Hormesis on life-history traits: is there such thing as a free lunch?

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Abstract
The term "hormesis" is used to describe dose-response relationships where the response is reversed between low and high doses of a stressor (generally, stimulation at low doses and inhibition at high ones). A mechanistic explanation is needed to interpret the relevance of such responses, but there does not appear to be a single universal mechanism underlying hormesis. When the endpoint is a life-history trait such as growth or reproduction, a stimulation of the response comes with costs in terms of resources. Organisms have to obey the conservation laws for mass and energy; there is no such thing as a free lunch. Based on the principles of Dynamic Energy Budget theory, we introduce three categories of explanations for hormesis that obey the conservation laws: acquisition (i.e., increasing the input of energy into the individual), allocation (i.e., rearranging the energy flows over various traits) and medication (e.g., the stressor is an essential element or acts as a cure for a disease or infection). In this discussion paper, we illustrate these explanations with cases where they might apply, and elaborate on the potential consequences for field populations.

Keywords Hormesis; Energy budget; Mechanisms; Life-history traits; Trade off

Introduction

The concept of hormesis is shrouded in confusion and controversy. The clearest and most practical definition was proposed by Kendig et al. (2010), who state that hormesis is a dose-response relationship for a single endpoint that is characterized by reversal of the response between low and high doses of a stressor. Essential in this definition is that hormesis is a *description* of a dose-response phenomenon, and thus independent of the underlying mechanism, which is unclear in most cases. However, identifying the mechanism is still essential to correctly interpret the relevance of the hormetic response (Mushak 2007; Thayer et al. 2005; van der Schalie and Gentile 2000). In this contribution, we will explore potential explanations for low-dose stimulation in ecotoxicology. Most of the hormesis discussion takes place in the toxicological literature, where the focus lies on protecting individuals. As a consequence, the endpoints of interest are usually at the sub-individual level (e.g., DNA damage). In contrast, ecotoxicology focuses on the protection of populations and ecosystems. Toxicity tests are usually conducted with individuals, but the endpoints of interest are life-history traits that determine population dynamics (reproductive output, growth and survival). The focus on life-history traits restricts the possible explanations that we can invoke for hormetic responses.

The first thing to realize is that chemical stress tends to affect different traits in different directions and/or in different degrees (Forbes 2000), and that the degree of effect depends on the exposure time (Alda Álvarez et al. 2006b). A correct interpretation of hormesis and its importance thus requires following multiple endpoints over a longer period of time (Mushak 2007; Thayer et al. 2005; Weltje et al. 2005). The example in Figure 1 shows a case were both body size and cumulative reproductive output are apparently increased by the lowest tested toxicant dose at all tested time points. The next thing to realize is that an individual organism needs to obey the conservation laws for mass and energy. This is one of the few hard rules that we can invoke in biology. An individual takes up resources from the environment, and these are distributed over various traits. Stimulation of one or more traits represents an increased use of resources that have to come from somewhere; the various traits must trade off due to energetic constraints (see Forbes 2000; Weltje et al. 2005). One popular explanation for hormesis is that it results from overcompensation of a repair process (Calabrese and Baldwin 2002). Although this is an interesting hypothesis, it remains highly speculative as a mechanistic underpinning is currently lacking (Kendig et al. 2010; Mushak 2007; Thayer et al. 2005). As a mechanistic explanation for hormesis on life-history traits, it is also insufficient because it does not specify where the energy for this repair process comes from.

