Title:

Toward a unified tolerance–resistance framework across biological stressors and scales

Authors:

Erik van Bergen [1]; Sara Magalhães [1,2]; Élio Sucena [1,2]; Elvira Lafuente [1 #]

Corresponding author: elafuentemaz@gmail.com

Affiliations:

[1] CE3C: Centre for Ecology, Evolution and Environmental Changes, Faculdade de Ciências, Universidade de Lisboa & CHANGE-Global Change and Sustainability Institute, Campo Grande, 1749-016 Lisbon, Portugal

[2] Department of Biology, Faculty of Sciences, University of Lisbon (FCUL), Lisbon, Portugal

Keywords:

immunotoxicology, environmental toxicology, biotic and abiotic stress, homeostasis, host defence, stress physiology, detoxification

ORCID IDs & emails:

Erik van Bergen: 0000-0002-9648-9837 - erikvanbergen.science@gmail.com

Sara Magalhães: 0000-0002-8609-7768 - snmagalhaes@fc.ul.pt

Élio Sucena: 0000-0001-8810-870X - jesucena@ciencias.ulisboa.pt

Elvira Lafuente: 0000-0002-2166-686X - elafuentemaz@gmail.com

Abstract

Ecotoxicology and immunology both explore how organisms cope with external stressors that disrupt homeostasis, yet these fields have developed largely in parallel. While immunology has formalized the distinction between resistance (i.e reducing stressor burden) and disease tolerance (i.e. mitigating damage without reducing burden), ecotoxicology has traditionally focussed on stressor fate, trophic transfer, and ecosystem-level consequences without consistently discriminating between these mechanistic strategies. Here, we argue that explicitly separating resistance from tolerance provides the conceptual clarity necessary to connect mechanistic, ecological, and evolutionary perspectives across these disciplines and bridge different biological scales.

Using examples from host–pathogen interactions and pollutant systems, we show that distinguishing between mechanisms that reduce stressor burden and those that mitigate damage enables more accurate predictions about contaminant persistence, bioaccumulation, transmission, and recovery. Conversely, ecological perspectives developed in ecotoxicology may extend resistance-tolerance theory and practice by incorporating stressor redistribution, food-web dynamics, and eco-evolutionary feedbacks into the host–pathogen interaction research programme. Finally, we discuss how resistance and tolerance evolve under different selective contexts, emphasizing the roles of reciprocal coevolution, stressor persistence, cross-talk between mechanisms, and eco-evolutionary feedbacks. By integrating mechanistic and ecological perspectives, propelled by a clear and shared definition of resistance and tolerance, we propose a unified framework for understanding how organisms deal with biotic and abiotic stressors across scales.

1. Introduction

Ecotoxicology addresses the impact of pollutants on ecosystems and their components (Truhaut, 1977; Moriarty, 1988), whereas immunology investigates organismal responses and adaptations to pathogen exposure (Pradeu, 2020). Although these disciplines developed largely independently, both are fundamentally concerned with how organisms cope with external agents that disrupt homeostasis. Ecotoxicology has traditionally emphasized the environmental sources, distribution, and ecological consequences of pollutants, while immunology has focused on the cellular and physiological mechanisms that protect the host against pathogens. These differences in emphasis largely reflect historical contingencies rather than conceptual incompatibility and may obscure a shared biological question: how do organisms maintain homeostasis when challenged by biotic or abiotic stressors (Fig. 1 and Fig. 2).

Physiological homeostasis (Kotas & Medzhitov, 2015) provides a conceptual anchor linking ecotoxicology and immunology, as both disciplines examine how external stressors perturb organismal steady states, how organisms resist or tolerate those perturbations, and how responses scale from physiology to populations and ecosystems. Pathogens and pollutants alike pose a common challenge for organisms: maintaining functional integrity in the face of disruption. This shared challenge provides a basis for considering responses to biotic and abiotic agents within a unified framework.

Elements of this integrative perspective have already begun to emerge, with studies examining the impact of toxic substances on organismal physiology and immunity (Tryphonas & Arnold, 2005; Tryphonas *et al.*, 2005; Sadd & Schmid-Hempel, 2009; Lafuente *et al.*, 2023), and others exploring how pathogens influence ecological processes (Seabloom *et al.*, 2015; Fischhoff *et al.*, 2020). However, the conceptual tools used to describe organismal responses are not always aligned across disciplines. In particular, the terms “resistance” and “tolerance” are widely used in both fields, yet in largely different contexts, often with different meanings and concomitantly distinct mechanistic, ecological, and evolutionary implications.

In ecotoxicology in particular, resistance and tolerance are not always defined in relation to internal burden and damage-fitness relationships. This can lead to the conflation of mechanistically distinct organismal responses, limiting our ability to predict contaminant persistence, trophic transfer, and ecosystem recovery. Conversely, although immunology has articulated a clearer

77 distinction between resistance and disease tolerance at the organismal level, this framework has
78 largely remained focused on host-pathogen interactions, with limited integration of ecosystem-level
79 consequences (Baucom & de Roode, 2011).

80 Here we argue that making explicit the mechanistic distinction between resistance and
81 tolerance provides a conceptual lens that connects ecotoxicology and immunology within a shared
82 framework anchored on homeostasis. We first distinguish between mechanisms that reduce stressor
83 burden (resistance) and those that mitigate damage without altering burden (tolerance) at the
84 organismal level. Then, we explore how this distinction helps to clarify how such responses scale to
85 ecological dynamics, evolutionary trajectories, and eco-evolutionary feedbacks across biotic and
86 abiotic stressors. By placing resistance and tolerance at the core of this shared framework, we aim to
87 sharpen concepts towards strengthened predictive links between physiological mechanisms,
88 ecological processes, and evolutionary outcomes.

2. Mechanisms of resistance and tolerance

In this section we review the mechanistic foundations of resistance and tolerance at the organismal level to help clarify how organismal responses to stressors can be compared across biotic and abiotic contexts. Immunology provides a particularly explicit formulation of this distinction, defining resistance as the reduction of pathogen burden and disease tolerance as the mitigation of damage without altering burden (Råberg, Sim & Read, 2007; Råberg, Graham & Read, 2009; Baucom & de Roode, 2011). Here, for readability, we will generalize the term "tolerance" and use it *sensu* "disease tolerance" rather than its strict adaptive immunity definition regarding the unresponsiveness to antigens resulting from lymphocyte maturation processes (Medawar, 1960; Murphy *et al.*, 2022).

We adopt this mechanistic distinction as a conceptual starting point and extend it to ecotoxicological systems, where analogous processes operate but are not always explicitly distinguished from one another. This approach will allow us to align terminology across disciplines (section 2) and link physiological mechanisms to ecological (section 3) and evolutionary consequences (section 4).

2.1. Definition of resistance and tolerance in immunology and ecotoxicology

In immunology, resistance refers to the ability of the host to prevent or eliminate infection, typically through two complementary processes: pathogen avoidance that minimizes exposure and pathogen clearance, which relies on immune mechanisms that detect and neutralize pathogens after infection and return the organism to a homeostatic steady-state (Restif & Koella, 2004; Råberg *et al.*, 2009; Boots, 2011). In contrast, tolerance concerns the ability of organisms to maintain their homeostasis, and therefore their fitness, despite infection and without directly affecting their pathogen load (Schneider & Ayres, 2008; Baucom & de Roode, 2011; Ayres & Schneider, 2012; Medzhitov, Schneider & Soares, 2012). Rather than preventing or clearing infection, tolerance mechanisms mitigate the damage caused by pathogens or their by-products through tissue repair, damage control, and physiological buffering (Read, Graham & Råberg, 2008; see Box 1).

The term "resistance" has historically been used broadly to describe the ability to prevent, survive, or recover from infection, eventually contributing to the emergence of the modern concept of "immunity" in the nineteenth century through the work of Jenner, Pasteur, Koch, Metchnikov, von

Behring, and Ehrlich (Silverstein, 1989). The concept of tolerance as a damage-mitigating process emerged from the recognition that survival may result from mechanistically distinct processes. This distinction also has roots in nineteenth-century plant pathology, particularly in the work of Nathan Cobb, and became increasingly developed throughout the twentieth century in plant biology and agronomy (Schafer, 1971; Pagán & García-Arenal, 2020). In the 1950s and 1960s, key conceptual advances clarified tolerance as distinct from resistance by moving beyond strictly host-centered measures (e.g., leaf damage or crop yield) to explicitly consider pathogen performance and the host–pathogen interaction (Dropkin, 1955; Caldwell *et al.*, 1958; Dropkin & Nelson, 1960). Schafer's influential 1971 definition - "*Tolerance may be defined as that capacity of a cultivar resulting in less yield or quality loss relative to disease severity or pathogen development when compared with other cultivars or crops*" - largely established the modern framework later adopted in animal immunology (Råberg *et al.*, 2007, 2009; Baucom & de Roode, 2011; Råberg, 2014; Kutzer & Armitage, 2016).

In ecotoxicology, such mechanistic distinctions between tolerance and resistance are not consistently made. Terms like "pesticide resistance" or "antibiotic resistance" are widely used but often agnostic as to whether the toxicant is eliminated, transformed, or remains biologically available within the organism. For example, resistance to organophosphates in the mosquito *Culex pipiens* may arise either through the overproduction of esterases that hydrolyse the pesticide (Raymond *et al.*, 1998), or through mutations in the acetylcholinesterase (ace-1) gene that reduce sensitivity of the molecular target (Labbé *et al.*, 2007). Despite their fundamentally different modes of action, both mechanisms are commonly classified as "resistance". Under a mechanistic framework informed by immunology, these strategies correspond to distinct categories: esterase-mediated hydrolysis constitutes resistance *sensu stricto*, as it reduces toxicant burden, whereas target-site insensitivity is more appropriately described as tolerance, as the pesticide remains unaltered and potentially bioavailable. Conflating these responses obscures their distinct ecological implications, including whether pollutants are detoxified or persist within organisms and ecosystems, with consequences for bioaccumulation, trophic transfer, and environmental recovery (cf. Section 3). This example illustrates how the clearer conceptual distinction between tolerance and resistance developed in immunology, may impact operationally ecotoxicology studies towards a clearer link between organismal mechanisms and eco-evolutionary outcomes. This does not imply that ecotoxicology lacks mechanistic insight; rather, making this distinction explicit clarifies how organismal responses translate into

ecological and evolutionary consequences. Importantly, the immunological definitions of resistance and tolerance hinge on the nature of the interactions between host and a living, hence proliferating, agent. This is not the case for abiotic stressors that, however, obey analogous dynamics in their interactions with organisms in time and space (cf. Section 3).

Taken together, the aforementioned definitions highlight that the key distinction between resistance and tolerance lies not in the identity of the stressor, but in how organisms interact with it to maintain homeostatic function. Below, we re-visit the main mechanisms of resistance and tolerance, building on the explicit formulation developed in immunology.

2.2. Mechanisms of resistance at the organismal level

In host–pathogen interactions, resistance is framed as operating along two complementary axes that reduce pathogen load: behavioural avoidance or expulsion and immune-mediated clearance (Heine, 2007; Murphy *et al.*, 2022)Fig. 2).

The first axis, avoidance and expulsion, includes processes whereby the agent is not modified. Avoidance is achieved through behavioural decisions that minimize contact with harmful agents (Buck, Weinstein & Young, 2018; Gibson & Amoroso, 2022). Such responses are well documented for biotic stressors: spider mites avoid plants harbouring pathogenic bacteria (Zélé *et al.*, 2019), and diverse pathogen avoidance behaviours have been described in *Drosophila* and *C. elegans* (Meisel & Kim, 2014; Vale & Jardine, 2017; Lei *et al.*, 2024). In plants, antixenosis - i.e. traits that deter or repel herbivores and other pests - similarly reduces harmful exposure by preventing feeding, reproduction, or settlement on the host . Although plants cannot behaviourally evade stressors, antixenosis functionally parallels avoidance in animals by limiting contact with biotic agents (Kogan & Ortman, 1978; Le Roux *et al.*, 2010).

