

**REVIEW**

# From silent spring to silent night: Agrochemicals and the anthropocene

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We are now living in the Anthropocene, the first time in Earth's history when synthetic chemicals—created by humans—are damaging the planet and contributing to a major loss of biodiversity. Pesticides are a particular problem in this regard. Agricultural practices changed dramatically following World War II. Methods for the production of nitrogen for manufacturing explosives were adapted for use as fertilizer in agriculture. Further, chemicals used to combat insect vectors for disease during World War II were adapted for the control of insect pests in agriculture. Eventually, herbicides used as defoliants to destroy food supplies and aid in combating soldiers using forests as cover, were customized to control weeds in agriculture. The heavy use of pesticides in agriculture has resulted in global exposure to these chemicals. Travelling through water, air, and in migrating animals, pesticides can be found in drinking water reservoirs, the atmosphere, on mountain tops, and even in remote areas in the Arctic where they are not used. The widespread exposure to agrichemicals has altered landscapes and ecosystems around the world. In addition to directly killing non-target organisms, target and non-target organisms can evolve resistance to pesticides, resulting in altered gene pools. Further, emerging data demonstrate that even low—formerly considered “non-toxic”—concentrations of pesticides can impact health, physiology, reproduction and development through endocrine-disrupting effects. The development of genetically modified crops that are resistant to pesticides and that produce pesticides themselves, and the financial incentive of the chemical companies that produce the genetically modified organisms (GMOs) have resulted in increased pesticide applications. There is probably no place on earth that is not affected by pesticides. The solution is the adoption of integrated pest management practices that reduce the use of chemical pesticides and fertilizers in agriculture and the decoupling of the agrichemical and seed industry.

**Keywords:** pesticides; endocrine disruption; agriculture

## 1. Introduction

We are in the Anthropocene and likely experiencing the Earth's sixth mass extinction. The current mass extinction is the first to be caused by a single species, humans. Chemical contaminants in the environment, especially pesticides, are playing an important role in the Anthropocene. Over 85,000 synthetic chemicals exist today (USEPA, 2014, USEPA, 2016b, NIH, 2014, USEPA). These chemicals represent compounds used in every aspect of life and can end up in the environment (air, water, soil, and biological tissues). Even personal care products and personal use chemicals (such as pharmaceuticals) can persist in the environment

(Yamamoto et al., 2009, D'Abrosca et al., 2008). Although there are many sources and types of chemicals in the environment, pesticides are a significant concern because they are applied directly in the environment in large amounts, particularly by the agricultural industry. Pesticides are defined by the U.S. Environmental Protection Agency as: “any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest; any substance or mixture of substances intended for use as a plant regulator, defoliant, or desiccant, or any nitrogen stabilizer” (USEPA, 2015c) and include herbicides, fungicides, nematocides, rodenticides, and agents to kill bacteria and viruses. Over the last 75 years, the use of pesticides has increased dramatically and continues to increase. Approximately 2.3 billion kilograms of pesticides are used annually worldwide with the U.S. alone accounting for over 0.45 billion kilograms per year (Alavanja, 2009, USEPA, 2017, USEPA, 2015b). Here, we review evidence that pesticides have altered the gene pool of target organisms and through direct toxic effects and so-called “low dose” effects (effects below concentrations considered safe) have altered landscapes and populations globally

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(references herein). The impact of these chemicals on non-target organisms and their impact on environmental health and public health are a growing concern. Here, we address: 1) the widespread use, transport, and persistence of pesticides in the environment; 2) growing concerns regarding low-dose effects of pesticides as endocrine disruptors: effects on reproduction, development, disease transmission, and epigenetic, trans-generational and other long-term effects; and 3) the trajectory for pesticide use and solutions to these concerns.

## 2. History of chemical use in agriculture

Agriculture has been a part of human civilization for over 10,000 years (IUPAC, 2010). Although pesticides have been used in agriculture for over 4,500 years, the early use of pesticides was mainly restricted to inorganic compounds, such as sulfur and copper, or even extracts from plants (e.g. pyrethrin). In the mid 1900's new synthetic pesticides were developed, however (IUPAC, 2010). For example, Dichloro-diphenyl-trichloroethane (DDT), first synthesized in 1874, is one of the most well-known synthetic insecticides. DDT was prized because it was inexpensive, not water soluble (so it did not wash away), persistent (so it did not have to be applied frequently), and a broad spectrum pesticide. DDT's effectiveness was discovered during World War II (WWII) where it was used to combat ticks and fleas that transmitted typhus in Europe. At the end of the war, DDT was used in agriculture (USEPA, 2015a), where over 36 million kilograms per year were produced and used worldwide. Likewise, the popular herbicide, 2,4-D was discovered during war time (Peterson et al., 2016). As one of the active components of "Agent Orange", 2,4-D was used as an herbicide to destroy food crops to starve people (such as during the Vietnam war), then also found a purpose in agriculture (as an herbicide to control weeds) following wartime. Other widespread pesticides were developed around this time as well, including the widely used herbicides atrazine (introduced in 1958) and glyphosate, among others.

