General criteria for an evaluation of the resistance risk of insecticides and tools for the risk mitigation

In general:

- The limited number of effective insecticides in small size segments of agriculture business (like stored product protection) requires a resistance risk evaluation to support these products.
- Prevention of resistance is better than resolving the problem of unsusceptibility.

Information:

- EPPO Guideline PP 1/213 (4)
- Resistance risk analysis and use of resistance management strategies, PSD, Efficacy guideline 606 (May 2008)
- IRAC website
- WHO website: WHOPES

Risk assessment and mangement			**Criteria for an evaluation of the resistance risk**	**Decision**
Resistance risk assessment Depends on characteristics of the pest and the pesticide	Inherent risk	Risk factors • Inherent in the compound • Its effect on pests • Result from a use pattern	• The factors associated with the pesticide that may favour the development of resistance can include: o persistent activity o single-site mode of action (MoA classification , see IRAC and ANSES) o resistance is based monogenic o simple metabolism o easy to generate resistant strains in laboratory or storage assays	
			• Past experience may also provide a guide to resistance risk; higher risk could be indicated in situations where a wide variation in existing sensitivity exist and where a target pest has already developed resistance to other active substances or where resistance to the active substance has already developed in other target pests -> There is a serious risk of resistance, a resistance management strategy will be required Have there been any reports of resistance in the target or related species after many years use of chemical pesticides -> There is some risk of resistance developing. A management strategy may be required	

			• This risk affects selection pressure on the development of resistance and is influenced by the particular characteristics of the crop, the geographic area in which the product is applied and the use pattern. The factors influencing the risk may include: o Application frequency: mono use or continuous use over long periods o Dosage o Persistance of effect/metabolizing: some active substance concentrations decreases with time after application, which may lead to the development of resistance o application technique o application/contact/residence time o no 100 % disinfestation/sanitation o other practices o need for high numbers of applications or long exposure to obtain control, because of the features of the specific use; o environmental conditions favouring more frequent generations or higher population densities of the pest o exclusive reliance on a single active substance o lack of diversity of available control measures o	
			• Those associated with the characteristics of the target pest that may favour the development of resistance can include: o Rate of reproduction: short life cycle/many generations; o Population isolation o high fecundity/widespread distribution of progeny; o high inherent genetic variability (including potential for spontaneous mutation); o existence of a mechanism in the pest to metabolize a range of active substances; o exihibition of cross resistance to a existing chemical group; mulitple resistance o high fitness of resistant strains o Diapause/egg - insensitive (low level of metabolism) developmental stages	

	Risk of practical resistance (inherent risk combined with agronomic risk) in unrestricted use = unmodified risk	Components of risk assessment	• Results of resistance tests (test methods see IRAC, INRA Review, FAO; Detia Degesch test kid for PH_3 resistance) o Resistance diagnostic assays (see R4P Network) ▪ Bioassays ▪ Biochemical assays ▪ Molecular assays o Are the tests accurate, sensitive, reliable? o How well do the theoretical assumptions of resistance apply to the practical use?	
			• Type of compound o For the re-registration of a known compound, the risk of resistance can be assessed from experience with that compound in the field, which can demonstrate whether practical resistance has occurred, or the success (or failure) of management strategies already being applied. o If it is a new compound belonging to an established group, then the resistance risk can be assumed to correspond to that of other compounds in the same group, unless demonstrated to be different. o In the case of a completely new type of compound (new chemical group), a risk of resistance development should be assumed, unless demonstrated otherwise by consideration of other risk factors; this is particularly true for insecticides and fungicides.	
			• Mode of action/mechanism of resistance o Site of action – different pesticides can have the same target site within the pest insect o Multiple resistance o A knowledge of the mode of action of a compound and, if known, the mechanism of resistance can be informative. For example, a mode of action involving a single biochemical site may indicate a potential higher risk, whereas 'multisite' action may indicate a lower risk. o Similarly, any mode of action which involves an existing mechanism to which resistance has already occurred would, in the absence of contrary evidence, be considered to indicate a high risk of resistance.	