Comparable avoidance strategies also occur in response to abiotic stressors (Mogren & Trumble, 2010). For example, spider mites avoid plants with high concentrations of toxic metals such as cadmium (Godinho *et al.*, 2024), while *Daphnia longispina* can detect copper and synthetic pyrethroids, actively swimming away from contaminated water masses (Lopes *et al.*, 2004). However, despite some illustrative examples, behavioural avoidance of abiotic stressors remains comparatively understudied in model organisms (but see e.g., Bahadorani & Hilliker, 2009; Pak & Murashov, 2021), limiting broader mechanistic comparisons across stressor types.

In contrast to avoidance, expulsion involves mechanisms that employ efflux systems to actively export harmful compounds, thereby alleviating the internal toxic burden. Clear examples include emetic responses (i.e. the reflexive expulsion of ingested contents through vomiting) triggered by ingested toxins or pathogens across the animal kingdom (Horn, 2017), as well as increased defecation in response to oral bacterial infections in *Drosophila* (Buchon *et al.*, 2009; Du *et al.*, 2016; but see Rubinić *et al.*, 2025). Comparable expulsion mechanisms also operate against abiotic stressors. For example, ATP-binding cassette (ABC) transporters are highly conserved across species (Ferreira *et al.*, 2014) and facilitate the export of xenobiotics and their metabolites across cell membranes, playing a critical role in organisms chronically exposed to pollution loads (Bard, 2000). Similarly, multidrug and toxic compound extrusion (MATE) transporters remove metal ions, such as cadmium and arsenic in bacteria, plants, and animals (Moriyama *et al.*, 2008; Takanashi, Shitan & Yazaki, 2014; Lu, 2016), while multidrug resistance-associated proteins (MRPs) expel polycyclic aromatic hydrocarbons (PAHs), pharmaceuticals, and dyes in aquatic invertebrates (Borst *et al.*, 2000; Sodani *et al.*, 2012).

The second axis of resistance involves transformation of the stressor through biochemical modification or biotransformation. In immunology, this axis is illustrated by antimicrobial defenses that chemically modify pathogens or their structural components. For example, lysozyme hydrolyses the peptidoglycan layer of bacterial cell walls, weakening cell integrity and inducing lysis (Ragland & Criss, 2017).

In ecotoxicology, a well-characterized class of such mechanisms includes enzymatic biotransformation pathways, which are often inducible and exhibit broader, less target-specific activity than immune responses. Cytochrome P450 monooxygenases, for example, catalyze oxidation reactions that convert hydrophobic pollutants (e.g., organochlorines, PAHs, pesticides) into hydrophilic metabolites (Stegeman & Lech, 1991). These metabolites can then be conjugated by UDP-glucuronosyltransferases (UGTs), facilitating their biliary and urinary excretion, as demonstrated in fish exposed to endocrine-disrupting chemicals (Wang, Huang & Wu, 2014). In plants, cytochrome P450 enzymes similarly metabolize herbicides and industrial contaminants (Siminszky, 2006; Schuler, 2011).

Notably, these enzymatic responses are also induced by pathogenic challenges in both animals and plants, highlighting conserved resistance mechanisms for coping with diverse stressors (Binggeli *et al.*, 2014; Tafesh-Edwards & Eleftherianos, 2023; see section 4.3). Similarly, glutathione-mediated responses are shared across taxa in the face of abiotic and biotic stressors, including pathogen

exposure (Dixon, Cummins & Cole, 1998; Cummins *et al.*, 2011; do Carmo Santos *et al.*, 2025). Together, these examples show that resistance to pollutants and immunological resistance rely on similar or diverse biochemical strategies that converge on a common outcome: reducing internal stressor burden and restoring homeostasis.

2.3. Mechanisms of tolerance at the organismal level

Tolerance includes mechanisms that prevent, repair, or mitigate damage, manage stressor-induced oxidative stress, and enable the accumulation and sequestration of foreign substances (Fig. 2). These mechanisms are widespread in nature and are particularly important in environments where avoidance or metabolic clearance may be limited.

One prominent class of tolerance mechanisms involves limiting physiological damage. In immunology, hosts can reduce infection-induced damage through tissue-protective responses that preserve organ function. For example, epithelial repair processes and mucus production can protect barrier tissues and limit damage during infection (Turner, 2009). Similarly, heavy-metal exposure in fish can induce morphological changes in gill epithelia (e.g., epithelial thickening and increased mucus production) that reduce physiological disruption and preserve ion balance despite continued exposure (Jezierska, Ługowska & Witeska, 2009). More broadly, organisms may upregulate protective proteins that stabilize membranes and reduce cellular injury under chronic pollutant stress (Abdallah *et al.*, 2024).

Another prominent form of tolerance is the management of oxidative stress. Pathogenic infections often induce the production of reactive oxygen species (ROS), which can damage host tissues if not properly controlled (Ma, 2013). Hosts therefore activate antioxidant and repair pathways to limit this damage and maintain cellular function (Lambeth, 2004; Nathan & Cunningham-Bussel, 2013). Similarly, pollutants such as metals, PAHs and pesticides generate ROS, leading to DNA damage, lipid peroxidation, and protein misfolding, which trigger antioxidant defenses and protein quality-control mechanisms, including heat-shock proteins and proteasomal degradation (Cabiscol, Tamarit & Ros, 2000; Steinbrenner & Sies, 2009).

Another axis of tolerance involves the accumulation and sequestration of pathogens or toxic substances into chemically inert forms or specialized compartments. This limits interference with core cellular processes despite the maintenance of high internal burdens. In immunology, this is exemplified by granulomas - organized aggregates of immune cells that form in response to persistent

stimuli, which restrict the spread of pathogens, as observed in tuberculosis and other chronic infections (Lyu *et al.*, 2024). An analogous strategy operates in response to abiotic stressors, where plants exposed to high metal concentrations bind metals to phytochelatins or metallothioneins and sequester them into vacuoles or root tissues, isolating them from key metabolic pathways (Clemens, 2006; Verbruggen, Hermans & Schat, 2009). In hyperaccumulator species, this strategy enables survival under metal concentrations that are lethal to non-adapted taxa. Comparable mechanisms occur in animals: bivalves store metals in lysosomal granules and storage vesicles (Zuykov, Pelletier & Harper, 2013), while marine polychaetes sequester petroleum hydrocarbons in lipid droplets (Cornelissen *et al.*, 2006). Together, these examples show that homeostasis can be achieved by compartmentalizing stressors rather than eliminating them and illustrate that both immunological disease tolerance and ecotoxicological tolerance enable organisms to maintain function without reducing contaminant load.

250

Box 1. Experimental criteria for distinguishing resistance and tolerance

Distinguishing resistance from tolerance requires going beyond phenotypic responses to exposure and explicitly considering internal stressor burden and damage–fitness relationships. Resistance reduces internal burden, whereas tolerance maintains performance despite sustained stressor levels by limiting damage and preserving function (Pradeu *et al.*, 2024).

Operationally, tolerance is detected as a change in the relationship between internal burden and fitness (or damage), such that organisms maintain higher performance at a given level of exposure without reducing stressor load (Kutzer & Armitage, 2016). Following the framework proposed by Råberg and colleagues (Råberg & Kautsky, 2007; Råberg *et al.*, 2009), resistance and tolerance can be distinguished by jointly quantifying (i) the relationship between exposure and internal burden, and (ii) the relationship between internal burden and fitness (Schneider & Ayres, 2008; Kutzer & Armitage, 2016). Resistance reduces internal burden for a given exposure, whereas tolerance alters the fitness–burden relationship. More recent work further shows that measuring dynamics of pathogen (or stressor) load and host fitness, particularly during early stages of infection, can help distinguish tolerance from resistance (Duneau *et al.*, 2017, 2025; Akyaw *et al.*, 2025).

Although developed in host–pathogen systems, this framework is directly applicable to ecotoxicology, where internal stressor burden can be quantified and related to performance metrics. Similar considerations regarding dynamic processes and endpoint measures are therefore likely to apply when distinguishing resistance from tolerance in these systems.

251

3. Ecological consequences

Ecotoxicology has long emphasized how pollutants move through ecosystems, accumulate across trophic levels, and persist in abiotic compartments. When interpreted through the clarified distinction between resistance and tolerance outlined above, these ecological processes reveal consequences that extend the resistance-tolerance dichotomy beyond its traditional host-pathogen framing. At the ecosystem level, resistance and tolerance differ fundamentally in whether the stressor agent is eliminated, retained, transformed, or redistributed through ecological interactions. Whereas immunology has been concerned with pathogen transmission, ecotoxicology provides a broader perspective in which stressors can accumulate, propagate through food webs, and re-enter the environment independently of host survival.

3.1. Stressor persistence and transmission

In host-pathogen systems, the ecological consequences of resistance and tolerance are often framed in terms of horizontal transmission of pathogens between hosts. Pathogens that transmit horizontally are approached under specific theoretical frameworks such as classical epidemiological models, like the Susceptible–Infected–Removed (SIR) models (Kermack & McKendrick, 1927; Harko, Lobo & Mak, 2014), which provide a basis for understanding how resistance and tolerance shape disease dynamics. For example, resistant hosts that effectively clear infections are expected to reduce pathogen prevalence and transmission at the community level (Råberg *et al.*, 2009). In contrast, hosts that tolerate infection without reducing pathogen load can act as reservoirs, maintaining viable pathogens and increasing transmission within and between species (Luis *et al.*, 2013; Hayman, 2016; Borremans *et al.*, 2019). Thus, tolerance can enhance transmission even when host fitness is only minimally affected.

Analogous, though not identical, dynamics occur in ecotoxicological systems. Species that tolerate harmful agents without eliminating them act as reservoirs of pollutants, facilitating trophic transfer and bioaccumulation. A well-documented example is mercury in aquatic ecosystems, where organisms tolerate methylmercury while retaining high internal burdens, leading to biomagnification in top predators (Lavoie *et al.*, 2013). Similarly, persistent organic pollutants such as PBDEs and organochlorine pesticides (e.g., DDT and metabolites) accumulate in tolerant organisms (Connell, 1988) and are transferred through food webs, extending exposure beyond the original contamination

site and timing (Windsor *et al.*, 2019). These processes may be further amplified under climate change, as shifts in species interactions and food-web structure increase trophic transfer (Barneche *et al.*, 2021).

Resistance mechanisms, by contrast, have more variable ecological consequences. Avoidance and antixenosis reduce individual exposure without altering environmental contamination (Stout, 2013). Other mechanisms, such as detoxification or biotransformation, can reduce environmental risk when contaminants are converted into less toxic or more readily eliminated forms, as is the case with cytochrome P450-mediated metabolism of organic pollutants (Stegeman, Hahn & Reyle-Hahn, 1994). However, when transformation produces persistent and toxic by-products, resistance may maintain or even increase environmental risk. Similarly, efflux-based mechanisms can either reduce or sustain contamination depending on whether compounds are exported in altered or intact forms.

Beyond transfer among organisms, both immunology and ecotoxicology involve processes through which harmful agents enter and persist in abiotic compartments. In host–pathogen systems, pathogen shedding, excretion, or host death increases the pool of infectious agents and the likelihood of subsequent infections (Anderson & May, 1992). In ecotoxicological systems, the release of pollutants similarly prolongs environmental exposure. In both cases, the potential for broader impact depends on how organisms process the stressor: whether pathogens remain viable outside the host, or pollutants are released intact or transformed, determines whether they continue to pose an environmental risk.

