x1)**
			1.3	2.7	4	**Partially modified (x0.67)**
			0.7	1.3	2	**IWM (x0.33)**
	Low (C3, E, F1, F3, H, K1, K3, L, N, Z + very low MOA)	1	1	2	3	**Unmodified Risk (x1)**
			0.7	1.3	2	**Partially modified (x0.67)**
			0.3	0.7	1	**IWM (x0.33)**

Fig. 2. Resistance risk matrix.



Overall score	Herbicide resistance risk
9	Very high risk
6	High risk
3 – 4	Moderate risk
0.3 – 2.7	Low risk

Fig. 3. Herbicide resistance risk classes.

scale from one (lowest) to three (highest risk) based on the propensity of weeds to evolve resistance to that MoA group based on global data (Table 1). Likewise, weed species were ranked on a one to three scale of risk (Fig. 2). The product of the herbicide and weed risk factors produces an overall resistance risk score for the *unmodified* use of the herbicide on the target weed (Fig. 3). The unmodified risk represents a 'worst case' scenario where there is total reliance on the herbicide for control of the target weed.

Where herbicide products containing two or more active ingredients with different MoA are being assessed, it is recommended that, initially, each component is assessed separately. The herbicide MoA with the highest risk then establishes the unmodified risk. The second herbicide MoA is then examined for its potential to act as a modifier on the same target weed.

The overall *unmodified* risk scores range from one to nine and equate with a herbicide resistance risk as designated in Fig. 3.

3.2. Modifying the resistance risk

Effective herbicide-resistance management requires the integration of a variety of chemical and non-chemical management practices in order to reduce selection pressure on weed populations (Shaner, 2014). The unmodified risk estimated initially in Figs. 2 and 3 is likely, in practice, to be reduced by use of a range of resistance management practices ("modifiers"). The use of multiplication factors in the matrix simplifies the incorporation of these modifiers into the overall risk evaluation. Initially, the multiplication factors used by Vencill et al. (2014) were incorporated into the matrix, but test evaluations indicated that these were likely to overestimate the impact of modifiers at reducing the resistance risk in the agronomic systems of EPPO member countries. Hence, more appropriate multiplication factors were used, as defined below.

In the resistance risk matrix (Fig. 2), '**partially modified**' indicates use of the herbicide under consideration with other herbicides with *different* MoA, either in mixture, sequence or alternation. There is some evidence that herbicide mixtures are more effective at combating resistance than herbicide alternations (using different herbicides in different years) (Diggle et al., 2003). However, herbicide mixtures should not be considered a complete solution to herbicide resistance management as, while they may delay resistance development, they are unlikely to prevent it (Evans et al., 2016). To justify a 'partially modified' status, these other herbicides would be expected to provide comparable levels of control of the target weed. Use of other herbicides with the *same* MoA as the herbicide under consideration should be assumed not to reduce the resistance risk although there are cases where this assumption is not valid, in which case evidence to the contrary would need to be provided. '**Partially modified**' is assumed to reduce the resistance risk by one-third, hence unmodified risk values are multiplied by 0.67 to obtain the revised figures and risk assessments in Figs. 2 and 3.

To justify full '**IWM**' (Integrated Weed Management) status in Fig. 2, use of herbicides would have to be integrated with *active* promotion of a range of non-chemical methods, proven to be of value against the target weed. In many cases, the use of non-chemical practices can reduce weed infestations and therefore lessen the dependency on herbicides. Proposed IWM practices should consider the impact of the whole crop rotation on the target weed, as well as more specific management practices. Many non-chemical methods of weed control are available and recent reviews of IWM include Beckie (2006), Harker & O'Donovan (2013), Melander et al. (2013, 2017) and Norsworthy et al. (2012). More specifically, Lutman et al. (2013) have reviewed the major non-chemical methods available for control of *Alopecurus myosuroides* (black-grass), currently the most problematic herbicide-resistant weed in Europe (Moss, 2017b). The characteristics of the particular weed/herbicide combination under consideration would need to be taken into account when deciding on the most appropriate strategy. '**IWM**' is assumed to reduce the resistance risk by two-thirds, hence unmodified risk values are multiplied by 0.33 to obtain the revised figures and risk

Table 3
Herbicide modifiers that can be used to reduce weed populations and the impact of herbicide resistance in annual grass and dicotyledonous weeds of arable crops. (Key: + + = high impact; + = low impact; 0 = no/little impact).

