Review of the Effects of Chemicals of Emerging Concern on the Environment

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Executive Summary:

Concerns over the group of contaminants labeled "emerging contaminants" has grown over the last decade. Part of the concern arises from the repeated measurement of these chemicals in various compartments of the environment but also due to the growing literature finding sublethal impacts of these compounds. The impacts of emerging environmental contaminants on the health of the Great Lakes and organisms associated with the Great Lakes is largely unknown. From the data that have been reviewed in this document regarding the potential impacts of emerging contaminants on wildlife and ecosystems suggests that more data is needed on:

1) sublethal chronic impacts of these chemicals at low and environmentally realistic exposures
2) impacts of mixtures of these chemicals with traditional pollutants and a way to measure effects in the field
3) impacts of byproducts or metabolites as they may be more toxic than the parent compounds
4) mechanisms of action at low chronic exposure levels
5) non-lethal endpoints such as growth, reproduction, behavior and metabolism
6) methods to monitor effects in the field and methods to tie laboratory studies to field studies
7) Lastly there is a need for investigating the impacts at the levels of populations, communities and ecosystems rather than just the individual organism level.

The review below is an overview of the toxicity information that exists for each class of compound, information that has been gathered regarding potential mechanisms of action, and information available as to potential impacts on natural populations and ecosystems with particular attention to the Great Lakes. Overall, the existing literature indicates an abundance of acute mortality information for several model species and a majority of the other effects research dedicated to reproductive effects in a subset of species and development in an even smaller subset of species (Table 1). Without information on more detailed endpoints (growth, reproduction, behavior, genetic damage etc.) the assessment of risk is somewhat limited. This is particularly true as many of these chemical exposures are at low levels and chronic. When one examines this literature in light of the concentrations organisms may truly be exposed the studies provide

limited information about realistic exposure levels. In Table 2 the studies marked in red were carried out at realistic environmental concentrations. More detailed mechanism of action information is also limiting in the literature and limited to a few species (see Table 3 summary). Data on mechanisms can provide another tool for monitoring the impact of emerging contaminants in natural populations of the Great Lakes. The most active area of research is the impact of emerging contaminants on the reproductive system and its related mechanisms (represented by ER, AR, EROD, Thyroid, Hormone, and Vt related pathways). As this may not be the only mechanisms impacted by these chemicals more research is needed on alternative mechanisms that may be disturbed during exposures on organisms that can be monitored within the Great Lakes.
The types of toxicity data here are necessary to fully inform risk to the Great Lakes from these substances and compliments any field related research efforts that are planned or ongoing. Using only field studies to assess risk leaves many questions as to what in the environment is actually causing an effect. Similarly laboratory studies on single organisms and single chemicals at high concentrations are limited in their relevance to realistic effects. Both types of studies are necessary to fully examine impacts of these chemicals.

The review was conducted using literature searches of primary literature using multiple search engines in addition to government documents or risk assessments and is extensive but not exhaustive due to constraints on time. Studies were evaluated for scientific quality and the use of standard methods and particular attention was paid to the concentrations of exposures discussed in the experiments and their relation to realistic environmental exposures.

I. Definition of Emerging Contaminants of Concern, Classes and Their Uses

The definition of emerging contaminant differs by organization**.** The U.S. Environmental Protection Agency and Department of Defense have defined an emerging contaminant as "a chemical or material that is characterized by a perceived, potential or real threat to human health or the environment ". A contaminant may also be "emerging" because of the discovery of a new source or a new pathway to humans, or a new detection method or treatment technology has been developed" (DoD 2006). The U.S. Geological Survey defines emerging contaminants as "any synthetic or naturally occurring chemical or any microorganism that is not commonly monitored in the environment but has the potential to enter the environment and cause known or suspected adverse ecological and (or) human health effects. These compounds are also labeled "trace organic compounds" by wastewater industries referring to environmental regulations as emerging contaminants are not yet regulated other than through controls on organic waste components.

