



Efficacy of low-risk substances and micro-organisms

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The updated criteria in the EU for low-risk substances (Regulation 2017/1432) more or less clearly define the characteristics of these substances in regards to certain physical-chemical, toxicological, ecotoxicological and environmental fate properties. With the exception of the very vague criteria given for micro-organisms, these low-risk requirements can be applied to any type of substance, setting the framework for registration strategies in these subject areas for each individual substance.

In addition, the criteria fixed for these subject areas also set the framework for possible incentives to foster the registration and availability of low-risk substances and products, for example, in regards to residue exemptions, reduced study requirements, reduced evaluation time-lines and, in some member states, lower authority fees.

With respect to economisation of the time and cost consuming efficacy studies and data requirements for a product authorisation, the low-risk criteria for active ingredients according to Regulation 2017/1432 offer no starting points.

As a basis for data/study requirements for low-risk product authorisations, the European and Mediterranean Plant Protection Organization (EPPO) published standard PP1/296(1) on the “Principles of efficacy evaluation for low-risk plant

protection products” in 2017 [the Standard].

The new standard also includes micro-organisms, in case they are of low-risk, and thus supplements EPPO standard PP1/276(1) of 2012 on the “Principles of efficacy evaluation for microbial plant protection products”.

In general, EPPO standard PP1/296(1) describes the framework for the minimum data requirements for demonstration of efficacy and crop safety for low-risk products. The Standard clearly does not substitute any of the EPPO standards in effect for non-low-risk plant protection products. On the contrary, the Standard makes reference to the existing applicable standards (see <https://gd.eppo.int/>) and emphasises consistently that there should not be a difference between the principles of efficacy evaluation for low- and non-low-risk products. The Standard ascribes possible differences in study conduct, testing strategy, trial programme, description and evaluation of results by authorities between low- and non-low-risk products solely to scientific reasons, based on the special characters of the individual low-risk ais. Even without considering different functions or modes of actions, the huge variety of low-risk ais is evident from the examples of the (very few) low-risk ais already authorised (12 substances) as well as the possible candidates identified in the ai renewal programme (64 substances;



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SAN-TE-2016-10616–rev 8 of October 2017). These 76 substances comprise biologically very different groups of micro-organisms – even from different domains and kingdoms – viruses, botanicals, inorganic salts, fatty acids, plant hormones, proteins, plant oils, gases, minerals and basic chemicals. Thus, the scientific, “more specialised”, approach to efficacy testing chosen by EPPO (“Good quality data and science are essential”) is reasonable and to be applauded in general.

For implementation of this scientific approach, certain principles are to be considered:

- Diversity of low-risk ais and products.
- General requirement for scientific explanations and justifications of claims.
- Flexibility of the efficacy evaluation in regards to the level of effectiveness where the Standard defines the primary criterion of acceptable efficacy as “results that are significantly superior to those recorded in the untreated control, i.e., that the use of the product is better than no use”. In the case of the use of a chemical product as reference product, the Standard highlights that the reference product is to be used to establish the validity of the trial and not for comparison of the level of efficacy.
- Use of lab trials and relevant published data as “important and valid source of information”.
- Acceptability of non-GEP data if scientifically sound.
- Further possible benefits of low-risk products, for example, regarding resistance management or suitability for IPM or special cultivation systems such as organic farming, that is the contribution of low-risk products to agricultural sustainability, are to be considered in the evaluation.
- Especially considering the level of effectiveness and the acceptable efficacy of low-risk plant protection products, the Standard highlights that the principle of relevant benefit applies, i.e., the effectiveness should be compared to untreated control and not a possible (chemical) reference product either stand alone or in a programme (for instance,

IPM). In addition, for the evaluation of the contribution of the use of low-risk products to agricultural sustainability and additional benefits such as short or no pre-harvest intervals, reduced or no residues, lower or no probability of resistance, less side-effects, for example, on non-target organisms or the unnecessary of risk mitigation measures are to be considered.

As key topics to be used in the scientific approach, the Standard mentions:

- Mode of action (MoA) where the Standard also defines categories of low-risk plant protection products, for which general scientific argumentation is possible. The categories are (bio) chemicals and substances derived from animals, botanicals, minerals, extracts from micro-organisms and synthetic substances with direct or indirect MoAs as well as micro-organisms with direct or indirect MoAs and semiochemicals including pheromones. In addition, the Standard acknowledges, that some ais belong to more than one category.
- Conditions and situations of minimum, optimum and maximum performance of low-risk ais and products such as, in the case of micro-organisms, biological/physiological parameters regarding survival, reproduction, colonisation and competition.
- Crop biology and physiology.
- Environmental conditions.

