EPPO Workshop on
Experiences with Implementation of
Zonal Evaluation of Plant Protection Products

Sofia, 2013-10-22/24

Extract from EPPO Report 13/19091

CONCLUSIONS ON THE SPECIFIC THEMES ANALYSED DURING THE WORKSHOP

Theme 1: Efficacy considerations when making changes to the chemical composition of plant protection products

The discussion focussed on efficacy considerations when making changes to the chemical composition of plant protection products with particular focus on the criteria for significant changes and on generating appropriate supporting data. Firstly the participants attempted to identify those components of a formulation that have a particular influence on effectiveness and crop safety properties. This included a discussion about whether the situation of use, particularly foliar vs soil applications, influenced which components were important. Participants also discussed whether minor changes in existing content could be permitted (without further supporting evidence), and if so at what level (% change) might these be accepted automatically. Secondly, participants discussed what type of information and data would be required where chemical composition changes were considered significant in terms of efficacy. To facilitate these discussions, a series of tables were presented for the commonest product types and uses.

Chemical components

There were some slight variations in opinions between Workshop attendees however, there was a general consensus regarding what would be considered a 'significant' and 'not significant' change in chemical composition of a formulation, both in terms of type of co-formulant where changes would trigger concern, and on percentage change of a co-formulant which would/would not be accepted without a requirement for further data. Generally, surfactants and solvents were considered critical (for foliar applications), and 'carriers' more important for soil applied granules/capsules. For seed treatments, changes were less important provided the retention of the active substance could be demonstrated. More specialised products had specific requirements, for example consideration of pellet palatability and integrity is important for molluscides. Generally the trigger value for a change in content to an existing component (same CAS number) ranged between 5% and 10%.
It was put forward that even where the 10% trigger was exceeded for a co-formulant, the resulting changes in effectiveness or crop safety are unlikely to be significant enough to be detectable in a small number of trials, and therefore it was suggested that there may not be justification for asking for comparability data where differences are unlikely to ever be demonstrated.

Evidence required supporting significant chemical composition changes

There was a general agreement that using some kind of tiered approach, rather than automatically requiring field data, was a sensible approach. For example, comparability could be initially tested in various controlled situations (e.g. the laboratory, glasshouse, or outdoor pot trials), with a requirement for field trials only where necessary in specific circumstances.

Requirements for a zonal bridging package were discussed. The general consensus was that field trials should be placed in challenging and representative locations, rather than automatically having to spread across each representative EPPO zone. Targets/crops chosen should principally reflect the major and/or most challenging uses.

Outcome

The various discussions and responses will be reflected upon further, and proposals included in the on-going EPPO draft on *Efficacy considerations and data generation when making changes to the chemical composition of plant protection products*, both to determine criteria for changes, as well as the type of supporting evidence required.

Theme 2: Registration of co-formulated products

Using some theoretical scenarios, the discussion around Theme 2 'Registration of co-formulated products' (those containing more than one active substance) highlighted a number of key issues which need to be considered in the development and registration of co–formulated products.

Participants agreed that a *justification* is needed. A clear benefit must be defined and demonstrated by the applicant. Benefits could include factors such as: increased spectra of activity, improved levels and/or greater duration of control, resistance management, reduced overall number of applications, avoidance of the need to tank mix and reduction in risk to operator. Potential disadvantages such as differential timing and non-optimised dose rates were also noted.

Regarding *zonal aspects*, the relevance/appropriateness of a co-formulated product across a regulatory zone should be demonstrated but is likely to be more difficult to establish than for solo products due to differences in pest occurrence/pressures. Different ratios/dose rates may be required in different regions. Co-formulated products are more likely to be developed on a sub-zonal scale.

A *ratio justification* should be addressed. It may be possible to do so using laboratory/semi field tests. It was also noted that, whereas justification can be made on an efficacy basis, there are other factors to consider such as regulatory, commercial and resistance management issues that may have an impact on choice of the most appropriate ratio.

Regarding *Minimum Effective Dose* trials, it was noted that where constituent active substances have no overlapping activity, this may be extrapolated from existing data packages. Field trials to demonstrate the effectiveness of the new co-formulated product should contain some lower doses to justify the dose rate for the product.