Major categories of emerging contaminants include:

Brominated flame retardants: This group of compounds are the most common additives used in fabrics, electronics, foams and fills to retard the progression of a fire. The majority of these flame retardants at the moment are hexabromocyclodecanes (HBCD), tetrabromobisphenol A (TBBPA), polybrominated diphenyl ethers (PBDE) (under this category there are deca, octa or pentabromodipheyl ethers). There are some new flame retardants that have been developed as alternatives to the previous PBDE's in particular. These include triaryl phosphate isomers, triphenyl phosphate, and a brominated group that is a mixture of 2-ethylhexyl 2,3,4,5-tetrabromobenzoate (TBB) and 2-ethylhexyl 2,3,4,5-tetrabromophthalate (TBPH) but there is limited information on their metabolism and toxicity.

Triclosan and triclocarban: Triclosan is a chemical that was introduced as a bacteriostat, fungistat, mildewistat, and deodorizer starting in 1969 and since its introduction, there has been substantial growth in the use of Triclosan and related Triclocarban as additives to soaps, deodorants, toothpaste, baby products and many other personal hygiene and commercial products.

Pharmaceuticals: This category is very broad as medications are composed of various chemicals for differing purposes. They have a variety of chemical forms and have been designed for a specific function in humans. These include hormones, pain relievers, psychopharmaceuticals, lipid reguators, antibiotics and others. Their impacts on other vertebrates is assumed to be similar by some organizations however exposures are often at doses much lower than therapeutic levels and since dose makes the mechanism it is possible that other effects occur at low dose exposures. In addition mechanisms may not be identical across all organisms in the environment.

Phytoestrogens: isoflavenoid plant products such as genistein and diadzein and their breakdown products. These compounds have similar structures to vertebrate hormones. They are found in many of the products that are produced using soy and have also been detected in surface waters where they are most concentrated near wastewater plants that process the waste from food processors that deal with soy products. They are also introduced into the environment from livestock operations (CAFO's) who are fed a large portion of the soy consumed in North America.

Perfluorinated surfactants: Perfluorinated surfactants (PS) are compounds that are used in paper refining, fire-extinguishing agents and in cleaning products. The main representatives of this group are perfluorooctanoic acid (PFOA) und perfluorooctane sulfonate (PFOS). PFOA and PFOS are used in polymers, that help with fire resistance and repel oil and water. They are incorporated into non-stick cookware and clothing, and are used in many industries for a variety of purposes.

Synthetic musks are fragrances in perfumes and personal care products or home products such as shampoos, soaps, candles, and cleaning products. This category is dominated with respect to volume manufactured by the polycyclic hydrocarbon compounds 7 - Acetyl - 1,1,3,4,4,6 - hexamethyl - 1,2,3,4 - tetrahydronaphthalene (AHTN) and 1,3,4,6,7,8-hexahydro- 4,6,6,7,8,8 - hexamethylcyclopenta - g - 2 - benzo-pyran (HHCB) . They are lipophylic and highly stable compounds that have been shown to absorb skin and accumulate in the food chain.

Chlorinated parafins are industrial chemicals that were used as a replacement for PCB's. They are used as additives in paint, coatings, sealants and flame retardants. They are straight chain hydrocarbons and are categorized as either short chains (10-13 carbons in length) medium (14-17 carbons) and long chain (greater than 17 carbons) compounds for purposes of detection and effect. In addition the level of chlorination varies and has an impact on reactability.

Phthalates: Phthalates are chemicals used to soften plastic, specifically polyvinyl chloride products and as carriers or additives to perfumes, cosmetics, hairsprays, lubricants and wood finishers. They are dialkyl or alkyl aryl esters of 1,2-benzenedicarboxylic acid and have analogues in the natural environment.

Bisphenol A: BPA was originally developed as an estrogenic substance for medical purposes. After other estrogens were developed its primary use became as an additive to plastics production of polycarbonate plastics and epoxy resins. It is used in plastic bottles and in the lining of metal food and beverage cans to prevent corrosion.

Nanomaterials: Nanomaterials are a new class of chemicals that are manufactured particulates less than 100 nm in size in one dimension. Due to

their size and chemical properties these materials have unique chemical and physical properties and behave differently than their larger counterparts. Nanomaterials are currently being incorporated into everything from medical diagnostics, pharmaceuticals, cancer therapies, cosmetics, sunscreens to a variety of industrial and environmental processes. The number of potential applications is rapidly growing each year.