3.2. Recovery *versus* hidden persistence

A key ecological consequence of tolerance is the potential disconnect between organismal or population performance and ecosystem recovery, a distinction particularly relevant for ecological risk assessments (Calow & Forbes, 2003). Indeed, when tolerance strategies predominate in ecological systems, populations may persist or even increase despite sustained exposure, while pollutants accumulate in organisms or circulate through food webs (Forbes & Calow, 2002; Fleeger, Carman & Nisbet, 2003; Luoma & Rainbow, 2008). Consequently, tolerance-driven persistence can mask underlying ecological stress, causing ecosystems to appear recovered despite ongoing or redistributed contaminant exposure. Thus, the extent to which ecosystem health assessments based on abundance or demographic performance underestimate the lasting impacts of contaminants depends on whether responses to stressors are dominated by tolerance or resistance mechanisms (Calow & Forbes, 2003).

For example, classic studies of polluted river systems show that biological recovery often lags behind chemical improvements, reflecting the delayed release and redistribution of stored contaminants (Frey, 1961). More recent research confirms that metals accumulated by tolerant organisms can be released long after external inputs cease, prolonging ecosystem contamination and hindering recovery (Luoma & Rainbow, 2008, 2009). In contrast, resistance-driven responses, which reduce or eliminate stressor burden, may shorten the time frame in which costs on organisms are expressed, but contribute more directly to ecosystem detoxification (Forbes & Calow, 2003; Ashauer & Escher, 2010). Therefore, the distinction between resistance and tolerance mechanisms is critically important to evaluate whether population persistence is a reliable indicator of environmental recovery, and to predict ecosystem trajectories in polluted environments.

321

Box 2. Ecological and evolutionary consequences of resistance and tolerance in Lepidoptera

Lepidoptera are phytophagous insects, and many species provide compelling examples of the evolution of resistance and tolerance to defensive secondary metabolites produced by their host plants. For example, diamondback moths (*Plutella xylostella*) produce a glucosinolate sulfatase that biochemically modifies host glucosinolates and prevents the formation of toxic hydrolysis products, actively reducing toxic burden and therefore exemplifying resistance through transformation of the harmful agent (Ratzka *et al.*, 2002; Chen *et al.*, 2020). In contrast, monarch butterflies (*Danaus plexippus*) cope with host-derived toxic cardiac glycosides through amino acid substitutions in the Na^+/K^+-ATPase, which reduce sensitivity to the toxin without altering its chemical structure (Vaughan & Jungreis, 1977; Holzinger, Frick & Wink, 1992). This well-studied example of target-site insensitivity illustrates a tolerance mechanism, as the harmful agent remains biologically active.

In contrast to metabolic detoxification of plant-derived toxins, the evolution of tolerance in herbivores can promote the transfer of these compounds through food webs, thereby influencing community dynamics and the evolutionary trajectories of populations from higher trophic levels. For example, cardenolide tolerance allows monarch butterflies to sequester these toxins in their tissues and repurpose them for defence against parasitoids and predators (Brower & Moffitt, 1974; Petschenka & Agrawal, 2015), deterring attacks by non-adapted enemies and driving the evolution of resistance and/or tolerance mechanisms in higher trophic levels. Recent work on a community of cardenolide-tolerant herbivores has provided compelling evidence for this phenomenon by demonstrating that at least four of their predators and parasitoids have convergently evolved target-site insensitivity in the Na^+/K^+-ATPase (Groen & Whiteman, 2021). Thus, the evolution of tolerance mechanisms can drive evolutionary cascades that extend across trophic levels.

These examples from Lepidoptera clearly illustrate how distinct mechanistic strategies can lead to fundamentally different ecological and evolutionary consequences and underscore the importance of employing clearly defined distinctions across subdisciplines of biological research.

322

4. Evolutionary consequences

The distinction between resistance and tolerance carries important evolutionary implications, as differences in how these strategies affect exposure, stressor fate, and interactions with other organisms translate into distinct selection pressures across generations. Below, we discuss how resistance and tolerance are studied from an evolutionary perspective and how they interact through cross-talk and eco-evolutionary feedbacks.

4.1. Contrasting evolutionary dynamics of biotic and abiotic stressors

Although we have emphasized similarities in how organisms respond to pollutants and pathogens, there is a fundamental difference between these stressors with major evolutionary consequences: unlike toxins, pathogens are living organisms and, thus, reproduce and evolve. As a result, pathogen evolution can directly shape host evolutionary trajectories. For example, pathogen replication within hosts is at the core of the virulence-transmission trade-off: while increased replication boosts transmission, it can also shorten infection duration due to premature host death (Alizon *et al.*, 2009). This trade-off is expected to select for lower virulence, with consequences for the evolution of host resistance and tolerance.

Moreover, evolutionary responses in the host can trigger counter-responses in the pathogen, potentially driving coevolution, with either Red Queen fluctuating dynamics or escalatory arms races (Woolhouse *et al.*, 2002). In turn, such coevolution will impact the evolution of tolerance or resistance in the host (Boots *et al.*, 2009). For instance, models of host-parasite interactions predict that tolerance is favored when hosts are exposed to parasites with a high growth rate (Restif & Koella, 2003). In contrast, resistance is expected to follow more dynamical coevolutionary patterns, making it less likely to become fixed compared to tolerance (Roy & Kirchner, 2000). Again, these fundamentally different predictions highlight the importance of empirical tests where the distinction between tolerance and resistance is unequivocal. Pollutants do not evolve, hence selection in polluted environments is driven primarily by persistence, transformation, and redistribution of stressors through ecological networks, rather than by coevolutionary feedbacks. Still, evolutionary consequences of host responses to abiotic stressors will also hinge upon the resistance or tolerance mechanisms involved (see section 4.3).

4.2. Approaches to address the evolution of resistance and/or tolerance

Adaptation to external stressors in ecotoxicology and immunity has been explored through a variety of complementary approaches, including local adaptation studies in natural populations, experimental evolution, interspecific comparisons of responses to similar stressors, and genetic analyses of adaptive mechanisms. A substantial body of literature tackles each of these approaches (e.g., Belliure, Montserrat & Magalhaes, 2010; Kawecki *et al.*, 2012; Koskella, 2014; Buck *et al.*, 2018; Paulo *et al.*, 2025), with certain study systems examining adaptation to stressors through multiple approaches. Despite this wealth of research, relatively few studies attribute adaptation to the evolution of resistance versus tolerance (but see e.g., Stowe, 1998; Paulo *et al.*, 2025). The results of some of these studies are summarized below.

Natural variation in responses of *Drosophila melanogaster* to copper is associated with the degree of urbanization, consistent with local adaptation to metal exposure. Transcriptomic analyses revealed that population differences in copper sensitivity were linked to differential expression of gut-expressed genes. RNAi knockdown of several candidate genes resulted in exaggerated gut acidification under copper exposure, indicating impaired capacity to mitigate copper-induced damage rather than reduced copper uptake. These results point to the evolution of tolerance - via gut damage control - rather than resistance in populations exposed to copper (Green *et al.*, 2022). Artificial selection experiments also using copper as the selective pressure also revealed phenotypic adaptation, but the response obtained could not be unambiguously attributed to either resistance or tolerance (Arnold & Everman, 2025).

Some host–parasite systems provide well-characterized examples in which adaptive responses can be directly attributed to resistance mechanisms. Bacteria, for instance, have evolved several strategies that allow them to defend themselves from phage infection (Hampton, Watson & Fineran, 2020; Watson *et al.*, 2021). One prominent example is the CRISPR–Cas system, first characterised in *Escherichia coli,* which provides sequence-specific degradation of invading viral genomes (Brouns *et al.*, 2008). Experimental evolution studies further showed that *Pseudomonas aeruginosa* evolves CRISPR-based resistance when exposed to the phage DMS3vir, alongside other defenses such as surface modification (Bondy-Denomy *et al.*, 2016; Broniewski *et al.*, 2021).

Notably, closely related species may deploy contrasting tolerance and resistance strategies when confronted with the same stressor, with distinct implications for ecological dynamics at higher levels of organization. For example, *Arabidopsis halleri* tolerates zinc concentrations that are toxic to

most plant species (Meyer *et al.*, 2010). This species efficiently translocates zinc to the shoots and sequesters it within vacuoles and leaf tissues, thereby maintaining physiological function despite a high internal zinc burden - an illustration of tolerance *sensu stricto*. In contrast, closely related *A. thaliana* maintain stricter control over zinc uptake and, under exposure to zinc excess , upregulates PCR2 expression in epidermal cells to enhance efflux and preserve cellular metal homeostasis (Kajala *et al.*, 2019). This response represents a resistance strategy, as it directly reduces internal metal burden. Contrasting strategies within the same genus underscore the diversity of evolutionary responses to identical stressors, with broad implications for ecological organization (Roosens, Willems & Saumitou-Laprade, 2008).

Resistance and tolerance mechanisms are not mutually exclusive and may evolve concurrently in the same system, as predicted by theory on host-parasite interactions (Restif & Koella, 2004). For example, a study on local adaptation of North American finches exposed to *Mycoplasma gallisepticum* bacteria shows the concurrent evolution of both mechanisms (Bonneaud *et al.*, 2019). Similarly, experimental evolution of mosquitoes exposed to microsporidia revealed the simultaneous evolution of both resistance and tolerance (Zeller & Koella, 2017). These findings underscore the importance of moving beyond binary classifications to identify the ecological and evolutionary conditions that favour the evolution of resistance, tolerance, or their combination, as well as the implications of these strategies for host fitness, stressor persistence, and broader ecological dynamics.

4.3. Correlated responses and eco-evolutionary feedbacks

As described in Section 2, resistance and tolerance differ fundamentally in their mechanistic bases and therefore have distinct evolutionary consequences for the host. However, the evolutionary consequences of these strategies on the host are unlikely to remain confined to the focal stressor. Indeed, a growing body of evidence shows that adaptation to one environmental challenge frequently alters responses to other stressors (Baker-Austin *et al.*, 2006; Martins *et al.*, 2013; Orr *et al.*, 2020; Bazzicalupo *et al.*, 2025). Of particular relevance to the framework proposed here is that evolutionary responses are often correlated both within and across abiotic and biotic stressors (Jansen *et al.*, 2011; Chauhan *et al.*, 2015; Foyer *et al.*, 2016; Biswas *et al.*, 2021; Rodgers *et al.*, 2025). Conceptual models have been proposed to address the effects of multiple stressors (Vinebrooke *et al.*, 2004; Piggott, Townsend & Matthaei, 2015), yet these frameworks have not explicitly incorporated whether responses to such stressors are mediated by tolerance or resistance mechanisms. Indeed, although concepts such as “co-

412 tolerance" (Vinebrooke *et al.*, 2004) and "cross-resistance" (Georghiou, 1972) are widely used, they
413 are seldom linked to the mechanistic basis underlying these responses. Attributing correlated
414 evolutionary responses to resistance or tolerance mechanisms may substantially improve our ability
415 to predict the net effects of adaptation to multiple stressors in natural systems.

416 The most fundamental distinction between tolerance and resistance lies in the fact that
417 tolerance implies that the stressor is retained within the focal organism. This may alter the responses
418 to subsequent abiotic or biotic challenges. For example, some plants tolerate metals through
419 sequestration in vacuoles, particularly in above-ground tissues. These accumulated metals can be co-
420 opted as an "elemental defence" against herbivores and pathogens (Rascio & Navari-Izzo, 2011),
421 thereby conferring an ecological advantage to metal-accumulating plants relative to their competitors
422 (Lin *et al.*, 2025). Tolerance may also generate cross-effects indirectly when adaptation involves
423 generalized homeostatic or damage-control mechanisms. For instance, maintaining homeostasis
424 under pollutant exposure often involves enhanced management of reactive oxygen species (ROS) and
425 increased cellular repair capacity (Andreau, Leroux & Bouharrour, 2012; Vilas-Boas *et al.*, 2024),
426 mechanisms that are also critical for limiting immunopathology during infection (Ayres & Schneider,
427 2012; Medzhitov *et al.*, 2012). As such, the existence of shared damage-control pathways renders
428 correlated responses across biotic and abiotic stressors highly plausible.