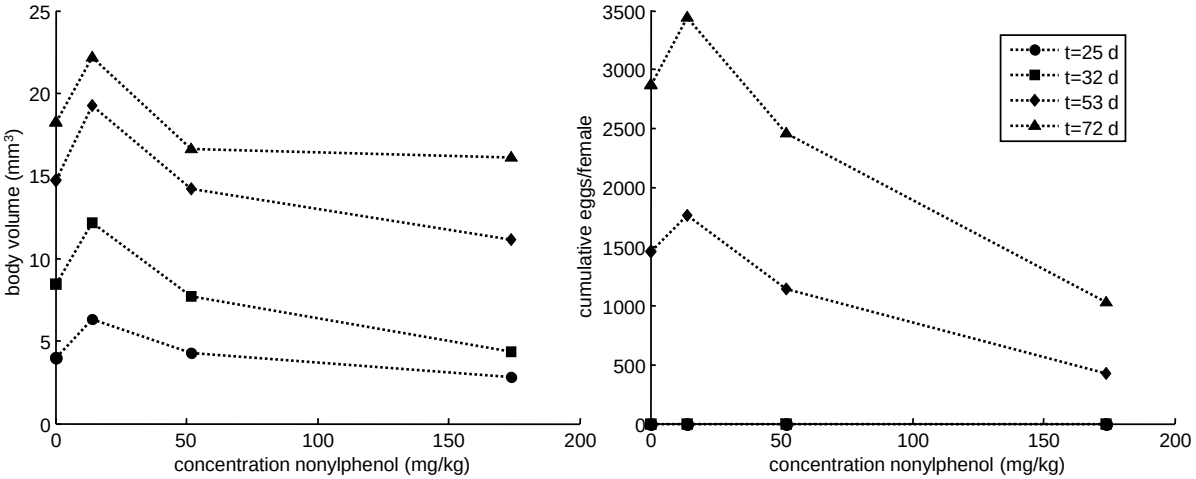

Figure 1. Example of hormesis on both growth and reproductive output, at various points in time. Data for the marine polychaete *Capitella teleta* from Hansen et al. (1999), and see analysis in Jager and Selck (2011).

The conservation laws leave us with a limited set of options for energy/mass management underlying the hormetic response. If we ignore the cases where hormesis is a statistical artifact (see Forbes 2000; Thayer et al. 2005), the remaining options can be classified into three broad categories: acquisition (i.e., increasing the input of energy into the individual), allocation (i.e., rearranging the energy flows over various traits) and medication (e.g., the stressor is an essential element or acts as a cure for a – unidentified – disease or infection). This is very similar to a well-balanced household budget: an increase in expenditure in one area requires either more income, reduction of other expenses, or remediation of unnecessary losses. To quantitatively explore these options for an individual, we need a consistent set of rules for the acquisition and use of resources over the life cycle of an individual. Fortunately, such a set of rules exist in the form of energy budgets, and the Dynamic Energy Budget (DEB) theory (Kooijman 2001; Sousa et al. 2008) is the best tested and most comprehensive framework in that area. In this discussion paper, we will use the DEB rules as a basis to discuss various options for hormesis on life-history traits, which respect the conservation laws. These options are connected to cases from the literature where they could have applied, and their consequences for field populations are discussed. It should be noted that we do not present new experimental evidence here, but rather lay the foundation for more mechanism-based research on hormetic responses in ecotoxicology.

Theoretical background

In our discussion of hormesis options, we refer to the standard DEB animal model (see Sousa et al. 2008) as schematically depicted in Figure 2 (equations are provided in the supporting information). Biomass is divided into structure which requires maintenance, and reserve which can be used to fuel metabolic processes. Energy from food is assimilated into the reserve, and allocated with a fixed fraction κ to the soma (structural growth and somatic maintenance). The remaining fraction 1- κ is allocated to maturation (increase in overall complexity), maturity maintenance (thought to include investment in the immune system) and reproduction. At a fixed maturity level, the animal starts to feed (defined as the moment of "birth"), and at a higher level of maturity (that corresponds to "puberty"), investment is switched from maturation into production of offspring.

