Concept Discussion Paper: A Generic Framework and Generic Risk Factors to Inform the Environmental Risk Assessment of Organisms

June 2019

*"The study of **invasiveness**, the **traits** that enable a species to invade a habitat, and **invasibility**, the habitat characteristics that determine its **susceptibility** to the establishment and spread of an invasive species, provide a **useful conceptual framework** to formulate the biological invasion problem in a modelling context. Another important aspect is the **complex interaction** emerging among the **invader species**, the **noninvader species** already present in the habitat, and the **habitat** itself."* (Marco et al., 2002)

Purpose of this discussion paper

This conceptual discussion paper proposes a generic framework for the environmental risk assessment (ERA) of organisms including a set of generic risk factors based on biological attributes of organisms and bio-physical characteristics of interactions of organisms with the environment.

The paper has been developed primarily to inform the approach of the Office of the Gene Technology Regulator for undertaking risk assessments of potential future applications for various types of genetically modified organisms (GMOs), whether they be GM plants, animals or microbes.

The paper is not intended to be a 'methodological template' or 'recipe' for conducting ERAs but seeks to identify common features of organisms (whether plants, animals or microbes) that can inform the ERA of various types of organisms in a variety of contexts. The framework is not intended to represent a fixed OGTR policy or approach in relation to potential future applications and assessments of GMOs.

The genesis of this paper involved comparisons of ERA for GMOs with risk assessment approaches for other organisms in a variety of contexts (e.g. weed risk assessment) to identify commonalities and it has subsequently been informed by literature from a range of regulatory and scientific 'disciplines'. The paper does not purport to have exhaustively reviewed the literature for all types of assessments of organisms but has sought to identify and reference relevant publications.

It is hoped that this concept paper may be useful for/inform the thinking of risk assessors of organisms other than GMOs. It is also hoped that it might contribute to ongoing dialogue, exchange of ideas, improve clarity of communication between risk assessors of various organisms.

The OGTR would welcome comments on this paper, particularly from risk assessment practitioners for the various types of organisms or risk assessment contexts. We invite feedback and suggestions for its improvement in terms of relevant information and references that might be included, any errors of fact, and reactions in relation to the logic (or flaws therein) and potential practicability of the proposed framework to inform ERA of organisms (whether GMOs or not). Comments may be sent to ogtr@health.gov.au using subject line – 'GRAFO'.

Summary

Various regulatory systems and risk assessment frameworks have been developed to address the potential risks posed by organisms to people and/or the environment, e.g. biosecurity (human, animal and plant health), biological control agents, food-borne pathogens, genetically modified organisms (GMOs). Comparison of these different frameworks reveals many commonalities despite differences in terminology and context. A generic framework applicable to the environmental risk assessment (ERA) of all types of organisms (plants, animals, microbes) is proposed. The framework describes risk relational terms: a risk source (the organism); harm to an object of value (people or the environment); and a causal pathway of events from the risk source leading to that harm. The framework is consistent with the problem formulation approach as adapted to ERA of GMOs with its focus on plausible pathways to harm. Organisms that cause harm are generally categorised as weeds (plants), pests (animals) and pathogens or parasites (microbes), each with generally accepted descriptors for harm. The generic framework comprises a set of risk factors based on the common biological attributes of harms caused by organisms.

Three classes of risk factors are described:

Invasiveness and infectivity, I 1-8, ability to establish, reproduce, disperse, persist, transfer and change of genes, tolerate biotic, abiotic and anthropogenic constraints;

Harm, **H 1-4**, increase toxicity or ill health, reduce the biotic or abiotic quality of the environment or the functional value of the environment (e.g. from ecosystem services);

Harm mitigation, **M 1-2**, ability of environment or host to suppress, avoid, reverse or recover from harm.

The framework also outlines the relevance of the concepts **vulnerability, resistance** and **resilience,** and the importance of distinguishing between events and harm for ERA of organisms. The generic risk factors and conceptual approach described in this framework would be relevant to the ERA of GMOs and other organisms in a range of contexts, including the increasing number of non-plant GMOs that have either been proposed, are in development, or are already being released to the environment.

1 Introduction and context

Many organisms are subject to control measures or regulation to manage the risks they may pose, for a variety of reasons and in a variety of contexts, including: organisms proposed for importation; invasive organisms; organisms for biological control; certain microorganisms that may contaminate food or water; genetically modified organisms (GMOs); organisms used as medicines (e.g. vaccines, probiotics); or agricultural/veterinary products (e.g. pesticides, animal vaccines).

A commonly used approach to regulation of organisms is the application of risk analysis[1] (comprising risk assessment, risk management and risk communication). Risk assessment is a central component of risk analysis and is used to support evidence-based decision making. In a regulatory context, the objective of the risk analysis is to protect people and/or the environment from harm, generally biophysical harm, in line with legislative obligations. The regulatory risk analysis of GMOs is one example.

Risk assessment frameworks have been developed and elaborated for many purposes (e.g. finance, engineering, biological) and have adopted a variety of terminologies. However, they all share intrinsic commonalities, including the objective of identifying harm to things that are valued (protection goals) and protecting against that harm.

Protection goals and what is considered to constitute harm to those goals are both underpinned by societal values. High level environmental and human health protection goals are often articulated or defined in legislation or policy. Protection goals provide context for the identification of potential harms but it is less common for what constitutes harm to the environment to be precisely defined (Sagoff, 2005; Evans et al., 2006; Sanvido et al., 2011).

Historically, frameworks for 'ecological risk assessment' (or 'environmental risk assessment', ERA) were developed primarily for assessing chemicals. For example, the ERA approach developed for

[1] depending on the framework and its terminology, the term 'risk management' may be used as the umbrella term rather than risk analysis

ERA of chemicals by the US Environmental Protection Agency (US EPA 1998) and literature of Suter and others (Suter, 2006) has been very influential in the regulatory risk assessment field. This includes the function expressing risk as 'Risk = Hazard x Exposure'.

Other risk frameworks describe risk as 'Risk = Likelihood x Consequence' (Standards Australia 2018). The OGTR Risk Analysis Framework (OGTR, 2013) adopts this terminology and OGTR's experience is that the likelihood and consequence approach is more suited to biological assessments i.e. the risk assessment of organisms.

Organisms may cause harm in a range of different contexts. Multiple regulatory systems and risk assessment frameworks have been developed to address the risks posed by organisms. These include: biosecurity (quarantine) for pests and diseases of humans, animals, plants, and invasive species; biosecurity (security) for control of weaponisable organisms (e.g. Biological Weapons Convention); biosafety (e.g. containment levels for laboratories and requirements for transport of disease agents); pre- and post-border weed risk assessments; biological control – species specificity, efficacy, pest potential; biopesticides and crop protection products (e.g. *Bacillus thuringiensis* (Bt) formulations for plant protection); and environmental release of live vaccines against disease agents.

GMOs are also subject to regulation requiring risk assessment in most jurisdictions around the world. Genetically modified (GM) plants represent the bulk of GMOs assessed and approved for commercial scale environmental release to date. However there is an increasing number of non-plant GMOs that have either been proposed (e.g. disease resistant poultry, microbes for bioremediation, biocontrol with 'sterile ferals' (e.g 'daughterless' carp), virally delivered fertility control), are in development (e.g. confined field trials of sterile mosquitoes for disease vector control, contained work on microalgae for biomass/biofuel production); or have already been released to the environment (e.g. live GMO vaccines) and/or commercialised (e.g. AquaAdvantage salmon in confinement). There is also ongoing research and development and discussions on the possible implications for risk assessment of synthetic biology and engineered gene drives.

While the objectives and contexts for all of these various regulatory risk analyses/assessments differ, they all have in common that organisms are the subject of risk analysis/assessment because they have the potential to cause harm. However, this common focus on organisms can be obscured by specific contexts (i.e. what is the protection goal or the nature of the harm), history of organisational development and category-specific use of risk terms (e.g. IPPC, 2018). For example, different risk frameworks use different terms for broadly comparable things. (Figure 2, also addressed in OGTR

Risk Analysis Framework[2]). In contrast to chemical risk assessments where harms to the environment, and their significance (e.g. lethality, dose response), may be (relatively) easily defined, for organisms this is less straightforward (Sagoff, 2005) and GMOs are a case in point (Sanvido et al., 2011).

This generic risk assessment framework for organisms (GRAFO) proposes terms and concepts and a set of risk factors that would be applicable to different types of organisms, including but not limited to GMOs, and for different risk contexts. It may be noted that Penk et al (2017) have also proposed a conceptual framework for assessment of novel organisms (invasives, GMOs, synthetic biology) based on trophic interactions, and that the framework described here shares certain features with it.

A specific and practical example of the application of this type of approach is the adoption and adaptation of the post-border weed risk management protocol (Standards Australia, 2006) in the assessment of GM plants (Keese et al., 2014). The post-border weed risk assessment (PBWRA) approach provides a structured and articulated basis for the risk assessment including criteria for likelihood, consequence and harm. OGTR's experience to date is that the potential harms postulated for GM plants are all described within the PBWRA and that the measurable characteristics for prediction of weediness potential are applicable (and have been applied) to GM plants. The OGTR has incorporated the PBWRA approach in documents on the biology of (unmodified) plant species which are used to inform regulatory risk assessments of GM plants (e.g. OGTR, 2017a, 2017b). The PBWRA approach has also informed the OGTR's data requirements for commercial releases of GM plants (OGTR, 2016).