In the US, pesticides are regulated by the U.S. Environmental Protection Agency, which is responsible for assessing the safety of pesticides and the risk that they pose to the environment and to human health. The U.S. EPA came into existence during the Nixon administration in 1972. Prior to the EPA, the Food and Drug Administration (FDA) and the U.S. Department of Agriculture (USDA) were responsible for evaluating and assessing the safety of pesticides, but there was little regulation. The Federal Insecticide Fungicide and Rodenticide Act (FIFRA) of 1947 called for stricter regulations, but this mandate did not become a reality until the establishment of the U.S. EPA 25 years later. Thus, many of the pesticides used in agriculture today were never adequately tested before registration and widespread use. This history left the U.S. EPA with over 80,000 chemicals to evaluate, including (according to the U.S. EPA) 1,235 active ingredients used to formulate 16,810 pesticide products, represented by 46,147 distributed products. In addition, many of the problems associated with pesticide over-use, such as endocrine-disrupting effects at low concentrations

(considered non-toxic by traditional toxicological standards) have only been recognized in the last two decades (Vandenberg et al., 2013, Vandenberg et al., 2012). So even chemicals that have been evaluated and reviewed and that are considered "safe" may cause previously unrecognized harm in the environment to a diversity of living organisms.

The size of the threat of pesticides is realized when one considers the sheer numbers of active ingredients, formulations, and environmental mixtures that have not been adequately examined or assessed. Further, the widespread use, persistence, transport and bioaccumulation in wildlife and food chain bio-magnification of these chemicals make the likely impact even more troubling.

## 3. Extent of chemical contamination

### 3.a. Wide spread use

An estimated 2.3 billion kilograms of active pesticide ingredients are used annually worldwide, with the U.S. using 22% of the total (USEPA, 2017). As an example, for three decades, DDT was heavily applied in agricultural and in public and military settings against insects to control insect-borne diseases. After 1972, many countries restricted the use of DDT and later the Stockholm Convention on Persistent Organic Pollutants in 2010 restricted its use to vector control of mosquitos (Anonymous, 2010). Still, however, the current global production volume of DDT is estimated at 3.3 million kilograms (Stockholm Convention 2010). Similarly, glyphosate, atrazine and 2,4-D are the three most applied herbicides, and also produced in the highest volumes with an estimated combined annual use of approximately 135 million kilograms in the U.S. alone (USEPA, 2017). Atrazine is used in the agricultural sector, 2,4-D in agriculture and in the non-agricultural sector (home, gardens and industry), and glyphosate in both (USEPA, 2017).

### 3.b. Persistence in the environment

In addition to the concerns associated with the sheer volume of pesticide ingredients produced and used each year, the persistence in the environment raises more concern. Even though environmental persistence is assessed prior to an approval, pesticides, their residues, and transformation products are omnipresent in groundwater, air, and sediment (Fenner et al., 2013). Pesticide removal processes include transport (e.g. atmospheric volatilization and deposition), abiotic processes (e.g. adsorption and photolysis), and biotic processes (e.g. by microorganisms and plants). Soil bacteria and fungi have proven most promising to degrade DDT, but still DDT and its transformation residues, such as DDE and DDD, persist in the environment (Yang et al., 2013, Turgut et al., 2012, Yang et al., 2012), animals (Beyer and Krynitsky, 1989), and in humans (Saoudi et al., 2014) for decades, if not longer. Similarly, habituated native microorganisms are key for removal processes of the three most popular herbicides, however degradation half-lives range from weeks to years (Borggaard and Gimsing, 2008, Boivin et al., 2005). The metabolites generated can survive environmental degradation, migrate into water supplies and exert similar or

different toxicological actions (for example see (Sanderson et al., 2002)). Thus, assessing the impact of transformation products is also important.

### 3.c. Transport to remote locations

In addition to widespread use and persistence, pesticides are also a significant threat because they spread well beyond the point of application. Pesticides and their byproducts, such as DDT and DDE, have been transported to remote locations (Simonich and Hites, 1995) such as the Arctic (Thomas et al., 1992), and to mountain tops (Devi et al., 2015, Dockalova et al., 2015, Mast et al., 2007, Ren et al., 2014, Yang et al., 2013) via atmospheric deposition (Bailey et al., 2000, Halsall et al., 1998), ocean currents, magnification in food web and migratory animals, and even in bark of trees across the world (Bailey et al., 2000, Blais et al., 2005, Kallenborn et al., 2013). Animal migration patterns (Deshpande et al., 2016, Dorneles et al., 2015) and climatic changes (including increases in global temperatures and alterations in ocean currents) can enhance the transport of pesticides (Gong et al., 2015, Nadal et al., 2015). The three most commonly applied herbicides, atrazine, glyphosate and 2,4-D, are less susceptible to transport to remote locations due to low volatility. Nevertheless, atrazine is found in Arctic seawater and ice (Jablonowski et al., 2011, Chernyak et al., 1996) and can travel over 1000 kilometers carried on dust and transported in clouds with an estimated 0.225 million kilograms per year coming down in precipitation in the U.S. alone (Thurman and Cromwell, 2000, Mast et al., 2007).

### 3.d. Bioaccumulation and biomagnification

Once an organism is contaminated, pesticides can be transferred biologically (Becker et al., 1992, Blomqvist et al., 2006, Ewins et al., 1992, Furusawa and Morita, 2001, Furusawa, 2002, George et al., 2006, Kamata et al., 2009, Kamata et al., 2013, Meiser et al., 2003). Pesticide residues are likely present in every larger organism on Earth including trees (Simonich and Hites, 1995). Pesticides, especially highly lipophilic xenobiotics such as DDT and its residues, accumulate in animal tissues and biomagnify in food webs to higher trophic levels (Alexander, 1999, Woodwell et al., 1967). For example, DDT and its residues are present in Adélie penguins (*Pygoscelis adeliae*) (Geisz et al., 2008), Galapagos sea lions (*Zalophus wolleabeki*) (Alava et al., 2011b, Alava et al., 2011c), killer whales (*Orcinus orca*) (McHugh et al., 2007), earthworms (*Aporrectodea turgida*) (Beyer and Krynitsky, 1989), and bald eagles (*Haliaeetus leucocephalus*) (Stokstad, 2007), among others. Furthermore, pesticides can be transferred to offspring, including transport across the placenta (Adetona et al., 2013, Elserougy et al., 2013, Li et al., 2014, Perera et al., 2003, Tyagi et al., 2015) and through breast milk (Al-Saleh et al., 2012), and can be found in egg yolk in birds (Faruga et al., 2008, Furusawa and Morita, 2001), reptiles (Alava et al., 2011a), and fish (Faruga et al., 2008, Lorenzen et al., 2003).