In DEB, toxicant effects are interpreted as a change in model parameters that are linked to a metabolic process, such as an increase in the maintenance costs per unit of structure, or in the costs per unit of structural biomass (Jager et al. 2010). In principle, any of the metabolic processes can be affected by a toxic stressor, and possibly even more processes simultaneously. However, for most chemicals, it is unclear what the affected processes are, so we have to use the patterns of effects on growth and reproduction to deduce the most likely target parameters (the "physiological mode of action", see Alda Álvarez et al. 2006a). For toxicants that exert a hormetic response, we follow the same reasoning, although different parameters may be affected, or in a different direction, compared to the non-hormetic response. In the following section, we consider several options for hormesis that are consistent with the budgeting rules in DEB theory, and discuss the consequences for growth and reproduction over the life cycle. We discuss hormetic effects on survival separately, as the energetic costs for such a response are less clear than for growth and reproduction.

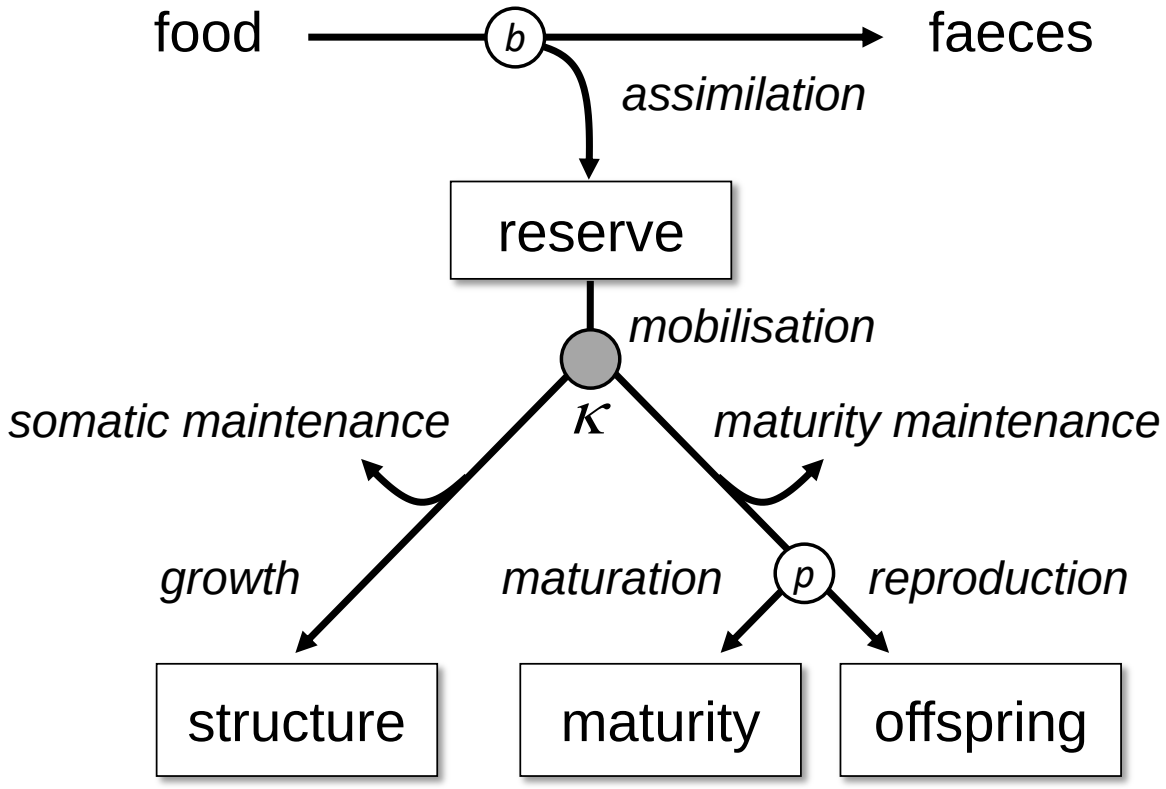

Figure 2. Schematic diagram of the mass and energy flows in a standard DEB animal. The circles *b* and *p* denote switches in life history (start of feeding and start of investment in reproduction, respectively). The mobilization flux is continuously split (grey circle) into a fraction κ allocated to somatic maintenance and growth, and 1-κ to maturation and reproduction.