429 In contrast to tolerance, resistance operates by avoiding, reducing, or eliminating the stressor
430 and, consequently, correlated responses associated with resistance often reflect allocation trade-offs,
431 whereby investment in resistance to one stressor constrains the capacity to cope with another stressor.
432 For example, predator avoidance in damselfly larvae is significantly impaired when individuals
433 simultaneously cope with zinc pollution (Janssens *et al.*, 2014), while pesticide exposure reduces the
434 ability of scarab grub hosts to evade nematode parasites through impaired host mobility (Koppenhofer,
435 Grewal & Kaya, 2000). However, resistance mechanisms may also generate positive cross-resistance
436 when a single defence pathway confers protection against multiple stressors. For instance, pollutant
437 exposure induces epidermal thickening in fish, reducing contaminant uptake and contact, while also
438 simultaneously lowering host susceptibility to parasite infection (Smallbone, Cable & Maceda-Veiga,
439 2016). These observations indicate that, although resistance is often associated with functional trade-
440 offs, shared defence mechanisms can also produce correlated increases in resistance across distinct
441 environmental challenges. We therefore propose that both co-tolerance (or cross-tolerance) and

cross-resistance may emerge as predictable outcomes of selection by co-occurring stressors, but the generality of these patterns would require more systematic comparative and experimental evaluation.

Organismal resistance and tolerance can also shape eco-evolutionary feedbacks (Fig. 3), which arise from reciprocal interactions between ecological and evolutionary processes (Matthews *et al.*, 2014; Govaert *et al.*, 2019). In both immunological and ecotoxicological systems, these feedbacks depend on how resistance or tolerance alter stressor fate and exposure pathways. Resistance mechanisms that reduce environmental concentrations or bioavailability can lower exposure for subsequent individuals, thereby relaxing selection over time, particularly when resistance carries maintenance costs or trade-offs (Forbes & Calow, 2002; McKean *et al.*, 2008; Ashauer & Escher, 2010). Such responses therefore generate negative eco-evolutionary feedbacks, in which adaptation progressively weakens the selective pressure that initially favoured it. However, detoxification or degradation processes may also sustain or redirect selection when pollutant transformation generates metabolites with distinct toxicological effects (Farré *et al.*, 2008; Ashauer & Escher, 2010).

In contrast, tolerance mechanisms facilitate the persistence of stressors in the system, maintaining chronic exposure across generations, and thereby reinforcing selection on tolerance traits through positive feedbacks (Post & Palkovacs, 2009; Hendry, 2020). Other tolerance mechanisms, such as sequestration or isolation, may temporarily reduce exposure, but delayed release of stressors through excretion, predation or decomposition extends exposure across generations, ultimately strengthening positive feedbacks (Luoma & Rainbow, 2008, 2009). Thus, distinguishing resistance from tolerance at the mechanistic level may improve our ability to predict long-term evolutionary outcomes in environments with biotic and/or abiotic stressors.

5. Concluding remarks and future directions

We have reviewed the mechanistic foundations of resistance and tolerance, clarified their distinction across biotic and abiotic stressors, and proposed a framework that integrates subdiscipline perspectives spanning biological scales. By explicitly separating these axes, the framework clarifies how organisms maintain homeostasis under stress and strengthens predictions of ecological and evolutionary consequences, including contaminant persistence, bioaccumulation, trophic transfer, and disease dynamics. This unified perspective highlights connections between resistance-tolerance theory and ecosystem-level processes, while linking physiological mechanisms to broader ecological and evolutionary dynamics across disciplines.

By integrating mechanistic clarity with ecological realism, this framework is also relevant to other biological subdisciplines, such as those involved with chemically mediated biotic interactions (Box 2). This is well illustrated by herbivore responses to plant chemical defences, which are often broadly grouped under the functional label of 'resistance' despite fundamental differences in how plant-derived toxins are eliminated, transformed, or retained in a biologically active form (Després, David & Gallet, 2007; Zhang *et al.*, 2019; López-Goldar *et al.*, 2026; but see e.g., Jeckel *et al.*, 2022). Furthermore, the use of shared conceptual definitions enables meta-analyses, enhances cross-system comparisons, and informs predictive modelling of ecological and evolutionary outcomes, including cascading effects within food webs and host populations under environmental change.

This bidirectional exchange between disciplines, in which immunology provides formalized definitions and evolutionary models of host defence mechanisms while ecotoxicology contributes insights into stressor fate, trophic transfer, and eco-evolutionary feedbacks, also promotes interdisciplinary collaboration and broadens our understanding of adaptive responses to environmental stressors as a whole. Greater integration across these fields will improve our understanding of resistance and tolerance mechanisms and strengthen predictions of how they shape health risks. More broadly, incorporating both pathogens and toxicants into environmental health research will better reflect real-world exposure scenarios and support more comprehensive frameworks for studying responses to multiple biological and chemical stressors. Such synthesis may ultimately enhance predictive power across disciplines and provide a more generalizable framework for understanding responses to homeostasis-disrupting challenges, consistent with the One Health perspective.

References

Abdallah, S.M., Muhammed, R.E., Mohamed, R.E., El Daous, H., Saleh, D.M., Ghorab, M.A., Chen, S. & El-Sayyad, G.S. (2024) Assessment of biochemical biomarkers and environmental stress indicators in some freshwater fish. *Environmental Geochemistry and Health* **46**, 464. Springer Science and Business Media LLC.

Akyaw, P.A., Paulo, T.F., Lafuente, E. & Sucena, É. (2025) Pathogen-induced damage in Drosophila: Uncoupling disease tolerance from resistance. *PLoS Pathogens* **21**, e1013482. Public Library of Science (PLoS).

Alizon, S., Hurford, A., Mideo, N. & Van Baalen, M. (2009) Virulence evolution and the trade-off hypothesis: history, current state of affairs and the future. *Journal of Evolutionary Biology* **22**, 245–259. Oxford University Press (OUP).

Anderson, R.M. & May, R.M. (1992) *Infectious diseases of humans*. Oxford University Press, London, England.

Andreau, K., Leroux, M. & Bouharrour, A. (2012) Health and cellular impacts of air pollutants: from cytoprotection to cytotoxicity. *Biochemistry Research International* **2012**, 493894. Hindawi Limited.

Arnold, K. & Everman, E.R. (2025) Artificial selection for resistance to copper and off-target physiological and behavioral effects in Drosophila melanogaster. *bioRxivorg*. Http://dx.doi.org/10.1101/2025.09.30.679338.

Ashauer, R. & Escher, B.I. (2010) Advantages of toxicokinetic and toxicodynamic modelling in aquatic ecotoxicology and risk assessment. *Journal of Environmental Monitoring* **12**, 2056–2061. Royal Society of Chemistry (RSC).

Ayres, J.S. & Schneider, D.S. (2012) Tolerance of infections. *Annual Review of Immunology* **30**, 271–294. Annual Reviews.

Bahadorani, S. & Hilliker, A.J. (2009) Biological and behavioral effects of heavy metals in Drosophila melanogaster adults and larvae. *Journal of Insect Behavior* **22**, 399–411. Springer Science and Business Media LLC.

Baker-Austin, C., Wright, M.S., Stepanauskas, R. & McArthur, J.V. (2006) Co-selection of antibiotic and metal resistance. *Trends in Microbiology* **14**, 176–182. Elsevier BV.

Bard, S.M. (2000) Multixenobiotic resistance as a cellular defense mechanism in aquatic organisms. *Aquatic toxicology* **48**, 357–389.

Barneche, D.R., Hulatt, C.J., Dossena, M., Padfield, D., Woodward, G., Trimmer, M. & Yvon-Durocher, G. (2021) Warming impairs trophic transfer efficiency in a long-term field experiment. *Nature* **592**, 76–79. Springer Science and Business Media LLC.

Bastamy, M., Raheel, I., Elbestawy, A., Diab, M., Hammad, E., Elebeedy, L., El-Barbary, A.M., Albadrani, G.M., Abdel-Daim, M.M., Abdel-Latif, M.A. & Orabi, A. (2024) Postbiotic, anti-inflammatory, and immunomodulatory effects of aqueous microbial lysozyme in broiler chickens. *Animal Biotechnology* **35**, 2309955. Informa UK Limited.

Baucom, R.S. & de Roode, J.C. (2011) Ecological immunology and tolerance in plants and animals: Tolerance in plants and animals. *Functional Ecology* **25**, 18–28. Wiley.

Bazzicalupo, A.L., Kahn, P.C., Ao, E., Campbell, J. & Otto, S.P. (2025) Evolution of cross-tolerance to metals in yeast. *Proceedings of the National Academy of Sciences of the United States of America* **122**, e2505337122.

Behringer, D.C., Karvonen, A. & Bojko, J. (2018) Parasite avoidance behaviours in aquatic environments. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*

373, 20170202. The Royal Society.

Belliure, B., Montserrat, M. & Magalhaes, S. (2010) Mites as models for experimental evolution studies. *Acarologia* **50**, 513–529. Les Amis d'Acarologia.

Binggeli, O., Neyen, C., Poidevin, M. & Lemaitre, B. (2014) Prophenoloxidase activation is required for survival to microbial infections in Drosophila. *PLoS Pathogens* **10**, e1004067. Public Library of Science (PLoS).

Biswas, R., Halder, U., Kabiraj, A., Mondal, A. & Bandopadhyay, R. (2021) Overview on the role of heavy metals tolerance on developing antibiotic resistance in both Gram-negative and Gram-positive bacteria. *Archives of Microbiology* **203**, 2761–2770. Springer Science and Business Media LLC.

Bondy-Denomy, J., Qian, J., Westra, E.R., Buckling, A., Guttman, D.S., Davidson, A.R. & Maxwell, K.L. (2016) Prophages mediate defense against phage infection through diverse mechanisms. *The ISME Journal* **10**, 2854–2866.

Bonneaud, C., Tardy, L., Giraudeau, M., Hill, G.E., McGraw, K.J. & Wilson, A.J. (2019) Evolution of both host resistance and tolerance to an emerging bacterial pathogen. *Evolution Letters* **3**, 544–554. Oxford University Press (OUP).

Boots, M. (2011) The evolution of resistance to a parasite is determined by resources. *The American Naturalist* **178**, 214–220. University of Chicago Press.

Boots, M., Best, A., Miller, M.R. & White, A. (2009) The role of ecological feedbacks in the evolution of host defence: what does theory tell us? *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* **364**, 27–36. The Royal Society.

Borremans, B., Faust, C., Manlove, K.R., Sokolow, S.H. & Lloyd-Smith, J.O. (2019) Cross-species pathogen spillover across ecosystem boundaries: mechanisms and theory. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* **374**, 20180344. The Royal Society.

Borst, P., Evers, R., Kool, M. & Wijnholds, J. (2000) A family of drug transporters: the multidrug resistance-associated proteins. *Journal of the National Cancer Institute* **92**, 1295–1302. Oxford University Press (OUP).

Broniewski, J.M., Chisnall, M.A.W., Høyland-Kroghsbo, N.M., Buckling, A. & Westra, E.R. (2021) The effect of Quorum sensing inhibitors on the evolution of CRISPR-based phage immunity in Pseudomonas aeruginosa. *The ISME Journal* **15**, 2465–2473. Oxford University Press (OUP).

Brouns, S.J.J., Jore, M.M., Lundgren, M., Westra, E.R., Slijkhuis, R.J.H., Snijders, A.P.L., Dickman, M.J., Makarova, K.S., Koonin, E.V. & van der Oost, J. (2008) Small CRISPR RNAs guide antiviral defense in prokaryotes. *Science (New York, N.Y.)* **321**, 960–964. American Association for the Advancement of Science (AAAS).

Brower, L.P. & Moffitt, C.M. (1974) Palatability dynamics of cardenolides in the monarch butterfly. *Nature* **249**, 280–283. Springer Science and Business Media LLC.