Description of herbicide modifier		Likely impact on weed infestation and resistance development	
		Grass weeds	Dicotyledonous weeds
Pre-emergence herbicides	Pre-emergence residual herbicides are affected by resistance but their use generally imposes a lower selection pressure compared with sole reliance on higher resistance-risk post-emergence herbicides.	+ +	+
Frequency of application	Limiting the numbers of applications of a mode of action against a weed species within a single crop, or over a period of years, will reduce selection pressure.	+ +	+ +
Efficacy of herbicides	Risks associated with specific MoA groups (see Table 1) is more important than herbicide efficacy. Low herbicide efficacy is likely to lead to inadequate control regardless of resistance status of weed.	+ +	+ +
Mixtures/Sequences (within a single crop)	Either as recommended tank mixes/sequences or as formulated product mixtures. To be effective modifiers, active ingredients must each give good control of the target weed and have different MoA.	+ +	+ +
Alternations (over crop rotation)	Involves using different herbicides in different years but herbicides must each give good control of the target weed and have a different MoA. Generally, mixtures/sequences applied in the same crop are more effective in combating resistance.	+	+
Timing of application	Applications should be made at times of the year and best crop and weed growth stage to achieve optimal weed control.	+ +	+ +

Table 4
Non-chemical control modifiers that can be used to reduce weed populations and the impact of herbicide resistance in annual grass and dicotyledonous weeds of arable crops. (Key: + + = high impact; + = low impact; 0 = no/little impact).

Description of non-chemical control modifier		Likely impact on weed infestation and resistance development	
		Grass weeds	Dicotyledonous weeds
Diverse crop rotations	Crops with differing sowing time and seedbed requirements enable a variety of cultural techniques to be used to manage specific weeds. A variety of crops in the rotation facilitate the use of herbicides with different modes of action. Crops with different growth characteristics provide disruptive competitive environments which tend to prevent the domination of any individual weed species.	+ +	+ +
Grass ley breaks (> 2yrs /Fallowing	Effectiveness in depleting soil seedbank depends on seed persistence of individual weed species. Prevention of further seed return is essential. Substantial financial penalties unless grass can be utilised effectively.	+ +	+ (depends on species)
Delaying sowing date	Delaying autumn crop sowing date allows more early germinating weeds to be destroyed prior to sowing instead of emerging within the crop. Performance of pre-emergence herbicide may also be enhanced. Sowing crops in spring can be even more effective, especially against predominantly autumn germinating grass weeds (e.g. ALOMY, LOLSS).	+ +	+ (depends on species)
Primary cultivations	Ploughing buries freshly shed weed seeds to a depth from which emergence is unlikely, although buried seeds may be brought back to the surface. Non-inversion tillage avoids bringing large numbers of buried seeds back to the surface so is preferable where little or no weed seed has been shed. Less soil disturbance may also reduce weed emergence. The best strategy depends on weed species and field conditions so generalized advice is inappropriate.	+ + (depends on species)	0/+ (depends on species)
Shallow post-harvest cultivations (stale seedbeds)	Aim is to stimulating weed seed germination post-harvest. Emerged weed plants are then destroyed by cultivations or with a non-selective herbicide before crop sowing.	+ (depends on species)	0/+
Increasing crop competition	Higher crop seed rates, narrow row spacing and more competitive crops or cultivars will increase the competitiveness of the crop at the expense of the weed and restrict weed seed production.	+	+
In-crop cultivations	Hoeing and harrowing can be effective methods of weed control although their use is limited mainly to crops planted in wide rows.	+	+
Preventing seed return and spread	Destroy patches of weeds to prevent seeding by cutting, spraying non-selective herbicides or removal by hand. These are very effective way of minimising seed return although only realistic on relatively small areas. Minimize spread of seeds and plants in combine harvesters, balers, cultivation equipment, straw, manure and crop seed.	+ + (on limited areas)	+

assessments in Figs. 2 and 3. Examples of non-chemical and herbicidal strategies that could be considered as potential modifiers to reduce resistance risk are presented in Tables 3 and 4.