			• Cross-resistance and multiple resistance o The existence of cross resistance between a new compound and other compounds of the same or other chemical classes can have profound consequences on the commercial use of a pesticide. It means, in effect, that resistance occurs already in the target organism even before the product is used. Bioassay tests are needed to detect the existence of cross resistance by attempting to control, with the new compound, the various populations of the pest that are known to have resistance to other compounds. o The existence of multiple resisatnce, that means more than one resistance mechanisms (metabolic/target site/reduced penetration/behavioural) o It may be useful to explore the possibility of negative cross resistance, in which resistance to one compound results in sensitivity to another, as its existence will influence the types of management strategies that might be used.	
			• Characterization of strains An understanding of whether and how resistant strains might develop in populations of the target pest may give useful indications of practical resistance o Test methods for sensitivity. Development of a test method to determine the sensitivity of the target pest(s) to the active substance is highly desirable because it provides the means of measuring the original level of sensitivity before the pest is subjected to the active substance (data generally needed for registration), of identifying resistant strains in laboratory studies, and of monitoring any shifts in response following widespread use. The method should be able to give realistic, quantitative, reproducible and readily understandable results. Many of the test methods used to determine sensitivity are somewhat difficult to perform and caution should therefore be applied in comparing results from different testing centres. Furthermore, there are many pests for which suitable methods are not yet available. Influence of unrestricted use on overall risk o Fitness: It could be useful to compare the fitness of sensitive wild-type strains and resistant strains in laboratory or glasshouse tests. Because resistant strains may lose a proportion of their ‘fitness’ so that, in practice, they would be unable to compete with fully fit, wild strains. o Rate of reproduction and density of population o Dynamics of resistance build-up: Mixtures of wild (sensitive) and resistant strains can be treated with repeated applications of the	

			active substance, and changes in the frequency of strains can be measured. Such experiments can reveal the potential risk and speed of build-up of resistance in relation to the number of applications, the level of initial resistance and the competitive abilities of wild and resistant strains. o Potential for spread. For some types of pest, the appearance of resistant strains in one geographical locality is quickly followed by their spread throughout the whole range of the species, because of the highly mobile nature of the organism. Resistant strains of other species have limited mobility (e.g. certain weed species) and remain localized at their site of origin. In assessing the risk, the mobility of the target pest(s) needs to be taken into account. o Genetics. Classical and molecular analysis of genetics can be used to identify resistance genes and to study their interactions; the results can provide further useful indications for predicting resistance risk and can suggest monitoring tools.	
			• Influence of unrestricted use on overall risk o The conditions under which the pesticide will be used should be considered to assess the degree of selection pressure that will result. o This will involve an analysis of the cropping system(s) where the pesticide will be used and should consider the use pattern. Factors that help to minimize the risk of practical resistance (e.g. rotation, the availability of several other chemical groups). o Other factors that could influence selection pressure as elements of the risk influenced by the proposed use.	
			• Magnitude of resistance risk o The risk of resistance is composed of the probability of the resistance occurring and the possible consequences if it does occur. o At the moment, there is no accepted method to quantify the overall risk, apart from the simple categorization into low, medium or high.	

			• Probability o An estimate of the probability of the occurrence of practical resistance can sometimes be gained from a consideration of existing cases of resistance or exhibition of restance in laboratory tests. If resistance to the chemical group to which the new biocide belongs or resistance to other biocides has been observed in the target species, the relevance of these cases to the situation being assessed should be considered.	
		Decision	Is the unmodified risk acceptable? • In resistance risk management, the decision is made whether the unmodified risk is acceptable; if it is,the process can stop. • The acceptability of the risk does not only depend on the magnitude of the risk (the combination of the probability of resistance occurring and the consequences if it does) but should also take account of the benefits to be obtained from the use of the pesticide, e.g. o a limited availability of suitable alternatives o advantages over other products like impact in the environment o comparative assessment: can the chemical diversity of the available a.s. within the identified alternative pesticide be considered as adequate to minimize the occurrence of resistance in the target harmful organism(s)) o Targets and related species have not previously developed resistance o It is difficult to generate resistant strains in laboratory or storage site assays o resistant laboratory strains are unfit or unstable o no change in sensitive seen before	☐yes ☐no

