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Review

Environmental risk assessment in agro-ecosystems: Revisiting the concept of receiving environment after the EFSA guidance document

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A R T I C L E I N F O

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A B S T R A C T

The environmental risk assessment (ERA) for genetically modified plants (GMPs) is a prerequisite for commercial approval of these new varieties according to regulatory systems worldwide. The first country to regulate GM crops was the USA and the issue of possible environmental impacts was based on the principles used in risk assessment of pesticides. Two main pillars of this approach are the use of surrogate species for testing effects on non-target organisms using a tiered assessment with clear thresholds to indicate the need to move between tiers. The latest EFSA guidance document on ERA of Genetically Modified Organisms considers specifically the receiving environment in preparation of ERA for commercial cultivation of GMPs. According to existing guidelines in the EU, the receiving environment is defined by three mutually interacting components: the characteristics of the environmental stressor (i.e. the GM plant), the bio-geographical regions where the commercial release of the crop is expected and the agricultural systems therein. Difference in agronomic and ecological conditions (e.g. use of different varieties, vegetation of adjacent areas, non-target species assemblages, sensitivity of local species to the stressors) suggests that explicit considerations of the receiving environments are necessary. Results from field experiments indicate that differences in cultivation practices, e.g. the herbicide regime used on herbicide-tolerant GM crops, may induce direct and indirect effects on wild plant distribution and abundance, with consequent repercussions on food webs based on these plants. Moreover, ecological literature indicates that the concept of surrogate species has clear limitations if applied broadly to any ERA. Starting from case studies regarding GMPs, this paper discusses some ecological and agronomic characteristics of agro-ecosystems, which have implications in the elaboration of both hazard and exposure analyses during ERA. The species selection approach indicated in the EFSA Guidance Document and the consideration of the area(s) of the expected release of the new variety may provide the basis to an ecologically sound ERA for a range of environmental stressors. The quality of the data that become available for risk managers with this approach may support a more transparent and dependable ERA and risk management for GMPs as well as for other potential environmental stressors in agro-ecosystems.

1. Introduction

The concept of receiving environment has traditionally developed in the framework of management of chemical pollution (e.g. Gambrell, 1981; Odjadjare and Okoh, 2010; Voulvoulis et al., 2015) to define areas and biological indicators where monitoring activities should be concentrated based on the expected exposure to environmental stressors.

In human-managed ecosystems, the purposeful introduction of a new product or technique (e.g. the use of a new crop variety, the introduction of a biological control agent) is considered also a potential stressor and therefore usually requires the provision of an environmental risk assessment (ERA) before commercial release. The preliminary consideration of the receiving environment can assist in framing the scope of ERA. Understanding the receiving environment in all its components will also help to ensure the consideration of the spatial extent and the proper timing to estimate environmental exposure to the stressor. Indeed, for each category of environmental stressors in the specific environment, the range of attributes necessary to detect environmental impacts might be different (DES, 2014).

In agriculture, most relevant experience of ERA for regulatory purposes has been gained with the approval of plant protection products. In

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this context, the goal of protection of valued species from harm is primarily based on the hazard characterization for the molecules. This is achieved performing standardized toxicity tests using a defined set of indicator organisms as surrogates for a group of valued species. When commercial release of genetically modified plants (GMPs) for cultivation started in the USA in the mid of the 90′s, pesticide legislation was the starting point to develop guidance for ERA of GM crops. For purpose of ERA, the US environmental protection agency introduced the concept of plant-incorporated protectants as the "pesticidal substances produced by plants *and* the genetic material necessary for the plant to produce the substance". Guidance for toxicity tests indicates that they should be performed according to a tiered approach, which may use laboratory data at lower tiers and semi field or field data at higher tiers, if uncertainty at lower tiers remains (e.g. US Environmental Protection Agency, 1998). The suggested criteria for selecting surrogate species are the different habitats (e.g., below the soil surface, soil surface, plant canopy), the ecological functions of the species (e.g., predator, parasite or decomposer), and taxonomic groups (e.g., relationship to the target pest). The species should also prove to be amenable for laboratory testing. In this framework, exposure analysis is mostly focussed on information regarding the source of the introduced materials, i.e. taxonomy, physiology, ecology and genetics of GMPs.