Resistance risk was also considered and it was concluded that where doses of active substances are below those for authorised solo products against the same pests particular attention must be paid to the potential impact on resistance management particularly for the at risk active substance and the at risk pest(s). Cross-resistance must be assessed. Co-formulated products containing two modes of action may not automatically represent a good anti-resistance strategy.

Regarding *data requirement*, a bridging approach is possible where the dose rates of the individual solo actives and the co-formulated product are similar. Co-formulated products containing much reduced doses of each active substance require more substantial supporting effectiveness data packages. Full data packages would be required to support new claims where no extrapolation is possible from the solo authorised products.

The *use of reference products in trials* was also discussed. The Workshop participants agreed that where the co-formulated product is essentially a combination of two existing solo actives and is applied at equivalent doses, the two authorised solo products should also normally be included in trials, such trials can provide a basis for a bridging approach. Where the co-formulated product applies much reduced doses of the authorised solo active substances a different reference product(s) may be included to demonstrate the effectiveness of the new product. The lack of unacceptable antagonism must normally be demonstrated. 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.

Future work

The existing EPPO Standard PP 1/277 *Insecticide Co-formulated Mixtures* was considered to contain some good guiding principles which are more widely applicable to other plant protection product co-formulations. It was acknowledged that further guidance was necessary particularly for herbicides and fungicides. It was proposed that EPPO develop a General principles paper for co–formulated mixture products, with separate appendices for the different plant protection product types. The potential for a tiered approach to testing should be considered taking into account the level/availability of existing knowledge, differences in dose rates of the existing actives and the claims made.

Theme 3 dRR and BAD: How to develop the dRR using the BAD as a basis in the zonal evaluation process

The aim of the discussion in the working group for Theme 3 was to describe the development of a dRR from the BAD in the zonal assessment process. In addition to the principal content of the documents, the purpose and the ownership of these documents have been identified.

The BAD (Biological Assessment Dossier):

- is a detailed summary which is submitted by the applicant;
- is classified in its entirety as non-public document as it is the intellectual property of the applicant;
- it is classified as a 'K document'.

It was debatable if the BAD could be classified as confidential or if data protection could be claimed. After some discussion it was agreed, that this question should be discussed by the Commission, and it would be desirable to have a dialogue between authorities and industry to define what data should be considered confidential. The BAD contains a summary of full individual efficacy trials, following the GAP (Good Agricultural Practice) table. In the BAD analysis and discussions of relevant data according to EPPO's standards are found as well as the statistical analysis of the individual trials. The GEP certificates (Good Experimental Practice) are also inside this document.

In contrast the RR (Registration Report) is the final concise summary, fully under the responsibility of the zRMS and available to the public. The following three main objectives characterise the RR:

1. The RR should be a standalone document,
2. It should contain all relevant summary tables as well as the conclusions of the evaluation;
3. The RR should be understandable without any reference to the BAD;

The relevance of statistics of the summary tables was discussed but without a specific conclusion.

The dRR (draft Registration Report):

- is the draft concise summary, written and submitted by the applicant and adopted by the zRMS within the evaluation process.
- is a working or living document in which the applicant submits the data to a critical evaluation in the given agronomic context.
- should be also a standalone document which ends up in a proposal for a conclusion. The structure and content should facilitate the evaluator's decision, but the decision process should be transparent.

The Working Groups debated if the dRR could be finalized by rewriting the document or by using commenting boxes. The general view of the evaluators was that commenting boxes require a very high quality of the initial dRR. In order to achieve this high quality document suitable working templates for the dRR efficacy section are needed. All annex points should be covered besides additional templates as e.g. maps of trial location per use and tables with trial summary details.

Theme 4: Evaluation of Plant Protection Products covering all EU zones

Under Regulation 1107/2009 Europe is considered one zone when it comes to the authorization of plant protection products for the use in glasshouses, for post-harvest treatment and for seed treatment. During the working group session for Theme 4 the following cases were discussed and, for each of the cases, the most relevant points concerning data requirements needed for the BAD and dRR (e.g. type of data, number and distribution of trials) were addressed.