2 Background

Our lives depend upon other organisms for our physical and mental well-being. Nevertheless, organisms can also cause harm, either directly (e.g. pathogens, plague locusts) or indirectly (e.g. as vectors for other harmful organisms such as mosquito vectors of disease-causing viruses or protozoa). Organisms of all three kingdoms (i.e. microbes, animals, plants) may cause harm to people, other organisms or the environment. Generally, plants that cause harm are referred to as weeds, animals that cause harm as pests (including predators of valued species, Richardson et al., 2000) or parasites, microorganisms that cause harm as pathogens. Invasive organisms, are considered to be a major source of risk to biodiversity and ecosystem functioning (Convention on Biological Diversity, 1993; MEA, 2005). The attributes of organisms categorised as weeds, pests, pathogens and invasive species

[2] OGTR's Risk Analysis Framework (2013) also compares terms used - Tables 2.1 and 2.2

have been articulated, as have the types of harms evident in those contexts. An inspection of those attributes, and types of harms from organisms reveals many commonalities, even though the focus of existing risk assessment frameworks is on the specific context – GMO, quarantine, biological control etc. These commonalities derive from the common biology of organisms and their attributes. Similarly, inspection of the various approaches and frameworks for environmental risk assessment and regulation of organisms indicates that there are many commonalities in key issues, concepts and approach, and some similarity of terminology. In particular, it may be noted that in preparing this paper, a significant level of conceptual overlap with invasion biology was evident (e.g. Blackburn et al., 2014; Davidson, 2017). Invasion biology seeks to predict invasions and environmental harmful impacts from alien species (i.e. risk assessment, Keller and Kumschick, 2017), albeit generally not in an 'application driven' regulatory context. Indeed, the convergence of invasive species and GMO risk assessment has been proposed by a number of authors (e.g. Bartz et al., 2010; Jeschke et al., 2013; Penk et al., 2017). A number of the terms used in this discussion paper are the same as or similar to those from invasion biology.

A number of international treaties, agreements and organisations are concerned with the harm to protection goals that may be caused by organisms and have developed standards or guidance for risk assessment and risk management. These include: the World Organisation for Animal Health (OIE, 2004), the International Plant Protection Convention (IPPC) (IPPC, 2016a), the UN Food & Agriculture Organisation (FAO, Codex Alimentarius Commission, 2003) and the World Health Organisation (WHO, 2001), and the Cartagena Protocol on Biosafety under the Convention on Biological Diversity (SCBD, 2000).

Many risk assessment frameworks have been developed for different types of organisms and for different purposes. As noted above, they all share similarities. However, no single widely accepted framework for the risk assessment of organisms has emerged. In invasion biology, for example, there are divergent views over unifying concepts or models (Blackburn et al., 2011; Blackburn et al., 2014; Dick, 2017b; Penk et al., 2017; Vonesh et al., 2017; Gallien et al., 2018; Fournier et al., 2019). Some of the reasons against a single unified framework may include:

- the success and wide adoption of the chemical risk assessment paradigm (USEPA, 1998), which places little emphasis on the relevance of distinct biological and ecological properties of organisms
- the complexity, diversity/variability and plasticity of organisms, and their interactions with the environment

- concerns about organisms vary considerably between people according to differences in values, policies and world-views – different protection and assessment contexts (e.g. location specific considerations, policies on GMOs)
- the use of different biological terms for the same or similar risk related concept (e.g. invasion, infection, colonisation, spread and persistence, naturalisation)
- discrete disciplines for similar risk assessment issues because of different categorisation (cf. Hoffmann and Courchamp, 2016)
- differing legislative requirements, including different protection goals, historical context and terms

To address these issues a generic risk assessment framework for organisms (GRAFO), including a set of generic risk factors, has been formulated with the following objectives:

- to provide a coherent, structured risk assessment framework for organisms that is practical and consistent with national and international best practice in risk analysis (risk management), including AS ISO 31000:2018 Risk management – Guidelines (Standards Australia, 2018) and with methods prescribed by international treaties, conventions and other international guidelines and guidance
- to identify key biological and ecological attributes that are relevant to risk assessment, which are considered useful and general across all types of organisms
- to facilitate communication across disciplines and between different regulatory authorities on risk from organisms
- to ensure OGTR's approaches for ERA are able to deal with new categories of organisms that may be proposed for environmental release in the future – e.g. GM microbes, GM animals, GMOs developed by new techniques (e.g. synthetic biology, genome editing) or GMOs with engineered gene drives.

In the context of these objectives, organisms refer to live and viable biological entities that include plants, animals and fungi, as well as microorganisms such as bacteria and viruses. Risks associated with other types of (non-viable) biological products, such as biological chemicals (including components for organisms), hormone and growth regulators, blood products, enzymes and vitamins, plant extracts and non-viable microbial products, are outside the scope of this framework.

3 Concepts and terms

The clear definition and usage of terms is important to distinguish between different issues and concepts and ensure clarity in communication, particularly where similar terms are used in different

contexts (Norman, 2002; Hodges, 2008). This also applies to risk analysis (and the development of OGTR's RAF has sought to ensure clarity of terms and their usage).

The risk related concepts and terms used in this document are based on AS ISO 31000:2018 Risk management - Guidelines (Standards Australia, 2018). Nevertheless, the interpretation and application of some key terms (risk, harm and vulnerability) are described in more detail below. As noted above, a number of terms are borrowed from other disciplines, such as invasion biology.

Risk is a widely used term with many variations in meaning. Generally, risk arises from an activity (e.g. driving a car) where there is potential for an undesirable outcome (e.g. accident). Therefore, risk relates to the effect of uncertainty (e.g. the possibility of an accident) on an objective or goal (e.g. arriving at a specified destination). Although the consideration or discussion of risk is often restricted to negative outcomes, outcomes may also be neutral or positive (Schlaepfer, 2011).

In addition, it is useful to distinguish two perspectives of risk that are relevant to risk assessment; one refers to the nature of risk, while the second refers to the level of risk.

The nature of risk can be described in relational terms (Boholm and Corvellec, 2011) with three essential elements (see also Figure 1), namely:

1. **risk source** (sometimes referred to as a hazard or stressor) – a progenitor of potential harm (which for the purposes of this document is an organism that is subject to risk assessment, regulation, and/or control measures).
2. **risk recipient (**a person or valued component of the environment) which may be harmed
3. **a causal linkage or pathway** between 1 and 2 – events or sets of circumstances required for **harm** to occur to the risk recipient because of the presence of the risk source.

For example, Hendra virus (element 1, risk source) that has the potential to cause life-threatening illness in people (element 2, risk recipient) through spread and persistence of Hendra virus in bat populations, followed by transmission to horses and then to a person who comes in contact with an infected horse (element 3, causal linkage).

In contrast to the nature of risk, the level of risk (Kaplan and Garrick, 1981) is derived from a combination of consequences (seriousness of harm, e.g. severity of disease or death of people infected by Hendra virus) and likelihood (chance that harm occurs, e.g. the probability of the causal pathway resulting in disease in people infected by Hendra virus occurring). In addition to this analytical approach, intuitive responses, which can vary between people, also play an important role in perception of the level of risk (Slovic, 1987; Slovic et al., 2004).

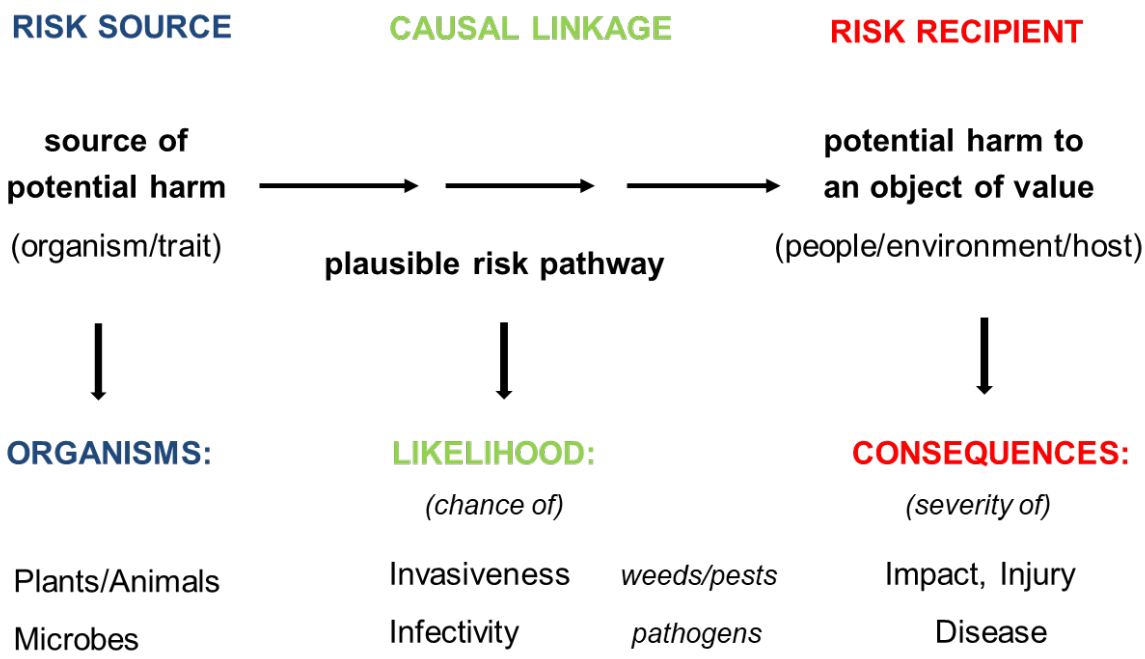

Figure 1 Risk of organisms in relational terms

Harm (adverse effect/negative impact) is an undesirable change to the health of people, environment, economy or social amenity. Harm is characterised as some form of damage, injury or illness to a valued object or process (risk recipient). In some cases a valued object or process may be described as a protection goal or ecosystem service. For the purposes here, consideration of harm is restricted to the health of people and the environment.

Importantly, attribution of harm involves a value judgement informed by individual and societal values. For example, intentional death of an organism may or may not be considered harmful: death of a person is usually considered harm, but not the death of a malarial parasite or pest animal. It may be noted that legislation (worldwide) generally places a priority on human protection.

Therefore harm is context dependent and can be difficult to define or determine. For example, organisms that are widely accepted as desirable and worthy of protection may not accord with actual practices or higher order values. One case is that of the honey bee (*Apis mellifera*), which is highly valued for honey production, pollination of obligate outcrossing crops, and a potential source of therapeutics (e.g. possible antimicrobial properties of honey, royal jelly or propolis). Society nevertheless 'allows' many activities that are detrimental to the presence of bees, including broad-acre planting of monocultures of wind-pollinated crops that do not satisfy the nectar requirements of bees, or the application of pesticides to crops to control pests but that will also be toxic to non-target

organisms such as bees. In addition, the honey bee is an introduced species in Australia and may be considered as having a detrimental environmental effect on the presence of native bee species (e.g. NSW Threatened Species Scientific Committee, 2002).