The Guidance document (GD) of the European Food Safety Authority (EFSA Panel on GMO, 2010) firstly elevated the importance of the receiving environment. The GD asks for a detailed recognition and evaluation of its specific elements and the analysis of the receiving environment is defined as one of the main crosscutting considerations for ERA of GMPs. This was deemed necessary because the receiving environment has implications for both hazard characterization and exposure assessment of living GM organisms and a more adequate consideration of its peculiarities for conducting ERA was required. This approach was further adopted in other legal frameworks (es. Ministry of Natural Resources and Environment of Malaysia, 2012). Further, the Convention on Biological Diversity adopted the concept of receiving environment in its Guidance on risk assessment of living modified organisms (Convention on biological Diversity, 2016). The Guidance document includes among the elements of the receiving environment to be considered for ERA: the environments and their degree of management, ecosystem functions and services of the potential receiving environment (e.g., relevant components of food webs), change in landscape patterns and sensitivity of the receiving environment.

There are at least two steps during ERA that, according to the EFSA GD, are necessary to select appropriate receiving environments that are representative of the whole European areas. The first one is to consider the expected scale of the environmental release of the GM variety under scrutiny. This will include the consideration of how the common agricultural practices in different areas may lead to possible impacts on the organisms living in the agro-ecosystem. The second aspect is to allow flexibility in the selection of non-target focal species on which toxicity tests are conducted, to attest that risk assessment is conducted considering the protection of biodiversity and existing protection goals at large.

In this paper, I will discuss scientific literature indicating some limitations of the traditional eco-toxicological methods, and how existing studies support the need of a more ecologically sound approach to ERA based on the definition of the components of the receiving environment.

2. A definition of receiving environment

According to the EFSA GMO Panel (2010) the receiving environment is defined as the environment into which the GM plant(s) will be released and into which the transgene(s) may spread. The definition of receiving environment(s) is a very important preliminary action of ERA, since ecological information needs to be provided which are relevant to the conditions of the most likely exposure scenarios for the deployment of the potential environmental stressor.

The receiving environment can be described by three components:

- The GM plant (e.g. plant species, genetic modification(s) and intended uses(s));
- The Biogeographical Zone (e.g. climatic conditions, altitude, soil, water, flora, fauna, etc.);
- The Management System (e.g. land use and production systems, cultivation practices, pest management, etc.).

A number of biotic and abiotic interactions characterize the above-mentioned factors for each receiving environment, which is not limited to the farmed areas but includes adjacent habitats, that are on ecological ground strictly linked to the fields where GM crops are cultivated (Marshall, 2002). These interactions develop at various spatial and temporal scales. For example, pollen expressing new toxins may be transported by wind or animal pollinators to nearby areas and interfere with the normal feeding activities of herbivores on wild plants (Perry et al., 2010; Holst et al., 2013). Plant residues may reach waterbodies making exposure to transgene products possible for organisms populating completely different habitats (Tank et al., 2010). Exposure to plant-expressed products may be extended in time beyond a cropping season and bioaccumulation of these products along trophic chains has been proven (Svobodová et al., 2017), though with different intensity according to the trophic system of study.

The three components of the receiving environment drive both hazard characterization and exposure assessment phases of ERA. The accurate description of the environmental stressor (i.e. the genetically modified plant) is the starting point for the hazard characterization phase foreseen by the agencies involved in risk assessment (e.g. US EPA, 1998) under different regulatory systems for GMOs. From the characteristics of the GM plants under evaluation (i.e. the plant species, the newly introduced trait(s), their intended use(s), the pattern of expression), the choice arises for the relevant assessment endpoints to be used in ecotoxicological tests. Indeed, the expression of novel compounds in different plant parts along the growing season is a primary information to estimate the possible exposure of non-target organisms and consumers to the introduced GM plant and its products. The molecular structure of the introduced genes will also influence the likelihood of gene transfer from GM plants to other organisms, which might be present in the receiving environment.

Once the nature and the characteristics of the stressor (e.g. the newly introduced variety) have been defined, relevant baseline information on the characteristics of the receiving environment(s) regarding climatic conditions, presence and distribution of native and cultivated plants and food web relying on this vegetation, is necessary.

The use of bio-geographical zoning is quite common in environmental regulations for different purposes. Common features related to abiotic and biotic factors are considered to identify similarities between adjacent territories and define agro-climatic zones in order to describe the likely conditions under which an environmental impact can occur. For example, the authorization for commercial use of pesticides in Europe is based on mutual recognition and zonal authorizations; the European Commission in Regulation (EC) No 1107/2009 established three zones at this purpose (Fig. 1). The European Plant Protection Organization proposed for the evaluation of PPPs, a slightly different zoning system based on four homogeneous zones, Mediterranean, Maritime, North-West, North-East. Additional zoning systems have been proposed to tailor ERA for specific goals (e.g. the EU Natura 2000, whose framework is the legislation for protection of habitats and species-based biodiversity).