Thus, the sheer amount of pesticides released into the environment annually, extensive transport, and persistence of these chemicals all raise concern. There is likely no habitat, geographical location, or organism that is free

from pesticide exposure. Even if organisms could migrate away from the sources of contamination, the persistence in biological tissues for many pesticides and the transfer from parent to offspring, means that even individuals that are not exposed directly are still at risk.

## 4. Low-dose effects

### 4.a. Resistance

In addition to direct adverse impacts of pesticides on non-target organisms – e.g. the detrimental effects of BT corn (genetically modified to produce toxins from the bacteria *Bacillus thuringiensis*) on monarch and other “non-target” butterflies and moths (Lang and Otto, 2010, Perry et al., 2010) and the proposed role of neonicotinoid insecticides in honey bee declines (Chaimanee et al., 2016, Christen et al., 2016, Hladik et al., 2016, Long and Krupke, 2016), among others – pesticides can also alter the adaptive evolution, hence the genetic make-up, of target and non-target organisms. Widespread use of pesticides can lead to the evolution of resistance in target and non-target organisms. As a result of intense use of herbicides and insecticides in agriculture, many resistance organisms have evolved over the last 70 years.

Resistance to insecticides was noted as early as 1897 (Forgash, 1984), but only 12 insecticide-resistant insects were known in 1946. From 1946 to 1954 (following the increased use of pesticides after WW II), however, one to two new resistant species were discovered per year and by 1980, 428 insecticide-resistant insects and spiders were known. Sixty one percent of the resistant species were agricultural pests at this time, thus, the widespread use of insecticides in agriculture that began after WW II contributed significantly to the evolution of resistant species. In fact, of the 25 most damaging insect pests, 17 are insecticide-resistant (Forgash, 1984). Although resistance depends on both genetic and other biological factors, the application frequency, distribution, and amount of pesticide is also an important factor. Historically, the response to insecticide-resistance was to apply more chemicals more frequently and more broadly, thus hastening the evolution of resistance.

DDT-resistance in insects was one of the first documented cases of resistance. The evolution of resistance to DDT was noted as early as 1946 (Incho and Deonier, 1947, Barber et al., 1948). Although DDT was used for several reasons, its use in agriculture was responsible for hastening the evolution of resistant insects. Resistance to other insecticides has been documented, including resistance to pyrethrins and pyrethroids (Dai et al., 2015, Ishak et al., 2015). In fact, some insects develop cross-resistance to multiple insecticides, in some cases, to pesticides with unrelated mechanisms of action (Ishak et al., 2015). Although cross-resistance (where insects evolve the ability to metabolize the insecticides via P450 enzymes) is common, in many cases, multiple resistance is due to independent selection via glutathione reductase induction (Han et al., 2016, Jacquet et al., 2015, Kamita et al., 2016, Pavlidi et al., 2017, Yang et al., 2016, Clements et al., 2017). The harmful consequences of the evolution of insecticide resistance is not only manifest in the harm to crops and

the use of even more insecticide (which leads to even more rapid and widespread evolution of resistance), but also seen in adverse impacts on public health, such as the progression of insecticide-resistance in insects that serve as vectors for human disease (e.g. malaria, yellow fever, dengue fever, and Zika virus) (Mulamba et al., 2014, Dang et al., 2015a, Dang et al., 2015b, Dang et al., 2015c, Dykes et al., 2015, Ishak et al., 2015, Owusu et al., 2015, Dalla Bona et al., 2016).

Likewise, intense herbicide use in agriculture has led to the evolution of herbicide-resistant weeds. The heavy use of herbicides also began post WWII. The earliest record of herbicide resistance was reported in 1957, when 2,4-D-resistant carrots were discovered (Shaner, 2014, Shaner and Beckie, 2014). 2,4-D is an herbicide that was discovered during WWII and later used as a component of Agent Orange to destroy crops of targeted populations in South East Asia. In 1968, however, widespread use of triazine herbicides (e.g. atrazine) resulted in the evolution of triazine-resistant groundsel (*Senecio vulgaris*) (Burgos et al., 2013, Busi et al., 2013, Shaner, 2014, Shaner and Beckie, 2014). The resistance was the result of a mutation at the target for triazine and was maternally inherited. Resistant groundsel and other triazine-resistant weeds succumbed to other herbicides, however. Concern over herbicides resistance rose, because multiple herbicide-resistance weed strains appeared. Between 1970 and 1995, at least four new triazine resistant weeds appeared per year, and by 1995, 191 herbicide-resistant weeds were identified. By 2013, over 400 herbicide-resistant weeds were described, including many with resistance to multiple herbicides (Varanasi et al., 2015, Owen et al., 2014, Shaner, 2014, Senseman and Grey, 2014). Interestingly, many of the weed species with multiple resistances are resistant as a result of alterations in the glutathione response (Cummins et al., 2013, Ma et al., 2016, Ma et al., 2013, Yu and Powles, 2014), the same mechanism that underlies cross-resistance to insecticides in insects (see references above).

