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Forecasting the impacts of chemical pollution and climate change interactions on the health of wildlife

Pamela D. NOYES[1*], Sean C. LEMA[2]

[1] Department of Environmental & Molecular Toxicology, Environmental Health Sciences Center, Sinnhuber Aquatic Research Laboratory, Oregon State University, Corvallis, OR, USA

[2] Biological Sciences Department, Center for Coastal Marine Sciences, California Polytechnic State University, San Luis Obispo, CA 93407, USA

Abstract Global climate change is impacting organisms, biological communities and ecosystems around the world. While most research has focused on characterizing how the climate is changing, including modeling future climatic conditions and predicting the impacts of these conditions on biodiversity, it is also the case that climate change is altering the environmental impacts of chemical pollution. Future climate conditions are expected to influence both the worldwide distribution of chemicals and the toxicological consequences of chemical exposures to organisms. Many of the environmental changes associated with a warming global climate (e.g., increased average – and possibly extreme – temperatures; intense periods of drier and wetter conditions; reduced ocean pH; altered salinity dynamics in estuaries) have the potential to enhance organism susceptibility to chemical toxicity. Additionally, chemical exposures themselves may impair the ability of organisms to cope with the changing environmental conditions of the shifting climate. Such reciprocity in the interactions between climate change and chemicals illustrates the complexity inherent in predicting the toxicological consequences of chemical exposures under future climate scenarios. Here, we summarize what is currently known about the potential reciprocal effects of climate change and chemical toxicity on wildlife, and depict current approaches and ongoing challenges for incorporating climate effects into chemical testing and assessment. Given the rapid pace of new man-made chemistries, the development of accurate and rapid methods to evaluate multiple chemical and non-chemical stressors in an ecologically relevant context will be critical to understanding toxic and endocrine-disrupting effects of chemical pollutants under future climate scenarios [*Current Zoology* 61 (4): 669–689, 2015].

Keywords Global warming, Toxicology, Metals, Endocrine disruptors, Risk assessment

1 Introduction

There is strong scientific consensus that rising anthropogenic greenhouse gas emissions are altering the Earth's climate and that shifts in climatic conditions are now impacting wildlife and plant species worldwide (IPCC, 2014a,c). Global average land and sea temperatures between 1983 and 2012 have been the warmest period in the Northern Hemisphere in the past 1,400 years (Arndt et al., 2014; IPCC, 2013). Accompanying these changes in global average temperature, annual mean sea ice extent in the Arctic and Antarctic has been declining at a rate of 3.5 to 4.1% and 1.2 to 1.8%, respectively, per decade since 1979. Terrestrial habitats in the Northern Hemisphere have seen a reduction in spring snow cover in combination with increasing soil temperatures and permafrost thawing (Blunden and Arndt, 2014). Climate changes are also leading to an enhanced frequency and severity of extreme temperature, drought, and precipitation events at a regional geographic scale (Hansen et al., 2012; Huntingford et al., 2013), which corresponds to predictions of climate change models (e.g., Diffenbaugh et al., 2005; Rahmstorf and Coumou, 2011).

The impacts of increasing atmospheric concentrations of non-water vapor greenhouse gases are not confined to terrestrial environments, and it has been estimated that ½ of the CO_2 generated by anthropogenic activities between 1800 and 1994 has been taken up by the oceans (Sabine et al., 2004). This uptake of CO_2 has caused a 26% increase in acidity (0.1 pH decrease) of the oceans since the start of the industrial era (c. 1,750 to 2,011). The upper 75 m of the world's oceans also increased in temperature by 0.11°C per decade between 1971 and 2010 (IPCC, 2013, 2014c). Rates of sea level change since the mid-1800s have been greater than during the previous two millennia with global mean sea level rising by 0.19 m from 1901 to 2010 (IPCC, 2014c),

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* Corresponding author. E-mail: pamela.noyes@oregonstate.edu or pnoyes@chevron.com

and the annual rate of sea level change over the past 20 years is estimated at ~3.2 mm·yr^{-1} (Arndt et al., 2014). Accompanying these changes in ocean pH and sea level, regional alterations in evaporation and precipitation rates are leading to changes in sea surface salinity with saltier ocean regions trending toward increased salinity and fresher ocean regions becoming even less saline (Durack et al., 2012; Pierce et al., 2012). These changes in sea surface temperature and salinity appear to be enhancing stratification of the upper ocean layer and lowering the mixed layer depth (Capotondi et al., 2012), which combined with shifts in the intensity of coastal winds are expected to alter the dynamics of upwelling of cold, nutrient-rich water in coastal zones (Roemmich and McGowan, 1995; Sydeman et al., 2014; Wang et al., 2015). Moreover, coastal hypoxia may become more prevalent with the combined impacts of changes in coastal ocean temperatures, vertical mixing (e.g., upwelling, surface mixing by winds), and freshwater runoff (Rabalais et al., 2010).

An increasing number of studies provide evidence of shifting habitat ranges, seasonal activities, phenology, predator-prey interactions, and migratory patterns of terrestrial, freshwater, and marine species to this changing climate (Doney et al., 2012; Forcada and Hoffman, 2014; IPCC, 2014a; Visser and Both, 2005; Walther et al., 2002; Zhang et al., 2014). Earlier mean arrival dates have now been documented for many species of birds migrating from winter to summer habitats (Miller-Rushing et al., 2008). There is now extensive evidence for geographic movement of fish, invertebrate, macroalgae, and phytoplankton populations to deeper water or to higher latitudes (Bernhardt and Leslie, 2013; Doney et al., 2012; Drinkwater, 2005; Frusher et al., 2014; Hiddink et al., 2015; IPCC, 2014c; Jonsson et al., 2015; Jueterbock et al., 2013; Jung et al., 2014; Okey et al., 2014; Pletterbauer et al., 2015). Terrestrial tree species also have been documented as experiencing range shifts toward higher latitudes, even as these species are also being affected by climate-associated changes in insect pest invasions and fire frequency (Iverson and Joranger, 1985; Tobin et al., 2014). Indeed, a large percentage of terrestrial and aquatic species are facing elevated risk of extinction with climate change acting as a major driving force that is worsened by interactions with other stressors including habitat fragmentation and modification, over-exploitation and harvesting, eutrophication, invading species, infectious disease, and chemical pollution (IPCC, 2014b; Stuart et al., 2004; Thomas et al., 2004). It is important to note that, ultimately, these impacts on individual species emerge as broader scale changes to biological communities and ecosystems. Tropical coral reef ecosystems, for instance, have suffered mass bleaching and live coral loss associated with elevated sea temperature events (Glassom, 2014; Hoegh-Guldberg et al., 2007), and it has been estimated that approximately one-third of the world's reef-building corals are at high risk for extinction due to the combined effects of climate change (e.g., elevated temperature, declining pH) and local anthropogenic impacts (e.g., overfishing, declining water quality) (Carpenter et al., 2008).

Despite widespread observations of climate change impacts on animal and plant species, the effects of a changing global climate on taxa are not uniform around the world (Frusher et al., 2014; IPCC, 2014b; Walther et al., 2002). Changes in temperature, precipitation, and other environmental parameters are spatially heterogeneous and often asymmetrical in magnitude across a species' geographic range, and this irregularity drives the non-uniform responses to climate change observed in populations. Animal and plant populations have adapted to their surroundings with unique genetic and phenotypic attributes that evolved due to selection pressures from the local environment and climate. Adaptive genetic variation underlying behavior and physiology across a species' geographic range may therefore make some populations more resistant to changing climate conditions, while other populations may lack the adaptive capacity to respond and be more susceptible to detrimental impacts from a rapidly changing climate (Chown et al., 2010; Hoffmann and Sgro, 2011).