However, the frequent variation of some environmental attributes due to land use, habitat fragmentation and climate change make the application of a fixed scheme to identify relevant zones for ERA more and more impractical. Availability of new hybrids and the constant increase of average temperature in the last decades are also moving the distribution area of some crops (e.g. maize currently being cultivated up

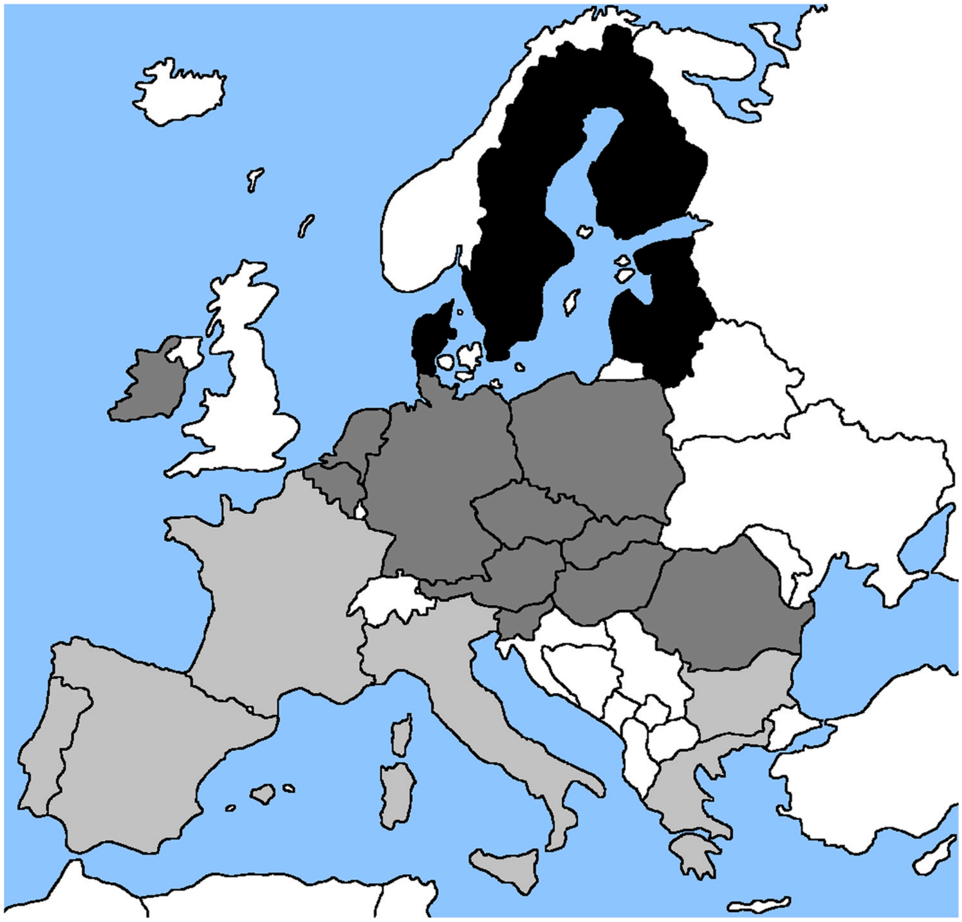

Fig. 1. Biogeographical zoning for the approval of plant protection products in the European Union. Black area = :Zone A, Northern; Dark grey = Zone B, Central; Light grey = Zone C, Southern.

to Sweden, Eckersten et al., 2012). Climate shift is affecting spatial distribution and dynamics of both terrestrial and aquatic fauna (e.g. Hoberg et al., 2017; Forister et al., 2018; Yin et al., 2019), so that a periodic revision of zoning systems considering both abiotic and biotic factors will become necessary. Distribution of wild/weedy plants outside the cropped field is also important information in the light of estimating possible spread of the transgene(s) in the environment via sexual hybridization. A specific case concerns the evaluation of risks for endangered or protected species. This necessity should be dictated by existing protection goals; in such cases, very specific conditions of the receiving environment, and often a restricted territorial range, need to be selected as appropriate.