Furthermore, organisms that are widely accepted as undesirable in one place (e.g. rabbits in Australia) may be valued in other circumstances (e.g. rabbits kept as pets, or in their natural range in Spain). Consequently, organisms may be considered desirable, undesirable and/or neutral depending upon the intended management goals, context, location, time and circumstances. Goats, pigs and olive trees provide other examples of organisms that are considered desirable when intentionally farmed, but may be considered undesirable when present in natural environments (e.g. Besnard and Cuneo, 2016). In addition, one harmful outcome can sometimes give rise to further downstream harms. For example, increased harms from weeds, pests, parasites or pathogens can lead to loss of biodiversity.

Environmental values can be contentious, however the environmental values and protection goals should be acknowledged and specified in a risk assessment. This helps frame the assessment to address whether or how the environmental values might be negatively impacted, including guiding the design of experiments or identification of information necessary for the assessment (Sanvido et al., 2012; Raybould and Macdonald, 2018). A risk assessment should ideally specify the outcomes that are considered harmful (Bartsch et al., 2009; Bartz et al., 2010; Heink et al., 2012; Devos et al., 2015; Dolezel et al., 2018; Raybould and Macdonald, 2018) taking into consideration acceptable management practices, protection goals or ecosystem services[3]. Clear articulation of the risk recipient is also important in identifying the nature of potential harm, and the concept of an 'assessment endpoint' (as used in the problem formulation approach for ERA of chemicals) may be helpful in this regard. An assessment endpoint is normally defined as an explicit expression of the environmental value to be protected, comprising an ecological entity (e.g. a particular species) and its attributes (e.g. its fecundity and recruitment, and amenable to measurement) (USEPA, 1998, 2016).

International standards (such as the International Standards for Phytosanitary Measures (ISPMs) (IPPC, 2016b), the Terrestrial Animal Health Code (OIE, 2017b) and Aquatic Animal Health Code (OIE, 2018), and national health and environmental legislation (Sheppard, 2016) can provide guidance on the values or entities to be protected from harm, including endangered, protected or iconic species or habitats. More specific consequence criteria may be derived from societal norms or

[3] Ecosystem services: the benefits provided to humans through the transformations of resources (or environmental assets, including land, water, vegetation and atmosphere) into a flow of essential goods and services e.g. clean air, water, and food (Costanza et al., 1997; DEWHA, 2009).

based on undesirable impacts from organisms categorised as weeds, pests, parasites or pathogens (Thorp, 2000; Standards Australia, 2006, 2010; Department of the Environment, 2013; Department of Environment & Energy, 2018).

For example, the Australian post-border weed risk management protocol (Standards Australia, 2006) specifies six categories of harm from weeds, including:

- reduced establishment of desired plants;
- reduced yield or amount of desired vegetation;
- reduced quality of products or services;
- restricted physical movement of people, animals, vehicles, machinery and/or water;
- reduced health of animals and/or people; and
- negative effects on environmental health (e.g. providing food or shelter to pests or pathogens, adverse changes to fire regimes, adverse changes to nutrient levels, increased soil salinity, reduced soil stability, or lowered soil water table levels).

Vulnerability is often considered to be an important concept in risk analysis, but there is no consensus on its definition and application (Haimes, 2009; Aven, 2011; Yellman and Murray, 2013). Vulnerability is usually described in terms such as 'the degree to which a system is susceptible to, and unable to cope with, injury, damage or harm' (De Lange et al., 2010). For example, people's vulnerability to influenza is a combination of susceptibility to infection (i.e. entry, establishment, replication and spread of the influenza virus) and sensitivity to harm from disease symptoms (e.g. tissue damage from fever) that result from the presence of the virus. A description of a cohort as vulnerable to influenza may refer to people who are either more prone to infection and/or attendant disease (e.g. immunocompromised people) or suffer more severe symptoms and disease impacts (e.g. older people or young children).

In this regard, there is close similarity between vulnerability and risk, where susceptibility equates to likelihood and injury/damage equates to consequences. The main difference is that risk is constructed from the perspective of the risk source i.e. the object that gives rise to potential harm, whereas vulnerability is viewed from the perspective of the risk recipient, the object that may be harmed. Therefore, vulnerability and risk can be seen as two sides of the same coin, namely, potential harm arising from the complex and dynamic interactions of an organism (risk source) with its environment/host (risk recipient) It may also be noted overall disease risk is expressed as a combination of the incidence (related to likelihood – the presence of the pathogen and susceptibility to infection) and severity of disease (related to consequences) (Seem, 1984).

While De Lange et al (2010) used the term vulnerability in relation to ecological risk assessment of chemicals, the same concept and terminology is also used in relation to risk assessments of organisms. For example, the terms vulnerability and invasibility (and corresponding term invasiveness) have been widely used in invasion biology to denote the susceptibility of an environment to invasion (e.g. Lonsdale, 1999; Milbau and Nijs, 2004; Richardson and Pyšek, 2006; Catford et al., 2012; Hui, 2016). The term susceptibility is widely used in disease biology in an analogous way.

Resistance is a term often used in relation to disease but may be more generally applied as the quality or ability of a risk recipient to not be susceptible to the risk source. It is thus related to the vulnerability of an environment to harm. This might be in terms of resistance to infection by a pathogen (e.g. the microbe cannot establish in a host), an insect is unaffected by a plant toxin, or qualities of an environment which prevent establishment of an organism. This concept has been used in invasion biology to describe the intrinsic abilities or attributes of native species (e.g. competitive ability), heterogeneity, and biotic and abiotic properties (often termed biotic and abiotic resistance) of an ecosystem to resist invasion (see Lonsdale, 1999; Von Holle and Simberloff, 2005; Menke and Holway, 2006; Melbourne, 2007; Richardson et al., 2011).

Resilience is also related to vulnerability (De Lange et al., 2010). However, resilience is usually restricted to consideration of tolerance to, or recovery from, injury/damage, namely the consequences dimension of risk. It might also be considered in terms of reversibility of impact, in that the environment overcomes the adverse effect. Ecology and invasion biology also use the term resilience– the ability of native ecosystems or species to recover from disturbance of the environment (see Lonsdale, 1999).

Resistance may be seen as pre-harm attributes of an environment or organisms that prevent establishment of, or harm from, organisms whereas resilience may be considered as post-harm attributes which enable recovery from harm.

Invasiveness *and* ***infectivity*** – in order for an organism to cause harm to other organisms and/or the environment it needs to be present, i.e. invade or infect the environment or host. These terms are used in this document as they are used in invasion (e.g. Marco et al., 2002) and disease biology (e.g. Casadevall and Pirofski, 2000) - to represent the abilities of organisms to establish, survive and spread in an environment, and their use is distinct from considerations of harm. These concepts are discussed further below.

4 Risk assessment

Risk assessment is a structured, reasoned approach to consider the nature and level of risk using scientific/technical evidence and taking into account and addressing uncertainty. Risk assessment of organisms is widely used in regulatory decision-making, e.g.: GMOs; biosecurity; biological control agents; invasion and conservation biology; and prioritisation in natural resource management. The focus of this risk assessment framework is environmental risk assessment of organisms rather than risk assessment of organisms in containment (e.g. laboratory, glasshouse, animal house). However, the principles can also be applied to containment requirements.

Despite a plethora of terms and methods, risk assessment typically encompasses three general processes or steps (Figure 2).

1. **Risk identification** (hazard identification, problem formulation) – examines the nature of risk based on decision-making/management requirements and attributes of the risk source or risk recipient that are relevant for identifying substantive risk.
2. **Risk characterisation** (risk analysis, risk profile, risk calculation) – assessment of risk in terms of consequences (seriousness of harm) and likelihood (chance that harm occurs).
3. **Risk evaluation** (risk estimate, risk acceptability) – combines the consequences and likelihood assessments to estimate the level of risk and establish the degree of concern and/or need for control measures to mitigate or reduce risk.

Risk Identification

Risk identification describes what could go wrong and how it could go wrong. Some of the considerations may include:

- establishing the context for the risk assessment (planning, preparation, scoping, terms of reference) to provide the ground rules and scope for conducting the assessment
- describing the factors that could give rise to risk, including the type of potential harm (hazard characterisation)
- postulating a risk model (exposure assessment, conceptual model, risk scenario, risk hypothesis) to describe the nature of risk
- developing a plan to characterise risk.

Risk identification may be an iterative process, e.g. gathering information on the characteristics of the risk source (i.e. the organism) can help to identify the components of the environment (risk recipient) that might be at risk and the environmental effects and causal pathways that might be

involved (Norton, 1992). Likewise, knowledge of the receiving environment can help identify relevant risk recipients (e.g. at the level of individuals, populations, communities) (Norton, 1992).

Establishing the risk context, or problem definition, is important but often overlooked as a discrete activity in risk assessment (e.g. it may not be explicitly questioned or described but left to implicit assumptions). Articulation of the risk context aids transparency of the risk assessment by describing the purpose, scope and parameters of the assessment. These parameters may include: the objective, including protection values and goals; the nature of the decision; requirements under national legislation; obligations under international treaties; organisational practices and processes; policies and guidelines; methodology and criteria to determine the level of risk; current or past activities with the organism; existing and proposed control measures; and/or relevant findings from previous assessments, feedback or monitoring mechanisms.

One of the difficulties for assessing risk from organisms lies in the complexity of their biology and the multitude of ecological interactions. Nevertheless, consideration of practical experience and the literature can indicate certain attributes of organisms (risk source) or the environment/host (risk recipient) that correlate with higher risk. The most significant attributes relate to greater establishment, spread and persistence of the risk source and/or increased seriousness of harm to the risk recipient. These attributes can then be used to postulate a risk model(s) or scenario(s) to describe the nature of risk and the pathway(s) to harm (Figure 1, 2). This process is also often described as problem formulation (particularly for ERA of chemicals, USEPA, 1998), and problem formulation terminology has also been advocated for GMO risk assessments (EFSA Panel on Genetically Modified Organisms, 2010; Wolt et al., 2010; Sanvido et al., 2012; Tepfer et al., 2013). Risk assessment of potential new pathogens of wildlife from biological invasions has also been framed using problem formulation terminology (Roy et al., 2017).