Studies to date have focused largely on the direct environmental alterations associated with climate change (e.g., temperature, ocean acidification, etc.). There is also a need to understand how the toxic and endocrine-disrupting effects of chemical pollutants are being affected by ongoing climate change. Humans and wildlife are now exposed to thousands of man-made chemicals. Research has shown that some chemicals released into the environment or present as legacy pollutants can impair the development, physiology and behavior of animals, and that the ecological context of chemical and chemical mixture exposures is an important consideration that can influence the nature and severity of adverse effects. As research efforts aimed at identifying and predicting the influences of climate change on organisms intensify, it will be crucial to consider how multiple stressors contribute to the sublethal and lethal effects of climate change via additive or synergistic interactions (Bozinovic and Pörtner, 2015; Helmuth,

2009). In the face of a changing global climate where a variety of environmental parameters are rapidly being altered, the toxicity of chemical pollution may be influenced by the environmental context of exposure and, conversely, exposure to chemical pollution has the potential to increase the susceptibility of species to climate change stressors (Hooper et al., 2013).

Our ability to evaluate climate change and chemical interactions on wildlife continues to be limited as there are numerous multi-dimensional aspects and many discrete, overlapping, and non-linear responses that make predictive analyses difficult. Some of these complex interactions may involve, for instance, the concentration, extent, and timing of chemical-climate stressor interactions (e.g., acute pulse vs low level chronic chemical exposures, organism life-stage, overlap with key phenological events), and the sequence of exposures relative to each stressor (e.g., chemical exposure followed by environmental stressor, chemical exposure and environmental stressor concurrently). Moreover, the geographical location and adaptive capacities of ecological populations will have important ramifications that influence responses (Moe et al., 2013). Understanding the dynamics and implications of chemical pollution in a changing global climate will thus require considering ecological context more fully in existing methodologies for chemical toxicity testing. Doing so presents considerable logistical difficulties, as studies with sufficient statistical power to detect interactive effects of chemical and climate stressors require complex experimental designs. Further development and implementation of alternative methodologies such as modeling using artificial neural networks provide one possibility for identifying and quantifying what are likely to be complex and nonlinear interactions among chemical and climate stressors (e.g., Bertin et al., 2013).

While these and other similar efforts hold promise for multi-stressor analyses, at present, the potential for climate change interaction with chemical toxicants continues to be understudied (Dalla Valle et al., 2007; Holmstrup et al., 2010; Noyes et al., 2009; Schiedek et al., 2007). To begin addressing this issue, a Society for Environmental Toxicology and Chemistry (SETAC) Pellston workshop was held in 2011 to explore how environmental parameters altered by the changing global climate could influence chemical toxicity and risk (Stahl et al., 2013). An important output from this workshop was a number of organizing principles and conceptual frameworks to better integrate climate change effects into chemical risk and injury assessments. Nonetheless, despite this effort, considerable challenges remain for studying and assessing the potential interactive effects of climate-chemical stress on wildlife. Therefore, the objective of this review was to provide an update on current research efforts to examine the reciprocal effects and ecological contexts of chemicals and climate change interactions, with particular focus on: (1) how important climate change-chemical interactions may be manifested; (2) how toxicity pathways could be influenced by climate change for important chemical classes that are environmentally problematic and prevalent (e.g., metals); and (3) how some chemical pollutants, such as endocrine disruptors, could hinder the physiological capacity (e.g., altered bioenergetics, thermal tolerances) of wildlife to respond to a rapidly changing climate. Finally, attention was focused on how toxicity testing and assessment approaches are evolving to allow for consideration of some of these simultaneously occurring events.

2 Climate Change - Chemical Stressor Interactions

The interactive effects of the dual stresses of climate change and chemical exposures are undoubtedly complex. As shown in Fig. 1, climate change may alter the sensitivity and susceptibility of organisms to chemical exposures, leading in some cases to increased chemical bioactivity and physiological perturbations (Hooper et al., 2013). Reversely, toxicants can impair the ability of organisms to respond to rapidly changing climate conditions and associated extreme weather events (Fig. 1). These reciprocal sensitivities to climate and chemical stressors could be influenced both geographically and temporally depending on a number of variables, such as the phylogenetic and microevolutionary history of affected species and populations, as well as the age, sex and health status of the exposed individual, inclusive of impacts from other environmental stressors that themselves may be altered by climate change. Such effects could occur in the short term wherein exposures to a chemical induces physiological or developmental defects that also impair the ability to cope physiologically or behaviorally with environmental change. Even over the longer-term, low level chemical exposures could lead to evolutionary tradeoffs wherein selection on developmental or metabolic pathways to make a population more tolerant to toxicant(s) could also retard evolutionary responses to new climatic conditions. Alternatively, the combined selective pressures could reduce genetic variation to the extent that population collapse

becomes more likely. There may thus be associated fitness costs to evolving chemical tolerance that reduce the capacities of populations to adapt to climate-related environmental stressors (Moe et al., 2013).

Current extinction rates are calculated at up to 1,000 times pre-human or natural background extinction levels (Barnosky et al., 2011; De Vos et al., 2015). Common elements of previous mass extinction events have included synergies between unusual climate dynamics, atmospheric changes, and intense ecological pressures that shape species lineages. Modern conditions associated with the rapidly warming climate, rising greenhouse gas levels, and human-related pressures on wildlife – such as chemical pollution – therefore constitute the types of interactive stressors that are predicted to intensify extinctions in the absence of mitigation efforts.

The expectation that many taxa will be at elevated extinction risk under a changing global climate contributes to an increased potential for large-scale shifts in the composition of biological communities or ecosystems over the next several decades. Such shifts may then impart heightened vulnerability to other stressors including chemical pollutants. The species predicted to suffer the greatest impacts of temperature changes associated with shifting climatic conditions are taxa that have evolved to be environmental specialists and have evolutionarily lost the ability to tolerate environmental conditions outside of a very narrow range (e.g., stenothermal taxa), or taxa already living in habitats with parameters near the upper limits of their thermal tolerance range (Bozinovic and Pörtner, 2015; Huey et al., 2012; Somero, 2010).

Although identifying taxa that are most vulnerable to the interacting effects of climate and pollution stressors may inform conservation efforts and policy making, it is important to point out that prior studies of mass extinctions provide lessons on how challenging it can be to distinguish vulnerability classifications accurately. For example, evidence from marine bivalves indicates that under previous mass extinction events, taxon persistence was promoted by broad geographical distribution at the genera-level but was not predicted by widespread species-level distributions or other factors such as dispersal capacities, species-richness, or generation times, all of which have been shown to be relevant lineage survival factors under background extinction dynamics (Jablonski, 2008). Thus, even more abundant, geographically widespread species could be vulnerable during mass extinctions linked to a changing climate interacting with other stressors like chemical pollution. In terms of terrestrial species, risk factors for extinction differ substantially depending on whether they are large or small bodied (< 3 kg) with larger bodied animals being more threatened by mass extinction events (Davies et al., 2008).

The context of biotic interactions (e.g., predators, competitors) has also been shown to influence the physiological and developmental impacts of some chemical pollutants (e.g., Relyea et al., 2012), and alterations to biotic community composition due to climate change have the potential to alter the ecological impacts of some chemical pollutants. Changes in species composition and species interactions due to climate change have already been detected in some biological communities (Tylianakis et al., 2008; Walther et al., 2002; Walther, 2010), and similar changes are expected to emerge in other communities of organisms occupying both terrestrial and aquatic environments (Dieleman et al., 2015, Inoue et al., 2013). The future of ecotoxicological research will therefore need to be one where evaluating the impacts of multiple stressors simultaneously – specifically, the interactions between chemical stressors and environmental stressors (e.g., temperature, ocean pH, predator presence) predicted to shift in intensity with climate change – will be paramount for understanding and predicting how the toxicity of chemicals may shift in the context of changing climatic conditions, as well as how changing conditions may influence the susceptibility of organisms to chemicals.

3 Climate-induced Changes in Exposures and Toxicity

3.1 Shifting chemical exposures

There are numerous ways in which climate change is predicted to affect chemical exposures among humans and wildlife. Perhaps one of the more well studied areas involves rising ambient temperatures that are leading to increased, regional-scale elevations in some air pollutants, notably ozone and particulate matter (IPCC, 2014 b,c). Related to this, melting sea ice, snow, and soils may liberate previously sequestered persistent organic pollutants (POPs), like polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), organochlorine pesticides, and methyl mercury, where they could become more bioavailable and enter food webs (Braune et al., 2005; Dalla Valle et al., 2007; Kong et al., 2014; Letcher et al., 2010; Pacyna et al., 2006). Areas that receive heavy or more frequent precipitation may experience elevated runoff of chemicals into water systems. This may be particularly relevant for surface runoff of

pesticides, fertilizers, petroleum products, and other nonpoint toxicants from agricultural and urban areas (Presley et al., 2006; Whitehead et al., 2009).