A third driving factor in describing the receiving environment(s) for ERA is the production system where the adoption of the new varieties is expected to occur. When agricultural ecosystems are considered, a relevant body of information about the production systems (starting from the choice of varieties, to pest control systems, crop rotation schemes and cultivation practices) are relevant in selecting the areas where the ERA will be conducted. For cultivation of GM crops, the appropriate geographical zones should firstly be considered in the context of the expected cultivation area. Consequently, proper ERA for different GM crop species evaluated for commercial cultivation (maize, soybean, rice, cotton, oilseed rape, ornamentals, etc.) can not rely on pre-defined regions for experimental testing. Even for the same crop species expressing different phenotypic characteristics (e.g. drought tolerance, cold tolerance, pest resistance) or for different end-use products (e.g. grain maize, forage maize and sweet maize) pre-defined regions for ERA seems to be inappropriate. Plant pest management is an important production practice, which has obvious implication for the environmental safety. Pest distribution is shifting due to an expansion of seasonal migration patterns (Bebber et al., 2013), a shift towards higher altitudes (González-Megías et al., 2016) or the continuous trans-boundary movement of arthropod alien species (Nentwig et al., 2018). Moreover, for the same crop species, pest distribution and incidence is quite variable (Fig. 2), therefore areas where the GM varieties may represent a benefit, vary as well.

Adoption of GM plants within a given agricultural production system may lead to significant changes in cultivation techniques. Such changes may be directly linked to the introduced trait, e.g. the case of GM herbicide tolerant crops, which aim at changing the herbicide regime (type of herbicide and application timing). The main benefit of herbicide tolerant GM crops is that specific herbicides can be used while crops are fully growing. The timing of herbicide application is particularly important in driving possible environmental consequences, due to a higher mortality of larger and reproductive weeds caused by the later herbicide application in GMHT crops (Heard et al., 2003) that tends to reduce the persistence of plant populations, their seed densities and, in turn, densities of emerged plants. This loss of food resources is likely to cause reductions in the abundance of key invertebrate groups (Hawes et al., 2003) and of species at higher trophic levels (Blaix et al., 2018). These GM plants can also indirectly induce changes in cropping practices (Firbank et al., 2003), e.g. promoting higher adoption of minimum tillage or no-till techniques or shorter crop rotation. Changes in herbicide regimes lead to a modification of the biodiversity (flora and fauna) in and around fields and the impact on biodiversity depends greatly upon the management of crops, rotations, and the availability of forage and habitat resources across the entire farmed landscape (Firbank et al., 2003). In the farm-scale study by Albajes et al. (2014), natural enemies

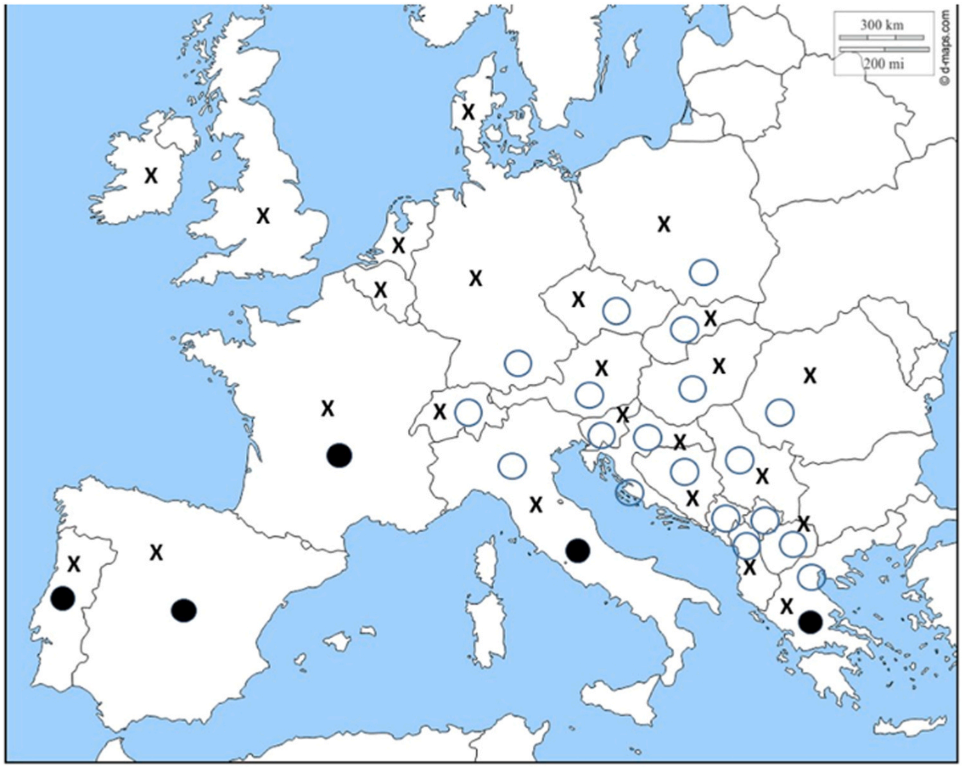

Fig. 2. Geographic distribution of the main maize insect pests in the European Union. Empty circles = *Diabrotica virgifera virgifera*; Close circles = *Sesamia nonagroides*; X = *Ostrinia nubilalis.*