Options for hormesis

Option 1: Acquisition

The increased performance of an animal exposed to a stressor might be explained by an increase in the uptake of energy from the environment, i.e., an increase in the feeding rate or in the assimilation efficiency of energy from food (e.g., related to food quality). Increasing the uptake of energy from the environment implies an increase in the growth rate and in

maximum size. Furthermore, there will be a decrease in the time to first reproduction, and an increase in the maximum reproduction rate (in terms of mass or energy output per time).

It is possible that up-regulation of feeding is an adaptive response of the organism to counteract the energetic losses due to toxicant effects (e.g., the induction of detoxification processes or damage repair, see Calow 1991). Some overshoot of this up-regulation could lead to increased performance on life-history traits such as growth and reproduction. If animals are indeed physiologically capable of increasing their feeding rate beyond control conditions, this raises an interesting evolutionary question. A mutant that always has this up-regulated feeding rate would reproduce earlier and more, and thus outcompete its conspecifics. So why did natural selection not lead to the maximum possible feeding rate? It is likely that there are fitness disadvantages of having an up-regulated feeding rate, which could relate to negative side effects of rapid growth (e.g., decreased survival probability), or of being large bodied (e.g., increased predation risk). If up-regulation of feeding occurs after exposure to toxicants, the response can be seen as a "free lunch" under laboratory conditions (the resources are not redirected from another metabolic process). However, we must be ready to expect negative fitness consequences under natural conditions. Furthermore, the lunch will be paid for by the organisms that make up the food source, and the competitors for the same source. In this way, the hormetic response may lead to shifts in inter-species relationships, the consequences of which will be hard to predict.

In experimental test systems, an increase in feeding or assimilation efficiency might result from a more indirect mechanism than up-regulation of the feeding rate. For example, it is possible that the toxicant (or the solvent used to introduce the toxicant in the test system) can be used as an energy source by the test species, or by micro-organisms, which in turn may serve as food for the test species. This option provided a quantitative explanation for the consistent increase in growth and reproduction shown in Figure 1 (Jager and Selck 2011). Another option is that the food itself is responsible for negative effects on the test organism. In many experimental tests, animals are fed with living organisms (e.g., algae for *Daphnia*, bacteria for bacterivorous nematodes). Many prey organisms exude secondary metabolites or build mechanical barriers (e.g., cuticles in plants, shells in animals) to decrease their palatability. When a toxicant weakens the defenses of the food organisms, this might lead to an increase in the feeding rate or the assimilation efficiency of the predator. This option has likely caused the stimulating effect of the herbicide diquat on the feeding rate of the pond snail *Lymnaea stagnalis* on lettuce (Ducrot et al. 2010). Small doses of this herbicide affected the cell walls of the lettuce provided as food for the snails, enhancing its palatability. Another example of toxicants enhancing palatability is in the work of Saiz et al. (2009), where PAHs were found to increase the feeding rate of the marine copepod *Oithona davisae*, by changing the properties of dinoflagellates used as food. A third option in this category is that a toxicant increases the quality of the food by limiting the growth of harmful bacteria or fungi. This possibility was for example discussed by Jager and Klok (2010) for earthworms feeding on dung, and shown to be a quantitatively consistent explanation for the increase in growth and reproduction simultaneously, at low copper concentrations.

These indirect increases in acquisition can be seen as artifacts of the experimental setup, rather than a physiological response to a toxicant effect. The hormetic response is expected to disappear when sufficient and appropriate food of a consistent quality can be provided. A tantalizing clue is provided by Winner et al. (1977), who observed hormesis of copper on reproduction of *Daphnia* when the animals where fed with algae, but not when fed on trout

food. Kooijman and Bedaux (1996) mention that hormesis in *Daphnia* sometimes disappears at lower food concentrations, implicating either the food (algae, producing polysaccharides) or bacteria (feeding on dead cells) for the reduced performance at high food. Unfortunately, for most (if not all) of the test organisms, it is not fully clear what their optimal nourishment is, which leaves room for a hormetic response. For example, the most popular test species in ecotoxicology, *Daphnia magna*, has a maximum length of some 5 mm, which is hardly ever reached in laboratory tests, possibly pointing at sub-optimal test conditions. For the pond snail *Lymnaea stagnalis*, Zonneveld and Kooijman (1989) estimated that "optimal" laboratory conditions represented only 70% of the maximum possible nutritional status.