Prolonged fire seasons are producing more frequent and larger wildfires in mid- and northern latitudes, notably boreal forests (Gillett et al., 2004; Moritz et al., 2012; Pitman et al., 2007). Increased wildfire activity may lead to elevated levels of polycyclic aromatic hydrocarbons (PAHs), dioxins/furans, and other pyrogenic byproducts at local and regional scales (Cai et al., 2014; Gouin et al., 2013). Related to this, for example, UV-A radiation (320–400 nm) has been shown to photo-activate and substantially enhance the toxicity of a variety of PAHs among amphibians (Blaustein et al., 2003) and other aquatic species (Ankley et al., 2003). Thus, increases in PAHs from more pervasive and intense wildfires in geographical areas projected to see intensified UV radiation may be an important climate-chemical synergism. These types of interactions take on heightened importance given the vulnerability and rapid declines of amphibian populations worldwide (Stuart et al., 2004).

3.2 Chemical uptake and disposition

Data show that the effects of chemical-climate stressor interactions will vary depending on the chemical contaminant itself and the life stage of the organism, among other variables (e.g., DeLorenzo et al., 2009). Some of these influences on chemical-climate interactions have been the subject of recent review and empirical evidence, including how rising temperatures alter the biological uptake and disposition of chemical toxicants, leading to generally elevated toxicity among exposed taxa exposed to organic chemicals (Holmstrup et al., 2010; Noyes et al., 2009). However, these toxicokinetic interactions are not straightforward. For example, rising ambient temperatures can enhance both the absorption and elimination of chemicals thereby increasing uptake but can also reduce their biological half-lives due to enhanced depuration. Bioconcentration kinetics for persistent organic chemicals can be described as a passive partitioning between lipids of an organism and its surrounding environment. It is well established in some ectotherms that environmental temperature affects lipid composition (saturated versus unsaturated fatty acids) and, in some cases, cholesterol content of cellular plasma membranes (Hazel and Williams, 1990; Robertson and Hazel, 1997), which alters the fluidity and permeability properties of these membranes. Such temperature-induced changes in membrane lipid composition have the potential to alter the accumulation and cellular entry of organic toxicants. In addition, some hydrophobic persistent organics, such as PCBs, PAHs, and organochlorine pesticides, can themselves alter lipid composition and metabolism as well as disrupt membrane functioning that in turn contributes to chemical uptake, disposition and toxicity (Elskus et al., 2005). Couple these changes in lipid composition and membrane dynamics with changes in cellular metabolic rate, food intake, and growth, as well as potential shifts in behaviors such as habitat selection and activity patterns, and one can see how the interactions between temperature change and chemical toxicity in an ecologically-relevant context become complicated rapidly.

Examples in which chemical movement, lipid/membrane alterations, and environmental variation have been studied concurrently are rare at present. Nonetheless, the limited data available suggest such interactions can result in intricate – and sometimes counterintuitive – dynamics of chemical toxicity. For instance, temperature increases are currently most pronounced at higher latitudes with warming in the Arctic increasing at nearly twice the global average (Chapin et al., 2005; Graversen et al., 2008; Kaufman et al., 2009). Rising levels of some PCBs have been detected recently in some Arctic fishes (i.e., burbot, *Lota lota*) despite the declines and stabilization of PCBs in the atmosphere since their phase-out (Carrie et al., 2010; Wang et al., 2010). It has been suggested that increased algal-derived organic matter linked to rising ambient temperatures has led to increased scavenging of PCBs and other persistent chemicals (methyl mercury, DDT), and this has in turn led to increased bioavailability and biomagnification. In addition to this temperature-enhanced bioaccumulation of PCBs, elevated water temperatures have been shown to increase the formation of bioactive hydroxylated PCBs (OH-PCBs), which are formed in biota by cytochrome P450 (CYP) catalyzed metabolic pathways. In particular, juvenile rainbow trout *Oncorhynchus mykiss* exposed to PCBs through the diet have been shown to form higher levels of OH-PCBs when co-exposed to elevated water temperatures (Buckman et al., 2007). Some OH-PCBs isoforms are persistent in blood and adipose tissues and elicit multiple adverse effects by inducing estrogenic activity (Kester et al., 2000; Shevtsov et al., 2003), by perturbing the thyroid system at several levels (Iwasaki et al., 2002; Purkey et al., 2004; Yang et al., 2008), and by inhibiting detoxification of environmentally prevalent PAHs (van den Hurk et al., 2002). In contrast to the temperature enhanced bioactivation of PCBs, a limited number of chemicals, including some

Type I pyrethroid insecticides – but not Type II pyrethroids – have less bioactivity and enhanced detoxification at elevated temperatures (Harwood et al., 2009; Materna et al., 1995; Ratushnyak et al., 2005).

Another informative example of climate change impacting bioactivation pathways relates to data showing enhanced toxicity in some aquatic fishes acclimated to different salinity conditions and exposed to organic chemicals (de Polo et al., 2014; Riou et al., 2012). In one study by Lavado and coworkers (2011), the organophosphate insecticide phorate was 30-times more lethal (measured as LC50) to coho salmon *Oncorhynchus kisutch* acclimated to elevated salinity conditions (32 $g \cdot L^{-1}$) than those fish maintained at salinities less than 0.5 $g \cdot L^{-1}$. The enhanced toxicity was attributable to increased formation of the highly toxic metabolites phorate oxon and phorate oxon sulfoxide in a number of tissues. This enhanced bioactivation under elevated salinities may be species dependent and has also been shown with other pesticides, notably carbamates, which also contain thioether moieties like organophosphate insecticides. For instance, research by the same laboratory in rainbow trout *O. mykiss* acclimated to elevated salinity and co-exposed to aldicarb for 96 hours showed elevated cholinesterase inhibition and increased formation of the toxic metabolite alicarb sulfoxide (Wang et al., 2001). However, this increased toxicity and altered metabolic profile was not observed in hybrid striped bass (*Morone saxatilis x chrysops*) subjected to the same salinity-aldicarb co-exposures. These data illustrate the potential for significant evolutionary differences among taxa in how chemical and climate stressors interact to shape toxicity.

3.3 Metals bioavailability and toxicity

Many of the environmental conditions being altered by climate change (pH, dissolved oxygen, temperature, and salinity) could impact metals speciation (i.e., changes to different ionic forms), biotransformation (e.g., methylation), and consequent bioavailability, accumulation, and toxicity potential (Anawar, 2013; Weiss, 2014; Sokolova and Lannig, 2008). Metals toxicology is unique from that of man-made organic chemicals in that metals are naturally occurring and their levels and speciation patterns can vary substantially by geographic region, water chemistry, and biogeochemical cycling. Moreover, some metals are essential nutrients (copper, selenium, zinc) necessary for proper health maintenance and physiological functioning, but all metals can be toxic depending on their concentration and form. Human activities, such as mining and fossil fuel burning, have been shown to redistribute and concentrate metals in some environments beyond natural background levels that are harmful to humans and ecosystems. Indeed, lead, mercury, cadmium, and the metalloid arsenic continue to rank in the top ten highest priority hazardous substances identified by the U.S. EPA and ATSDR in their priority hazardous substances list (http://www.atsdr.cdc.gov/spl/).