such as *Orius* spp., Araneae and Coccinellidae predators were more abundant in plots treated twice with glyphosate compared with conventional pre-emergence treatment, a result probably due to the lower density of weeds and larger populations of canopy dwelling herbivores, mainly leafhoppers. However, the abundance of phytophagous arthropods among plots managed with different herbicide treatments was statistically significant in one of the 3 years of the experiment. The change in the herbicide regime in a field study in a different area of Spain did not reduce weed density in glyphosate treated maize plots; however abundance of Mymaridae parasitoids was lower under this herbicide regime in one year (García-Ruiz et al., 2020).

Bürger et al. (2015) developed a simulation model to predict impacts on plant and arthropod biodiversity due to changing farming practices after introduction of GM maize varieties. Their simulations showed that the changes accompanying the introduction of GM maize varieties affected weed flora as well as weed-related biodiversity and crop production loss, but that the consequences depended on local conditions. Most of these consequences were caused by simplifications in the cropping systems made possible by the GM varieties, rather than by the use of glyphosate associated to GM varieties.

The cropping practice regime then becomes a relevant component in evaluating the environmental consequences of the introduction of the GM variety. The diversity of cropping practices between agro-ecosystems in different zones makes the selection of the most appropriate receiving environments challenging, therefore recommendations to risk managers for the appropriate management of herbicide tolerant GM varieties are usually included in the scientific opinions by regulatory authorities (e.g. EFSA Panel on Genetically Modified Organisms, 2009).

All this ecological information needs to guide the hazard characterization, by selecting appropriate areas to conduct ERA, and the selection of relevant focal species for testing (e.g. ecological service providing organisms) related to existing protection goals.

An effective exposure assessment also needs to be rooted on such locally relevant ecological and agronomic information, in order to select focal species most likely under threat. Arpaia et al. (2018) estimated the possible exposure of butterfly species to maize pollen in two protected areas in Italy, characterized by different climatic conditions and different agrarian landscapes, where several Lepidoptera species are common in proximity to maize cultivations. In a Northern area where maize grain varieties are most often cultivated, occurrence of butterfly larvae on neighbouring wild plants and maize pollen emission overlapped. On the contrary in the Southern site silage maize was prevalent and flowering of such varieties occurred in mid-summer, when several butterfly species undergo an aestivation period due to hot and dry conditions. The evaluation of different plant and insect phenology finally led to very different exposure scenarios in this study, where locally grown varieties play a paramount role in effectively estimating exposure to the stressor in natural conditions.

3. Limitations of the surrogate species concept in ERA

The use of predefined surrogate species for risk assessment for NTO shows clear limitations when applied broadly to any GM crop. A first and paradigmatic case is related to the risk assessment of non-target Lepidoptera to GM maize expressing Cry 1f toxin. When a request for the commercial use of GM maize 1507 in Europe was submitted (Notification C/ES/01/01), EFSA evaluated the risk assessment provided by the applicant giving a favourable opinion to its commercial use. In particular, the evaluation of possible risk for non-target Lepidoptera was based on the results of the paper by Hellmich et al. (2001) who compared the toxicity of different Bt toxins in laboratory studies using the monarch butterfly, *Danaus plexippus,* as a surrogate species. The authors reported a >10.000 times lower toxicity of the Cry1F toxin (as produced in 1507 maize) on monarch butterfly first instars as compared with other Cry toxins (e.g. CryIAb). The study clearly showed that monarch larvae were not affected when fed a diet consisting of 1507 maize pollen. Even considering the higher expression in pollen in the event 1507 compared with other GM maize events, the estimate LC_{50} calculated for monarch larvae was >24,750 pollen grains. Based on these results, the EFSA GMO Panel "*agrees with the assessment of the applicant that risk of exposure of non-target lepidoptera to harmful toxin concentrations* via *1507 maize pollen is negligible and that adverse impacts on populations are very unlikely*" (EFSA Panel on Genetically Modified Organisms, 2005). However, studies conducted with butterfly species living outside of the American continent (see Wolt et al., 2005 and references therein) indicated a generally higher sensitivity to Cry1f compared to the Monarch butterfly (the opposite case of Cry1Ab). Moreover, natural variation in sensitivity to Cry1F toxins among populations of the same species have been detected in some cases (Gaspers et al., 2011; Farias et al., 2014). In the light of the scientific data become available, and according to the criteria of the newly adopted Guidance Document, EFSA issued an updated ERA of maize 1507 (EFSA Panel on Genetically Modified Organisms, 2011) basing the risk assessment for non-target Lepidoptera on the mathematical model, developed by Perry et al. (2010). The GMO Panel concluded that reductions in populations of certain highly sensitive non-target Lepidoptera are possible if high proportions of their populations are exposed over successive years to high levels of maize 1507 pollen. In situations where highly sensitive non-target Lepidoptera populations might be at risk, the EFSA GMO Panel recommended the adoption of mitigation measures to reduce exposure.