Buchon, N., Broderick, N.A., Poidevin, M., Pradervand, S. & Lemaitre, B. (2009) Drosophila intestinal response to bacterial infection: activation of host defense and stem cell proliferation. *Cell Host & Microbe* **5**, 200–211. Elsevier BV.

Buck, J.C., Weinstein, S.B. & Young, H.S. (2018) Ecological and evolutionary consequences of parasite avoidance. *Trends in Ecology & Evolution* **33**, 619–632. Elsevier BV.

Cabiscol, E., Tamarit, J. & Ros, J. (2000) Oxidative stress in bacteria and protein damage by reactive oxygen species. *International Microbiology: The Official Journal of the Spanish Society for Microbiology* **3**, 3–8.

Caldwell, R.M., Schafer, J.F., Compton, L.E. & Patterson, F.L. (1958) Tolerance to cereal leaf rusts.

Science (New York, N.Y.) **128**, 714–715. American Association for the Advancement of Science (AAAS).

Calow, P. & Forbes, V.E. (2003) Peer reviewed: Does ecotoxicology inform ecological risk assessment? *Environmental Science & Technology* **37**, 146A – 151A. American Chemical Society (ACS).

do Carmo Santos, M.L., Silva Santos, A., Pereira Silva de Novais, D., Dos Santos Lopes, N., Pirovani, C.P. & Micheli, F. (2025) The family of glutathione peroxidase proteins and their role against biotic stress in plants: a systematic review. *Frontiers in Plant Science* **16**, 1425880.

Chauhan, E., Bali, A., Singh, N. & Jaggi, A.S. (2015) Cross stress adaptation: Phenomenon of interactions between homotypic and heterotypic stressors. *Life Sciences* **137**, 98–104. Elsevier BV.

Chen, W., Dong, Y., Saqib, H.S.A., Vasseur, L., Zhou, W., Zheng, L., Lai, Y., Ma, X., Lin, L., Xu, X., Bai, J., He, W. & You, M. (2020) Functions of duplicated glucosinolate sulfatases in the development and host adaptation of Plutella xylostella. *Insect Biochemistry and Molecular Biology* **119**, 103316. Elsevier BV.

Clemens, S. (2006) Toxic metal accumulation, responses to exposure and mechanisms of tolerance in plants. *Biochimie* **88**, 1707–1719. Elsevier BV.

Connell, D.W. (1988) Bioaccumulation behavior of persistent organic chemicals with aquatic organisms. *Reviews of Environmental Contamination and Toxicology* **102**, 117–154. Springer New York, New York, NY.

Cornelissen, G., Breedveld, G.D., Naes, K., Oen, A.M.P. & Ruus, A. (2006) Bioaccumulation of native polycyclic aromatic hydrocarbons from sediment by a polychaete and a gastropod: freely dissolved concentrations and activated carbon amendment. *Environmental Toxicology and Chemistry* **25**, 2349–2355. Oxford University Press (OUP).

Cummins, I., Dixon, D.P., Freitag-Pohl, S., Skipsey, M. & Edwards, R. (2011) Multiple roles for plant glutathione transferases in xenobiotic detoxification. *Drug Metabolism Reviews* **43**, 266–280. Informa UK Limited.

Després, L., David, J.-P. & Gallet, C. (2007) The evolutionary ecology of insect resistance to plant chemicals. *Trends in Ecology & Evolution* **22**, 298–307. Elsevier BV.

Dixon, D.P., Cummins, I. & Cole, D.J. (1998) Robert Edwards Glutathione-mediated detoxification systems in plants Current Opinion in Plant Biology. *Current Opinion in Plant Biology* **1**, 258–266.

Dropkin, V.H. (1955) The relations between nematodes and plants. *Experimental Parasitology* **4**, 282–322. Elsevier BV.

Dropkin, V. & Nelson, P. (1960) The histopathology of root-knot nematode infections in soybeans. *Phytopathology* **50**, 442–447.

Du, E.J., Ahn, T.J., Kwon, I., Lee, J.H., Park, J.-H., Park, S.H., Kang, T.M., Cho, H., Kim, T.J., Kim, H.-W., Jun, Y., Lee, H.J., Lee, Y.S., Kwon, J.Y. & Kang, K. (2016) TrpA1 regulates defecation of food-borne pathogens under the control of the Duox pathway. *PLoS Genetics* **12**, e1005773. Public Library of Science (PLoS).

Duneau, D., Ferdy, J.-B., Revah, J., Kondolf, H., Ortiz, G.A., Lazzaro, B.P. & Buchon, N. (2017) Stochastic variation in the initial phase of bacterial infection predicts the probability of survival in D. melanogaster. *eLife* **6**. eLife Sciences Publications, Ltd.

Duneau, D., Lafont, P.D.M., Lauzeral, C., Parthuisot, N., Faucher, C., Jin, X., Buchon, N. & Ferdy, J.-B. (2025) A within-host infection model to explore tolerance and resistance. *eLife* **14**, e104052. eLife Sciences Publications, Ltd.

Ehsani, J., Movahedinia, A., Abdi, R., Safahieh, A. & Salati, A.P. (2024) Gill alterations of whiteleg shrimp (Litopenaeus vannamei) exposed to cadmium under different experimental salinities. *Veterinary Medicine and Science* **10**, e1494. Wiley.

632 Farré, M. la, Pérez, S., Kantiani, L. & Barceló, D. (2008) Fate and toxicity of emerging pollutants, their
633 metabolites and transformation products in the aquatic environment. *Trends in Analytical*
634 *Chemistry: TRAC* **27**, 991–1007. Elsevier BV.

635 Ferreira, M., Costa, J. & Reis-Henriques, M.A. (2014) ABC transporters in fish species: a review.
636 *Frontiers in Physiology* **5**, 266. Frontiers Media SA.

637 Fischhoff, I.R., Huang, T., Hamilton, S.K., Han, B.A., LaDeau, S.L., Ostfeld, R.S., Rosi, E.J. & Solomon,
638 C.T. (2020) Parasite and pathogen effects on ecosystem processes: A quantitative review.
639 *Ecosphere (Washington, D.C)* **11**. Wiley.

640 Flannagan, R.S., Heit, B. & Heinrichs, D.E. (2015) Antimicrobial mechanisms of macrophages and the
641 immune evasion strategies of Staphylococcus aureus. *Pathogens* **4**, 826–868. MDPI AG.

642 Fleeger, J.W., Carman, K.R. & Nisbet, R.M. (2003) Indirect effects of contaminants in aquatic
643 ecosystems. *The Science of the Total Environment* **317**, 207–233. Elsevier BV.

644 Forbes, V.E. & Calow, P. (2002) Population growth rate as a basis for ecological risk assessment of
645 toxic chemicals. *Philosophical Transactions of the Royal Society of London. Series B, Biological*
646 *Sciences* **357**, 1299–1306. The Royal Society.

647 Forbes, V.E. & Calow, P. (2003) Population growth rate as a basis for ecological risk assessment of
648 toxic chemicals. In *Wildlife Population Growth Rates* (eds R.M. Sibly, J. Hone & T.H. Clutton-
649 Brock), pp. 269–283. Cambridge University Press, Cambridge.

650 Foyer, C.H., Rasool, B., Davey, J.W. & Hancock, R.D. (2016) Cross-tolerance to biotic and abiotic
651 stresses in plants: a focus on resistance to aphid infestation. *Journal of Experimental Botany* **67**,
652 2025–2037. Oxford University Press (OUP).

653 Frey, D.G. (1961) The biology of polluted waters. *Limnology and Oceanography* **6**, 98–98. Wiley.

654 Georghiou, G.P. (1972) The evolution of resistance to pesticides. *Annual Review of Ecology and*
655 *Systematics* **3**, 133–168. Annual Reviews.

656 Gibson, A.K. & Amoroso, C.R. (2022) Evolution and ecology of parasite avoidance. *Annual Review of*
657 *Ecology, Evolution, and Systematics* **53**, 47–67. Annual Reviews.

658 Godinho, D.P., Fragata, I., de la Masseliere, M.C. & Magalhães, S. (2024) Spider mites collectively
659 avoid plants with cadmium irrespective of their frequency or the presence of competitors. *Peer*
660 *Community Journal* **4**. Peer Community In.

661 Govaert, L., Fronhofer, E.A., Lion, S., Eizaguirre, C., Bonte, D., Egas, M., Hendry, A.P., De Brito
662 Martins, A., Melián, C.J., Raeymaekers, J.A.M., Ratikainen, I.I., Saether, B., Schweitzer, J.A. &
663 Matthews, B. (2019) Eco-evolutionary feedbacks—Theoretical models and perspectives.
664 *Functional ecology* **33**, 13–30.

665 Green, L., Coronado-Zamora, M., Radío, S., Rech, G.E., Salces-Ortiz, J. & González, J. (2022) The
666 genomic basis of copper tolerance in Drosophila is shaped by a complex interplay of regulatory
667 and environmental factors. *BMC Biology* **20**, 275. Springer Science and Business Media LLC.

668 Groen, S.C. & Whiteman, N.K. (2021) Convergent evolution of cardiac-glycoside resistance in
669 predators and parasites of milkweed herbivores. *Current Biology* **31**, R1465–R1466. Elsevier BV.

670 Ha, E.-M., Oh, C.-T., Ryu, J.-H., Bae, Y.-S., Kang, S.-W., Jang, I.-H., Brey, P.T. & Lee, W.-J. (2005) An
671 antioxidant system required for host protection against gut infection in Drosophila.
672 *Developmental Cell* **8**, 125–132. Elsevier BV.

673 Hampton, H.G., Watson, B.N.J. & Fineran, P.C. (2020) The arms race between bacteria and their phage
674 foes. *Nature* **577**, 327–336. Springer Science and Business Media LLC.

675 Harko, T., Lobo, F.S.N. & Mak, M.K. (2014) Exact analytical solutions of the Susceptible-Infected-
676 Recovered (SIR) epidemic model and of the SIR model with equal death and birth rates. *Applied*

677 *Mathematics and Computation* **236**, 184–194. Elsevier BV.

678 Hayman, D.T.S. (2016) Bats as viral reservoirs. *Annual Review of Virology* **3**, 77–99. Annual Reviews.

679 Heine, H. (ed) (2007) *Innate immunity of plants, animals and humans*, 2008th edition. Springer, Berlin,
680 Germany.

681 Hendry, A.P. (2020) *Eco-evolutionary dynamics*. Princeton University Press, Princeton, NJ.

682 Holzinger, F., Frick, C. & Wink, M. (1992) Molecular basis for the insensitivity of the Monarch (Danaus
683 plexippus) to cardiac glycosides. *FEBS Letters* **314**, 477–480. Wiley.

684 Horn, C.C. (2017) *The Physiology of Vomiting" in Nausea and Vomiting*. Springer International
685 Publishing Switzerland.

686 Jansen, M., Coors, A., Stoks, R. & De Meester, L. (2011) Evolutionary ecotoxicology of pesticide
687 resistance: a case study in Daphnia. *Ecotoxicology (London, England)* **20**, 543–551. Springer
688 Science and Business Media LLC.

689 Janssens, L., Dinh Van, K., Debecker, S., Bervoets, L. & Stoks, R. (2014) Local adaptation and the
690 potential effects of a contaminant on predator avoidance and antipredator responses under
691 global warming: a space-for-time substitution approach. *Evolutionary Applications* **7**, 421–430.
692 Wiley.

693 Jeckel, A.M., Beran, F., Züst, T., Younkin, G., Petschenka, G., Pokharel, P., Dreisbach, D., Ganal-
694 Vonarburg, S.C. & Robert, C.A.M. (2022) Metabolization and sequestration of plant specialized
695 metabolites in insect herbivores: Current and emerging approaches. *Frontiers in Physiology* **13**,
696 1001032.