II. Laboratory Toxicity Studies of Classes of Emerging Contaminants

Single organism laboratory studies

A majority of the effects research regarding the potential impacts of emerging contaminants on wildlife is derived from laboratory toxicity studies on single chemicals with a limited number of species or ecosystem representatives. Many of the studies reviewed here have been completed at concentrations above that which is found in the environment. Realistically most exposures are low dose and chronic and there are fewer studies documenting effects from long-term exposures. Although there is some information regarding mechanism of action, in general the mechanisms investigated are limited (focused on hormonal pathways and oxidative stress) and may not provide a complete picture of how a chemical impacts physiology. In addition, mechanisms can change with the dose of exposure and therefore mechanistic information should be evaluated with the dose in mind. There are also gaps in measuring sublethal effects and outcomes, such as growth and reproduction that would allow for use of this data in modeling effects in natural populations. Presented here is a short summary of the data that is available for each category of chemical.

Brominated flame retardant compounds: There are several hundred compounds in this category yet toxicity information is lacking for half of the known compounds (Birnbaum and Staskal 2004). Toxicity information is more plentiful for the known high use compounds from the last several decades. PBDEs are the most common flame retardants in use but are currently banned or are under regulatory consideration in some countries. They are often found in a mixture within a commercially available retardant however most studies examine singe BFR components. The major compounds in this category have been shown to have low acute toxicity, but several rat and mouse studies indicate they can significantly affect development and the developing nervous system and may cause major behavioral changes, hyperactivity, and changes in gross motor function (Kuriyama et al. 2005, Fischer et al. 2008, Cheng et al. 2009). These neurobehavioral studies show effects at doses as low as 0.4 mg/kg, which is relevant to an environmental exposure (Eriksson et al. 2001, Eriksson et al. 2002, Viberg et al. 2002). As of 2004 the ATSDR set a minimal risk level (MRL) of 0.03 mg/kg/day for acute oral exposures to lower polybrominated diphenyl ethers (PBDEs) (ATSDR, 2004).

Specific ecological effects information for PBDE's is limited. Acute toxicity assays have shown that most PBDE's are very toxic to crustaceans at concentrations available in the environment and as many PBDE's are hydrophobic and attach to organic particulates, particle uptake may be the primary route of exposure and account for an even greater uptake rate and risk from these compounds (Wollenberger et al. 2002, Breitholtz et al. 2003). PBDE's at environmentally realistic aquatic concentrations negatively impact offspring production and increase mortality in Daphnia (Nakari and Huhtula 2008). Fish and frog studies also indicate acute developmental toxicity at environmental levels (Balch et al. 2006, Van Boxtel 2008) but low acute toxicity to adult organisms (Boon et al. 2002, Balch et al. 2006, Bearr et al. 2010). Exposure to PBDE's has sublethal impacts on growth, development, behavior and reproduction. Exposure to PBDE's at environmentally relevant levels impacts growth of whitefish (Kuo et al. 2010), alters locomotion in zebrafish with effects similar to those seen in mice and rats (Chou et al. 2010) and affects pair bonding behavior in birds such as the American Kestrel (Fernie et al. 2008). However at these same concentrations PBDE's do not alter fertility or embryonic survival of rainbow trout (Schultz et al. 2008). There is variation in effects due to the type of PBDE concerned and there may be some PBDE's that are more relevant to wildlife exposures (such as PBDE 47). Many of these studies find that the less brominated the PBDE are more toxic.