Articulating plausible pathways to harm has been highlighted in problem formulation literature for GMOs (e.g. Raybould, 2011) and chemicals (e.g. Norton, 1992) as well as guidance for pest risk analysis (IPPC, 2016a). The pathway concept is also important in invasion biology (e.g. Williamson, 2006; Blackburn et al., 2011; Hulme, 2015; McGeoch, 2016) and a number of stages have been articulated: transport; introduction/colonisation; establishment; landscape spread (e.g. Williamson, 2006; Blackburn et al., 2011; Roy et al., 2017) with some authors arguing that impact should be considered as a separate stage (e.g. Theoharides, 2007; Lockwood, 2013; Downey, 2016). The concept of ‘adverse outcome pathways’ utilised in ecotoxicology of chemicals (e.g. Ankley et al., 2010) may also be informative for ERA of organisms. Adverse outcome pathways describe and

consider the linkages and dependencies from an initiating event to a level of organisation relevant to risk assessment (e.g. individuals, populations, communities).

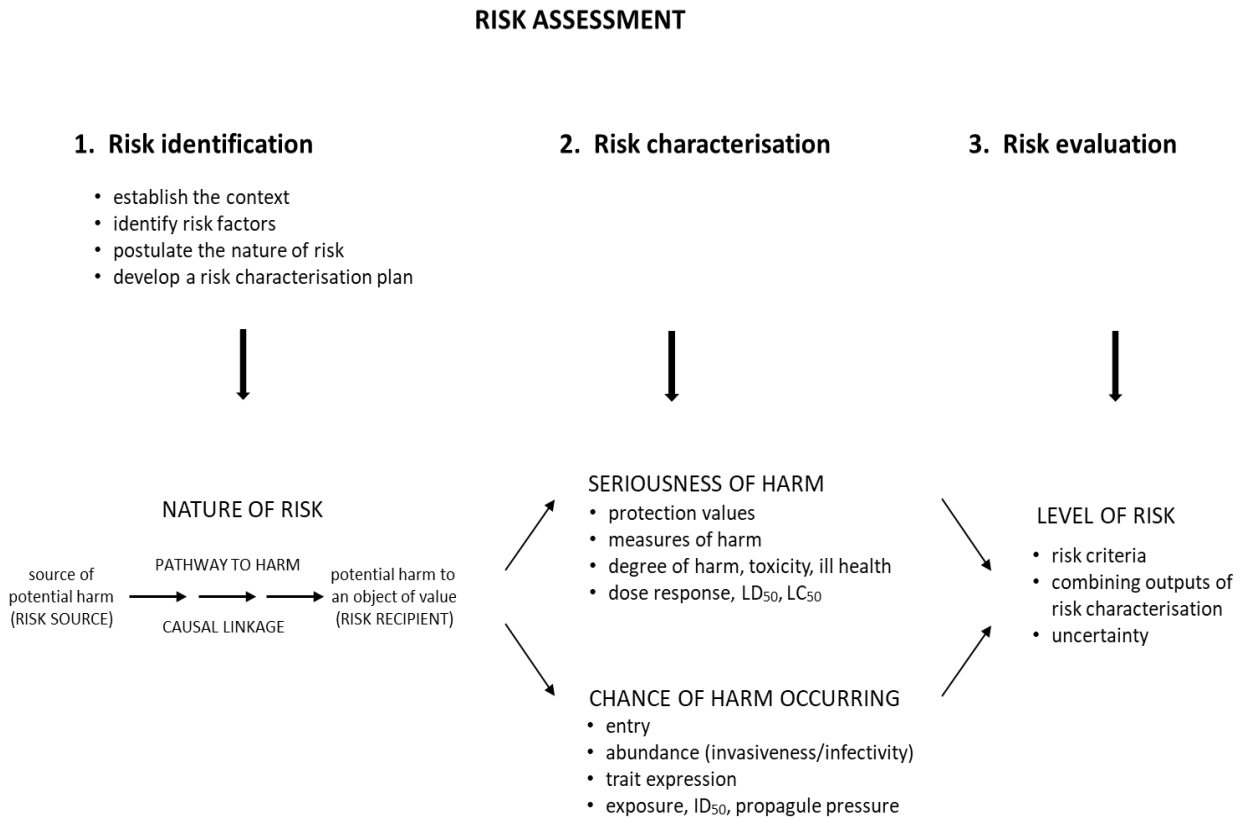

Figure 2 Conceptual steps and terminology used in risk assessment. (A comparison of analogous terms used in other risk assessment frameworks is presented in Table 1.)

The risk model takes into account the values (protection goals/ecosystem services) in order to identify potential harm to people or a desirable (valued) entity. To determine if these values are adversely affected the risk model expresses those values in observable, measurable terms. In addition, the risk assessment should specify the degree of change to protection goals that is considered significant to assess the seriousness of harm (OGTR, 2013; Blackburn et al., 2014; Devos et al., 2015).

Table 1 Comparison of terms used to describe components of risk assessment in GRAFO and other risk frameworks

TERMS USED IN GRAFO	RELATED TERMS DESCRIBED IN OTHER RISK FRAMEWORKS
Risk identification	**Hazard identification, Problem formulation**
Risk context	Protection goals, values, Planning, Scoping, Problem definition
Postulate the nature of risk	Conceptual model, risk model, risk hypothesis, risk scenario

TERMS USED IN GRAFO	RELATED TERMS DESCRIBED IN OTHER RISK FRAMEWORKS
Develop a risk characterisation plan	Analysis plan
Risk source	Hazard
Pathways to harm	Exposure, events, sets of circumstances
Risk recipient	Assessment endpoint
Risk characterisation	**Risk analysis, Risk profile**
Seriousness of harm	Consequences, hazard assessment
Measure of harm	Measurement endpoints, measures of effect
Chance of harm occurring	Likelihood, exposure assessment
Risk evaluation	**Risk estimation, Risk acceptability, Risk calculation**

The concepts of an assessment endpoint and measures of effect (cf. problem formulation terminology, USEPA, 1998, 2016) may be useful in this context. An assessment endpoint is an explicit expression of a valued environmental entity and its attributes (e.g. pollinator abundance). Measures of harm (measurement endpoints, measures of effects) are measureable characteristics related to, and able to detect or predict effects, on the assessment endpoint. Specific studies or observations of the measures of harm may be chosen to estimate harm to the valued entity. These measures of harm can serve as the endpoint in assessing risk models.

Risk characterisation

The information prepared during risk identification is used in risk characterisation. Some common approaches for developing a plan to characterise risk include: directly scoring certain biological or environmental risk factors, with the scores combined to determine the overall risk; developing simple risk models for individual risks based on the most important risk factors; or developing a complex risk model (e.g. a Bayesian network, Monte Carlo simulation) that captures the interactions of multiple risk pathways.

The simple depiction of the nature of risk in Figure 1 can mask complex, conditional pathways that link a risk source to the risk recipient. More detailed risk pathways may be developed using techniques such as Bayesian networks, decision trees, fault tree analysis, event trees, or concept maps (Hayes et al., 2004; Standards Australia, 2013). In addition, alternative approaches may be used to

generate a risk model such as multi-criteria decision analysis or strategic foresighting (Cook et al., 2014).

Risk characterisation considers the consequences (dose response (e.g. lethal dose, LD_{50}, lethal concentration, LC_{50}), hazard characterisation, impact) and likelihood (exposure (including infectious dose, ID_{50}), probability, conditional probabilities i.e. the probability of an event A, given that another event B has already occurred) of risk.

The likelihood that harm occurs from the presence of an organism is a combination of the probabilities of several events or steps in a pathway occurring, including:

- the arrival of an organism at a location or region of interest (entry, establishment)
- abundance of an organism (or some undesirable 'passenger' organism), which arises from spread and persistence of an organism (invasion/infection)
- expression of a particular characteristic of an organism that gives rise to harm (effect trait)
- interaction of an organism or trait[4] with people or other desirable components of the environment (exposure).

In order to ensure clarity in risk assessment it is useful to have terminology that distinguishes between likelihood (e.g. of the presence or abundance of an organism), consequence (e.g. environmental impacts from the organism) and overall risk (OGTR, 2013). The terms invasion and infection are colloquially used in a pejorative sense connoting harm and are sometimes used as the sole proxy for determining likelihood when estimating the level of risk from an organism (Standards Australia, 2006), and/or alien (invasive) species (Simberloff, 2005). However for the purposes of this paper (and in other literature) they are also used in the sense of presence and spread with authors arguing that consequent harm/impact should be treated separately from presence/abundance (Parker, 1999; Casadevall and Pirofski, 2003; Sagoff, 2005; Theoharides, 2007; Kumschick et al., 2012; Lockwood, 2013; Blackburn et al., 2014) and abundance is not always directly correlated with impact (Sofaer, 2018). Similarly, the term 'invasive' plant or animal is frequently used to encompass harm caused by such organisms, however Richardson et al (2000) noted that there are well established terms for harmful species (whether native or alien) – weeds for plants and pests for all kinds of organisms. Interestingly, the IPPC (IPPC, 2018) has adopted the term 'pest' as "any species, strain or biotype of

[4] For GMO environmental risk assessment, the importance of considering the biology of the organism, the introduced trait, the receiving environment and the interaction between them was articulated by the OECD (OECD, 1993).

plant, animal or pathogenic agent injurious to plants or plant products", thus encompassing organisms from all three kingdoms that are considered to cause harm.

The interaction of the risk source with the risk recipient and the environment as a conceptual framework to inform modelling, prediction and risk assessment in invasion and disease biology and for GMOs has been represented as a triangle. The 'disease triangle' presents disease as the result of interactions of pathogen, host and environment, and was first articulated in plant pathology but the concept has been extended to human and animal disease (Scholthof, 2007; Gurr et al., 2011; Turner, 2011; James et al., 2015). The explicit addition of time as a fourth parameter (ie a disease pyramid) has also been suggested (Allen, 2012). Similarly, the 'invasion triangle' consists of invader attributes, site biotic characteristics (including resident organisms) and site environmental conditions (Perkins et al., 2011). Interestingly, also in invasion biology, interactions of (invasive) species traits, regional characteristics (sites) and pathways for assessing invasion risk (Essl et al., 2015) have been represented using a triangle (McGeoch, 2016). Application of the disease triangle concept has also been advocated for considering biological control, comprising the control organism, host and environment (McEvoy, 2018). For GMO risk assessment, OECD guidance has stressed the importance of considering the biology of the unmodified organism, the introduced trait (i.e. genetic modification), the receiving environment and the interaction between them (OECD, 1993).