697 Jezierska, B., Ługowska, K. & Witeska, M. (2009) The effects of heavy metals on embryonic
698 development of fish (a review). *Fish Physiology and Biochemistry* **35**, 625–640. Springer Science
699 and Business Media LLC.

700 Kajala, K., Walker, K.L., Mitchell, G.S., Krämer, U., Cherry, S.R. & Brady, S.M. (2019) Real-time whole-
701 plant dynamics of heavy metal transport in Arabidopsis halleri and Arabidopsis thaliana by
702 gamma-ray imaging. *Plant Direct* **3**, e00131. Wiley.

703 Kawecki, T.J., Lenski, R.E., Ebert, D., Hollis, B., Olivieri, I. & Whitlock, M.C. (2012) Experimental
704 evolution. *Trends in Ecology & Evolution* **27**, 547–560. Elsevier BV.

705 Kermack, W.O. & McKendrick, A.G. (1927) A contribution to the mathematical theory of epidemics.
706 *Proceedings of the Royal Society of London. Series A, Mathematical and Physical Sciences* **115**, 700–
707 721. The Royal Society.

708 Kogan, M. & Ortman, E.F. (1978) Antixenosis-A new term proposed to define painter's
709 'nonpreference' modality of resistance. *Bulletin of the Entomological Society of America* **24**, 175–
710 176. Oxford University Press (OUP).

711 Koppenhofer, A.M., Grewal, P.S. & Kaya, H.K. (2000) Synergism of imidacloprid and
712 entomopathogenic nematodes against white grubs: the mechanism. *Entomologia experimentalis*
713 *et applicata* **94**, 283–293. Wiley.

714 Koskella, B. (2014) Bacteria-phage interactions across time and space: merging local adaptation and
715 time-shift experiments to understand phage evolution. *The American Naturalist* **184 Suppl 1**, S9–
716 S21. University of Chicago Press.

717 Kotas, M.E. & Medzhitov, R. (2015) Homeostasis, inflammation, and disease susceptibility. *Cell* **160**,
718 816–827. Elsevier BV.

719 Kournouto, G.G., Giannopoulou, P.C., Sazakli, E., Leotsinidis, M., Kalpaxis, D.L. & Dinos, G.P. (2020)
720 Oxidative damage of mussels living in seawater enriched with trace metals, from the viewpoint
721 of proteins expression and modification. *Toxics* **8**, E89. MDPI AG.

Kutzer, M.A.M. & Armitage, S.A.O. (2016) Maximising fitness in the face of parasites: a review of host tolerance. *Zoology (Jena, Germany)* **119**, 281–289. Elsevier BV.

Labbé, P., Berticat, C., Berthomieu, A., Unal, S., Bernard, C., Weill, M. & Lenormand, T. (2007) Forty years of erratic insecticide resistance evolution in the mosquito Culex pipiens. *PLoS Genetics* **3**, e205. Public Library of Science (PLoS).

Lafuente, E., Carles, L., Walser, J.-C., Giulio, M., Wullschleger, S., Stamm, C. & Räsänen, K. (2023) Effects of anthropogenic stress on hosts and their microbiomes: Treated wastewater alters performance and gut microbiome of a key detritivore (Asellus aquaticus). *Evolutionary applications* **16**, 824–848.

Lambeth, J.D. (2004) NOX enzymes and the biology of reactive oxygen. *Nature Reviews. Immunology* **4**, 181–189. Springer Science and Business Media LLC.

Lavoie, R.A., Jardine, T.D., Chumchal, M.M., Kidd, K.A. & Campbell, L.M. (2013) Biomagnification of mercury in aquatic food webs: a worldwide meta-analysis. *Environmental Science & Technology* **47**, 13385–13394. American Chemical Society (ACS).

Lei, M., Tan, Y., Tu, H. & Tan, W. (2024) Neuronal basis and diverse mechanisms of pathogen avoidance in Caenorhabditis elegans. *Frontiers in Immunology* **15**, 1353747. Frontiers Media SA.

Le Roux, V., Dugravot, S., Brunissen, L., Vincent, C., Pelletier, Y. & Giordanengo, P. (2010) Antixenosis phloem-based resistance to aphids: is it the rule. *Ecological Entomology* **35**, 407–416. Wiley.

Lin, T., Manan, A., Yang, S., Zhu, G., Wang, Y., Dai, Z., Vrieling, K. & Li, B. (2025) Heavy metal pollution enhances pathogen resistance of an invasive plant species over its native congener. *Functional Ecology* **39**, 1096–1111. Wiley.

Lopes, I., Baird, D.J. & Ribeiro, R. (2004) Avoidance of copper contamination by field populations of Daphnia longispina. *Environmental Toxicology and Chemistry* **23**, 1702–1708. Oxford University Press (OUP).

López-Goldar, X., Rubiano-Buitrago, P.A., Hastings, A.P. & Agrawal, A.A. (2026) Costs of toxin ingestion versus costs of sequestration in a community of specialized herbivores. *Proceedings. Biological Sciences* **293**, 20260044. The Royal Society.

Luis, A.D., Hayman, D.T.S., O'Shea, T.J., Cryan, P.M., Gilbert, A.T., Pulliam, J.R.C., Mills, J.N., Timonin, M.E., Willis, C.K.R., Cunningham, A.A., Fooks, A.R., Rupprecht, C.E., Wood, J.L.N. & Webb, C.T. (2013) A comparison of bats and rodents as reservoirs of zoonotic viruses: are bats special? *Proceedings. Biological Sciences* **280**, 20122753. The Royal Society.

Lu, M. (2016) Structures of multidrug and toxic compound extrusion transporters and their mechanistic implications. *Channels (Austin, Tex.)* **10**, 88–100. Informa UK Limited.

Luoma, S.N. & Rainbow, P.S. (2008) *Metal contamination in aquatic environments*. Cambridge University Press, Cambridge, England.

Luoma, S.N. & Rainbow, P.S. (2009) *Metal contamination in aquatic environments: Science and lateral management*. Cambridge University Press, Cambridge, 2008.

Lyu, J., Narum, D.E., Baldwin, S.L., Larsen, S.E., Bai, X., Griffith, D.E., Dartois, V., Naidoo, T., Steyn, A.J.C., Coler, R.N. & Chan, E.D. (2024) Understanding the development of tuberculous granulomas: insights into host protection and pathogenesis, a review in humans and animals. *Frontiers in Immunology* **15**, 1427559. Frontiers Media SA.

Ma, Q. (2013) Role of Nrf2 in oxidative stress and toxicity. *Annual Review of Pharmacology and Toxicology* **53**, 401–426. Annual Reviews.

Martins, N.E., Faria, V.G., Teixeira, L., Magalhães, S. & Sucena, É. (2013) Host adaptation is contingent upon the infection route taken by pathogens. *PLoS Pathogens* **9**, e1003601. Public Library of Science (PLoS).

768 Matthews, B., De Meester, L., Jones, C.G., Ibelings, B.W., Bouma, T.J., Nuutinen, V., van de Koppel, J. &
769 Odling-Smee, J. (2014) Under niche construction: an operational bridge between ecology,
770 evolution, and ecosystem science. *Ecological Monographs* **84**, 245–263. Wiley.

771 McKean, K.A., Yourth, C.P., Lazzaro, B.P. & Clark, A.G. (2008) The evolutionary costs of
772 immunological maintenance and deployment. *BMC Evolutionary Biology* **8**, 76.

773 Medawar, P. (1960) Immunological Tolerance. Nobel Lecture. *NobelPrize.org*.
774 Https://www.nobelprize.org/prizes/medicine/1960/medawar/lecture/ [accessed 3 March 2026].

775 Medzhitov, R., Schneider, D.S. & Soares, M.P. (2012) Disease tolerance as a defense strategy. *Science*
776 *(New York, N.Y.)* **335**, 936–941. American Association for the Advancement of Science (AAAS).

777 Meisel, J.D. & Kim, D.H. (2014) Behavioral avoidance of pathogenic bacteria by Caenorhabditis
778 elegans. *Trends in Immunology* **35**, 465–470. Elsevier BV.

779 Meyer, C.-L., Kostecka, A.A., Saumitou-Laprade, P., Créach, A., Castric, V., Pauwels, M. & Frérot, H.
780 (2010) Variability of zinc tolerance among and within populations of the pseudometallophyte
781 species Arabidopsis halleri and possible role of directional selection. *The New Phytologist* **185**,
782 130–142. Wiley.

783 Meyer, J.N., Nacci, D.E. & Di Giulio, R.T. (2002) Cytochrome P4501A (CYP1A) in killifish (Fundulus
784 heteroclitus): heritability of altered expression and relationship to survival in contaminated
785 sediments. *Toxicological Sciences: An Official Journal of the Society of Toxicology* **68**, 69–81. Oxford
786 University Press (OUP).

787 Mogren, C.L. & Trumble, J.T. (2010) The impacts of metals and metalloids on insect behavior.
788 *Entomologia experimentalis et applicata* **135**, 1–17. Wiley.

789 Moriarty, F. (1988) Ecotoxicology. *Human Toxicology* **7**, 437–441. SAGE Publications.

790 Moriyama, Y., Hiasa, M., Matsumoto, T. & Omote, H. (2008) Multidrug and toxic compound extrusion
791 (MATE)-type proteins as anchor transporters for the excretion of metabolic waste products and
792 xenobiotics. *Xenobiotica; the Fate of Foreign Compounds in Biological Systems* **38**, 1107–1118.
793 Informa UK Limited.

794 Murphy, K., Weaver, C., Berg, L., Barton, G. & Janeway, C.A. (2022) *Janeway's Immunobiology*. W.W.
795 Norton and Company,.

796 Nathan, C. & Cunningham-Bussel, A. (2013) Beyond oxidative stress: an immunologist's guide to
797 reactive oxygen species. *Nature Reviews. Immunology* **13**, 349–361. Springer Science and Business
798 Media LLC.

799 Orr, J.A., Vinebrooke, R.D., Jackson, M.C., Kroeker, K.J., Kordas, R.L., Mantyka-Pringle, C., Van den
800 Brink, P.J., De Laender, F., Stoks, R., Holmstrup, M., Matthaei, C.D., Monk, W.A., Penk, M.R.,
801 Leuzinger, S., Schäfer, R.B., et al. (2020) Towards a unified study of multiple stressors: divisions
802 and common goals across research disciplines. *Proceedings. Biological Sciences* **287**, 20200421.
803 The Royal Society.

804 Pagán, I. & García-Arenal, F. (2020) Tolerance of plants to pathogens: A unifying view. *Annual Review*
805 *of Phytopathology* **58**, 77–96. Annual Reviews.

806 Pak, E.S. & Murashov, A.K. (2021) Drosophila passive avoidance behavior as a new paradigm to study
807 associative aversive learning. *Journal of Visualized Experiments: JoVE*. MyJove Corporation.

808 Paulo, T.F., Akyaw, P.A., Paixão, T. & Sucena, É. (2025) Evolution of resistance and disease tolerance
809 mechanisms to oral bacterial infection in Drosophila melanogaster. *Open Biology* **15**, 240265. The
810 Royal Society.

811 Petschenka, G. & Agrawal, A.A. (2015) Milkweed butterfly resistance to plant toxins is linked to
812 sequestration, not coping with a toxic diet. *Proceedings. Biological Sciences* **282**, 20151865. The
813 Royal Society.

814 Piggott, J.J., Townsend, C.R. & Matthaei, C.D. (2015) Reconceptualizing synergism and antagonism
815 among multiple stressors. *Ecology and Evolution* **5**, 1538–1547. Wiley.

816 Post, D.M. & Palkovacs, E.P. (2009) Eco-evolutionary feedbacks in community and ecosystem
817 ecology: interactions between the ecological theatre and the evolutionary play. *Philosophical*
818 *Transactions of the Royal Society of London. Series B, Biological Sciences* **364**, 1629–1640. The Royal
819 Society.