The within taxa variation of sensitivity to pollutants is not a peculiar case for Cry toxins, but rather a common feature across different stressors, environments and taxa. Several studies with non-target species addressed the issue. For example, Vaal et al. (1997) studied the variation in the sensitivity of aquatic species to environmental pollutants and found variations in species sensitivity as large as 10^5 to 10^6. Prabhaker et al. (2007) found large variation in sensitivities to several active compounds, e.g. acetemiprid, thiamethoxam, imidacloprid, among four important parasitoid natural enemies. Extent of difference was higher than 20.000 folds in some cases. Significant ranges of sensitivity to five different pesticides were also detected among the coccinellid predators *Coccinella septempunctata*, *Adalia bipunctata*, *Propylea quatuordecimpunctata* and *Harmonia axyridis* (Jansen and Hautier, 2006). *A. bipunctata* was generally the most sensitive species, while *C. septempunctata* showed a general low sensitivity to the selected active ingredients with LC_{50}s up to 600 times higher compared to other ladybird species. The basis of such diversity of responses can be ascribed to insect genomes, but cases of variability between populations of the same species are also known (e.g. Sugahara et al., 2017). The difference in sensitivity between taxonomically related species will not be captured if inappropriate surrogate species are used, even considering that during *in vitro* tests organisms are exposed to concentrations of the toxin exceeding (usually 10–100 times) conservative estimates of field exposures (Raybould et al., 2011).

In consideration of the problematic outcomes of many field studies highlighting negative effects of expected "selective'' insecticides on natural enemies, Banks et al. (2014) used a modelling approach to predict population trajectories of four different parasitoid species: *Diachasmimorpha longicaudata*, *Psyttalia fletcheri*, *Fopius arisanus* and *Diaeretiella rapae*. The results of their study indicate that parasitoid wasp species show different population responses to toxicants and it is not possible to predict how all four species will react to pesticide exposure by extrapolating from the response of any one of them. More recently, Banks et al. (2019) considered three different aquatic species commonly used as indicators, *Ceriodaphnia dubia*; *Daphnia magna*; and *Daphnia pulex*. Feeding a mathematical model with laboratory-derived life history data, the authors showed that Daphniid species' responses to toxicants make them poor surrogates for one another. Even with a similar sensitivity to a stressor, because of differences in life history parameters (i.e. decreased survivorship and fecundity) their responses to a stressor are quite different leading to very different population-level impacts. The authors conclude that caution should be exercised in using any Daphnid species as surrogate during ERA for pesticide risks to aquatic environments.

Furthermore, different responses to the same stressors are not only linked to different physiological parameters. Paula et al. (2016) describe a fourth example in which the use of a "wrong" selection of surrogate species might fail. In their study, larvae of two related aphidophagous coccinellid predators, *Cycloneda sanguinea* and *Harmonia axyridis*, were exposed to Cry1Ac and Cry1F toxins. During laboratory bioassays the majority of *H. axyridis* larvae ingested both Cry toxins, and bioaccumulated them from their aphid food. In contrast, only a few *C. sanguinea* larvae took up either Cry toxin and, when uptake occurred, the concentration was low. Both species were insensitive to the two toxins; however, these results suggest that the lack of ecological effects in the two species is due to different behavioural mechanisms.