Risk evaluation

Risk evaluation establishes the degree of concern, which will inform whether or not there is a need for risk treatment measures. Some of the considerations may include:

- criteria for establishing the level of risk (risk acceptability, potential interactions of risk, feasibility of controls etc.)
- estimating the level of risk from the outputs of the consequence and likelihood assessments
- significance of residual uncertainty.

The degree of concern is expressed in terms such as: negligible, low, moderate, high risk (e.g. OGTR, 2013; Downey, 2016); articulation of the magnitude of the impacts (e.g. Blackburn et al., 2014); acceptable, tolerable, unacceptable risk (e.g. Hunter, 2001); or appropriate level of protection (ALOP) (WTO, 1995).

Three commonly used approaches to evaluate risks from organisms may be described:

1. The risk relevant attributes of the risk source and risk recipient are scored and the total score used directly in the decision making process (pre-border weed risk assessment as per (Pheloung et al., 1999).
2. The likelihood and consequence assessments from individual risk scenarios are combined using a risk matrix to derive a qualitative estimate of the level of risk (e.g. import risk analysis as per DAWR, 2016).
3. The probabilities (likelihood) of specified outcomes (consequences, harms) are determined quantitatively from a network of causal pathways (WHO/FAO, 2008, 2009; Standards Australia, 2013).

In addition, risk evaluation should consider the nature and level of uncertainty. Uncertainty is an intrinsic part of risk and is an integral part of risk identification and risk characterisation. Some typical measures to address uncertainty in risk assessment include:

- establishing parameters for data quality;
- obtaining additional data;
- identifying and correcting errors;
- applying conservative estimates and/or safety factors;
- using upper and lower bounds of estimates; refining models; using expert opinion;
- providing clear definitions and interpretations of key terms;
- re-evaluating outcomes against objectives, scope and risk criteria; and/or
- considering risk perception issues such as heuristics and biases.

Nevertheless, there always remains some degree of residual uncertainty regarding the overall level of risk, which may warrant higher tier uncertainty analysis (e.g. sensitivity analysis or meta-analysis) or additional control measures to manage risk.

It may be concluded that all risk assessments of organisms share a common purpose that seeks to identify, characterise and evaluate risk (Figure 2). The nature and level of risk is strongly shaped by particular factors, including: the abilities (traits) of organisms to establish, reproduce and disperse; as well as contingencies that arise from complex and dynamic interactions of an organism with its environment. Such factors are widely used in risk assessment of any type of organism. Nevertheless, the type of analysis and degree of effort used in each stage of the risk assessment should be commensurate with the level of risk and importance of the decision (Keeney, 2004). The concept of proportionality is also relevant to risk management (including measures recommended or required) and/or regulatory burden should be proportionate with risk (OECD, 2010). For example, the World

Trade Organisation's Sanitary and Phytosanitary (WTO SPS) agreement requires that measures imposed should be scientifically justified to achieve a country's ALOP (WTO, 1995). A country's ALOP should be clearly articulated and may be in legislation, a standard or a national policy. Similarly, the intergovernmental Gene Technology Agreement states that the Australian gene technology regulatory scheme should ensure that regulatory burden is commensurate with risks (GTMC, 2008).

5 Concepts for risk factors for organisms – invasiveness/infectivity and harm

Attributes of the risk source (organism) and risk recipient (receiving environment or host, including potential responses) are both important for determining key factors associated with predicting, risk that might result from organisms. Generic risk factors (i.e. identified based on the common biological and physical attributes of, and harms caused by. organisms, and of the environment) would be of utility to support risk assessments to predict the likelihood and consequences of harm posed by organisms.

Invasiveness / infectivity

The likelihood of harm occurring from organisms is related to the presence and abundance of the organism under consideration (Keller et al., 2011; Garnier, 2012; Strayer, 2012). Abundance of an organism is the result of its ability to establish, grow, reproduce, disperse and survive/persist over space and time. Abundance also describes the density of a population.

As noted earlier, the terms invasiveness (plants and animals) or infectivity (micro-organisms), are sometimes used as indicators of harm but that it is important to distinguish between presence/abundance and harm. Mutation, and/or selection of genetic variants in a population (i.e. mutations) also contribute to an organism's ability to survive over time. However, the characteristics of the organism are also subject to influences of other organisms and the abiotic environment. Ricciardi and Cohen (2007) note that the use of the term 'invasive' in a policy context necessarily implies harm (e.g. international discussions under the CBD about control of invasive alien species), but that in the scientific context of invasion biology the same term relates to rate and scale of colonisation and spread with harm considered separately, and that invasiveness is not necessarily predictive of impact. There are examples where the harm caused by an organism is disproportionate to its abundance, as evidenced by example of the functional responses of predators on prey in the environment (e.g. Paterson et al., 2013; Paterson et al., 2015).

For the purposes of this framework, the terms invasiveness and infectivity are limited to the presence and abundance of an organism, not necessarily the occurrence of harm. While each of these terms are

commonly used in a pejorative sense, implying that the presence/existence of the organism is of itself an undesirable outcome is not necessarily the case. Only when the organism causes harm is there concern. Infection may be used to describe a process leading to pathogenesis or to mutualism/symbiosis (e.g. nitrogen fixing rhizobia that infect legumes to establish root nodules (Soto et al., 2006). Establishment through invasion or infection is nevertheless a part of the pathway to harm. Disease biology sometimes makes the distinction between infection and colonisation, and the terms infection and infectivity are used to describe the ability to establish and impact (severity) of disease dealt with separately (e.g. Casadevall and Pirofski, 2000).

There is a considerable body of literature from the disciplines of invasion biology, ecology and biological control that traverses similar conceptual issues, despite definitional and terminological differences (see Richardson et al., 2011 for invasion biology terms and concepts). While it is not practicable for this paper to attempt an exhaustive synthesis of that literature, it may be concluded that familiarity with the concepts developed for invasion biology would be of benefit to risk assessors of organisms in many other contexts. Invasion biology also uses the terms invasibility, resilience, resistance (e.g. Miller AL, 2014) and susceptibility.

Traits, characteristics of the organism – risk source

ERA of GMOs includes a focus on the genetic modification (genotype) and the traits that such modifications confer on the GMO and whether they result in novel phenotypes which might lead to harm to the environment. Similarly, in other fields of risk assessment of organisms there has been a focus on identifying traits that predispose the organism to establish and ultimately cause harm. Examples include invasion biology (e.g. Milbau and Nijs, 2004; Blackburn et al., 2009; Pyšek et al., 2012; Moravcová et al., 2015; Lodge et al., 2016; Lembrechts et al., 2018) and infectious diseases (e.g. Casadevall and Pirofski, 2009; OECD, 2011) and parasites (e.g. Cable et al., 2017; Ghosh et al., 2018). There has also been attention to identifying invasiveness traits across various taxa (e.g. Kumschick and Richardson, 2013; Davidson, 2017; Emiljanowicz et al., 2017). Traits considered important for invasiveness have formed the basis for scoring systems for the assessment of weed potential of plants (e.g. Pheloung et al., 1999; Standards Australia, 2006; Virtue et al., 2008) and invasive potential of animals (Williams, 2010).

Traits, characteristics of the environment – risk recipient

Invasion biology also frames the stages of the invasion pathway (described earlier) with barriers to be overcome by the invader including geography, captivity/confinement/cultivation, survival (post-escape), reproduction, dispersal, environmental (e.g. Blackburn et al., 2011; Catford et al., 2012; Lockwood, 2013). The magnitude of such barriers or resistance to the organism determine the level

of vulnerability of the environment. Thus traits of the organism (risk source) and of the environment (risk recipient) may relate to vulnerability to harm, resistance to harm and resilience from harm.

Harm – interactions between risk source, risk recipient and environment

Interactions between the traits of organisms and the receiving environment ultimately govern the abundance of the organism and resultant harms (e.g. OECD, 1993; Warren II et al., 2012; Barney et al., 2016; O'Reilly-Nugent, 2016; Ghosh et al., 2018; Lembrechts et al., 2018). As already noted, only when the organism causes harm is there concern. A pathogen may be highly infectious but nevertheless not result in severe disease (e.g. the common cold) or conversely not particularly infectious but result in significant harm to the host.

When the characteristics of the risk recipient and/or environment and their interactions change, organisms whose presence is normally considered benign may become harmful, as exemplified by opportunistic pathogens (e.g. Price et al., 2017). For example, *Escherichia coli* is an abundant commensal organism present in the gut of many animals, including humans. Generally, its abundant presence in the gut may not be considered harm (Conway and Cohen, 2015). However there are distinct pathotypes of *E. coli* that can cause disease (Sousa, 2006). When people come into contact with a strain of *E. coli* that expresses certain toxins (e.g. enterohemorrhagic *E. coli* O157:H7) harm is manifested as illness and can even result in death. Presence of *E. coli* in the environment may indicate presence of other faecal pathogens (NHMRC and NRMMC, 2011). Conversely, due to mutation and recombination some *E.coli* strains are adapted to be free-living and their presence in the environment does not represent faecal input or harm (Power et al., 2005).

Risk from organisms depends not only on the presence of the organism (risk source) but also harm (injury, ill health) to desirable components of the environment (the risk recipient) that may arise from exposure to the organism. Organisms may cause a broad range of adverse effects. Harm may be mediated by the presence of the organism (via its phenotype) directly (competition, predation, herbivory, disease, parasitism, biophysical damage) or its properties or traits (e.g. production of toxins). Harm is also determined by the interaction of the organism with the environment/host. In the case of GMOs the introduced trait (phenotype conferred by the genetic modification) is one of the key risk assessment considerations, together with the interaction with the biology of the unmodified organism and environment (OECD, 1993). In assessing the level of risk posed by an organism it is important to consider the impact. A classification of invasive species on the basis of level of impact has been proposed, including with different impact classes (Blackburn et al., 2014). Weed risk assessment protocols are often framed around categorisation of the potential impacts of the plant (e.g. Randall, 2017).While potential harms have been presented in four overarching risk factors, it is

obvious that harms could be categorised in finer detail. For example, Blackburn et al (2014) propose a greater number of 'impact mechanisms' and 'impact classes' for invasive species, though each of these may be subsumed into the four harm categories proposed in this paper.