1) The application of a systemic insecticide in protected fruiting vegetables (*Cucurbitaceae* and *Solanaceae*) for the control of whiteflies (*Bemisia* and *Trialeurodes*) using two different application techniques (spray and drip application).
2) The application of a seed treatment with an insecticide to control flea beetles, cabbage root fly and virus transmitting aphids in oil seed rape.
3) The application of a fungicide to be used in different countries in the south of Europe (ES, IT and GR were considered as examples) to control storage diseases (*Penicillium* spp., *Alternaria citri*) in citrus using two different application methods.

Different aspects relevant to the authorization were discussed using these three selected cases. Some important points, for which agreement was achieved or a need for further action and harmonization was highlighted, are presented below. Because of time restrictions not all aspects were discussed during the Workshop and there may be the need for additional points to be addressed in the future.
Furthermore, it was noted that two relevant examples to accompany EPPO Standard PP 1/278 *Principles of zonal data production and evaluation* are in preparation for seed treatment and ornamentals under protected conditions.

Glasshouse

- A specific dRR for glasshouse crops for the whole zone should be developed in addition to separate zonal dRRs for each EU zone for field crops. Different BAD or one clearly structured BAD should be presented for these different indoor and outdoor uses.
- Separate phytotoxicity studies for insecticides and fungicides in glasshouse uses, including tested doses, should be considered and further discussed by the EPPO Fungicide and Insecticide Panel as well as by the EPPO Panel on General Standards.
- Regarding the distribution of effectiveness trials within concerned Member States in both Northern and Southern European countries, the majority of trials should be carried out in the countries with the highest pest pressure and the minority of trials in those with low pest pressure.
- When dealing with minimum effective doses, different rates should be considered for areas with high pest pressure and low pest pressure.
- Different application techniques, growing conditions and structures should ideally be considered separately.

Seed treatment

- Availability of maps and/or data presenting the uses of treated seeds in the main EU areas is important.
- For trial distribution the distribution of pests should be taken into account.
- It is hoped that the chapter on labelling in the new EU guidance on seed treatment will solve the indistinctness of different dose rate authorizations within one crop to control different pests.

- Minimum effective dose trials are to be done on major pests.
- Different (sensitive) varieties should be tested for selectivity.
- Dose expression (per kilogram or per number of seeds, depending on the crop) and the use of units of seeds are to be further harmonized beyond the actual recommendations in EPPO Standard PP 1/239 *Dose expression for plant protection products*[1].
- Harmonization is needed regarding how to deal with effectiveness of seed treatments on seed that is subsequently stored for one year.

Post-harvest treatments

- When dealing with minimum effective doses: different susceptible varieties should be tested.
- Different origins and different methods for harvesting should be considered when choosing citrus fruits to be tested.
- Different application techniques and different storage conditions need also to be taken into account.
- Both, data on processing and taint are needed for citrus fruit.

[1] Extract from the EPPO Standard PP 1/239 *Dose expression for plant protection products*: *Treatment of seeds and propagating material / Seeds : For seeds sold by specific number per unit, such as sugar beet, maize and sunflower, dose should be given in g or kg or mL or L per unit. The unit should be specified. For seeds sold by weight, such as wheat, dose should be given in kg or L per 100 kg of seed. For seeds with a small thousand-seed weight that can vary significantly (e.g. leeks and crucifers), it is acceptable to express the dose in g or mL per number of seeds, even if the seeds are sold by weight. As the efficiency of seed treatment can vary greatly according to the equipment used and the characteristics of the seeds, the amount of active substance actually present on the seeds should be verified. This will allow definition of the target dose in relation to the efficacy results. The maximum amount of seeds and maximum amount of product per hectare should be recorded.*

GENERAL CONCLUSIONS AND RECOMMENDATIONS

The introduction of the Regulation 1107/2009 has led to a fundamental change in the efficacy assessment for plant protection products within the EU. Previously, under Directive 91/414/EC, it remained a National issue whereas now assessments are conducted by one Member State on behalf of several others within a regulatory zone. This has placed a new emphasis and responsibility on both industry and Member States to consider the relevance of the proposed uses and supporting data package on a regional basis. Within this context the role of EPPO has become critical in providing a framework of agreed principles and harmonized guidance that underpin zonal data generation and assessments. This has provided a great impetus to review existing EPPO Standards as well as to develop new guidance, as well as challenges to achieve this in a relatively short time within the on-going EPPO plant protection programme.