Finally, another case study involving parasitoids, whose physiology is strictly linked to the development of their host, shows the need of considering exposure via tritrophic experiments in order to mimic natural conditions under which exposure to a toxicant ingested by a host herbivore may or may not occur. The polyembryonic egg-larval parasitoid *Copidosoma floridanum* lay numerous eggs into the body of caterpillars and the newly born larvae consume the entire host rapidly (Tian et al., 2018). On the contrary, other larval parasitoids like *Cotesia marginiventris* only feed on specific host tissues, and may possibly avoid tissues containing Bt toxins such as the gut (Ramirez-Romero et al., 2007). A basic assumption of the use of surrogate species is that the species should respond to the toxin with similar physiological processes existing in other non-target organisms (e.g. Godoy et al., 2015). This assumption is not met in the two latter biological systems described above.

Overall, there is increasing evidence in the scientific literature indicating that the ability to predict the fate of a suite of species using the response of a surrogate species is widely variable and potentially misleading. Favreau et al. (2006) extensively discussed the shortcoming of the surrogate species concept and indicated a number of issues that should be better addressed for supporting the selection of such indicators for conservation purposes. Among the priorities indicated by the authors, there is a recommendation to taking advantage of data-rich regions and consider more openly the spatial and temporal pattern of species composition in the habitats.

The EFSA Guidance Document for ERA of GM plants (EFSA Panel on Genetically Modified Organisms, 2010) is in line with these indications and in order to overcome some shortcomings in the use of the surrogate species concept in ERA frameworks, suggested a stepwise approach for selecting focal species for the assessment of non-target effects. Focal species selected for ERA should be representative of ecological services providing guilds and being relevant for the receiving environment where GM crops are expected to be cultivated. Examples of the application of the EFSA approach to species selection were conducted for different agroecosystems. The selection process for prioritizing relevant herbivore species in potato agroecosystems conducted by Lazebnik et al. (2017) selected aphids as generally suitable candidate non-target herbivores. In the study by Van Capelle et al. (2016), the geographical distribution of earthworm species in maize fields suggested instead, that site-specific soil-inhabiting indicators might better reflect species assemblages in the receiving environment in some cases.

4. Conclusions

Agriculture is considered one of the human activities with high environmental impacts, leading to hampered provision of ecological services, loss of biodiversity and ultimately even to species extinctions (e.g. Tilman, 1999).

Trying to address the possibility of environmental impacts on NTOs means unavoidably the choice of a few focal species or ecological functions, as indicators of the biotic communities providing ecological services in agro-ecosystems.

Common approaches to ERA in agro-ecosystems are mostly derived from the pre-market eco toxicological assessment of pesticides.

However, the rapid adoption of biotechnological innovations (especially genetically modified crop plants) and the delayed discovery of negative environmental effects of widely used insecticides (e.g. Goulson, 2013) indicate that it is timely to rethink some keystone of the traditional approach to ERA.

In Europe, there are ongoing initiatives to harmonize ERA in different fields of application. Preserving biodiversity is one of the goals in different legislations including the regulation of plant protection products, genetically modified organisms, plant health. It was recognised that ERA schemes have evolved independently in the different areas and that further harmonisation might be possible (EFSA Scientific Committee, 2016). The suggested approach is to firstly identify species or ecological processes providing ecosystem services and relevant for the specific receiving environment, which will define the framework in which risk assessors operate when performing ERA. Life history traits of focal species, species assemblage in field conditions, agro-environmental differences in the receiving environments are specific aspects that need to be evaluated. This could provide a harmonised methodological framework using the ecosystem service concept to derive environmental protection goals, regardless of the regulated product or organism that is being assessed. One of the issues, which receives attention, is that modelling could prove a useful approach to derive specific protection goals, as it would allow taking into consideration different environmental conditions including the action of multiple stressors (Aasmo and Wendell, 2018). However, no explicit consideration of other aspects of the receiving environment for ERA is currently being made.