Mammalian studies have shown a deca-BDE compounds in particular to be carcinogenic (National Toxicology Program 1986). Metabolically, PBDE's have been shown to impact the endocrine system affecting androgen, progesterone and estrogen and the most sensitive endpoints appear to be the impact of exposure of PBDE's on thyroid function and development in mammals and ecologically relevant species (National Toxicology Program 1986; WHO 1994, Fowles et al. 1994; Hallgren et al. 2001; Zhou et al. 2001, 2002, Balch et al. 2006, Kuiper et al. 2007; see Costa et al. 2008 and Talsness 2009 for reviews). Thyroid effects are also seen in frogs and kestrels at environmentally relevant concentrations (Fernie et al. 2005, Balch et al. 2006). Cellular assays have demonstrated that PBDE's can be either agonistic or antagonistic to the AHR depending on the individual PBDE and it's level of bromination (Meerts et al., 1998). PBDE's have also been shown to competitively bind ER and serve as an estrogen mimic (Meerts et al. 2001; Thayer et al. 2000). Alternatively PBDE's may act by increasing ethoxyresorufin-O-deethylase and pentoxyresorufin-O-deethylase activities in mammals (Chen et al., 2001; Zhou et al., 2001) and have been shown to increase cytochromes Cyp1A, Cyp2B, Cyp1A1 and Cyp4A (Bruchajzer et al. 2010) but this may be mammalian specific as the same effects are not seen in at environmentally relevant concentrations in fish (Chen et al., 2001; Holm et al. 1994, Boon et al. 2002, Kuiper et al. 2007).

The effects of PBDE's extend beyond hormonal influences as PBDE's also affect metabolism in the liver and cause an increase in liver weight (Darnerud et al. 2001; Hardy 2002, McDonald 2002). PBDE's in mammals have been shown to cause oxidative stress in the brain and nervous system during development

(Giordano et al. 2008; He et al. 2008, Cheng et al. 2009, Dreiem et al. 2010) and in adult rats (Belles et al. 2010) and liver tissue in fish (Kling et al. 2008). Exposure also induces apoptosis in the nervous system with changes in neuronal maturation mediated by Gap43 in the cortex (Alm et al. 2008). PBDE's have also been shown to activate MAP Kinase pathways in rodent models (Fan et al. 2010). In kestrals PBDE's induces hepatic oxidative stress and an increase in lipid peroxidation, and alters thyroid hormone and vitamin A concentrations (Fernie et al. 2005).

The main PBDE components that impact these pathways may not be the actual commercial products but the hydroxy-metabolites of the PBDE's in the environment which have been shown to be more toxic than their respective parent compounds in cell cultures, lab mammals and ecologically relevant species (Meerts et al. 2000, Zhou et al. 2001, Hallgren and Darnerud 2002, Zhou et al. 2002, Chen and Bunce 2003, Stoker et al. 2004, Canton et al. 2006, Van Boxtel et al. 2008). Hydroxylated BDE-47 competitively binds to thyroid transport proteins which results in reduced levels of total and free thyroid hormones in serum (Meerts et al. 2000, Hallgren et al. 2001, Zhou et al. 2001, Hallgren and Darnerud 2002, Zhou et al. 2002). A recent evaluation of gene transcription in zebrafish during development found that hydroxylated BDE 47, and not the native or methoxy form, impacts proton transport and carbohydrate metabolsm and disrupts oxidative phosphorylation and electron transport (Van Boxten 2008).

HBCD and TBBPA's also have been shown to have similar toxicities and mechanisms of action in laboratory studies. Nether are acutely toxic in whole animal studies in mammals (IUCLID 2000,) but each are acutely toxic at relatively low doses in invertebrates and algae and in fish (WHO/ICPS, 1995). HBCD has been shown to impact thyroid metabolism (van der Ven et al. 2006) and have a high affinity for the thyroid hormone receptor (Yamada-Okabe et al., 2005) and antagonistic activity with with the androgen (AR), estrogen (ER), progesterone (PR), and aryl hydrocarbon (AhR) receptors at environmentally relevant concentrations (Hamers et al., 2006) and similarly affect cytochrome P450's (Germer et al. 2006). TBBPA's have also been shown to impact Cyp17 (Canton et al. 2006). They are also neurotoxic in cell cultures (Reistad et al. 2006) and inhibit the uptake of neurotransmitters. HBCD has also been found to induce genetic changes in mammalian cell cultures related to carcinogenesis (Helleday et al.1999) and in cell cultures of clams (Smolarz and Berger 2009). TBBPA has been shown in mammalian cell cultures to be cytotoxic, neurotoxicant, a thyroid hormone agonist and weakly estrogenic (Mariussen and Fonnum 2003, Kitamura et al. 2005); and the immunotoxic potential of TBBPA has been recently demonstrated (Pullen et al., 2003, Reistad et al., 2002, 2005). TBBPA has been shown to interfere MAP kinases and protein kinase C (Strack et al. 2007, Reistad et al. 2005).