Perhaps some of the more compelling evidence that climate change can exacerbate chemical toxicity relates to research showing that rising ambient temperatures may alter toxicokinetic and energy metabolism pathways that in turn potentiate the toxicity of some metals. The exact mechanisms are not fully understood, but dysfunction of mitochondrial energetics, increased thermal and oxidative stress, and impaired respiration/oxygen production and consumption have been reported in teleost fishes and terrestrial and aquatic invertebrates exposed concurrently to elevated temperatures and several metals, including cadmium, lead, mercury(II), and copper (Cherkasov et al., 2006; Khan et al., 2006; Kimberly and Salice, 2014; Kumar and Gupta, 2006; Lannig et al., 2006; Legeay et al., 2005; Li et al., 2014; Mo et al., 2013; Rao and Khan, 2000; Rathore and Khangarot, 2002). Indeed, mitochondria are important metabolic and homeostatic structures that function in maintaining thermal tolerance ranges, and as such are highly sensitive to temperature variations (Blier et al., 2014). The effects of temperature on metal toxicity have also been measured in higher level vertebrates including tree swallows *Tachycineta bicolor*, whereby elevated ambient temperatures were associated with reduced reproductive output during early nestling periods among birds with elevated blood levels of mercury compared to bird residing at uncontaminated sites (Hallinger and Cristol, 2011; Hooper et al., 2013). Temperature effects on metals bioaccumulation have also been observed for some aquatic plants with increasing temperatures leading to increased bioaccumulation of cadmium and lead (Fritioff et al., 2005).

Changing salinity patterns of aquatic habitats are another parameter that could influence the bioavailability and toxicity of metals although the relationships are less clear than for temperature. Many metals have been shown to be more toxic with declining environmental salinities. This interaction has been fairly well described and is thought to be attributable to more free metal ion being available for biological uptake (i.e., less metals complexation) as well as the osmoregulatory physiology of exposed animals (Hall and Anderson, 1995; Henry et al., 2012; Heugens et al., 2002; Weiss, 2014). In addi-

tion, as salinities rise there is thought to be more competition for binding sites on the biotic ligand (e.g., gill) such that aqueous cations (Na^+, Ca^{2+}, and Mg^{2+}) may confer some protection from metals binding. An important pathway of acute metal toxicity has been shown to proceed through impairment of osmoregulatory functioning of gill Na^+/K^+-ATPase (Monseratt et al., 2007; Roast et al., 2002; Weis, 2014). Among euryhaline and marine organisms that may experience a range of salinity regimes, there is evidence suggesting that impaired osmoregulation leading to disrupted ion homeostasis is a major factor influencing metals acute toxicity with metals complexation and ligand competition being less important.

For example, research in the euryhaline teleost *Fundulus heteroclitus* exposed to copper (Grosell et al., 2007) and in the crustaceans *Litopenaeus vannamea* and *Excirolana armata* exposed to nickel (Leonard et al., 2011) found that elevated internal to external Na^+ gradients (i.e., disrupted osmoregulation) were the key parameter influencing acute toxicity with less of a role for salinity-related changes in levels of the more bioavailable free metal fraction. Furthermore, like many marine invertebrates, *L. vannamea*, and likely *E. armata*, are osmoconformers but will osmoregulate at lower salinities, which may make them more sensitive to metals. Related to these findings, there is some evidence that the influence of salinity on metals toxicity may depend on previous salinity regimes. Specifically, euryhaline sheepshead minnow *Cyprinodon variegatus* acclimated to low salinity levels and subsequently exposed to free cupric ion (Cu^{2+}) experienced greater disruptions in Na^+/K^+-ATPase activity and reduced Na^+ plasma levels, among other osmoregulatory disturbances, than copper-exposed minnows acclimated to higher salinities. These findings provide further support for the proposition that coincident exposures to metals contamination and pulses of aqueous freshening may exacerbate osmoregulatory disturbances that may in part depend on previous salinity conditions to which the animal was exposed (Adeyami et al., 2012). Therefore, species residing in habitats experiencing increased and extreme precipitation events linked to climate change may be more susceptible to disrupted ion homeostasis and metals toxicity. Conversely, metals bioavailability and consequent toxicity could be reduced in metals-contaminated habitats experiencing increased salinity associated with precipitation reductions, drought and diminished snowpack runoff. Salinity impacts on metals toxicity may be particularly pertinent for euryhaline and marine species residing in areas that experience salinity fluctuations and receive both freshwater and saltwater, such as coastal bays, wetlands, and estuaries.

Whereas metals toxicity has been shown to be generally augmented with decreasing salinity, exceptions to these inverse relationships have been measured. For instance, in at least one study, increasing environmental salinity caused an increase in the oxidation of selenomethionine to its reactive selenoxide form that in turn was associated with depleted levels of the antioxidant glutathione and developmental toxicity (Lavado et al., 2012). While selenium levels were unaltered by changing salinity levels, the authors suggested a mechanism of altered oxidative metabolism that could be linked to salinity-related increases in the expression and activity of flavin-containing monooxygenases (FMOs), which are involved in osmoregulation and xenobiotic metabolism and of which organoselenides act as strong substrates. It is also the case that climate change-metal interactions are complicated by the fact that populations of organisms have evolved under differing background environmental levels of metals and therefore may have regionally specific intrinsic tolerances to metals that influence their adaptive capacities. Thus, taken together, a great deal of caution is merited when trying to derive general unifying principles concerning how metals toxicity will be influenced by climate change.

4 Chemical Exposures may Enhance Susceptibilities to Climate Change

4.1 Multiple stressors and organism energy balances

With climate change it is possible, even likely, that many species are experiencing multiple rapid environmental changes simultaneously (Harley et al., 2006), and chemical pollutant exposure could hinder an organism's ability to acclimate to the new suite of environmental conditions (Fig. 1). For example, exposure to trace metals can impair respiratory functioning in some aquatic invertebrates such as crustaceans and mollusks (Spicer and Weber, 1991), leading to altered oxygen consumption and metabolic rates (Giacomin et al., 2014; Xuan et al., 2013). Changes in oxygen consumption, metabolic rate, and gill Na^+/K^+-ATPase activity caused by exposure to metals – or other chemicals such as organochlorine pesticides – have been observed in fishes as well (Beyers et al., 1999; Peles et al., 2012; Pistole et al., 2008). Although such chemical-induced changes in oxygen consumption and metabolism clearly have significance for food consumption and growth, these changes also could have profound implications for the

ability of ectothermic organisms to cope with changing temperatures and food availability, because both of those environmental parameters can have their own impacts on metabolism.

As a conceptual framework for thinking about potential implications of such interactions, it is useful to consider how chemical exposure and climate change stressors might interact to impact energy balance in organisms. An organism's energy budget is an accounting of how the energy gained by the organism (e.g., energy acquired from food consumption) balances against the energy either 1) lost as unassimilated (i.e., excreted as feces), 2) used by the organism for respiration (i.e., basal metabolic costs), or 3) devoted toward somatic growth and reproduction (Sokolova et al., 2012). These components of an organism's energy budget are linked functionally by the maximum metabolic ability (e.g., cellular respiration capacity) of an organism to convert energy consumed, which itself is limited by mitochondrial efficiency as well as oxygen availability and transport rates (Guderley and Pörtner, 2010). Ultimately, the significance of these interrelationships is a tradeoff in energy allocation; allocation of energy for basal metabolic processes (e.g., basal metabolic rate) holds priority over energy allocation for growth and reproduction.

4.2 Chemicals, energetics and thermal tolerances

To begin to illustrate how those functional interrelationships between the components of an organism's energy budget are relevant to chemical pollution and climate stressor interactions, it is helpful to consider an organism's thermal performance curve (TPC) (Hofmann and Todgham, 2010; Huey et al., 2012; Pörtner, 2010). The TPC describes the relationship between temperature variation and 'performance' or 'fitness' (Huey et al., 2012), with performance typically assessed using some indirect, proxy measure of relative fitness such as aerobic metabolism (e.g., O_2 consumption rates) or another physiological or behavioral measures (e.g., sustained swimming ability; prey capture ability; reproductive rate) linked to survival and fitness (Amarasekare and Savage, 2012; Huey and Stevenson, 1979). In ectotherms, TPCs characterize both an organism's thermal tolerance and its temperature range of near-optimal