In addition, Climate change increases the rate of herbicide metabolism and the frequency of herbicide resistant weeds (Matzrafi et al., 2016). To add to the concern, when mosquitos (*Aedes aegypti*) are exposed to herbicides (such as atrazine) as larvae, they can become insecticide resistant as adults (Jacquet et al., 2015). This species is a vector for yellow fever, dengue, and chikungunya virus. So, overuse of herbicides can lead to increased public health concerns as it renders insecticides less effective in controlling insect vectors.

#### 4.b. Endocrine disruption

In addition to changing the genetic landscape via the evolution of resistant pests (Mulamba et al., 2014, Gellatly et al., 2015, Kudom et al., 2015, Wanjala et al., 2015) as a result of widespread heavy use, many pesticides also produce adverse effects on development, growth and reproduction at concentrations well below levels previously considered toxic. In particular, endocrine-disrupting effects have been identified in controlled laboratory studies, are correlated with effects on exposed wildlife,

and are associated with adverse effects on human health (references below). Endocrine disruption can occur via a number of mechanisms, including increases or decreases in hormone production and/or hormone half-life, or via binding to hormone receptors (as agonist or antagonist), and by inhibiting, inducing, or increasing hormone action. These effects are especially concerning because endocrine-disrupting effects of pesticides can be unpredictable, due to underlying mechanisms of action that are unrelated to the mechanism by which the chemical regulates the target organism. For example, DDT kills insects by opening sodium channels in the nervous system which leads to spasms and death (Holan, 1969). DDT's endocrine disrupting effects in vertebrates, however, are unrelated to this mechanism.

DDT is most well-known for causing eggshell-thinning in birds (Bitman et al., 1969, Burnett et al., 2013, Cecil et al., 1972, Cecil et al., 1971, Cecil et al., 1969, Holm et al., 2006). The mechanism that underlies this effect is still not completely clear, however. Early studies suggested that metabolites of DDT inhibited prostaglandin production in birds leading to decreased calcium deposition by the shell gland (Lundholm and Bartonek, 1992), even though other studies showed that ortho-para isomer of DDT (o,p'DDD) and at least one metabolite (p,p'DDD) stimulate prostaglandin production in the uterus of mammals (Juberg and Lochcaruso, 1992). More recent studies suggest that estrogenic effects of DDT lead to decreased capillaries and carbonic anhydrase expression which results in reduced calcium deposition in eggs by the shell gland in birds (Holm et al., 2006).

Also, unrelated to its mechanism of action in insects, DDT and some of its metabolites inhibit androgen action by binding to and inhibiting the androgen receptor (antagonist) (Maness et al., 1998, Zhuang et al., 2012, Song et al., 2014, Monteiro et al., 2015, Rivero et al., 2015, Wong et al., 2015). Inhibition of androgen-dependent developmental events have dramatic effects on development, including reproductive malformations in developing males and decreased reproductive behavior and function in exposed wildlife and humans (Daxenberger, 2002). Metabolites of DDT can act as estrogen agonists (mimics) as well, however (Gaido et al., 1997, Gaido et al., 2000, Miyashita et al., 2004, Hoekstra, 2006, Li et al., 2008, Naidoo et al., 2008, Katsu et al., 2010, Zhuang et al., 2012, Rivero et al., 2015). Effects are difficult to predict, because specific binding affinities of DDT and its metabolites to estrogen receptors and the ability of these compounds to activate the receptors vary between receptor types and between species (Miyagawa et al., 2014, Tohyama et al., 2015).

In addition, these dual effects of DDT and its metabolites (acting as androgen antagonists and estrogen agonists) make predicting the impact of exposure on development, physiology, reproduction and health complicated. Through its estrogenic actions, DDT and its metabolites can produce a number of effects through the estrogen receptors: ER $\alpha$ , ER $\beta$ , or ER $\gamma$  (Zhuang et al., 2012, Pestana et al., 2015). Effects include feminization of males during developmental exposure or exposure during adulthood (Sikka and Wang, 2008). DDT metabolites also stimulate

breast cancer cells *in vitro* (Zhuang et al., 2012) and DDT exposure is associated with breast cancer (Cohn et al., 2007, Soto and Sonnenschein, 2015). Furthermore, developmental exposure (even *in utero*) can affect outcomes later in life (Cohn et al., 2007). For example, DDT exposure *in utero* may increase the likelihood of developing breast cancer in adulthood (Cohn et al., 2007). So, measuring DDT in tissues in adulthood underestimates exposure and effects (or may not relate at all). Although the effects of DDT on breast cancer are correlational, DDT and its metabolites affect estrogen receptor-positive breast cancer cells *in vitro* and decrease cell proliferation and viability, but increase invasiveness (Pestana et al., 2015). These multiple effects of DDT, acting as an androgen antagonist and an estrogen agonist, also mean that exposure can produce a combination of demasculinizing and feminizing effects, depending on the timing of exposure and the mixture of metabolites, along with other pesticides present during exposure. Furthermore, the complex effects of DDT and its metabolites can cause pre-term labor by its alteration of estrogen to progesterone ratios (Longnecker et al., 2001).