In some sense, this indirect mechanism for hormesis might also be viewed as a "free lunch". For the focal species in the test, there are no negative consequences of the hormetic response. However, it is not the action of the toxicant on the metabolism of the animal that underlies the response, but the sub-optimal laboratory conditions. An increase in acquisition due to an indirect mechanism can also occur in the field, and the toxicant might thus provide a real fitness benefit for the focal species. For other species in the system, however, this may have negative consequence; weakening the prey's defenses is bad news for the prey, and limiting the growth of harmful fungi is bad news for the fungi. So again, there are costs for this lunch, but they are being paid by other species.

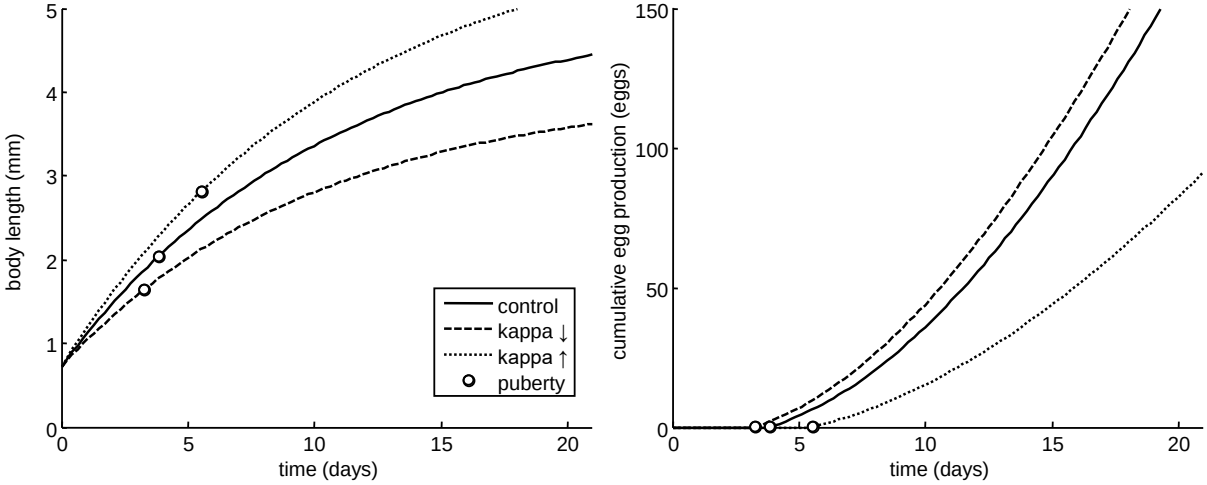

Figure 3. Model simulation for hormesis due to a change in the allocation parameter κ (see Fig. 2). Model parameters are representative for *Daphnia magna*. Details of the model and parameter values are provided in the supporting information.

Option 2: Allocation

In response to a stressor, the individual might allocate the same amount of available energy in a different manner. This leads to an increase in the performance of one trait, but a decrease on another trait. However, the consequences of the decreased trait might not have been observed in the toxicity test, for example, because the test is too short, does not follow all endpoints, or because the trait is only important under other environmental conditions (e.g., when suffering disease or food limitation).