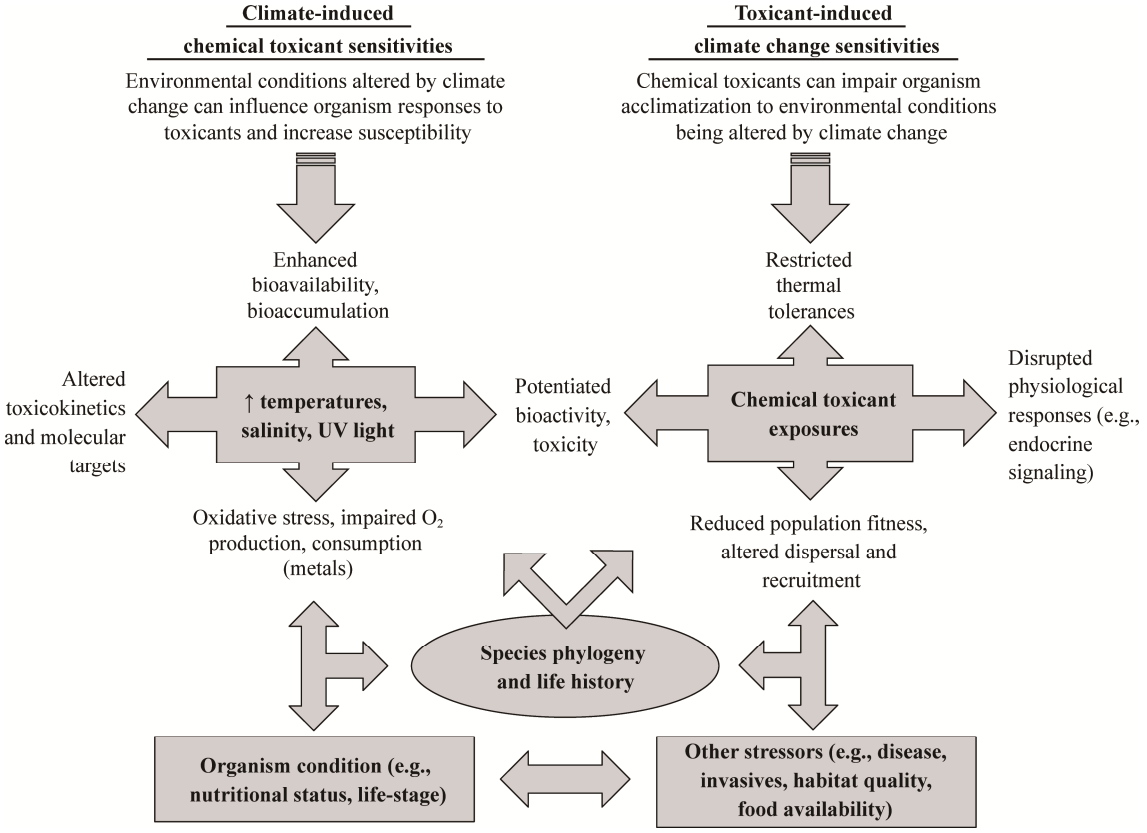

Fig. 1 Depiction of interactions between climate change and chemical stressors

Climate change could perturb an organism's response to a chemical exposure and chemical exposures could perturb species adaptive responses to the changing climate. Individual variation in condition and genetic composition, genetic differences among populations, and other environmental stressors that may or may not be directly linked to climate change can each influence how species respond to these climate-chemical interactions.

performance ('performance breadth'), and are typically asymmetrical in shape around the optimal performance temperature (T_{opt}) with a rapid decline in performance as the organism approaches its critical thermal maximum (CT_{max}) temperature (Fig. 2A). The CT_{max} and critical thermal minimum temperature (CT_{min}) bounds of a TPC arise from limits to aerobic scope, which is restricted at high temperature by deficient oxygen uptake to meet metabolic demand, but by insufficient mitochondrial capacity at low temperatures (Pörtner, 2001). Ecotherms exposed to temperatures above these CT values transition to anaerobic mitochondrial metabolism, and eventually may enter a 'repair' state where the expression of heat shock protein (HSPs) becomes elevated to cope with the increasing loss of structural integrity of proteins at thermal extremes (Pörtner, 2002, 2010). In many species, TPCs show some degree of plasticity both over ontogeny and as organisms acclimate physiologically to different environmental temperature regimes on a seasonal or geographic basis by altering cellular mitochondrial density or by shifting expression of HSPs or oxidative stress defenses (Fig. 2B) (Pörtner, 2002, 2010; Schulte et al., 2011).

4.3 Chemical impacts on thermal tolerances

The empirical study of TPCs has been used to identify broad-scale geographic variation in thermal tolerances among ectothermic taxa, and results from these studies indicate that taxa in the tropics may be at a higher risk of extinction from climate change than taxa in temperate latitudes (e.g., Deutsch et al., 2008; Dillon et al., 2010). What hasn't been considered, however, is that chemical exposures might alter TPCs by disrupting metabolic processes either directly or indirectly. Such alterations could occur via several mechanisms including chemical interactions with nuclear receptors underlying metabolic regulation (Casals-Casas et al., 2008; Grün and Blumberg, 2006), interference with hormone pathways that regulate metabolism (Casals-Casas and

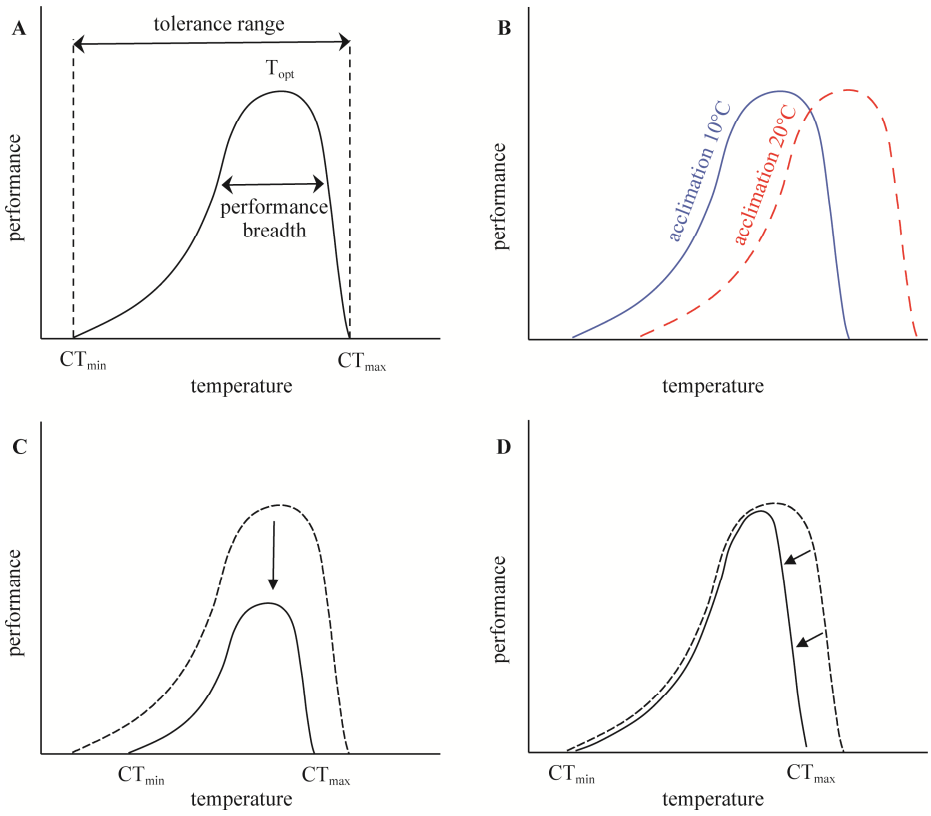

Fig. 2 Illustration of how chemical exposure might impact thermal performance curves (TPCs)

A. TPC for a typical ectothermic animal. The critical thermal minimum (CT_{min}) and maximum (CT_{max}), optimal performance temperature (T_{opt}), near-optimal performance breath, and overall temperature tolerance range are indicated (adapted from Huey, 1982). B. TPCs have been shown to shift in many ectotherms with acclimation to differing environmental temperatures, and such acclimation ability is predicted to be critical in responding to climate change (Hofmann and Todgham, 2010). Exposure to chemical contaminants has been found to alter the TPC, in some cases both decreasing the CT_{max} and increasing the CT_{min} to result in a reduced tolerance range compared to the organism's 'unexposed' TPC (indicated by dotted line) (C) (e.g., Heath et al., 1995), while in other scenarios chemical exposure may depress CT_{max} without any change in CT_{min} (D) (e.g., Heath et al., 1997). Acclimation temperature may be critical to how the TPC changes under chemical exposure. While both scenarios C and D reduce performance across a range of temperatures, the differing implications for tolerance range in these two scenarios may be critical for interpreting how chemical exposure impacts the ability of an organism to survive changing temperature conditions.