Resistance risk management strategies for avoiding or delaying the appearance of resistance	Modifiers to reduce the risk plus the selection pressure and to prolong the useful life of and insecticidal MoA If the unmodified risk is not acceptable, possible modifiers are then analysed to determine whether they can be used to mitigate the risk.		• There is a range of modifiers that can be used in a resistance management strategy. The integrated use of combinations of different modifiers is likely to be most beneficial. The characteristics of the particular pest/product combination that affect resistance development and have been identified in the assessment of resistance risk should be taken into account when deciding on the exact strategy. In addition, the strategy should take account of the overall pest management in the crop concerned: o Ensuring best practice: Good agricultural practice/ good crop hygiene, appropriate use by training and education, labeling o Checking the need of using the special pesticide o Frequency of application of pesticides with the same MoA o Timing o Dose rate, sufficient dose – disinfestation/eradication better than reducing an infestation! o Exposure time/residential time o Application technique o Mixtures of pesticides with different mode of actions/combination of control measures/innovative substances o Alternations/Rotation of pesticides with other/multi-side MoA: changing the MoA between and/or within generations of pest organisms to break in the selection pressure what allows a recovery of susceptible species (under failing resistance pressure, susceptible species are often fitter than the selected resistant species) o Mixture with other pesticides and different MoA o Mosaic Spraying (Silos on various neighbouring farms etc) o Recommendations on the product label o Early starting/regular monitoring, reporting and reaction to changes in performance (e.g. baseline sensitivity. - tolerance) o Avoiding of non-effective concentration in the environment (non-target effects) o Aiding product choice for optimum efficacy and sustainable control o Only professional use to prevent inappropriate use through education and training programs / special recommendations on the label for consumer use o Combination of pesticides with non-chemical methods and products (biological, mechanical, physical); target specific pest control e.g. combination with biopesticides o Specific use patterns/claims (temperature, development stages,	

			exposure time, timing, …) o Reduction of pest source via ▪ cleanliness and hygiene: remove old stored goods before warehousing, proper cleaning (vacuum cleaner) and disinfestation of rooms, storage containers etc. ▪ wide crop rotation in storage rooms o Restricting the area of use (indoor, outdoor) o Avoiding the spread of resistance o Baseline sensitivity/monitoring the susceptibility during practical use/detection of resistance at low frequency in the population to establish an IRM early/ o Resistance factor RF: RF = LC50 resistant population/LC50 susceptible population o Resistance labeling provides an indication of e.g. MoA, IPM, GAP, risk of resistance o Label advice: Read accompanying instructions before use o Label with warnings and instructions (see www.kemi.se; EPA ‘Pesticide Registration Notice (PRN)2017-1’ : to avoid the build-up of resistance comply with the instructions for use; see PSD 601 ’Resistance Warnings and estrictions on Labels of insecticide and Acaricide Products) o Manual: clear and detailed information about the correct use and avoiding/handling resistance in the instructions of use. o Combination with non-chemical controlantagonists o Using of resistant crops ➢ Integrated Resistance Management (IRM) - sustainable eradication ➢ In stored product protection: usually just 1 fumigation/year and crop ➢ Notification of any observed resistance to authorities and applicants/manufactures of the pesticide ➢ Maintain efficacy of pesticides for agriculture use	
⇨	**Management strategy** If suitable modifiers exist, the conclusion of the resistance risk analysis will be a resistance management strategy		There is a range of modifiers that can be used in a resistance management strategy. The integrated use of combinations of different modifiers is likely to be most beneficial. The characteristics of the particular pest/product combination that affect resistance development and have been identified in the assessment of resistance risk should be taken into account when deciding on the exact strategy. In addition, the strategy should take account of the overall pest management in the crop concerned and interrupt the spread of resistant species to preserve a portfolio of PPP. The use of pesticides in borderline cases must be considered, related to the similar	