The Workshop:

- Acknowledged that the main challenges when dealing with the zonal evaluation approach are creating trust among countries through transparent procedures, secure communication between evaluators and with the applicants, improving knowledge on crops, cropping systems, climatic conditions and registered plant protection products in the zone and finally establishing common agreement on data requirements. Communication should be also improved between all stakeholders involved (EU, EPPO, ECPA, MS) about on-going developments of guidance papers fostering harmonisation.
- Recommended that the outcome of the discussions in the working group session (Theme 1) are taken aboard by the EPPO Panel on General Standards in preparation of the draft Standard on *Efficacy considerations when making changes to the chemical composition of plant protection products*.
- Acknowledged that further guidance is necessary on Registration of co-formulated products, in particular, for herbicides and fungicides. It was proposed that EPPO, based on the published Standard PP 1/277 *Insecticide Co-formulated mixture*s and on the outcome of the working groups discussion (Theme 2), develops a Standard on general principles for co–formulated mixture products, with separate appendices for the different plant protection product.
- Recognized that it is still debatable if the BAD could be classified as confidential or if data protection could be claimed. It was agreed that this question should be discussed at European Commission level and it would be desirable to set up a dialogue between authorities and industry on this matter.
- Encouraged further development and adoption of the EPPO extrapolation tables as well as the use of the EUMUDA[2] database in order to cover *minor uses*.
- Recognized that general information and data are needed by zonal evaluators on:
    - Agricultural practices e.g. plant protection product application techniques, crop rotations, row distances, seeding densities, crop structure, type of cultivars and
    - Crop area, pest presence and pest damages. ECPA and IBMA might be in charge of delivering such information. EPPO and EU, in cooperation with ECPA and IBMA, should collaborate to set up the relevant framework and update procedures. Eurostat data has been indicated as a possible relevant source of information to be better exploited (in particular for cropping areas).
- Recommended that crop groups and target pest groups should be developed by EPPO and included in the EPPO code system. Ideally EPPO should cooperate with the EC on this activity. The possible need to reactivate the *Ad hoc* Panel on harmonization of data on plant protection products, which developed a Standard PP 1/248 *Harmonized classification and coding of the*

[2] http://www.eumuda.eu/

uses of plant protection products was proposed. Further discussion is also needed on whether trials should be conducted in all intended crops or on indicator crops and on all intended targets or on indicator species.

- Noted that, on resistance, it should be clarified when there is a need for sensitivity data. Harmonization and guidance from EPPO is required (see also conclusions of the EPPO Workshop on Herbicide Resistance Analysis in the Framework of Zonal Evaluation (Berlin, 2012-10-23/25). Further guidance on resistance issues with respect to the sensitivity data will be provided through a revision of the existing EPPO Standard PP 1/213 *Resistance risk analysis* (in progress).
- Considered that EPPO should take further actions (in addition to the existing ones) to disseminate information about recently published standards. A lack of awareness about new EPPO's standards was noted, for example for EPPO standard PP 1/277 *Insecticide co-formulated mixtures*.
- Recommended that a dialogue among the EC, EPPO Secretariat and countries concerned by zonal evaluation should be improved to better develop and implement processes. EU funds allocation should also be encouraged to implement specific technical actions which might cover, for example, dose expression (harmonizing expressions of doses/units for seed treatment), maps on pest distribution (in addition to the existing work conducted by ECPA).
- Considered that EPPO should undertake a survey to explore/clarify what is meant by an authorized dose (Is it a range? Is it a fixed dose and only this specified dose may be applied? or is it a maximum dose with a possibility for applications of lower doses?). As this is a regulatory issue relating to National policies and National labelling, it should also be discussed with the EC.
- Recognized that Good Experimental Practices (GEP) greatly vary among countries. It was recommended that, in order to facilitate better understanding and the use of GEP certificates translation into English and the creation of a database of GEP managers would be helpful (Belgium and UK volunteered to support EPPO in approaching the EC on this issue).
- It was proposed that a further Zonal procedures Workshop in 2015 may be valuable to discuss progress, experience and further requirements.