In the case of biological control, a significant consideration is the host range of control agents (e.g. van Lenteren et al., 2006; Barratt, 2011; Barratt et al., 2016; Van Driesche and Hoddle, 2017) which are traits/attributes of the organism under assessment, though related to potential harm rather than invasiveness/infectivity *per se*.

6 Proposed generic risk factors for ERA of organisms

Three classes of risk factors for organisms are proposed based on the concepts articulated above – Invasiveness and infectivity I-1 – I-8), Harm (H-1 – H-4) and Harm Mitigation (M-1, M-2). The risk factors are outlined below and summarised in Tables 2, 3 and 4 respectively. Figure 3 illustrates how the proposed risk factors relate to interactions between the abilities and attributes of an organism (risk source) and the attributes of the environment or host (risk recipient).

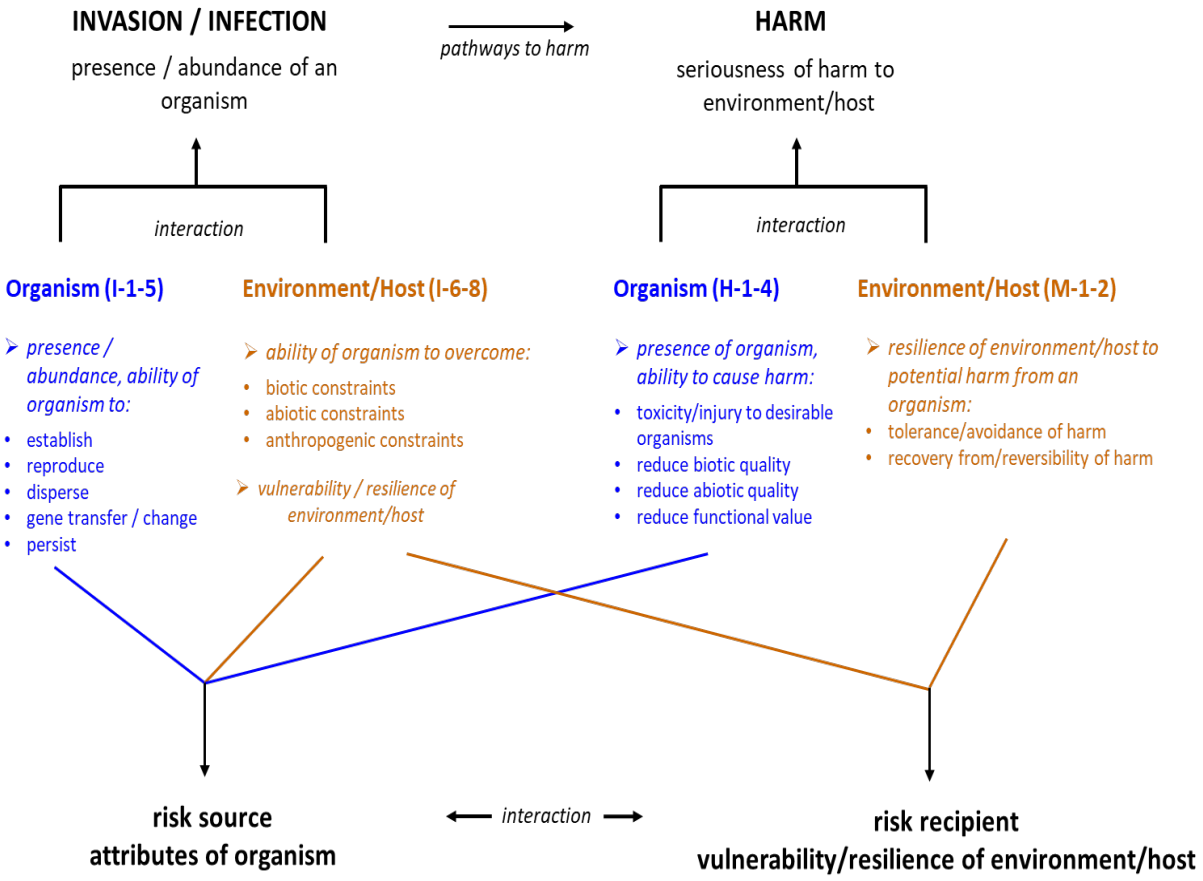

Figure 3 Biological and environmental factors relevant to the risk assessment of organisms.

A diagrammatic representation of the relationship and interaction between generic attributes of organisms and the environment or host that underpin the generic risk factors for Invasiveness and infectivity (I-1 – I-8), Harm (H-1 – H-4) and Harm mitigation (M-1, M-2).

6.1 Invasiveness / infectivity: Proposed risk factors I-1 to I-8

Eight risk factors are proposed that relate to the invasiveness and/or infectivity characteristics (traits) of organisms (summarised in Table 1). Invasion/infection by organisms is determined by interactions between the organism and the environment or host.

Five risk factors (I-1 to I-5) relate to specific intrinsic attributes of the risk source (the organism), namely establishment, reproduction, dispersal, gene transfer & genetic change, and persistence of the organism. The remaining three risk factors (I-6 to I-8) relate to the risk recipient (in the receiving environment) that restrict or facilitate the presence of the organism, namely, biotic, abiotic and anthropogenic constraints and the abilities of the risk source organism to overcome these constraints.

These, or analogous, characteristics of organisms are also detailed in risk assessment guidance relevant to GMOs and other organisms e.g. OECD for GMOs (OECD, 2006) and IPPC for pests and diseases (IPPC, 2017b) and biological control agents (IPPC, 2017c).

A focus on identifying invasive traits is evident in invasion biology research (e.g. Blackburn et al., 2009; Pyšek et al., 2012; Moravcová et al., 2015). For plants the use of functional traits[5] and responses for predicting invasiveness has been proposed (e.g. Drenovsky et al., 2012; Díaz et al., 2013; MacKinnon et al., 2014; Schwartz et al., 2015; Bourgeois et al., 2019). Functional traits may be split into effect traits (determining effects on the environment whether or not the trait confers an adaptive advantage) and response traits (influence the organism's ability to colonise, thrive, persist in the environment) (Díaz et al., 2013; Nock et al., 2016). A similar concept, functional feeding traits, has been investigated for prediction of alien fish invasiveness (Nagelkerke et al., 2018). However many authors note that the complexity of environmental interactions means a universal suite of predictive attributes is unlikely (Tecco et al., 2010; Van Kleunen et al., 2010). There is some overlap between the risk factors proposed here and the terms used in six stage invasion schemes (Catford et al., 2009).

[5] Various definitions of 'functional traits have been proposed, for example: "readily measurable morphological, chemical, physiological and phenological attributes of plants that interact with surrounding biotic and abiotic factors" (Drenovsky et al., 2012); and morphological, biochemical, physiological, structural, phenological, or behavioral characteristics that are expressed in phenotypes of individual organisms and are considered relevant to the response of such organisms to the environment and/or their effects on ecosystem properties" Díaz et al (2013).

Disease biology also focuses on traits of pathogens that determine infectivity and/or impact, variously referred to as virulence factors (e.g. Cao et al., 2001; Surico, 2013), pathogenicity factors (OECD, 2011).

Table 2 Risk Factors I-1 – I-8: Invasiveness / Infectivity

	Risk Factor	Attribute	Explanation
Risk source (organism)	I-1	Establishment	Organism's ability to establish in the environment or host
	I-2	Reproduction	Organism's ability to reproduce in the environment or host
	I-3	Dispersal	Organism's ability to disperse / spread in the environment or to hosts
	I-4	Gene Transfer & Genetic change	Organism's ability to transfer genes to other organisms in the environment, and capacity for genetic change
	I-5	Persistence	Organism's ability to persist in the environment or host
Risk recipient Vulnerability & Resistance to invasion / infection	I-6	Biotic constraints	Organism's ability to tolerate / overcome biotic constraints
	I-7	Abiotic constraints	Organism's ability to tolerate / overcome abiotic constraints
Constraints of the receiving environment on the organism	I-8	Anthropogenic constraints	Organism's ability to tolerate / overcome constraints from human activity

Risk Factor I-1. What is the organism's ability to <u>establish</u> in the environment/host?

Animals and plants that have greater survival of offspring have a greater potential to colonise. In the case of animals, this may involve consideration of factors such as the number and size of offspring,

parental care, or rate of development. In the case of plants, this involves consideration of parameters such as seed size, rate of root development, and requirements for water, light and nutrients. The organism's environmental requirements will also form part of this consideration e.g. temperature, water, humidity, sunlight requirements for plants.

The concepts/terms of propagule pressure (i.e. number of individuals introduced to found a population) and infectious dose have been widely used in invasion biology (D 'antonio et al., 2001; Von Holle and Simberloff, 2005; Cassey et al., 2018) and disease (Buchanan et al., 2017).

Establishment of parasites/pathogens is determined by properties that facilitate host entry and, where necessary, movement to a suitable site that allows reproduction or replication to occur. There has been considerable attention to virulence and pathogenicity factors of pathogens, including the traits which facilitate establishment and spread, as well as disease impacts (cf RF H-1) (Casadevall and Pirofski, 2009; OECD, 2011; Cressler et al., 2015).

Knowledge or an organism's habitat requirements, niche and climatic suitability, geographic origin and current distribution can inform predictions (e.g. by habitat modelling) of whether it may establish in new environments or locations (OECD, 2006; VanDerWal et al., 2009; Gallien et al., 2018; Braasch et al., 2019; Cope et al., 2019; Fournier et al., 2019).

Risk Factor I-2. What is the organism's reproductive ability?