	(comprising one or more modifiers) that can be applied when the product is used commercially.		use in different fields against the same pest organism. It is important to communicate a strategy as well as the resistance.	
⇨	Risk of practical resistance in restricted use = **modified risk**			Is the modified risk acceptable? ☐yes ☐no
Resistance test ⇨	Laboratory test		• WHO resistance tests (WHO/CDS/CPC/MAL/98.6 • Resistance test kid – Detia • In most instances, resistance is tested using the standard Food and Agriculture Organization of the United Nations (FAO) technique of injecting phosphine into gastight desiccators (FAO 1975). Two discriminating doses are used. A lower one discriminates between susceptible and resistant insects and a higher one is designed to detect resistances higher than the common 'weak' resistance (Daglish and Collins 1999). (aus E.J. Wright, M.C. Webb and E. Highley, ed., Stored grain in Australia 2003. Proceedings of the Australian Postharvest Technical Conference, Canberra, 25–27 June 2003. CSIRO Stored Grain Research Laboratory, Canberra.) • Two other assay methods are also used. The 'rapid test', originally developed by Reichmuth (1991) and Bell et al. (1994), is used to give a quick yes–no answer with field-collected insects—i.e. resistant or not—allowing immediate action (control, eradication, quarantine) to be taken where appropriate. The drawback with this type of method is that it is difficult to determine the strength of resistance in some species (Daglish and Collins 1999). • A third method is the flow-through technique that exposes mixed-age cultures of insects to a continuous flow of phosphine at a constant concentration (Winks and Hyne 1997; Daglish et al. 2002). This method is very laborious and lengthy but it gives an accurate prediction of the time required for complete extinction of an insect population at a nominated phosphine concentration (Daglish and Collins 1999). It is used to characterise the resistance and predict concentrations and exposure periods needed to control insects in the field.	

⇨	Field data		• Monitoring results? • Past experience: in pratical use or EU approval of the active substance? • Longterm tests?	
Registration ⇨	Decision ⇨	Elements needed for a registration decision	Elements needed for a **registration decision** • an assessment of risk of resistance has been performed; • the method of assessment is appropriate, i.e. that this EPPO Standard or an acceptable equivalent has been followed; • the data needed for the risk assessment was correctly obtained and adequate; • the conclusion of the resistance risk assessment is realistic; • sensitivity data is provided (or assurance that a sensitive biotype will be available) so that development of resistance can be assessed in the future; • announcement/note of observed reasonable suspicition to the national authorization agency • aiding product choice for optimum efficacy and sustainable control; • the management strategy proposed is practical, likely to be effective and will be properly communicated; • mutually acceptable expert opinions, such as independent experts or Resistance Action Committees; • opinions of other regulatory authorities; • decision already taken in other countries.	
⇨	Authorized use ⇨	Unrestricted	Submitted label and use (GAP) submitted by the applicant	
	⇨	Modified	Required provisions: Labelling phrases e.g.: • List the 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).* • *Total reliance on one pesticide will hasten the development of resistance. Pesticides of different chemical types or alternative control measures should be included in the planned programme. Alternating insecticides with different modes of action is a recognised anti-resistance strategy and [product name] should always be used in conjunction with other insecticides of a different mode*	

			of action. This includes consideration of sequences involving soil treatments followed by foliar sprays. Where a neonicotinoid soil treatment has been used, the first subsequent foliar spray should be a non-neonicotinoid containing product with a different mode of action.	
Monitoring, reporting ⇨	Post application		Monitoring resistance/sensitivity of pest against the pesticide during use, to register a dynamic development of resistance and spread.	
			Does an overall resistance management strategy for high and low pest pressure exist, e.g. insecticide use in cereals?	