DDT and its metabolites also affect the adrenal corticosteroids. Mitotane (*o,p'* DDD) destroys adrenocortical tissue leading to decreased cortisol production and is, in fact, used in clinical treatments for Cushing's disease (Komissarenko et al., 1978). Other DDT metabolites, e.g. *o,p'* DDT and *p,p'* DDT act as glucocorticoid antagonist to the glucocorticoid receptor (Zhang et al., 2016). *In vitro* *o,p'* DDT, *p,p'* DDT, and *p,p'* DDE can all reduce expression of glucocorticoid regulated genes (Zhang et al., 2016). So DDT and its metabolites can inhibit glucocorticoids by decreasing synthesis and by directly blocking glucocorticoid action at the receptor. Given that glucocorticoids play a significant role in regulating tumor suppressor genes (An et al., 2016, Barr et al., 2009), interference with cortisol by DDT and its metabolites may be another indirect way that these compounds might influence cancer incidence. Further, although the mechanisms is still unknown, DDT also produces an effect similar to the mandibular fenestration associated with exogenous glucocorticoid exposure in amphibians (Hayes et al., 1997).

On the other hand, other studies show that DDT and its metabolites, when mixed with other pesticides, can increase glucocorticoid production: Zimmer et al. (Zimmer et al., 2011) extracted pesticide contaminants from burbot (*Lota lota*) exposed in the wild and then applied similar pesticides mixtures to H295R cells and examined steroidogenesis *in vitro*. Mixtures containing DDT increased cortisol production at low doses, and increased cortisol and estradiol at higher doses, while decreasing testosterone production. Pesticide mixtures can also increase glucocorticoid production which leads to immunosuppression and increased disease rates in amphibians (Falso et al., 2015).

DDT and its metabolites affect the thyroid axis as well. DDT and its metabolites affect thyroid action via several mechanisms: DDT and its metabolites result in hypothyroidism (Goldner et al., 2013) by decreasing thyroid stimulating hormone levels (Liu et al., 2014) (resulting in decreased circulating thyroid hormone levels (Liu et al.,

2011, Tebourbi et al., 2010, Yaglova and Yaglov, 2014)), increasing thyroid hormone receptor expression in the hypothalamus (which presumably increases negative feedback and results in decreased thyroid production) (Liu et al., 2011, Liu et al., 2014, Tebourbi et al., 2010), decreasing thyroid hormone plasma binding protein levels (Liu et al., 2011, Liu et al., 2014), increasing hepatic enzymes that metabolize thyroid hormones (Liu et al., 2011, Liu et al., 2014, Tebourbi et al., 2010), decreasing enzymes that produce thyroid hormone (Liu et al., 2014), and inhibiting internalization of the TSH receptor (De Gregorio et al., 2011). Given the important role of thyroid hormones in growth, metabolism, and neural development and function, not to mention possible impediment of *cross-talk* mechanisms between steroid and thyroid hormones (Duarte-Guterman et al., 2014), these adverse effects are significant, especially considering that DDT and its metabolites can cross the placenta and affect developing fetuses (Li et al., 2014, Lopez-Espinosa et al., 2010, Adetona et al., 2013, Elserougy et al., 2013, Torres-Sanchez et al., 2013). DDT and its metabolites are also associated with decreased thyroid function in wildlife (Crain et al., 1997).

Likewise, herbicides can act as endocrine disrupters via mechanisms unrelated to their actions in plants and (as shown for atrazine, below) can function through many mechanisms as well. Historically, there was a false sense of safety associated with the assumption that herbicides that targeted processes specific to plants would not affect animals. This assumption has proven false. For example, atrazine kills weeds by inhibiting a protein involved in electronic transport in photosystem II in weed targets (Chereskin et al., 1984). Crop species where atrazine is used (such as corn) are resistant to atrazine due to the glutathione response (Shimabuk et al., 1971), the same mechanism associated with the evolution of resistance to herbicides in weeds. Because animals do not perform photosynthesis, it seemed that exposed animals would be unaffected by atrazine, however this is not the case. The U.S. EPA recently concluded that the herbicide, atrazine, is harmful to plants, fish, amphibians, reptiles, birds, and mammals and that harmful levels were exceeded several-fold in the environment (USEPA, 2016a). Similarly, the state of California's Office of Environmental Health Hazard Assessment listed atrazine and related compounds as reproductive toxins under the state's proposition 65 (OEHHA, 2016). These decisions were based on over twenty years of studies showing that atrazine is a potent endocrine disruptor in animals, through mechanisms that are unrelated to its mode of action in plants.

Atrazine was first identified as an endocrine disruptor in studies conducted by the manufacturer, which showed that atrazine increased the incidence of mammary tumors in rats (Eldridge et al., 1999, Greiner et al., 2000, Ueda et al., 2005), potentially through its ability to increase estrogen production. Later studies showed that the mammary tumors in rats exposed to atrazine were indeed estrogen-dependent (Ueda et al., 2005). Shortly after, the mechanism by which atrazine induces aromatase and increases estrogen was shown in human cell lines (Sanderson et al., 2002, Sanderson et al., 2001, Sanderson et al., 2000,

Fan et al., 2007a, Fan et al., 2007b, Suzawa and Ingraham, 2008). Atrazine inhibits a phosphodiesterase that results in increased cAMP, which in turn increases aromatase (*cyp19*) gene expression, and result in excess and inappropriate estrogen production. This mechanism is ubiquitous across vertebrate classes (Hayes et al., 2011), but other effects, such as decreases in androgen production and action are also observed across species (Fraitses et al., 2011, Victor-Costa et al., 2010, Rey et al., 2009, Rosenberg et al., 2008, Hecker et al., 2005, Friedmann, 2002, Stoker et al., 2000, Šimic et al., 1991, Babic-Gojmerac et al., 1989, Kniewald et al., 1980, Hayes et al., 2011, Hayes et al., 2010b, Hayes et al., 2006b, Hayes et al., 2002a).