During the authorisation process, both the estimate of resistance risk, and any measures proposed to modify that risk, must be subject to a critical and thorough evaluation. Any resistance management strategy proposed must be shown to be relevant and appropriate for both the herbicide under evaluation and the target weed(s). Simply listing many of the elements included in Tables 3 and 4 is insufficient. Resistance management guidelines have little or no impact unless they are effectively communicated to the end user (Ulber and Rissel, 2018). Hence, a critical part of the authorisation process must be a thorough appraisal of how resistance management strategies are to be communicated and their effectiveness monitored.

3.3. Examples of resistance risk evaluations for different MoA herbicide/weed combinations

See Tables 1 and 2 for the categorisation of inherent herbicide and weed resistance risks and Figs. 2 and 3 for calculation of scores and risk classes. The assessments below appear to represent a fair representation of the known resistance risks associated with the herbicide MoA groups and weed species used in each of the four scenarios.

3.3.1. High risk MoA/high risk weed

ACCase inhibitor (HRAC group A) e.g. clodinafop-propargyl/*Alopecurus myosuroides* (Black-grass/ALOMY): Unmodified risk = 9 (very high risk); Partially modified = 6 (high risk); IWM = 3 (moderate risk).

Herbicide-resistant populations of *A. myosuroides* occur in at least 14 countries with resistance to ACCase inhibitors (HRAC group A) and other herbicides widespread, making this species the most problematic resistant weed in Europe (Moss, 2017b). Diversity in control measures is the key to successful long-term management of *A. myosuroides* with greater use of non-chemical methods and less reliance on herbicides.

3.3.2. Medium risk MoA/medium risk weed

Synthetic auxin (HRAC group O) e.g. mecoprop-p/*Stellaria media* (Common chickweed/STEME): Unmodified risk = 4 (moderate risk); Partially modified = 2.7 (low risk); IWM = 1.3 (low risk).

Herbicide-resistant populations of *Stellaria media* have been recorded in 15 countries worldwide, but most cases involve ALS inhibiting herbicides (Heap, 2018). However, resistance to synthetic auxin herbicides (HRAC group O) has been reported in both the UK and China. Hence a 'moderate resistance risk' assessment for the unmodified use of synthetic auxin herbicides against this species seems appropriate. The fact that resistance to ALS herbicides has been reported much more frequently worldwide, means that proposals to modify the resistance risk must aim to prevent the development of multiple resistance to both synthetic auxins and ALS inhibitors within the same weed population. Although not so far recorded in *Stellaria media*, this has been reported in 12 weed species worldwide, including *Papaver rhoeas* (Common poppy) in France, Italy and Spain.

3.3.3. High risk MoA/low risk weed

ALS inhibitor (HRAC group B) e.g. metsulfuron-methyl/*Aphanes arvensis* (Parsley piert/APHAR): Unmodified risk = 3 (moderate risk); Partially modified = 2 (low risk); IWM = 1 (low risk).

Resistance has never been reported in *Aphanes arvensis* to any herbicide anywhere in the world (Heap, 2018). However, this weed species is widespread in arable fields in Western Europe and many ALS inhibitors give good control. Despite the lack of documented cases of resistance, sole reliance on ALS inhibitors would be unwise as there are over twice as many weed species resistant to ALS inhibiting herbicides as to any other single herbicide MoA group (Table 1). Hence a 'moderate resistance risk' assessment for the unmodified use of herbicides of this group seems appropriate. This risk can be reduced relatively easily by use of sequences, alternations or mixtures with herbicides from other groups which have activity on this weed (e.g. pendimethalin, HRAC group K1).