820 Pradeu, T. (2020) *Philosophy of immunology*. Cambridge University Press (Virtual Publishing),
821 Cambridge, England.

822 Pradeu, T., Thomma, B.P.H.J., Girardin, S.E. & Lemaitre, B. (2024) The conceptual foundations of
823 innate immunity: Taking stock 30 years later. *Immunity* **57**, 613–631. Elsevier BV.

824 Råberg, L. (2014) How to live with the enemy: understanding tolerance to parasites. *PLoS Biology* **12**,
825 e1001989. Public Library of Science (PLoS).

826 Råberg, L., Graham, A.L. & Read, A.F. (2009) Decomposing health: tolerance and resistance to
827 parasites in animals. *Philosophical Transactions of the Royal Society of London. Series B, Biological*
828 *Sciences* **364**, 37–49. The Royal Society.

829 Råberg, L., Sim, D. & Read, A.F. (2007) Disentangling genetic variation for resistance and tolerance to
830 infectious diseases in animals. *Science (New York, N.Y.)* **318**, 812–814. American Association for
831 the Advancement of Science (AAAS).

832 Råberg, S. & Kautsky, L. (2007) A comparative biodiversity study of the associated fauna of perennial
833 fucoids and filamentous algae. *Estuarine, Coastal and Shelf Science* **73**, 249–258. Elsevier BV.

834 Ragland, S.A. & Criss, A.K. (2017) From bacterial killing to immune modulation: Recent insights into
835 the functions of lysozyme. *PLoS Pathogens* **13**, e1006512. Public Library of Science (PLoS).

836 Rascio, N. & Navari-Izzo, F. (2011) Heavy metal hyperaccumulating plants: how and why do they do
837 it? And what makes them so interesting? *Plant Science: An International Journal of Experimental*
838 *Plant Biology* **180**, 169–181. Elsevier BV.

839 Ratzka, A., Vogel, H., Kliebenstein, D.J., Mitchell-Olds, T. & Kroymann, J. (2002) Disarming the
840 mustard oil bomb. *Proceedings of the National Academy of Sciences of the United States of America*
841 **99**, 11223–11228. Proceedings of the National Academy of Sciences.

842 Raymond, M., Chevillon, C., Guillemaud, T., Lenormand, T. & Pasteur, N. (1998) An overview of the
843 evolution of overproduced esterases in the mosquito Culex pipiens. *Philosophical Transactions of*
844 *the Royal Society of London. Series B, Biological Sciences* **353**, 1707–1711. The Royal Society.

845 Read, A.F., Graham, A.L. & Råberg, L. (2008) Animal defenses against infectious agents: is damage
846 control more important than pathogen control. *PLoS Biology* **6**, e4. Public Library of Science
847 (PLoS).

848 Restif, O. & Koella, J.C. (2003) Shared control of epidemiological traits in a coevolutionary model of
849 host-parasite interactions. *The American Naturalist* **161**, 827–836. University of Chicago Press.

850 Restif, O. & Koella, J.C. (2004) Concurrent evolution of resistance and tolerance to pathogens. *The*
851 *American Naturalist* **164**, E90–E102. University of Chicago Press.

852 Rodgers, E.M., Baldanzi, S., Collins, M., Dowd, W.W., Feugere, L., Mottola, G., Vermandele, F. & Gomez
853 Isaza, D.F. (2025) Protective multi-stressor interactions in the Anthropocene: Key
854 considerations for investigating cross-tolerance in a conservation context. *Conservation*
855 *Physiology* **13**, coaf052. Oxford University Press (OUP).

856 Rolot, M. & Dewals, B.G. (2018) Macrophage activation and functions during helminth infection:
857 Recent advances from the laboratory mouse. *Journal of Immunology Research* **2018**, 2790627.
858 Wiley.

Roosens, N.H.C.J., Willems, G. & Saumitou-Laprade, P. (2008) Using Arabidopsis to explore zinc tolerance and hyperaccumulation. *Trends in Plant Science* **13**, 208–215. Elsevier BV.

Roy, B.A. & Kirchner, J.W. (2000) Evolutionary dynamics of pathogen resistance and tolerance. *Evolution; international journal of organic evolution* **54**, 51–63.

Rubinić, M., Arias-Rojas, A., Martinez, K., Klimek, W., Paczia, N., Alagesan, K., Duneau, D. & Iatsenko, I. (2025) Sex differences in *Drosophila* intestinal metabolism contribute to sexually dimorphic infection outcome and alter gut pathogen virulence. bioRxiv. *bioRxiv*. Http://dx.doi.org/10.1101/2025.05.22.655590.

Sadd, B.M. & Schmid-Hempel, P. (2009) Principles of ecological immunology: Principles of ecological immunology. *Evolutionary Applications* **2**, 113–121. Wiley.

Schafer, J.F. (1971) Tolerance to plant disease. *Annual Review of Phytopathology* **9**, 235–252. Annual Reviews.

Schneider, D.S. & Ayres, J.S. (2008) Two ways to survive infection: what resistance and tolerance can teach us about treating infectious diseases. *Nature reviews. Immunology* **8**, 889–895.

Schuler, M.A. (2011) P450s in plant-insect interactions. *Biochimica et biophysica acta* **1814**, 36–45. Elsevier BV.

Seabloom, E.W., Borer, E.T., Gross, K., Kendig, A.E., Lacroix, C., Mitchell, C.E., Mordecai, E.A. & Power, A.G. (2015) The community ecology of pathogens: coinfection, coexistence and community composition. *Ecology Letters* **18**, 401–415. Wiley.

Silverstein, A.M. (1989) *A history of immunology*. Academic Press, San Diego, CA.

Siminszky, B. (2006) Plant cytochrome P450-mediated herbicide metabolism. *Phytochemistry Reviews: Proceedings of the Phytochemical Society of Europe* **5**, 445–458. Springer Science and Business Media LLC.

Smallbone, W., Cable, J. & Maceda-Veiga, A. (2016) Chronic nitrate enrichment decreases severity and induces protection against an infectious disease. *Environment International* **91**, 265–270. Elsevier BV.

Sodani, K., Patel, A., Kathawala, R.J. & Chen, Z.-S. (2012) Multidrug resistance associated proteins in multidrug resistance. *Chinese Journal of Cancer* **31**, 58–72. Editorial Office of Chinese Journal of Cancer.

Song, W.-Y., Mendoza-Cózatl, D.G., Lee, Y., Schroeder, J.I., Ahn, S.-N., Lee, H.-S., Wicker, T. & Martinoia, E. (2014) Phytochelatin-metal(loid) transport into vacuoles shows different substrate preferences in barley and Arabidopsis. *Plant, Cell & Environment* **37**, 1192–1201. Wiley.

Stegeman, J.J., Hahn, M.E. & Reyle-Hahn, M. (1994) Biochemistry and molecular biology of monooxygenases: Current perspectives on forms, functions, and regulation of cytochrome p450 in aquatic species. *Aquatic Toxicology: Molecular, Biochemical and Cellular Perspectives*.

Stegeman, J.J. & Lech, J.J. (1991) Cytochrome P-450 monooxygenase systems in aquatic species: carcinogen metabolism and biomarkers for carcinogen and pollutant exposure. *Environmental Health Perspectives* **90**, 101–109. Environmental Health Perspectives.

Steinbrenner, H. & Sies, H. (2009) Protection against reactive oxygen species by selenoproteins. *Biochimica et biophysica acta* **1790**, 1478–1485. Elsevier BV.

Stout, M.J. (2013) Reevaluating the conceptual framework for applied research on host-plant resistance. *Insect Science* **20**, 263–272. Wiley.

Stowe, K.A. (1998) Experimental evolution of resistance in Brassica rapa: Correlated response of tolerance in lines selected for glucosinolate content. *Evolution; International Journal of Organic Evolution* **52**, 703–712. Oxford University Press (OUP).

904 Tafesh-Edwards, G. & Eleftherianos, I. (2023) The Drosophila melanogaster prophenoloxidase
905 system participates in immunity against Zika virus infection. *European Journal of Immunology* **53**,
906 e2350632.

907 Takanashi, K., Shitan, N. & Yazaki, K. (2014) The multidrug and toxic compound extrusion (MATE)
908 family in plants. *Plant Biotechnology (Tokyo, Japan)* **31**, 417–430. Japanese Society for Plant Cell
909 and Molecular Biology.

910 Truhaut, R. (1977) Ecotoxicology: objectives, principles and perspectives. *Ecotoxicology and*
911 *Environmental Safety* **1**, 151–173. Elsevier BV.

912 Tryphonas, H. & Arnold, D. (2005) The use of old world nonhuman primates as models for evaluating
913 chemical-induced alterations of the immune system. In *Investigative Immunotoxicology* pp. 211–
914 227. Informa Healthcare.

915 Tryphonas, H., Fournier, M., Blakley, B.R., Smits, J. & Brousseau, P. (eds) (2005) *Investigative*
916 *Immunotoxicology*. CRC Press, Boca Raton, FL.

917 Turner, J.R. (2009) Intestinal mucosal barrier function in health and disease. *Nature Reviews.*
918 *Immunology* **9**, 799–809. Springer Science and Business Media LLC.

919 Vale, P.F. & Jardine, M.D. (2017) Infection avoidance behavior: Viral exposure reduces the motivation
920 to forage in female Drosophila melanogaster. *Fly* **11**, 3–9.

921 Vaughan, G.L. & Jungreis, A.M. (1977) *Insensitivity of lepidopteran tissues to ouabain -physiological*
922 *mechanisms for protection from cardiac glycosides*.

923 Verbruggen, N., Hermans, C. & Schat, H. (2009) Molecular mechanisms of metal hyperaccumulation
924 in plants. *The New phytologist* **181**, 759–776.

925 Vilas-Boas, V., Chatterjee, N., Carvalho, A. & Alfaro-Moreno, E. (2024) Particulate matter-induced
926 oxidative stress - Mechanistic insights and antioxidant approaches reported in in vitro studies.
927 *Environmental Toxicology and Pharmacology* **110**, 104529. Elsevier BV.

928 Vinebrooke, R.D., L. Cottingham, K., Jon, N.M.S., I. Dodson, S., C. Maberly, S. & Sommer, U. (2004)
929 Impacts of multiple stressors on biodiversity and ecosystem functioning: the role of species co-
930 tolerance. *Oikos (Copenhagen, Denmark)* **104**, 451–457. Wiley.

931 Wang, Y., Huang, H. & Wu, Q. (2014) Characterization of the zebrafish Ugt repertoire reveals a new
932 class of drug-metabolizing UDP glucuronosyltransferases. *Molecular Pharmacology* **86**, 62–75.
933 Elsevier BV.

934 Watson, B.N.J., Steens, J.A., Staals, R.H.J., Westra, E.R. & van Houte, S. (2021) Coevolution between
935 bacterial CRISPR-Cas systems and their bacteriophages. *Cell Host & Microbe* **29**, 715–725.
936 Elsevier BV.

937 Windsor, F.M., Pereira, M.G., Tyler, C.R. & Ormerod, S.J. (2019) Biological traits and the transfer of
938 persistent organic pollutants through river food webs. *Environmental Science & Technology* **53**,
939 13246–13256. American Chemical Society (ACS).

940 Woolhouse, M.E.J., Webster, J.P., Domingo, E., Charlesworth, B. & Levin, B.R. (2002) Biological and
941 biomedical implications of the co-evolution of pathogens and their hosts. *Nature Genetics* **32**,
942 569–577. Springer Science and Business Media LLC.

943 Zélé, F., Santos-Matos, G., Figueiredo, A.R.T., Eira, C., Pinto, C., Laurentino, T.G., Sucena, É. &
944 Magalhães, S. (2019) Spider mites escape bacterial infection by avoiding contaminated food.
945 *Oecologia* **189**, 111–122. Springer Science and Business Media LLC.

946 Zeller, M. & Koella, J.C. (2017) The role of the environment in the evolution of tolerance and resistance
947 to a pathogen. *The American Naturalist* **190**, 389–397. University of Chicago Press.