Considering the huge variety of (possible) low-risk substances and their special characters, the commitment to a scientific approach in regards to efficacy evaluation itself is a huge benefit for applicants. Furthermore, the scientific case-to-case approach, with certain exceptions, renders additional efficacy or crop safety guidance for low-risk ais types as unnecessary. For low-risk substances, a reduction of the financial burden in the efficacy area is of special interest, not only as many applicants are SMEs. First and foremost, as many of these substances are able to control diseases and pests in crops of lower economic importance or situations for which no pest control method is available until now but for which big investments in efficacy trial programmes are not justified.

Based on the scientific approach, economisation of efficacy data/study requirements is also considered in the present standard on the “Principles of efficacy evaluation for low-risk plant protection products” to a huge extent.

The Standard sets the minimum number of fully supportive direct efficacy trials required for an area of similar conditions as six for a major pest on a major field crop, four for a major pest under protected conditions and three for other uses. At first glance, this is quite similar to the minimum requirements for plant protection products given in Eppo standard PP1/226(2) which, of course, is already a clear reduction of studies required. But in addition, the numbers of efficacy trials given in The Standard do not only apply for a single pest or crop, but to pest and crop groups where The Standard explicitly refers to the existing extrapolation possibilities for minor uses as described in Eppo standard PP 1/257(2) as well as the relevant extrapolation tables developed by Eppo (refer to: https://www.eppo.int/PPPRODUCTS/minor_uses/minor_uses.htm) and the use of these extrapolation possibilities not only for minor but also for major uses.

Furthermore, depending on the characteristics of the individual ais/product for example, an extrapolation from worst-case circumstances to intermediate or less-critical conditions is considered feasible by Eppo. Similar for extrapolation between agro-climatic zones as – considering the special characteristics of many low-risk ais – comparable conditions do not depend on climatic factors only but also on edaphic and agronomic factors, crop biology, pest/crop interrelationships, soil conditions, application and cultivation techniques. Due to the huge variety of low-risk ais, extrapolation outside Eppo PP 1/257(2) may also be possible for low-risk products.

In addition, the Standard establishes possibilities for exemptions from the requirement of dose justification field trials, for example, based on MoAs as well as minimum effective dose trials. For reproducing micro-organisms, the minimum effective dose approach is considered difficult or not appropriate. Instead, the Standard proposes that a

range of doses should be provided which reflects the scientific and practical facts. A similar approach applies for semiochemicals. In case of selectivity/phytotoxicity trials Eppo concludes that even for special low-risk herbicides and plant growth regulators appropriate analysis of the effectiveness trials may be sufficient, given that no phytotoxicity symptoms are observed in these trials. The same is the case for effects on plant parts used for propagation or side effects on succeeding or adjacent crops.

As evident, full implementation of the possibilities and benefits of the Eppo standard PP1/296(1) on the “Principles of efficacy evaluation for low-risk plant protection products” in the registration strategy for a low-risk product obliges applicants to use a completely different (new) approach to efficacy testing and dossier preparation. In addition, standard PP1/296(1) requires in-depth knowledge of applicants not only in regards to their individual low-risk ais and products, but also on crop biology and physiology, environmental and agricultural conditions, application and cultivation techniques such as IPM.

As practical experiences with the implementation of the new principles for efficacy evaluation for low-risk plant protection products is currently very limited, there are several open questions on the future impact of this standard. The two key points are: (i) whether applicants are willing and able to provide a scientifically sound dossier [Biological Assessment Dossier (BAD) and dRR], scientifically explaining and justifying their claims and (ii) whether authorities are willing and able to follow the scientific approach, accepting the special character of many low-risk substances and the study/data reduction approach.

If these two points can be met, Eppo standard PP1/296(1) represents a valuable incentive for plant protection product authorisation applications, fostering the availability of low-risk plant protection products on the market. This may, in future, even include possibilities to fully exploit the potential of low-risk ais including their use against abiotic stresses or in the scope of IPM programmes for which an efficacy testing guideline would be much needed.