An obvious option in the DEB scheme is a change in the allocation between the soma (growth and somatic maintenance) and maturation/reproduction (κ), which is simulated in Figure 3. An increase in κ would lead to an increased investment in the soma, and decreased investment

in maturation and reproduction. As a consequence, growth is stimulated and the individual reaches a larger size than the control organisms. However, an increase in κ also delays the start of reproduction, increases the size at first reproduction, and decreases the reproduction rate (when comparing individuals of the same size, and expressed as a mass or energy flux). This pattern of effects is well known for some parasitic infections, although reproduction is generally fully halted as the parasite uses this energy for its own purposes (Hall et al. 2007). A decrease in κ will have an opposite effect: less growth, an earlier start of reproduction at a smaller size, and enhanced reproduction (for its size). This pattern of effect is for example seen in *Daphnia* when exposed to chemicals released by their fish predators (kairomones, e.g., Stibor 1992). Note that when κ is decreased too much, the reproduction rate will become lower than the control as the feeding rate is also linked to size in DEB. A similar rationale might also explain the increased reproduction and decreased growth of the snail *L. palustris* exposed to hexachlorobenzene (Baturo et al. 1995).

Shifts of allocation in either direction have been indicated in response to (suspected) endocrine disrupting chemicals in nematodes (Höss and Weltje 2007). However, a quantitative analysis will be needed to see if these changes can indeed be explained by a change in κ. Weltje et al. (2005) argue to make a distinction between hormesis and stimulation due to endocrine disruption. However, the definition of hormesis that we adopted (see introduction), does not allow such a distinction. Endocrine disruption must also obey the conservation laws, so if there is stimulation of a life-history trait, the explanation must fit into one of our three categories. A change in allocation is a likely place to start detailed investigations.

Another option for a change in allocation within DEB models is an increase in the mobilization rate of the reserve. This increases the growth and reproduction rates, but only temporarily. After some time, the reserve density will reach a new equilibrium, at a lower level, and growth and reproduction rates return to normal. Increasing mobilization thus leads to a short-term boost of both growth and reproduction, but no effect on the ultimate size and the ultimate reproduction rate. This boost might be considered as beneficial (it increases the population growth rate under optimal conditions), but the associated cost is a decreased reserve density. This means that the individual becomes more sensitive to fluctuations in the food availability; a disadvantage that will easily escape attention in a laboratory toxicity test. We are not aware of any example where this explanation can be used, so it remains a theoretical option for now.

The last option that we need to discuss is a decrease in the energy investment per offspring. Such a decrease implies that the reproduction rate (in numbers of offspring per time) increases, but smaller offspring are produced. This pattern of effects was for example shown by a toxicant in *D. magna* (Hammers-Wirtz and Ratte 2000). These smaller offspring had a lower fitness compared to large ones, so there are clearly costs associated with this apparent increase in performance. Such a trade off might easily escape attention in toxicity tests, as measuring offspring weight or quality is certainly not routine procedure.

Within the category of allocation options for hormesis, there are a few more possibilities, which we consider less likely than the previous ones. If an animal is able to reduce its somatic maintenance costs, the results will be qualitatively similar to an increase in feeding rate: growth to a larger size and increased reproduction (because large animals can eat more). It seems unlikely that organisms are able to decrease their somatic maintenance costs without

major adaptations (e.g., as in hibernation or torpor) or major effects on the quality of their tissues. However, Kooijman (Acc.) speculates on the possibility that species waste resources (increase their somatic maintenance beyond what is needed) to remain small and grow fast, in order to fully exploit temporal food abundance. If this mechanism is corroborated by further evidence, it would open up a pathway for hormetic responses appearing as a decrease in maintenance costs. Theoretically, hormesis could result from a decrease in the overhead costs for growth, maturation and reproduction. This seems unlikely using an evolutionary rationale: if such costs are easily reducible, this would provide a straightforward gradient for natural selection to work on. The maturity maintenance costs may however be more flexible. In DEB theory, these maintenance costs are assumed to be associated with defense systems against infections (Sousa et al. 2008). A decrease in the maintenance costs for these systems leaves more energy available for maturation and reproduction, at a cost of an increased susceptibility to disease. Such a cost might easily go unnoticed in a well-controlled laboratory setting.