948 Zhang, X., van Doan, C., Arce, C.C.M., Hu, L., Gruenig, S., Parisod, C., Hibbard, B.E., Hervé, M.R.,

949 Nielson, C., Robert, C.A.M., Machado, R.A.R. & Erb, M. (2019) Plant defense resistance in natural
950 enemies of a specialist insect herbivore. *Proceedings of the National Academy of Sciences of the*
951 *United States of America* **116**, 23174–23181. Proceedings of the National Academy of Sciences.

952 Zuykov, M., Pelletier, E. & Harper, D.A.T. (2013) Bivalve mollusks in metal pollution studies: from
953 bioaccumulation to biomonitoring. *Chemosphere* **93**, 201–208. Elsevier BV.

Statements

Author contributions:

EL initiated and coordinated the development of the manuscript, working closely with all authors throughout the process. EvB, SM, and ES contributed to the development of the conceptual framework and to drafting specific sections of the manuscript. The figures were conceptualized collaboratively by all authors and prepared by EL and EvB. All authors contributed to the critical revision of the manuscript and approved the final version.

Funding:

This work was supported by the Portuguese Foundation for Science and Technology (FCT) through CE3C unit funding UID/00329/2025 (DOI: 10.54499/UID/00329/2025) and grants 2022.08248.CEECIND/CP1722/CT0014 and 2024.16230.PEX (DOI: 10.54499/2024.16230.PEX) to EL; PTDC/BIA-BIO/4693/2021 to ES; 2024.08432.CEECIND to EvB; 2022.04172.PTDC (DOI: 10.54499/2022.04172.PTDC) to SM.

Conflict of interest:

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Figures

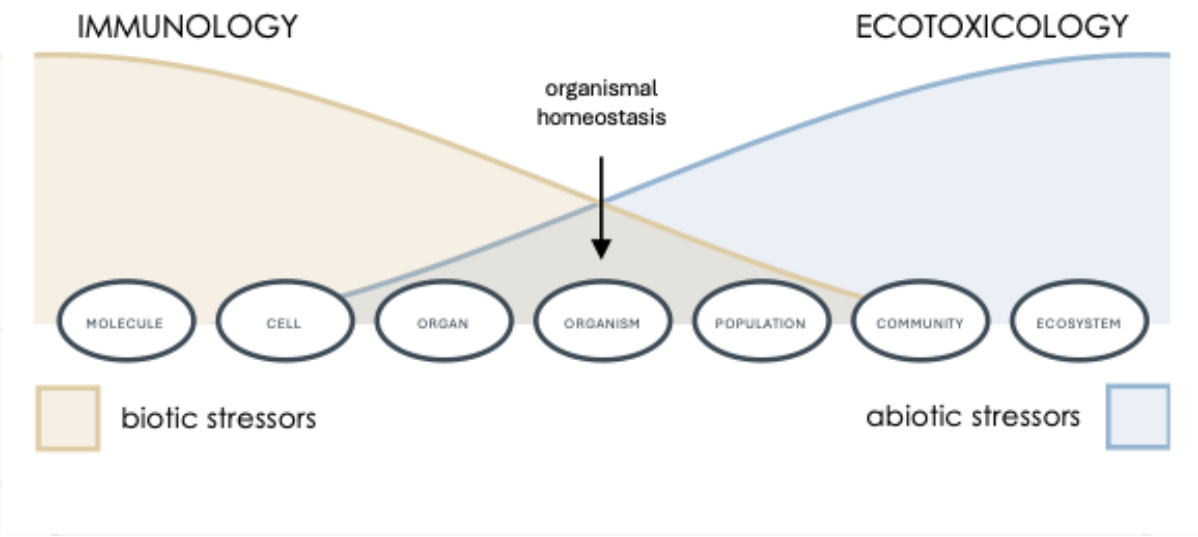

Fig. 1. Conceptual convergence of ecotoxicology and immunology across biological scales.

Ecotoxicology has historically focused on higher levels of biological organization, including populations, communities, and ecosystems, whereas immunology has primarily examined processes operating at lower levels, from molecules and cells to tissues and organs. Organismal homeostasis constitutes the central integrative scale at which these disciplines converge: both biotic and abiotic stressors disrupt physiological stability, and both resistance and tolerance mechanisms can improve organismal performance and fitness under stress. By framing homeostasis as a shared functional framework, the figure highlights a conceptual and operational bridge linking molecular responses to ecological processes and outcomes.

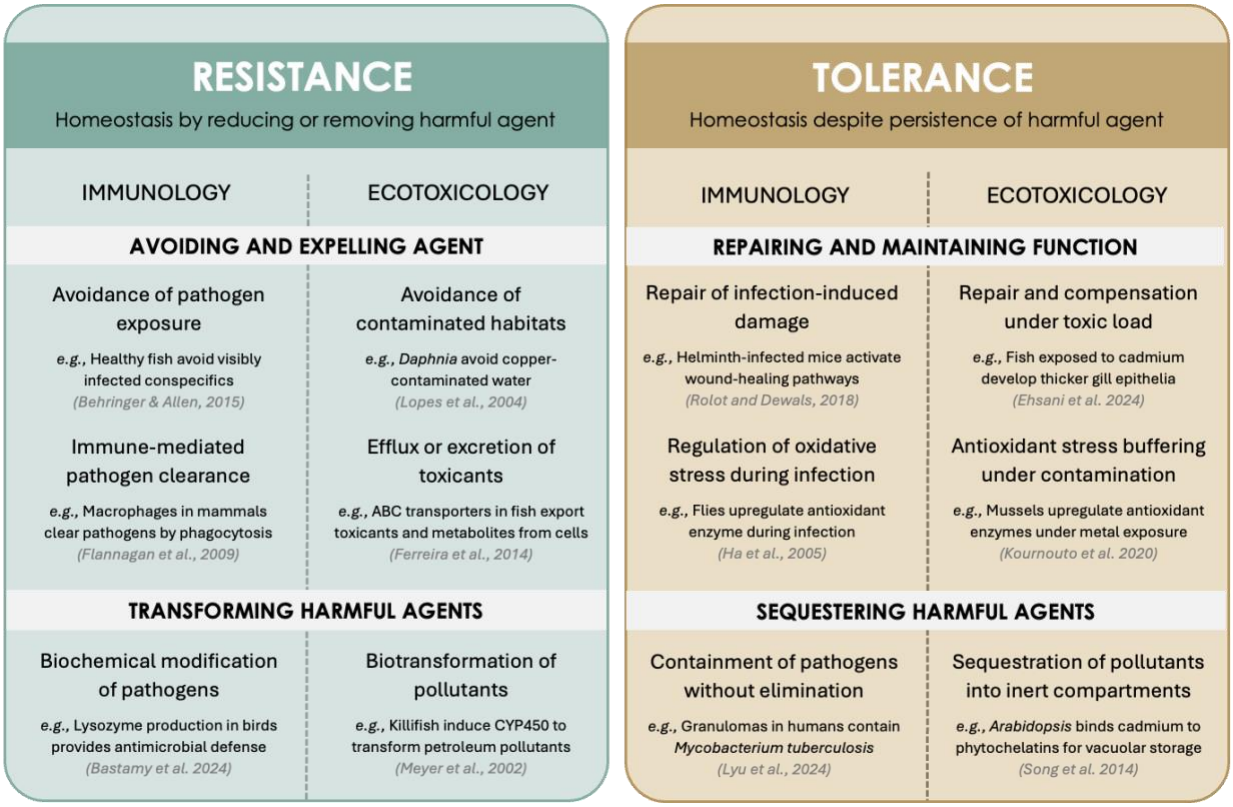

Fig. 2. Mechanistic parallels between resistance and tolerance in immunology and ecotoxicology.

Resistance reduces or removes harmful agents through avoidance, expulsion, or biochemical transformation, thereby lowering internal burden. Tolerance maintains organismal function despite continued presence of the agent through damage repair, physiological buffering, or sequestration. Although developed in separate disciplines, analogous mechanisms operate across biotic and abiotic stressors. Explicitly distinguishing whether organisms reduce burden or mitigate damage clarifies ecological and evolutionary consequences across scales.

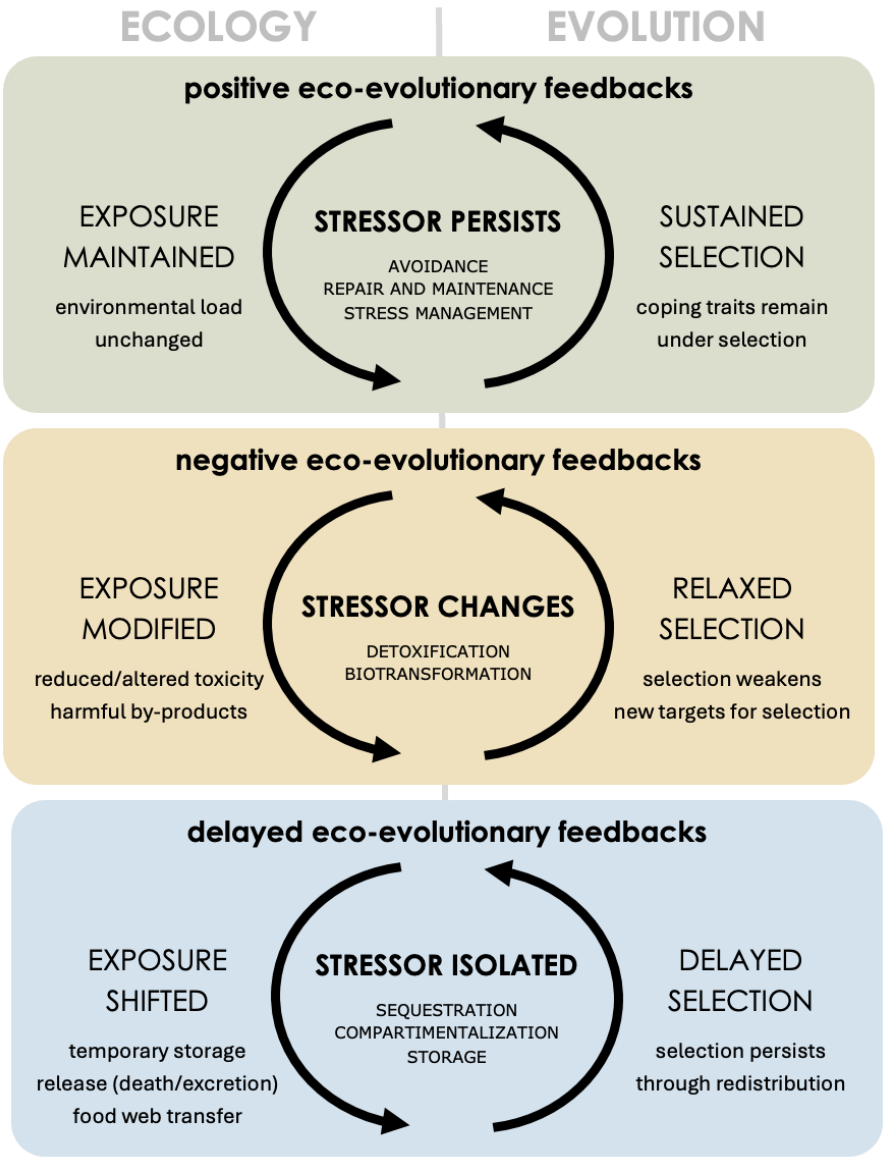

Fig. 3. Mechanistic drivers of eco-evolutionary feedbacks under environmental stress.

Physiological strategies that determine whether stressors persist, are transformed, or are isolated within organisms shape ecological exposure and how selection acts across generations. Stressor persistence maintains chronic exposure and positive feedbacks, transformation can relax or redirect selection and generate negative feedbacks, while sequestration and delayed release prolong exposure through trophic and ecological interactions.