Higher rates of reproduction increase the potential abundance of the organism. This includes consideration of shorter time to maturity, more cycles of reproduction in a season, larger numbers of offspring, or a greater rate of replication in the case of viruses or single-celled organisms. In addition, greater reproductive ability is associated with multiple modes of reproduction. There is a significant body of literature on the influence of reproductive ability for organism success, especially in invading and persisting in new habitats, for example weed risk assessment protocols.

Risk Factor I-3. What is the organism's ability to disperse?

Organisms with greater dispersal ability commonly move long distances or transfer to many hosts. Dispersal ability depends on the number of dispersal modes, the frequency of each mode and the dispersal distance/number of hosts. Dispersal may occur by natural means such as self-locomotion (walking, flying, swimming) or indirectly through the movement of air or water, attachment to other organisms/vectors, transmission via offspring of the host, or via secretion of bodily/cellular fluids and waste products in the case of seeds, parasites and pathogens.

In addition, a major mode of dispersal involves assistance by people, intentional and accidental (e.g. on vehicles, ships, machinery, produce, or domesticated animals). The increase of global trade, transport, travel and tourism opens growing opportunities for many types of organism to disperse well beyond their native range. As for reproductive ability, there is a significant body of literature on the role and mechanisms of dispersal that facilitate colonisation or expansion of an organism's range. Both of these factors feature prominently in GMO risk assessments to date.

Risk Factor I-4. What is the organism's ability for gene transfer and genetic change?

Gene transfer and gene flow as used in this paper refer to transfer of genetic material between individuals rather than the broader sense used in population biology which includes migration of individuals or whole populations. Gene transfer is a very common consideration in GMO risk assessments. As for GMO assessments, it is important to distinguish between the occurrence of a gene transfer event (likelihood) and the harm that might result. Gene transfer *per se* is generally not considered a harmful outcome.

Organisms can spread throughout the environment by direct dispersal of the whole organism. Alternatively, only some proportion of an organism's genetic complement may be spread by gene transfer through sexual means (hybridisation) or asexual means (horizontal gene transfer). Deliberate genetic modification by human agency may be considered a particular case of gene transfer.

This risk factor may also be considered to encompass genetic change - the organism's ability to evolve / acquire new traits ('evolutionary potential') that alter its ability to survive over time and invade/infect and/or cause harm. This may occur through transfer of genes to the organism (i.e. the risk source) from other organisms in the environment, creation of new genotypes through sexual reproduction, the selection of genotypes already present in the organism (i.e. its population) or mutation of the organism's genes (Lavergne and Molofsky, 2007; Prentis et al., 2008; Whitney and Gabler, 2008; Hodgins, 2018). The importance of mutations is widely acknowledged in the fields of invasion and infection biology the evolution. For example, increased human infectivity of Ebola was explained by viral mutations (Bedford and Malik, 2016; Ueda et al., 2017). Mutation rate may therefore be viewed as a trait of an organism that might affect the invasiveness/infectivity (Butin et al., 2005; Clune et al., 2008; Cobben et al., 2017). Mutation may be an (one) important factor in novel host evolution (Engering et al., 2013).

Hybridisation involves the interbreeding of individuals from genetically distinct populations of the same species or from related species that are sexually compatible. Hybrid progeny can deviate from the parental fitness through the expression of either heterosis (hybrid vigour) or outbreeding

depression, which may lead to loss of the genetic identity of desirable populations (Byrne et al., 2011). Blackburn et al. (2014) list hybridisation as an impact mechanism for invasive species (in the context of eroding native genotypes). Hybridisation may also provide an organism (i.e. risk source) with new genetic material that affects its ability to survive or cause harm in the environment (Ellstrand and Schierenbeck, 2000; van Kleunen et al., 2015).

Horizontal gene transfer refers to the stable transfer of genetic material from one organism to another without reproduction or human intervention (Keese, 2008). It occurs frequently in viruses and single celled organisms such as bacteria, but almost never in plants and vertebrate animals. Horizontal gene transfer may involve small amounts of genetic material or substantially more in the case of plasmids or integration of a complete viral genome into a host genome. The insecticidal endotoxins produced by *Bacillus thuringiensis* bacteria ('Bt toxins') are often encoded on plasmids and may be moved between strains through horizontal gene transfer (Nair et al 2018). There is also large diversity in the types of Bt toxins and individual strains may produce multiple toxins (Nair et al., 2018).

Although horizontal gene transfer can potentially transfer genes across broad taxonomic groups, it more frequently occurs between closely related organisms. Of particular relevance to risk assessment is the transfer of genes that have potential to increase the ability of the recipient organism to cause harm. For example, transfer of bacterial plasmids (which often contain genes encoding pathogenic determinants) or viral re-assortment (in an infected host) can lead to changes in pathogenicity.

This risk factor intersects with other risk factors, in that potential genetic changes in an organism may affect its abilities to: establish and persist in (I factors); cause harm to (H factors); or interact with the environment (M factors).

Risk Factor I-5. What is the organism's ability to <u>persist</u>?

Certain organisms demonstrate adaptations that allow the organism to survive extended periods of unfavourable conditions. These adaptations include specialised structures (e.g. seeds or spores), physiological responses (e.g. hibernation or dormancy), or behavioural traits (e.g. migration or habitat reconstruction). Therefore, persistence can increase abundance of an organism by overcoming biotic and abiotic constraints (see risk factors I6 and I7) and providing opportunities to rapidly increase population size when conditions are more favourable (e.g. locust plagues). Persistence is a recurring theme and factor in invasion biology.

Persistence can be an important consideration when evaluating the feasibility and effectiveness of control measures to reduce the abundance of an undesirable organism.

Risk Factors I-6 – I-8 – Abilities of the organism (risk source) to overcome environmental constraints and vulnerability of the environment (risk recipient) to the organism.

In the case of GMOs, especially GM plants or animals developed for agricultural production purposes, it may be noted that introduced traits are frequently intended to increase toleration of abiotic (e.g. drought) or biotic (e.g. diseases or pests) in the production context (e.g. cultivated fields). A focus of GMO risk assessment is whether such traits might give such organisms a competitive advantage in other environments which might lead to harm (Eastick and Hearnden, 2006)

Risk factors I-6 to I-8 are related to the harm mitigation risk factors M-1 and M-2 as vulnerability of the environment (risk recipient) mirrors or parallels the abilities/traits of the organism (risk source) to overcome environmental constraints. This is also represented in Figure 3. An organism's adaptability/plasticity (cf I-4, potential for genetic change, level of genetic variation) or specificity/narrow niche requirements will influence/underpin its abilities to overcome environmental constraints. Similarly, the adaptability of the receiving environment will affect its ability to resist or recover from harm (risk factors M-1, M-2).

Risk Factor I-6. What is the organism's ability to <u>tolerate biotic constraints</u>?

Biotic factors that restrict the presence of organisms include: competition, pest pressures, diseases, herbivory, predation; availability of suitable habitat/food source; behavioural adaptations such as grooming; or host resistance/immunity properties. For example, a plant species that is introduced to a new area with fewer of its concomitant pests and diseases may have an increased propensity to become invasive (Mitchell and Power 1995). The importance of biological constraints can also be inferred from the success of biological control programs e.g. use of the moth *Cactoblastis* sp. to control the invasive cactus prickly pear (*Opuntia* species) in Australia.

In the case of parasites, the most common biotic constraints include availability (abundance) of the host(s) and/or vector, as well as host properties that provide resistance or immunity to establishment or replication of the parasite. These constraints include surface and cellular barriers, and simple enzymatic processes such as inflammation, complement systems, adaptive immunity, or RNAi. Antigenic variation is a common 'strategy' of parasites and pathogens to evade the immune system of the host, and the trypanosome parasite of African sleeping sickness is a well known example (Deitsch et al., 2009). Many parasites and pathogens are able to survive outside of the host(s) with multiple mechanisms described (Morris et al., 2009).

Risk Factor I-7. What is the organism's ability to tolerate abiotic constraints?

Abiotic factors that may constrain the presence of organisms include: climate, rainfall patterns, soil properties (e.g. nutrient profile, salinity, pH, particle composition, water table levels etc), water availability/quality, light, and fire regimes. Abiotic factors determine the potential distribution of the organism. Greater significance is given to organisms that can colonise a broad range of climates and habitats. Parasitic microorganisms are generally less affected by abiotic constraints other than indirectly via host availability. Nevertheless, some abiotic factors may play a role at different parts of the life cycle, such as during transmission between hosts. These factors may include temperature, pH, oxygen levels, nutrients or radiation levels.

Risk Factor I-8. What is the organism's ability to tolerate anthropogenic constraints?

People also constrain the presence of organisms through the use of antibiotics and vaccines, as well as weed and pest control, including through application of herbicides and pesticides. In addition, people exert indirect effects on organisms through food and fibre production, land clearing, habitation, or as a result of transport, storage and use of energy, chemicals or other goods.

6.2 Harm: Proposed risk factors H-1 to H-4

These four risk factors relate to attributes/traits of the organism (risk source) to cause harmful impacts on other organisms. The types of harm that may result from the presence of the organism have been grouped according to four risk factors H-1 to H-4, summarised in Table 3. As noted above, such harms may be mediated by a pathway of interactions between the organism and the receiving environment. In addition, the seriousness of harm may be mitigated by properties of the environment/host (risk factors M-1 and M-2).

Risk factors H-1 to H-4 are expressed in terms of the degree of impact from the organism (risk source) on the risk recipient. However the vulnerability of the risk recipient is also relevant to these considerations. As noted above, there is a large number of ways that organisms can effect harm on other organisms or the environment and these are widely described (e.g. Blackburn et al., 2014 for impacts from invasive plants). For invasive animal species, the 'functional response' of the (potential) invader (e.g. extent of predation by predator, herbivory by herbivore) has been proposed as a predictor (e.g. Paterson et al., 2013; Alexander et al., 2014; Dick, 2014; Dick, 2017a; Cuthbert et al., 2018). The functional response may be considered as a characteristic or trait of the species. For invasive plants, it has been proposed that some species traits (e.g. life form, pollination syndrome) may be predictive of impact (Pyšek et al., 2012). However, for both plants and animals, identifying common traits predictive of impact remains elusive (see Drenovsky et al., 2012). More recently, also for

invasive species, a ‘relative impact potential’ has been proposed (Dick, 2017b). For disease agents, the damage-response framework (e.g. Casadevall and Pirofski, 2009) may be relevant. Differentiation between impacts on individuals and populations (e.g. Tompkins et al., 2011; Lachish et al., 2012)(e.g. Tompkins et al. 2011, Lachish et al 2012), including severity and frequency of impact, should also be borne in mind.