Adverse effects of atrazine on reproduction occur across vertebrates (Hayes et al., 2011). Under controlled experimental conditions, atrazine causes a decline in sperm production in fish (Moore and Waring, 1998), amphibians (Hayes et al., 2010b), reptiles (Rey et al., 2009), birds (Hussain et al., 2011), and mammals (laboratory rodents (Victor-Costa et al., 2010, Kniewald et al., 2000)) and is associated with low sperm count and decreased fertility in humans (Swan et al., 2003) exposed to atrazine at levels 24,000 times lower than levels farm workers experience (Lucas et al., 1993). These effects are all likely the result of atrazine's inhibitory effect on androgen production and action (cited above).

The estrogenic effects of atrazine are also recognized by the mounting evidence that atrazine feminizes fish and amphibians and results in testicular oocytes in fish (Tillitt et al., 2008), amphibians (Hayes et al., 2002b, Hayes et al., 2002c), and reptiles (De Solla et al., 2006). Likely through the same mechanisms (aromatase induction), atrazine increases mammary cancer incidence (Stevens et al., 1994) and prostate disease in rodents (Stanko et al., 2010, Kniewald et al., 1978, Rayner et al., 2007). Atrazine exposure during gestation can even result in prostate disease in neonatal rodents (Stanko et al., 2010). Atrazine is also associated with breast cancer (Kettles et al., 1997) and is correlated with an 8.4 fold increase in prostate cancer incidence in men working in an atrazine production facility (MacLennan et al., 2002).

Atrazine also produces reproductive abnormalities in vertebrates under controlled laboratory conditions. For example, atrazine causes partial or complete sex reversal in fish (Tillitt et al., 2008, Suzawa and Ingraham, 2008), amphibians (Hayes et al., 2002a, Hayes et al., 2006b, Hayes et al., 2010b, Hayes et al., 2002b, Hayes et al., 2002c), and reptiles (De Solla et al., 2006). Similar effects have been documented in amphibians in the wild (Reeder et al., 1998, Hayes et al., 2002b). In addition, abnormalities in secondary sex characters (e.g. small penis) is experienced in reptiles exposed under controlled laboratory conditions (Rey et al., 2009). In humans, atrazine is likewise implicated as a cause of birth defects (Winchester et al., 2009), many of which are consistent with a decrease in androgens and/or an increase in estrogens when males are exposed *in utero* (Waller et al., 2010). These effects include hypospadias, cryptorchidism, and micropenis, all effects associated with a decrease in fetal androgen exposure (Gray et al., 1994, Kalfa et al., 2011, Sikka and

Wang, 2008, Gray et al., 1998) or excessive fetal exposure to estrogen (Gray et al., 1998, Harrison et al., 1997, Palmer et al., 2009, Zhang et al., 2009, Agras et al., 2007, Kalfa et al., 2015, Sikka and Wang, 2008), and consistent with well-documented mechanisms and effects of atrazine across vertebrates (Hayes et al., 2011). Atrazine is also correlated with gastroschisis (Mattix et al., 2007, Waller et al., 2010) which is associated with excess estrogen production during pregnancy (Lubinsky, 2012).

Although many of the effects of atrazine are explained by its ability to induce aromatase, like DDT, atrazine acts through many other mechanisms (Hayes et al., 2011) including adverse effects on the hypothalamus, the anterior pituitary, and gonads (see references in (Hayes et al., 2011)) that involve alterations in hormone synthesis and/or secretion that appear independent of action on aromatase or androgen synthesis and action. Also atrazine affects the stress axis (Fraitses et al., 2009, Laws et al., 2009), behavior (Carr et al., 2003, Rohr et al., 2003, Alvarez and Fuiman, 2005, Belloni et al., 2011, Britson and Threlkeld, 1998, Dessi-Fulgheri et al., 2007, Fraites et al., 2011, Kunze, 1989, Liu et al., 2016, Mendez et al., 2009, Neuman-Lee and Janzen, 2005, Neuman-Lee and Janzen, 2003, Rodriguez et al., 2005, Saglio and Trijasse, 1998, Walters et al., 2015, Tierney et al., 2007) and immune function (Brodtkin et al., 2007, Cantemir et al., 1987, Christin et al., 2003, Filipov et al., 2005, Forson and Storfer, 2006a, Forson and Storfer, 2006b, Gendron et al., 2003, Hooghe et al., 2000, Whalen et al., 2003, Zeljezic et al., 2006, Schwab et al., 2005) in addition to its adverse effects on reproduction. Thus, given the many mechanisms by which atrazine can act as an endocrine disruptor, there can be multiple developmental and physiological cascade effects which can be difficult to predict. Given the ubiquity of atrazine contamination and the severity of effects at low ecologically relevant doses, these findings are a significant concern for both wildlife and humans.

Less information is known about the other two heavily used herbicides 2,4-D and glyphosate. Like atrazine, glyphosate was considered safe because its herbicidal mechanism of action was through a pathway not present in vertebrates (Myers et al., 2016). Recently designated a probable carcinogen (Guyton et al., 2015), glyphosate is also a potent endocrine disruptor (Gasnier et al., 2009, Mesnage et al., 2015). Glyphosate alters the structure of the ovaries and affects expression of SF 1, a gene important in sex differentiation and regulation of sex steroid production (Armiliato et al., 2014), which is also affected by atrazine (Fan et al., 2007c, Fan et al., 2007a). Glyphosate alters aromatase expression in testes and adversely affects sperm production (Cassault-Meyer et al., 2014). Glyphosate also decreases male fertility by inhibiting gonadotropin expression (Romano et al., 2012), again similar to effects of atrazine. Furthermore, glyphosate causes a decrease in male fertility because it causes necrosis and apoptosis in testicular cells and a decrease in testosterone (Clair et al., 2012, Romano et al., 2010). Glyphosate also alters estrogen-regulated genes (Hokanson et al., 2007) and stimulates breast cancer cells via the estrogen receptor

(Thongprakaisang et al., 2013). Data regarding endocrine disrupting effects of 2,4-D are lacking. The studies simply have not been conducted (or published).