Desvergne, 2011), alteration of storage or mobilization of metabolic substrates such as glucose, glycogen, and protein (De Smet and Blust, 2001; Fabbri et al., 2003; Jyothi and Narayan, 1999; Sancho et al., 1998), or impairment of food intake rates or foraging efficacy (Smith et al. 1995). Supporting this idea, several studies have found that chemical exposure can decrease CT_{max} values in ectotherms (Becker and Wolford, 1980; Heath et al., 1994; Johnson, 1976; Messaad et al., 2000; Patra et al., 2007; Poulton et al., 1989; Watenpaugh et al., 1985). There are relatively few studies, however, that have examined how both CT_{max} and CT_{min} values might be affected by chemical exposures, even though quantification of both CT_{max} and CT_{min} can provide crucial information about how a specific chemical contaminant might impact survival in the face of changing environmental temperatures. For example, exposure to some chemicals could cause a general depression of the TPC (Fig. 2C). Such a TPC depression would be indicated by both a decrease in CT_{max} and increase in CT_{min}, as well as by a decrease in performance at intermediate temperatures across the TPC. Under such a scenario, acclimation may still shift the temperature range of thermal tolerance, but because performance is reduced across all temperatures, the organism would likely still suffer reduced fitness in any tolerable thermal regime even with acclimation. In an alternate scenario where chemical exposure results in a horizontal shift in an animal's TPC toward lower temperatures but does not result in a decrease in maximum performance (Fig. 2D), physiological acclimation to a warmer environment may aid significantly in overcoming the detrimental effects of the chemical on temperature-related performance by shifting the TPC back toward a warmer range of temperatures.

Evidence for both of these patterns of chemical-induced TPC alternation has been observed in experimental studies. Heath and coworkers (1994) found a decrease in CT_{max} and increase in CT_{min} in fathead minnows *Pimephales promelas* exposed to the pyrethroid pesticide cyfluthrin; that finding suggested a general depression in performance across all temperatures (Fig. 2C). This observation contrasts, however, to the finding of a decrease in CT_{max} but no alteration of CT_{min} (similar to Fig. 2D) for *P. promelas* exposed to the pesticide carbofuran (Heath et al., 1997). Evidently chemical exposure can induce varied types of changes to an organism's TPC depending on the chemical, developmental stage and other factors. The pattern of TPC alteration (e.g., change in thermal tolerance, T_{opt}, and performance breadth) caused by chemical exposure may however be critical to understanding how an organism will respond to elevated thermal regimes associated with climate change, as well as what role physiological acclimation might play in remediating the toxic effects of chemicals on an organism's TPC.

Empirical studies that evaluate how TPCs are altered by chemical exposure have the potential to provide new insights into idenfying ectotherms that will be most at risk under the combined influences of chemical pollutants and changing environmental temperatures. However, other environmental parameters (e.g., salinity, desiccation stress, pH) predicted to shift with climate change also influence metabolic processes and are likely to have synergistic interactions with temperature variation. For instance, active regulation of osmotic and ionic homeostasis by an organism has metabolic costs. Such costs are evident in aquatic taxa where a change in salinity conditions alters metabolic rate (Tseng and Hwang, 2008). However, such salinity effects do not occur in isolation, and the thermal environment wherein active regulation of hydromineral balance occurs can influence the efficacy of osmotic regulation and ability to tolerate elevated salinities (e.g., Stuenkel and Hillyard, 1981). Multiple stressors are thus likely to interact and shape how the tolerance range to any single environmental parameter is altered by chemical exposure, and future toxicological studies should begin emphasizing experimental designs that examine toxicity effects of chemical contaminants in the context of multiple dimensions of environmental and physiological variability. Such studies should not be limited only to empirical measurement of TPCs, but also incorporate alternative approaches such as dynamic energy budget (DEB) modeling (Kooijman, 2010), which links the energetics of organisms to population-level responses by incorporating environmental conditions (e.g., temperature, food availability, toxin exposure) into energetics models (Baas et al., 2010; Jager and Zimmer, 2012), or other bioenergetics frameworks based on predictions from oxygen- and capacity-limited thermal tolerance (OCLTT) models (e.g., Sokolova et al., 2012).

4.4 Endocrine disrupting chemicals

Beyond the need for better incorporation of multiple stressors into studies of chemical toxicity, there are also certain categories of chemical effects that may have a greater likelihood of affecting how organisms respond to the changing climate. Chemicals that disrupt endocrine system functioning, for instance, are of particular concern. Hormone systems are highly sensitive to envi-

ronmental cues such as temperature, food availability, body water and ion concentrations, photoperiod, and social interactions, and are considered one of the first physiological responses to respond to changes in an organism's environment (Lema, 2014). Moreover, many of the structural and functional features of endocrine systems are well-conserved across vertebrates with research demonstrating common mechanistic responses of fish and mammals to endocrine disrupting chemicals (EDCs; Ankley and Gray, 2013). Thus, EDC interactions with climate change are a priority concern because of their potential for widespread impacts and common targets across a range of taxa and given the integrated role of endocrine systems in the maintenance of physiological homeostasis in response to environmental variability and homeostatic perturbations.

Endocrine signaling systems are multi-dimensional regulatory pathways that include not just the hormone signal molecule, but also transport proteins, conversion enzymes, membrane transporters, and receptors (Lema and Kitano, 2013). Many studies targeting EDCs have focused on how chemical exposure alters circulating hormone concentrations, and there is abundant evidence that endocrine-disrupting effects often occur simultaneously at several levels of an endocrine signaling pathway. Over the last decade, research on EDCs has shown that many agricultural chemicals (pesticides, herbicides, fertilizers), industrial chemicals and pharmaceuticals have the ability to alter hormone signaling within several of the major endocrine signaling axes, including the hypothalamic-pituitary-gonadal (HPG) axis that regulates reproduction, the hypothalamic-pituitary-adrenal/interrenal (HPA or HPI) axis that controls physiological and behavioral responses to many environmental stressors, and the hypothalamic-pituitary-thyroid (HPT) axis that regulates metabolic processes, somatic growth, and neural system development (Bergman et al., 2012; Khetan, 2014; Noyes and Stapleton, 2014).

Interactions between EDCs and environmental parameters linked to climate change are now beginning to be documented among individual species and populations. One recent study measured male-skewed sex ratios among inbred and outbred zebrafish *Danio rerio* co-exposed to elevated temperatures (33°C representing IPCC worst-case projections for India by 2100) and the fungicide clotrimazole, which disrupts estrogen biosynthesis by inhibiting aromatase (Brown et al., 2015). In addition to an increase in the expression of *cyp19a1a* genes encoding aromatase in fish exposed to elevated temperatures and/or fungicide, male-biased sex ratios caused declines in estimated population growth rates that were most severe among smaller, inbred populations. These data demonstrate how ecological context may amplify climate-EDC impacts markedly among inbred species and populations that occupy narrow niches with limited genetic diversity (e.g., threatened or endangered species) or those that display environmental sex determination. In another study examining the interactive effects of perfluorooctane sulfonic acid (PFOS) and elevated dissolved CO_2 concentrations (0.3% increase of dissolved CO_2 representative of predicted ocean conditions in the year 2300) found that PFOS exposure in combination with the 0.3% increase in CO_2 induced different effects including a short-term elevation in skeletal muscle testosterone concentration and changes in hepatic estrogenic gene expression in patterns dissimilar to those following exposure to PFOS or elevated CO_2 alone (Preus-Olsen et al., 2014). Temperature has also been shown in several studies to influence the effect of xenoestrogens like ethinylestradiol on vitellogenin yolk protein expression in fish (Jin et al., 2009; Korner et al., 2008). It has also been found that some environmental conditions themselves may disrupt endocrine signaling. Environmental hypoxia (generally defined as dissolved $O_2 < 2\ mg \cdot L^{-1}$) has been implicated to depress the HPG and HPT axes in fish resulting in impaired reproductive function (Martinovic et al., 2009; Thomas et al., 2007; Wu et al., 2003). Likewise, nitrate (NO_3^-) has been proposed as potentially having endocrine-disrupting effects in aquatic environments (Guillette and Edwards, 2005).