3.3.4. Formulated herbicide mixture with high risk MoA + low risk MoA/high risk weed

ACCase inhibitor (HRAC group A) e.g. clodinafop-propargyl + Lipid inhibitor (HRAC group N) e.g. prosulfocarb/*Apera spica-venti* (Loose silky bent/APESV): Unmodified risk for Group A herbicide = 9 (very high risk); Unmodified risk for Group N herbicide = 3 (moderate risk). As the herbicide MoA with the highest risk (clodinafop-propargyl) establishes the unmodified risk, the overall unmodified risk should, initially, be considered 'very high'. However, as the second active ingredient (prosulfocarb) also has good activity on the target weed, is from a different MoA group and has a lower resistance risk, the overall resistance risk can be reduced. How much it should be reduced would depend on the relative efficacy of the two active ingredients on the target weed and the extent of resistance. An assessment of 'high risk' for the partially modified use would appear appropriate, which would then require robust IWM strategies to reduce the risk further.

Herbicide-resistant populations of *Apera spica-venti* occur in at least nine European countries with resistance recorded to both ACCase and ALS inhibitors (HRAC groups A & B). Although resistance to HRAC group N herbicides has not been reported in *A. spica-venti*, resistance has been demonstrated in 10 other grass-weed species, including resistance to prosulfocarb (Heap, 2018). Hence, as with other problematic grass-weeds, diversity in control measures is the key to successful long-term management.

4. Discussion

The matrix approach appears robust and produces realistic and balanced assessments of the herbicide resistance risks associated with the four scenarios tested. This more quantitative approach is more appropriate and easier to adopt than the qualitative resistance risk evaluation scheme proposed by Rotteveel et al. (1997).

Within the current EPPO Standard for resistance risk analysis, applicants are required to provide details of the resistance risk assessment performed on the unrestricted ('unmodified') use pattern of the product for which they are seeking authorisation (EPPO, 2015). Applicants are then required to comment on this resistance risk and argue whether this level of risk should be considered acceptable or not. Where this risk is considered unacceptable, a management strategy designed to minimize the impact of resistance is required.

However, little guidance is provided within the EPPO Standard on how to quantify this resistance risk. A matrix to evaluate the resistance risk associated with fungicides has recently been proposed by Grimmer et al. (2014). However, that matrix does not quantify the impact of individual chemical and non-chemical agronomic practises. The resistance matrix approach outlined in this paper will have benefits in allowing a more objective assessment of resistance risks, both 'unmodified' and 'modified'. Although the EPPO Standard has a clear application to the European legislative process, the matrix approach and principles described in this paper can easily by adapted for use in other regions of the world. For example, in countries where the extensive use of herbicides is a relatively recent development, and where there is currently limited knowledge and expertise on herbicide resistance.

An important issue is how to assess the resistance risk for weeds that are not the primary targets of a herbicide being evaluated for authorisation. Clearly, it is unwise to assume that, simply because a weed species is not included on a herbicide label, it is unaffected by that herbicide and thus not subject to selection for resistance. However, it is unreasonable to expect applicants to demonstrate the efficacy of a herbicide against all the possible weed species that might be encountered in practice. There is no simple solution, but a pragmatic approach would be to focus attention, and request efficacy information, on the relatively small number of weed species that pose a significant resistance risk.

The assessments of resistance risks for both active ingredients and weed species are based on the Herbicide Resistance Action Committee (HRAC) International Survey of Herbicide Resistant Weeds (Heap, 2018). This freely accessible online resource documents cases of herbicide resistance worldwide and provides regularly updated information on individual active ingredients and weed species. In addition, a considerable amount of other relevant information is accessible. The database has some limitations as it is dependent on researchers providing up to date information but it represents a unique global resource for assessing herbicide resistance risks (Kniss, 2018). Consequently, although the actual matrix is relatively simple, the assessment of risk should be robust as it is based on a considerable body of information from an authoritative, global database. Table 2 provides an overview of weed species and genera with a medium or high inherent risk of resistance development within the EPPO region. However, the individual inherent resistance risk of the target weed species in each country, geographical region or authorisation zone needs to be assessed at a local level as both the agronomic importance and the level of resistance development within the target species may vary widely.

The matrix strikes the right balance between over-complexity and over-simplification. While the categorisation is approximate and risk scores arbitrary, this approach produces credible estimates in the light of current knowledge. The risk scores alone should not be used to determine whether or not to authorise a specific plant protection product. However, they do act as a good indicator of the likely resistance risk and focus attention on the resources required both to develop strategies for reducing the risk to an acceptable level, and to monitor the resistance situation post-authorisation.

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