The options within the category of allocation effects cannot be considered experimental artifacts; these options represent actual changes in the physiology of the organism. The increased performance on a trait is accompanied by a decrease in performance in another trait. In principle, these trade-offs are all measurable, although in practice, many will easily escape attention because of the limitations imposed by the (standard) test protocols. Some trade-offs might only incur negative consequences at another developmental stage, in another generation, or under different environmental conditions. For example, a decrease in the quality of the immune system will only reduce fitness under conditions where disease regularly strikes.

Option 3: Medication

Some toxicants are essential elements (e.g., metals such as copper and zinc). If the animals are deficient, a small dose may lead to an obvious enhancement of performance. Only for a limited number of chemicals can this hypothesis be invoked, and these chemicals are mostly known. A more common situation might be that the toxicant acts as a medicine, helping to fight off an infection that was not recognized by the experimenters. As an example, fungi might affect the test organisms (or their eggs), and these fungi might be more susceptible to the toxicant than the test organisms. These explanations for low-dose stimulation are discussed by Forbes (2000), but she does not consider them to be “hormesis”. With the definition that we adopt (see introduction), “medication” responses should however be included. Forbes refers to two studies where this option was suggested as an explanation for the stimulatory effect, although there was no supporting evidence in these cases. In fact, we are not aware of a single study where this mechanism was actually demonstrated to cause a hormetic response. This does not necessarily imply that this situation is rare; it probably reflects the reluctance of ecotoxicologists to return to the laboratory for further experimentation after observing a hormetic response.

In a laboratory setting, this category can be considered as an experimental artifact; the hormetic response is expected to disappear when there is no deficiency or disease in the test population. However, many diseases or deficiencies do not lead to large detrimental effects on the organisms, so this situation might be more common than we like to think, and difficult to identify in practice. In the field, organisms also suffer from infections and disease, so a mild chemical stress may incur a real fitness advantage for the species of interest. In some sense, this is a “free lunch” for the focal species, but not for its food source, its competitors, or the organism causing the disease (which was, apparently, more sensitive than the focal species).

Again, this option for hormesis has the potential to shift inter-species relationships in ecosystems.

What about an increase in survival?
In some life-cycle experiments, an increase in survival in response to toxicant stress is seen (e.g., Jager et al. 2004). Increased longevity is the common response to reduced food intake (caloric restriction), also in non-mammals (Gerhard 2001), so it is possible that such toxicants decrease the feeding rate (either by avoidance or a direct toxic effect) or that they decrease the assimilation efficiency. There is a close link between metabolic processes (i.e., the energy budget) and organismal ageing, which can explain the link between feeding and longevity (Van Leeuwen et al. 2010). The trade-offs of a longer life lie in the consequences of reduced feeding: slower growth, delayed start of reproduction and lower reproduction rates. In this way, increased longevity is unlikely to imply an increase in fitness. Jager et al. (2004) show that cadmium exposure in the springtail *Folsomia candida* increases longevity and decreases growth and reproduction. The calculated net effect on the population growth rate was however always negative. An increase in survival by decreasing assimilation can thus be considered as a special case of our "allocation" category. However, it is unlikely that this is the whole picture of senescence, and more work will be needed to elucidate the trade-offs (if any) related to various life-extending treatments.

Practical recommendations

Several of the mechanisms in the categories "acquisition" and "medication" should be considered experimental artifacts, because they do not follow from a direct toxic effect on the test animals. Even for popular test species, it is unclear what their nutritional requirements are; a situation that can easily create sub-optimal test conditions and bias in toxicity tests (Zimmer et al. Acc.). Furthermore, we can never test a species in isolation; other organisms are inevitably present in the test system (as food item, parasite, symbiont, micro-flora etc.). A toxicant effect on these non-focal species can easily shift inter-species balances in the test system. When a hormetic response is observed, it therefore makes sense to start by scrutinizing the experimental setup. The examples we provided hint at the possibility that such experimental artifacts may be more common that we like to think. Sub-optimal conditions and effects on species interactions will also occur in the environment, which implies that a chemical stress can incur a real fitness advantage for the organism of interest. In some sense, this is a free lunch for the focal species, although this response has the potential to shift inter-species relationships in an exposed ecosystem.