Ecological information should constitute the central paradigm of ERA, without neglecting that the efforts needed for conducting ERA should be proportionate to the potential risks highlighted during the preliminary problem formulation phase. For instance, the experience accumulated in the last two decades with some traits expressed in the 'first generation' of GM crops could allow to safely resolving some concerns arising during the ERA process. However, making it simple does not mean making it clumsy and the availability of abundant ecological data, in part commented in this paper, should not be ignored. The use of laboratory bioassays on a set of pre-conceived surrogate species to estimate effects of potential stressors to NTOs has shown serious shortcomings. The species selection phase should be conducted considering additional ecological and physiological criteria other than the taxonomic relatedness to the NTOs of interest, and should be flexible enough to drive the choice of different testing species case by case. Differences in species life histories even with a similar toxicological sensitivity can result in very different impacts at population level. This is generally ignored in ERA and represents an added weakness of the whole process. Taxonomic similarities alone can not guarantee to mirror the biological characteristics of NTOs in the agro-ecosystem of interest. For instance, even insect species within the same order are known to show quite a different sensitivity to Cry toxins (Van Frankenhuyzen, 2009). Moreover, species assemblages in and near cultivated fields are sometimes strongly influenced by their geographic distribution and the surrounding landscape. Therefore, the necessity arises to select test species to be used as indicators, which are good representatives of the biodiversity in the expected receiving environments where the stressor is to be released. This is even more urgent nowadays, since the natural trend of ecosystems evolution is accelerated by climate change and increased habitat fragmentation. Once the analysis of the ecological features of the receiving environments has been conducted, priority should be given to non-target species which can be efficiently used for experimental purposes in laboratory or field studies.

In order to tackle some of the limitations of the existing ERA schemes, the European Food Safety Authority introduced in its Guidance document on the environmental impacts of GMOs (EFSA Panel on GMO, 2010) several criteria, and especially calls for the open consideration of the receiving environments where GM crops are to be released. The interactions between the GM plant under assessment, the bio-geographical zones in Europe where the new release is expected and the operating agricultural system of interest are considered in the EFSA's view as "triangular components" of the representing receiving environment. Environmental risk assessment needs, at a certain stage of the process, to collect regional ecologically relevant information (e.g., on NTOs) that is deemed important in providing ecological services in a particular agro-ecosystem. Under the regulatory system for GMOs in Europe, scientific opinions express a global judgment considering the possible deliberate release of the GM varieties in the whole European Union. Collecting enough information for a thorough estimate of ecological services Europe-wide may represent a massive effort, which goes beyond the scope and possibilities of an ERA aimed at the approval of a new crop variety. Local resources and expertise should then be involved, also after the approval of a new GM event, to confirm that biotech products are exploiting their potential and are managed in a way to support the sustainability of agriculture. It is also task of local risk managers, to evaluate if the diversity of local cultivation practices, might lead to unexpected environmental effects, which need to be investigated during ERA or with appropriate post-market monitoring plans. The preparation of an ERA based firstly on the ecological criteria as discussed in this review, provides a transparent process, which puts risk managers in a position to judge if approval of cultivation of GMPs, or other innovation in farming practices, will need management measures tailored to their territories and protection goals.

The same limitations of the eco-toxicological approach to ERA discussed in this paper mostly considering GMPs, also apply to other possible environmental stressors in agrarian landscapes. For instance, Lee et al. (2020) specifically proposed the use of locally based indicators for the protection of cultural ecosystem services. Differences in susceptibility to pesticides among species should also be evaluated when selecting locally relevant focal species for toxicity tests aimed at the approval of plant protection products. Regionally relevant species assemblages need to be considered in estimating potential negative effects of the introduction of exotic natural enemies in a new area. Loomans (2020) highlights the importance of including in the risk assessment framework for generalist biological control agents a detailed evaluation of the receiving environment. The consideration of the host/prey range of the introduced arthropod, the likelihood of encounters of certain hosts/preys and the likelihood of dispersal and establishment of the alien species considering local climatic and agronomic characteristics are key parameters to be evaluated during ERA.

Obviously, the consideration of the very nature of the specific stressor (a GM plant, a chemical, a change in crop management) shall lead the process, since both exposure analysis and hazard characterization are driven by a specific problem formulation. In this phase, the relevant attributes of the stressor (e.g. intrinsic toxicity, possible indirect effects, mode of action, pathways of exposure, etc.) need to be evaluated.

Differences in the agricultural practices between regions and the increasing tendency in saving cultivation inputs as a goal of sustainable agriculture need to be included in a transparent assessment of new plant protection products or other farming practices (e.g. reuse of wastewater) involving the use of chemicals in agricultural fields. These reflections trigger the need of building more communication activities between risk assessors and risk managers at different levels. This will support a proportionate and flexible ERA for different environmental stressors, based on a common approach including the accurate consideration of the ecology and the production systems in receiving environments. In this framework, risks are to be considered firstly at large scale, using tools like mathematical models and scenario analyses for the ecological processes involved, and the adequacy of the outcome of ERA, performed on a subset of relevant species, is further monitored locally based on clearly defined protection goals.

Declaration of Competing Interest

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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