Fungicides are also potentially important endocrine disruptors, but have not been adequately addressed in the literature. Miconazole and related fungicides disrupt steroidogenesis, however, and can reduce both androgen and estrogen production (Kjaerstad et al., 2010, Trosken et al., 2006). The fungicide tebuconazole also decreased estrogen production and resulted in elevated androgens in the gonads and plasma of an amphibian *Xenopus laevis* (Poulsen et al., 2015). Another fungicide, vinclozolin (Benachour et al., 2007, Gray et al., 1994, Hecker et al., 2006, Makynen et al., 2000, Rivers et al., 2016, Sanderson et al., 2002, Thibaut and Porte, 2004, Uzumcu et al., 2004) may act as a direct antagonist to the androgen receptor and interfere with reproductive development and function in exposed males. This field of study is worthy of more attention.

#### 4.c. Transgenerational effects

In addition to the effects associated with direct exposure, pesticides can have transgenerational effects. For example, atrazine retards growth and development in rodents for two generations even without exposure to F2 (Rayner et al., 2005, Rayner et al., 2004, Rayner et al., 2007, Stanko et al., 2007). This effect across two generations is the result of impaired mammary development in females exposed *in utero*. The resulting F1 are unable to provide adequate milk to the F2 generation which then suffer from retarded growth and development. In addition, there is a growing concern for epigenetic effects in exposed organisms. For example, altered gene expression and effects on development and physiology after the maternal or even paternal parent is exposed to a chemical, can be observed in the next generation even though the individuals in the next generation are not exposed themselves (Heindel et al., 2006, Nilsson and Skinner, 2015, Perera and Herbstman, 2011, Skinner, 2011, Stuppia et al., 2015, Vandegehuchte and Janssen, 2011). For example, atrazine inhibits meiosis in mice, but also affects gene expression in ways that can be inherited through the germline in the next generation (Gely-Pernot et al., 2015). Similarly, DDT exposure can result in transgenerational effects (Skinner et al., 2013b, Kabashe and Skinner, 2014, Song et al., 2014) and at least two fungicides can have transgenerational effects (Skinner, 2011, Skinner et al., 2013a, Skinner et al., 2011, Skinner et al., 2014). These observations create an even greater concern. Not only are pesticides widespread, effectively ubiquitous, but even after their use is restricted, they can persist in the environment for decades if not longer. Furthermore, even after they no longer persist, effects can occur across generations even without direct exposure.

#### 5. The future and solutions

Rachel Carson warned in *Silent Spring* (Carson, 1962) that the decline of birds (primarily due to DDT-exposure) was a warning of environmental collapse and that human health was intricately tied to environmental health. Extinction rates have increased continuously over the last 100 years.

The loss is exemplified by amphibians, a vertebrate class that survived the last four mass extinctions. As much as 70% of all amphibian species are threatened globally (Alford and Richards, 1999, Blaustein and Wake, 1990, Vredenburg et al., 2008, Wake and Vredenburg, 2008). This sixth mass extinction, experienced in the *Anthropocene* (Waters et al., 2016, Williams et al., 2016, Zalasiewicz et al., 2015, Barnosky, 2014, Barnosky et al., 2011, Wake and Vredenburg, 2008), is inarguably due to human activity. While habitat loss is surely the most direct cause of amphibian declines (and other animals and plants), environmental contaminants, especially pesticides, which contaminate the remaining refuges in degrading habitats and remote areas where many species persist, are key factors in declines (Hayes et al., 2010a, Lenhardt et al., 2015, Wagner et al., 2014, Bruhl et al., 2013, Hayes et al., 2006a, Hayes, 1997). Even in cases where disease (Berger et al., 1998, Bosch et al., 2007, Bovero et al., 2008, Briggs et al., 2005, Fellers et al., 2007, Fellers et al., 2001, Frias-Alvarez et al., 2008, Garner et al., 2005, Goldberg et al., 2007, Green and Dodd, 2007) and invasive species (which in many cases introduce pathogens) (Silvano and Segalla, 2005, Woodhams et al., 2006) directly impact amphibian populations, the immunosuppressive effects of pesticides play a synergistic role as does climate change (Bosch et al., 2007, Rohr et al., 2003, Hayes et al., 2006a). These interactions are very important, because there is no single cause for amphibian decline. Likewise, several interactions between changes associated with the *Anthropocene* and pesticides will inevitably result in collapse if not mitigated: Climate change is increasing the development and evolution of resistance to herbicides and likely insecticides (Matzrafi et al., 2016), increased use of pesticides (in response) will increase the number of resistant pests, increased pesticide use will exacerbate the damage, resulting in more resistance weed species which will decrease productivity and more resistant insects which will both decrease crop yields and increase the spread of vector-borne diseases.