Another area of special concern relates to how the impacts of chemicals that perturb metabolism, growth and development may become even more severe under changing temperatures. The disruption of metamorphosis in aquatic breeding amphibians provides a clear example of the potential for such interactions. In anuran amphibians, the metamorphic transition from water-based tadpoles to more terrestrial-living juveniles depends primarily on programmed secretions of thyroid hormone along with other coordinated endocrine signaling events (e.g., HPA axis). Rising temperatures and other climatic changes such as drought and water shortages could have important ramifications for amphibian populations subjected to concurrent chemical exposures that impair thyroid functioning. Temperature and moisture are important factors regulating metamorphic transitioning, and amphibians subjected to unusual drying or warming conditions have been shown to undergo accelerated metamorphosis, which is thought to be an adaptive stress response (Denver et al., 1998; Walsh et

al., 2008). Exposures to thyroid perturbing chemicals could impair the physiological plasticity of these adaptive responses in some amphibian species subjected to these climate change pressures (Hooper et al., 2013).

It is important reaffirm that interactions between EDCs and climate change stressors such as temperature, UV light, salinity, pH and dissolve O_2 are likely to be involved. To exemplify this point, one can look at the role of thyroid hormones in metabolic regulation in vertebrates. In mammals, it is well established that the thyroid hormone triiodothyronine (T_3) stimulates thermogenic mechanisms that increase metabolic heat production, making T_3 an important regulator of mammalian body temperature (Silva, 1995). In Actinoperygiian fishes, however, the effects of thyroid hormones on metabolism appear to vary with environmental temperature. Recent evidence indicates that T_3 may mediate metabolic and cardiac regulation associated with thermal acclimation at low temperatures, but not at high temperatures (Little et al., 2013; Little and Seebacher, 2014). As this example of evolutionary divergence in the regulation of metabolism by thyroid hormones illustrates, phylogenetic context needs to be considered when testing hormone function and endocrine signaling regulation for additive or synergist EDC-climate change interactions. Even closely-related organisms have been found to vary in responses to chemicals under different environmental regimes due to past selection for disparate environments (e.g., Mo et al., 2013), and such evolution will continue as populations adapt to local variation in changing climatic conditions (Moe et al., 2013).

5 Considering Climate Change in Chemical Toxicity Testing

It has long been acknowledged that there needs to be improved methods, tools, and approaches for examining and assessing the impacts of multiple chemical and non-chemical stressors on humans and wildlife. One of the major obstacles to evaluating how climate change stressor impacts chemical toxicity, and vice versa, arises from the daunting reality that – even with all the research efforts in toxicology to date – little is known about the toxicity potential of most environmental chemicals for most species, let alone how different life stages, sexes, or populations may vary in susceptibility to any toxic effects (Dix et al., 2007; Grandjean and Landrigan, 2006). There are tens of thousands of chemicals in use today throughout the world, and bioactivity and toxicity data on most of these chemicals is limited or lacking entirely. Moreover, humans and wildlife are exposed to varying and complex mixtures of chemicals and metals, typically but not always at low levels, over the course of a lifetime. The role of these long term exposures in contributing to disease outcomes and population declines continue to be generally poorly described.

To date, most ecotoxicity (and human health related) testing used in risk assessments has focused on direct measurements of apical endpoints of concern, such as development during early life, reproductive functioning, and survival. Such assessments often rely on data from *in vivo* models and the application of uncertainty factors to extrapolate any observed toxicity findings across taxa and chemical exposure concentrations. Typically, studies supporting these assessments are conducted at 'normal' ambient temperatures (e.g., 25°C) so that impacts of the surrounding environment on the test animal are neutralized to avoid confounding effects. Thus, mechanistic data describing the targets and underlying pathway of toxicity, such as altered gene expression, changes in protein activity, altered metabolite profiles and receptor interactions, are seldom used in chemical risk assessment and regulatory toxicology. Moreover, the interactive or synergistic effects of chemical-environment interactions are rarely subjected to systematic evaluation in any context.

The 'test and extrapolate' approach has been important in identifying hazard-risk issues for some chemicals, especially certain pesticides, but this approach is increasingly recognized as impractical due to the logistical challenges of implementation for an ever-increasing number of chemicals and novel chemistries (e.g., nanoparticles) being used. Coupled with our fast developing capacity to detect chemicals at exceedingly low concentrations (ppt – ppb levels) in biota and the environment, this single chemical testing paradigm is now being replaced by new methods to more quickly measure, in some cases, many thousands of biological endpoints simultaneously using advances in 'omics' technologies (transcriptomics, proteomics, metabolomics), computational biology, and other high throughput models and technologies. Stemming in part from the increasing use of molecular and genetic biotechnologies in chemical testing, the field of toxicology has been shifting focus from traditional empirical testing methods with whole organisms and single chemical analyses to more predictive-based approaches that strive to characterize early molecular pathway responses to chemical exposures to identify chemical classes that require enhanced scrutiny and testing. In 2007, for instance, the U.S. National Research Council (NRC) concluded that a transformational

shift was required in human health toxicity testing from whole animal test systems to *in vitro* methods and bioinformatics to better evaluate biological perturbations and toxicity pathways (NRC, 2007). In alignment with these NRC findings, ecological endpoints have also been the target of focus, including a recent SETAC Pellston workshop that examined how to better incorporate mechanistic data into predictive ecotoxicity testing and ecological risk assessment (Villeneuve and Garcia-Reyero, 2011).

This shift in emphasis toward understanding toxic chemical perturbations to biological pathways – particularly those earliest molecular initiating events – as opposed to whole-organism endpoints has led to increasing interest in the use of *in vitro* and non-mammalian models, such as embryonic zebrafish, as biosensors to test for potential human and ecological effects. To help prioritize chemicals for testing, the U.S. Environmental Protection Agency (EPA), National Institute of Environmental Health Sciences (NIEHS), and Food and Drug Administration (FDA) formed a consortium "Tox21" to apply high-throughput technologies to screen ~10,000 chemicals and characterize molecular and physiological pathways underlying toxicity (http://www.epa.gov/ncct/Tox21/). In addition, the U.S. EPA launched its ToxCast™ program in 2007 to further develop high-throughput screening platforms with cell-based approaches and embryonic zebrafish to screen toxicity for a large chemical library (Kavlock et al., 2012; Padilla et al., 2012; Truong et al., 2014). These programs have focused on characterizing chemical mechanisms and targets for use in understanding potential health effects, and have recently been used to understand the toxicity of other large chemical categories (e.g., flame retardant chemicals) with widespread global distributions but poorly understood toxicity pathways (Noyes et al., 2015). These types of high throughput screening platforms provide a meaningful opportunity to screen for interactive effects of multiple chemicals and environmental stressors, including those being altered by climate change.

Layered on these high-throughput screening programs, there is also an expanding use of non-traditional organisms in toxicological studies. The use of non-traditional organisms is based on our increasing knowledge of biological pathway conservation across species, which then allows for the selection of test organisms based on conserved (or divergent) systems and responses. These types of pathway-based approaches for chemical assessment are resulting in less distinction between traditional human health and ecological hazard/risk characterizations. Nevertheless, there continue to be fundamental challenges with implementing toxicity pathway-based approaches in hazard-risk assessment in both human and ecological systems. One of the primary challenges remains translating data collected at lower levels of biological organization (e.g., molecular, biochemical) into endpoints that are meaningful for the individual fitness and population consequences of chemical exposure. This translation across levels of biological organization is particularly difficult with data from *in vitro* testing (e.g., receptor binding assays) where there are substantial limits and uncertainties in delineating whether a positive result is an adverse effect or adaptive response to a chemical exposure.