If experimental (and statistical) artifacts can reasonably be excluded, we have to explore which of the remaining options best explains the response to the toxicant. The common single-endpoint studies are, however, not useful for this purpose (Mushak 2007). It is advisable to follow as many traits as possible in the toxicity test (e.g., also measure offspring quality in reproduction tests), over a longer period of time, and possibly under different environmental conditions (e.g., different food levels). Energy budget models can subsequently be used to test these responses quantitatively (see e.g., Jager and Klok 2010), thus ensuring mass and energy conservation. An optimal way forward would be to perform several iterations of experiments and modeling. When the experiments reveal hormesis, explore the possible mechanistic options with a model. Next, use the model to predict where the trade-offs should occur, and subsequently set up a dedicated experiment to test that prediction (and repeat this process until satisfied by the explanation). However, such a cycle requires a close

and flexible link between experimenters and modelers, which is still rather uncommon in ecotoxicology.

We need a mechanistic explanation for hormetic responses to interpret its ecological consequences. If it is an artifact of the test system, we might wish to ignore this response (e.g., use the treatment with the highest performance as the "control"). If it is not an artifact, we have to proceed carefully. Ecological risk assessment should not treat life-history traits in isolation; the effects on all traits must be integrated into a measure of fitness to interpret the consequences of the hormetic response (Forbes 2000). However, we also should not look at a single species in isolation. In an ecosystem, species inevitably interact with each other, and shifting these interactions might have undesirable consequences. These potential indirect consequences of hormesis seriously complicate ecological risk assessment (van der Schalie and Gentile 2000). Finally, we also should not focus on a single set of environmental conditions; what is "beneficial" in one environment might be "detrimental" in another. For these reasons, we should be very careful to view hormesis on life-history traits as beneficial; it seems likely that there are always some negative consequences associated with the hormetic response, which require careful consideration.

Conclusions

Hormesis is best defined descriptively; as a certain shape of the dose-response relationship (Kendig et al. 2010). In this way, the definition does not rely on any speculative underlying mechanisms. The hormetic response, however, does require a mechanistic explanation to interpret what the impact of the stressor under natural conditions is (van der Schalie and Gentile 2000), or even put hormesis to commercial use (Belz et al. 2011). Individual organisms must obey the conservation laws for mass and energy; they cannot create more body tissue or more offspring out of thin air. Such free lunches are not served. However, some form of free lunch *is* implied in some of the explanations that we put forward. There is a fitness benefit for the focal species in the toxicity test, at the expense of other species in the ecosystem. There is no way around it: the conservation laws ensure that all lunches have to be paid by someone, somewhere, in the end.

We put forward a series of explanations for hormesis that obey the conservation laws, falling into three broad categories: acquisition, allocation and medication. Several of the mechanisms in acquisition and medication can be viewed as experimental artifacts; the hormetic response is expected to disappear under different (more optimal) experimental conditions. The remaining options represent changes in the physiology of the organism, where the increased investment in a trait is either paid from up-regulated feeding or by decreased investment in another trait (which might easily go unnoticed in a laboratory setting). Whether such changes should be seen as adaptive (as proposed by Calabrese and Baldwin 2002), or as a toxic effect, requires a mechanistic underpinning, which is currently lacking (Mushak 2007; Thayer et al. 2005). We expect that these changes in physiology are always associated with negative consequences, either at the level of the individual or at the ecosystem level. In the end, it will be up to risk management to weigh all effects of the chemical with its benefits.

To conclude, the first step in explaining hormesis should be to scrutinize the experimental setup for possible artifacts. The next step should be to investigate the remaining options and look for the trade-offs. The all-too-common avoidance strategy (call the response "hormesis"

and use a different curve to fit the data) is neither going to progress the science of ecotoxicology, nor supporting ecological risk assessment.

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