It is not clear if lessons were learned from our Silent Spring (bird decline) and likely our Silent Night (amphibian decline) is occurring because of many of the same concerns and practices (increasing pesticide use) addressed by Carson. Now, there is virtually no habitat or organism that is free from pesticide exposure or effects of pesticides. It is clear that increasing pesticide applications (sheer volume and number of active ingredients) increases the evolution of resistance (and ultimately render the active ingredients ineffective) and increases the widespread low-level contamination that leads to endocrine disruption and transgenerational effects.

Despite lessons from over-use of pesticides (e.g. more is not better), the current genetically modified organism (GMO) crop strategy rapidly moves us towards increased pesticide applications and more widespread use, as more crop species are rendered pesticide-resistant. The production of GMO crops has increased and will continue to increase the use of pesticides, in particular, herbicides. Although the earliest promise of GMO technology was to develop drought resistant (Hanson et al., 1994, Newton et al., 1991) or frost resistant crops (Jain and Pehu, 1992,

Nichols et al., 1992), to increase yields, to increase nutritional value of the crop (Burkhardt et al., 1997, Chopra and Vageeshbabu, 1996, George and Delumen, 1991), or to decrease insecticide applications into the environment with the use of BT crops (Peferoen, 1997) the strategy has changed. In fact GMO technology has increased and will continue to increase pesticide use and applications. For example, corn and soy are the top two crops in the U.S. and the number one and sixth (respectively) most planted crops in the world. At present, 80–90% of all corn and soy planted in the U.S. are glyphosate resistant (“Roundup-ready”) crops (Dill, 2005, Dill et al., 2008) and, more GMO crops are being developed with the use of “stacking” where plants are rendered resistant or tolerant to more than one herbicide. These herbicide resistant varieties will permit (and require) the use of even more herbicides (see the case for glyphosate (Benbrook, 2016)). As Dill concluded in 2008, regarding glyphosate resistant crops (GRCs): “GRCs represent one of the more rapidly adopted weed management technologies in recent history. Current use patterns would indicate that GRCs will likely continue to be a popular weed management choice that may also include the use of other herbicides to complement glyphosate. Stacking with other biotechnology traits will also give farmers the benefits and convenience of multiple pest control and quality trait technologies within a single seed.” (Dill et al., 2008). Thus, all of the problems associated with heavy pesticide use (evolution of resistant weeds, endocrine-disrupting effects, carcinogenicity, transgenerational effects, etc.), will become even more widespread and problematic.

In addition, since Silent Spring, science has uncovered many of the mechanisms of action on non-target organisms, yet manufacturers and regulators seem to ignore this new information. The manufacturers (and the scientists that support them) have even been accused of misreporting science (Rohr et al., 2009, Hayes, 2004, Sass and Colangelo, 2006) or misrepresenting science (Hakim, 2017) and released chemicals with the knowledge that they are harmful. For example, after a ban on atrazine by the European Union in 2003 (Sass and Colangelo, 2006), an almost chemically identical triazine herbicide, terbuthylazine was approved for use in Europe, even though the manufacturer had knowledge that it had even greater adverse effects than atrazine. The manufacturer wrote, regarding the herbicide terbuthylazine (TBA), “TBA may be a bit more potent than atrazine, lower doses cause same effects” and commented that terbuthylazine caused an “increase in mammary tumors” and an “increase in testicular tumors” (Syngenta, 2004). In addition, terbuthylazine can persist in soils three times as long as atrazine (Stipicevic et al., 2015). The U.S. EPA seems complicit in accepting the manufacturers’ misrepresentation of data: “It is unfortunate but not uncommon for registrants to ‘sit’ on data that may be considered adverse to the public’s perception of their products...science can be manipulated to serve certain agendas. All you can do is practice suspended disbelief.” (Tom Steeger, U.S. Environmental Protection Agency, personal communication (USEPA, 2003)) and accept that chemicals cause harm: “a monetary value is assigned to disease, impairments, and shortened lives and

*weighed against the benefits of keeping a chemical in use”* (Aviv, 2014). The problem is that the cost of these chemicals is paid by wildlife and individuals from low income and minority populations, while the benefits are reaped by others. Many health disparities between minority populations (African Americans and Hispanic Americans) and Caucasians in the U.S. are likely related to differential exposure to environmental factors (Bonner et al., 2005, DeLancey et al., 2008, Demicheli et al., 2007, Gatto et al., 2007, Gerend and Pai, 2008, Jones, 1989, Lantz et al., 2006, Menashe et al., 2009, Sarker et al., 2007). The impact on human health is manifested both by the effects of direct exposure (e.g. cancer, impaired fertility, birth defects etc.) and by the increase in pesticide-resistant insect vectors for human diseases.

Finally, at the heart of the problem is the intertwining of the chemical industry and the seed industry. An overwhelming percentage of the seeds used in agriculture are distributed by six chemical companies (Howard 2009). Thus, the financial incentive to generate pesticide resistant crops (or chemically dependent agriculture) is driving the increased use of chemical pesticides. This strategy is in direct opposition to an integrated pest management (IPM) approach, which first emerged under the Nixon administration. Completely eradicating pests is usually unrealistic and certainly not possible without harming other non-pest species. IPM practices (which may incorporate chemical control methods), instead seeks to reduce yield loss to an economically acceptable level and limit damage to the environment by chemical practices. The increased use of GMO technology to produce crops that require pesticide application will continue to limit the ability to use an IPM approach. The solution is to decouple the seed industry and the pesticide industry (a regulatory ruling to require the separation of the chemical industry and seed industry) and to provide incentives to growers to use less and fewer chemical pesticides. This is the only way to avoid more widespread damage due to overuse of pesticides.

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### Author contributions

Hayes wrote the majority of the manuscript with contributions and edits from Hansen.

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