Even so, there have been important efforts to address these limitations. In particular, adverse outcome pathways (AOPs) represent a conceptual framework to depict linkages between molecular initiating events of toxicity (e.g., chemical interaction with a subcellular target) and the consequent cascade of responses that elicit an adverse phenotypic response in an organism and ultimately wildlife population (Ankley et al., 2010; Villeneuve et al., 2014). These types of AOP approaches build on previous ecological risk assessment concepts to provide a framework for integrating and translating mechanistic data into fitness-related endpoints at higher level of biological organization that are critical to effective risk assessment. They also provide an organizing platform for integrating mechanistic data derived from 'omics' studies and other multi-dimensional data outputs to anchor molecular initiating events and other key molecular observations to downstream phenotypic outcomes (e.g., deformity, impaired reproduction, population impact).

Considering global climate change in AOP frameworks is one promising approach for predicting and diagnosing potential adverse effects elicited by climate change and chemical interactions as AOPs can be modified to incorporate environmental exposure components into testing regimes (Hooper et al., 2013; Moe et al., 2013). Figure 3 (from Hooper et al., 2013) provides an instructive AOP that describes the potential interactive effects of climate change with EDCs demonstrated to impact thyroid system functioning in amphibians and other taxa. For this AOP example, there exists a fairly robust dataset describing the underlying targets and mechanisms of thyroid dysfunction for several classes of chemicals. Therefore, this type of AOP construct allows for the linkage of several chemical initiating events of thyroid system perturbations to downstream outcomes that are meaningful for risk assessment with

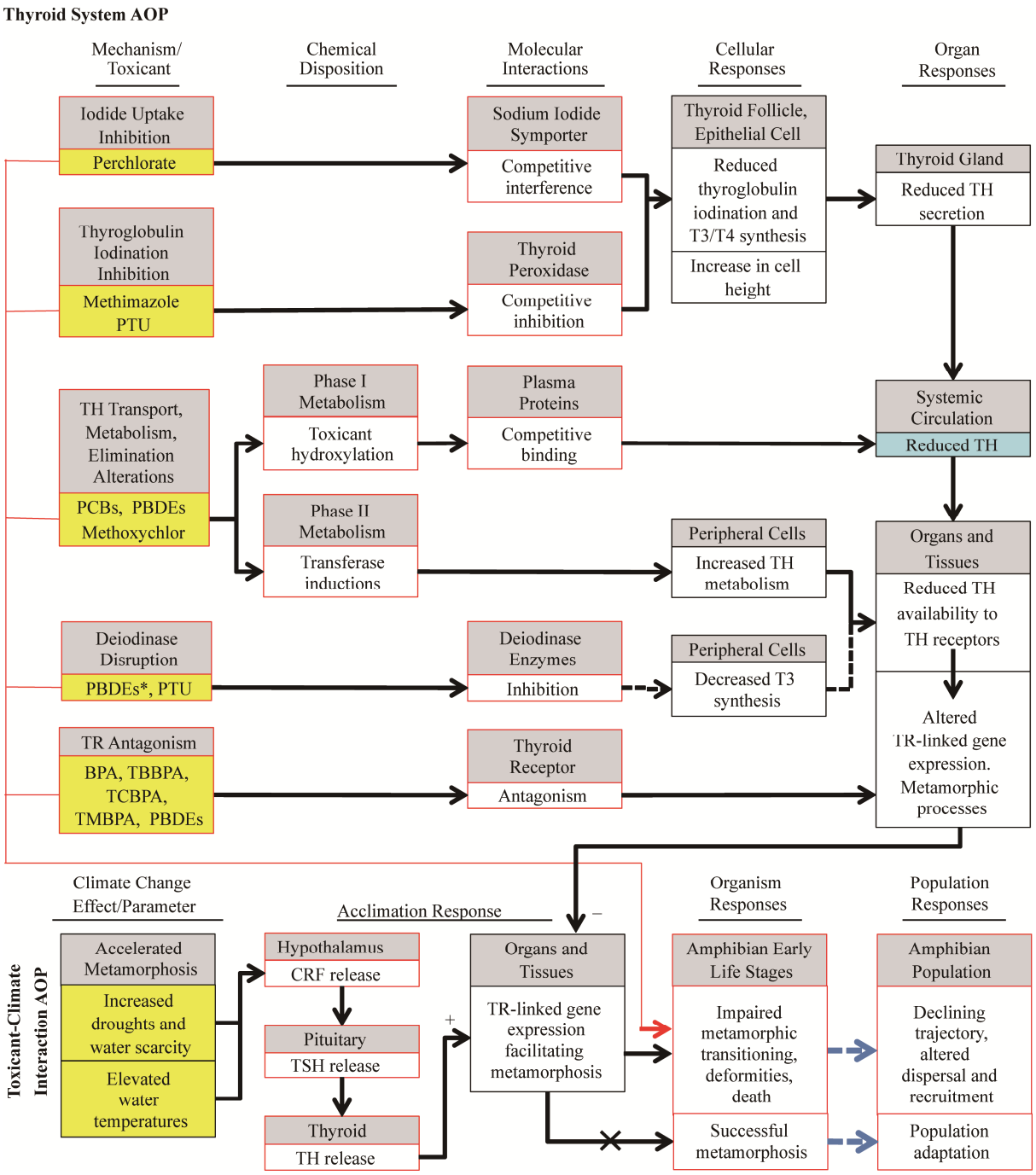

Fig. 3 Representation of an adverse outcome pathway (AOP) for chemical-induced sensitivities in amphibians that depict the potential reciprocal interactions between climate change and thyroid disrupting chemicals

Five chemical toxicity mechanisms are outlined with unique molecular initiating events that can lead to reduced thyroid hormone levels and impaired metamorphosis. These chemical AOPs in turn share common outcomes under climate change that could impair accelerated metamorphosis under some climate change scenarios (e.g., drought, warming). The blue box (reduced TH) represents a potential biomarker that can be used to identify chemicals operating by this pathway. Red arrows represent empirical linkages based on quantitative exposure-response data. Black arrows represent established mechanistic linkages with quantitative data. Black and blue dotted arrows represent plausible and predicted linkages, respectively. BPA = bisphenol A; PBDE= polybrominated diphenyl ether; PCB = polychlorinated biphenyl; PTU = propylthiouracil; TBBPA = tetrabromobisphenol A; TCBPA = tetrachlorobisphenol A; TMBPA = tetramethylbisphenol A; TH = thyroid hormone; T3 = triiodothyronine; T4 = thyroxine; TR = thyroid receptor; CRF = corticotropin-releasing factor; TSH = thyroid stimulating hormone (from Hooper et al., 2013).

explicit integration and consideration of possible climate change interactions. It serves as a diagnostic tool to systematically predict when and how chemicals and climate change stressor interactions might occur (i.e., providing a clarifying tool for identifying species, populations, and geographical regions or 'hot spots' that

could merit further examination and protection), rather than relying on collections of disparate empirical data to make decisions. As can be seen in Fig. 3, even with the mechanistic information now available on several thyroid disruptor chemicals, there is comparatively less clear information on the environmental stressors being altered by the changing climate (e.g., droughts, loss of moisture). Thus, AOPs can identify data gaps and uncertainty. This approach can also be used retrospectively to begin to understand observations in wild populations that lack explanatory data. Whether used in retrospective or prospective types of examinations, the AOP framework represents a promising avenue to systematically integrate molecular and physiological mechanisms data for improving identification and evaluation of chemical toxicity in a global climate change context.

6 Conclusions

Although uncertainties remain in predicting the extent of biodiversity loss over the coming decades, increased extinction risks are predicted under all current climate change scenarios due to the magnitude and rate of climate change (IPCC, 2014b). Environmental chemical pollutants will be a contributing factor to these elevated extinction risks. The toxicity or endocrine-disrupting impacts of chemicals vary with environmental context, and more research into the interactive effects of chemicals and environmental factors is needed to predict future impacts for organismal health and fitness. Such efforts will require both refining experimental and assessment approaches to more fully incorporate theory from environmental physiology and prioritizing studies that conduct toxicity tests in contexts that simulate multiple environmental stressors. Climate change is expected to be the most urgent environmental challenge of the 21st century, and studies of toxicology that consider the context of multiple environmental stressors have much to contribute toward understanding how a changing global climate will affect the health of both wildlife and ourselves.

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