Table 3 Risk Factors H-1 – H-4: Harm

	Risk Factor	Effect	Explanation
Risk source – characteristics and **Risk recipient – vulnerability & resilience**	H-1	Toxicity / ill health / injury	Degree to which the organism could increase toxicity or ill health in people or desirable organisms.
	H-2	Biotic quality	Degree to which the organism could reduce biotic quality of the environment through decrease of desirable organisms or increase of undesirable organisms, or reduce biodiversity or ecological functions.
	H-3	Abiotic quality	Degree to which the organism could reduce abiotic quality of the environment.
	H-4	Functional value	Degree to which the organism could reduce functional value of the environment such as ecosystem services.

As noted above under I-4, mutations and evolution of the organism/population may effect longer term seriousness of harm. In the case of parasites/pathogens, ongoing mutations of the host are also relevant e.g. co-evolution of rabbits and the myxoma virus towards less severe disease (Best and Kerr, 2000; Peng et al., 2016), as is the interplay of pathogen, host and environment (e.g. Engering et al., 2013). Therefore, the seriousness of harm can vary over time (e.g. different harms from: influenza virus infecting people depending on the strain; or variation / changes in host-pathogen specificity).

Risk Factor H-1. To what degree could the organism <u>increase toxicity/ill health</u> to people or desirable organisms?

Toxicity or ill health for people, livestock, crops, domesticated animals and wildlife is a major concern in risk assessments of organisms. In particular, ill health of people has the greatest significance. Negative impacts include disease, toxicity/allergenicity or injury/death. Organisms may cause toxicity or ill health directly (e.g. ingestion toxic plants) or indirectly (e.g. as a vector or reservoir for certain pests, parasites and pathogens). Predation and herbivory by organisms represent another direct route to harm. Toxicity/ill health is generally the major consideration for negative

impacts from microorganisms (as pathogens and parasites), which may occur directly through impacts on the host or indirectly by consumption of an infected host (including zoonoses). The concept of dose response and lethal dose for toxins and toxicants will be relevant here, as well as the organsim's life history traits including toxin/toxicant production dynamics (e.g. amount, spatial and temporal scales).

Risk Factor H-2. To what degree could the organism reduce biotic quality of the environment?

Organisms may reduce environmental biotic quality, including biodiversity and ecological functions, by two different means. One way involves (directly) decreasing the presence of desirable organisms (e.g. endangered or protected species, crops, or native species), most notably through reduced establishment of juveniles from desirable organisms. The second way involves (indirectly) increasing the presence of undesirable organisms (weeds, pests, parasites, pathogens) due to the provision of food, shelter or resources (e.g. including as a host or vector for a disease or pest). Organisms may also affect community or ecosystem structure, for example if the organism represents a new functional group the change would be qualitative and may be greater than if an introduced organism only differs from native species in degree only (Catford et al., 2012).

Plants may reduce establishment of other desirable plants by preventing germination through dense shading or forming physical barriers to water movement. Plants may also kill seedlings by production of allelopathic chemicals, or outcompeting them access to soil moisture, sunlight and nutrients (e.g. pine trees suppressing establishment of other species). Animals may reduce establishment and/or reproductive output of desirable plants through herbivory (Cooke and McPhee, 2007); other animals through preying on juveniles or adults, or damaging reproductive organs; or by competing directly with native fauna for food supply or burrows. Microbes may also affect biotic quality by affecting community structure by removing or denuding particular species (e.g. change to forest structure with losses of American chestnuts, Loo, 2009).

Risk Factor H-3. To what degree could the organism reduce abiotic quality of the environment?

Organisms may have negative impacts on the abiotic environment through, for example: reduced water quality by means such as fouling, sediment disturbance, silting or reduced oxygen levels; reduced soil quality through increased salinity, acidification, soil erosion, reduced water table levels, or undesirable changes in nutrient levels; or reduced air quality through increased greenhouse gas emissions or undesirable changes in fire regimes. Reduction of abiotic quality might result from impacts on ecosystem processes including biogeochemical cycling. A number of the harmful impacts categorised for invasive plants and animals are harms to the abiotic environment (e.g. see Blackburn

et al., 2014). Microbes may also have impacts on the abiotic environment, e.g. algal blooms in waterways can significantly affect oxygen concentration and water quality.

Risk Factor H-4. To what degree could the organism reduce functional value of the environment?

Depending on the intended use of the environment under consideration its functional value (e.g. the quality of ecosystem services or products**)** might be reduced by the presence of the organism that is the subject of assessment. The use of 'functional value' in this paper is analogous to that of Smith et al (2008). They parsed ecological functions into three categories – functional value, as well as biodiversity and conservation value, and that the latter two are analogous to biotic quality addressed in Risk Factor H-2. Generally, ecological functions, characteristics and processes are understood to encompass the biophysical relationships in an environment whereas ecosystem services are the benefits humans derive from functioning ecosystems (see de Groot et al., 2002; Granek et al., 2010; Costanza et al., 2011).

For example, organisms might reduce the yield, purity or quality of the appearance of farming/forestry/fishery produce. In urban areas, negative impacts might include physical damage to infrastructure or reduced social amenity. In nature reserves, negative impacts may include reduced suitability for nature conservation or nature-based tourism.

In addition, organisms may restrict the movement of people, water, vehicles, domesticated stock or other desirable organisms. Plants (weeds) may restrict movement by forming dense mats in aquatic systems or dense, spiny thickets on land. For example, plants may limit movement by: slowing of stock mustering; blocking farm machinery; tyre punctures; slowing water flow in irrigation channels; interfering with boat access; interfering with thinning operations in forestry; preventing stock access to pasture and/or water; or preventing animal access to nesting sites. Animals (pests) may harass domestic livestock or native animals, limiting their access to water, feed or suitable habitat (e.g. nesting sites). In addition, the presence, or potential presence, of microorganisms (pathogens), plants (weeds, weed seeds) or animals (pests) may result in human imposed restrictions on the movement of people, other organisms or goods indirectly as a result of quarantine impositions (e.g. ebola, fruit fly or *Fusarium*).

6.3 Harm mitigation: Proposed Risk Factors–M-1, M-2

The two proposed harm mitigation risk factors are related to resilience attributes of the risk recipient and/or receiving environment and its ability to tolerate or avoid harm (M-1), or to recover from or reverse harmful effects (M-2) from organisms. Table 4 summarises the two factors. Theses harm

mitigation factors may also be viewed as the counterpoint to the vulnerability/susceptibility of the receiving environment.

A number of general principles underpinning resilience and vulnerability can be discerned from invasion and disease biology/ecology. The degree of disturbance of an environment is often correlated with susceptibility to invasion or its 'invasibility' (e.g. Didham et al., 2007; Mächler and Altermatt, 2012).

As noted for the I and H risk factors, the abilities of organisms or populations can evolve through mutations, genetic exchange or genetic selection. The abilities of the other organisms in the receiving environment may contribute to the environment's capacity to resist or recover from harm (caused by the organism that is the subject of risk assessment). In both plant and animal invasion biology, the community structure, including its genetic diversity, has been invoked as a factor in invasibility (e.g. Crutsinger et al., 2008). However a direct correlation between species or genetic diversity and resistance to invasion is not a given (e.g. see Richardson and Pyšek, 2006; Chang and Smith, 2012). Similar observations have been made for microbial invaders (Jousset et al., 2011). For pathogens, it is well recognised that limited genetic diversity in a host population may predispose to significant disease impacts.

Table 4 Risk Factors M-1, M-2: Harm Mitigation

	Risk Factor	Effect	Explanation
Risk recipient – resilience & vulnerability	M-1	Suppression / Avoidance	Degree to which the environment or host could suppress or avoid harm from the organism
	M-2	Reversal / Recovery	Degree to which the organism could reduce biotic quality of the environment through decrease of desirable organisms or increase of undesirable organisms

Risk Factor M-1. To what degree could the environment/host <u>suppress/avoid harm</u>?

This risk factor considers the circumstances where the organism is present but the potential harm it might cause is suppressed or avoided because of the characteristics of the receiving environment, and as noted is the counterpoint of susceptibility/vulnerability. In the case of diseases some organisms may tolerate the presence of, or have resistance to infection by, a parasite or pathogen and show

minimal disease. This may be at the level of individuals (e.g. different genotypes, age cohorts) or species. It has been proposed that functional traits of resident plant species in a community influence the invasion outcome (e.g. Fried et al., 2019). The concept of biotic resistance is also relevant to such considerations (Byun and Lee, 2017).

Risk Factor M-2. To what degree could the environment/host reverse or recover from harm?

This risk factor considers potential reversibility of harmful outcomes where the organism is present and does result in harm or disease. Greater significance is given to harm that is chronic and irreversible. In some cases recovery from harmful outcomes may involve reduction in the presence of the antagonist organism. Reversibility or recovery from harm involves consideration of the ecological scale (e.g. individual, population, community, ecosystem), management goals, availability and suitability of potential interventions and time scale. In the context of invasion biology, environmental recovery through restoration of the native species by human interventions (as opposed to removal of invaders) has been a focus of research and management (e.g. Byun and Lee, 2017).

7 Conclusion

This discussion document has proposed a generic conceptual framework which should be applicable to inform environmental or other risk assessment of organisms. A set of generic risk factors related to the nature of organisms and the receiving environment are proposed as a key aspect of this framework – invasiveness and infectivity, harm and harm mitigation. Many of the concepts articulated are not new and many of the terms used have been informed by and/or borrowed from literature for other risk assessments or academic disciplines.

As noted at the beginning of the document, this is a discussion piece and is not intended to be a 'finalised tool'. The concepts articulated will help to inform OGTR's evaluation of GMOs and elements of it may be incorporated in future updates of the Risk Analysis Framework.

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