Little mechanistic or chronic toxicity information is available in ecologically relevant species for these two categories of flame retardants. TBBPA does

activate kinase mediated cell signaling in Mytilus cell cultures (Canesi et al. 2005). HBCD as been shown to have a multigenerational impact on reproductive behavior and success in kestrels (Marteinson et al. 2010).

Triclosan and Triclocarban: Triclosan and triclocarban have been implicated as potential endocrine disrupting compounds (Witorsch and Thomas 2010). However the impacts of these compounds is debated among authors. Most of the animal data involve cell culture data and results have not been verified at environmentally relevant levels in whole organism trials. The EPA 2007 report on triclosan for their Reregistration Eligibility Decision (RED) determined that current data did not indicate a developmental or reproductive effect for *in utero* and post-natal exposure to triclosan in mammals. However, since this time studies have shown that triclosan disrupts thyroid hormone homeostasis, and interacts with androgen and estrogen receptors. Windsor rats exposures to concentrations of 30 mg/kg and higher impacts T4 and testosterone in males (Zorilla et al. 2007). The exposure of TCS to female windsar rats affected estrogen-mediated responses in the pubertal and weanling female rate. TCS significantly altered thyroid hormones in these animals. Triclosan has been shown to bind with the estrogen receptor and supported growth of the estrogen-dependent MCF-7 cell line and binds to the rat androgen receptor (Min et al. 2003). Triclosan has also been shown to impact the activity of adenylyl cylcase which leads to disruption of steroid production at 1 uM (Kumar et al. 2008).

Environmental models raise the most concern for this class of compounds, particularly for lower organisms such as bacteria and algae. Triclosan and triclocarban have been found to be acutely toxic to fish, crustaceans, and algae at environmentally relevant concentrations (Tatarazako et al. 2004) and to cause detrimental malformations to fish embryos (Oliveira et al. 2009). Triclosan has been shown to affect hatchability of embryos and cause some endocrine disruption in males with exposure levels consistent with environmental concentrations (Ishibashi et al. 2004). At higher concentrations the exposure of TCS in western mosquitofish (*Gambusia Affinis*) at concentrations of 350nM (101.3 mg/L) for 35 days caused an elevation of vitellogenin mRNA expression, a decline in sperm counts and an increase in the mean hepatosomatic index (Raut and Angus 2010). However these effects are only seen when they are exposed to 100 times a maximal environmental level. Studies in general suggest that these compounds may be slightly estrogenic. Murray et al. (2010) have named triclosan to be one of the one of the highest priority pollutants for regulation and treatment due to the frequency with which it occurs in freshwater and the fact that it may pose a health hazard at concentrations found in the environment. However a review by Rodricks et al. (2010) indicates that triclosan is not of concern. More studies need to be conducted to verify whole-organism effects at levels that are environmentally relevant.

Pharmaceuticals: This category represents a wide variety of compounds with varying mechanisms of action as each pharmaceutical is designed to impact

particular pathways in humans. A review of every class would be an entire paper in itself. There are however some generalizations that can be made regarding the research on the effects pharmaceuticals on in the environment. Most research to date has attempted to examine the predicted effects based on the therapeutic use of a particular medication. However several issues arise. First, concentrations found in the environment are much lower than medically relevant doses of these chemicals which may change the mechanisms of these compounds. There are potential side effects with any medication indicating there may be additional pathways that are important in determining their impacts on Great Lakes species. Lasly, there is a question as to whether they have the same impact in other species who may not have the intended receptors or may interact with the medication in a different manner. In addition, risk assessment from an ecological perspective often relies on population, community, or ecosystem endpoints where there is a lack of information. Since this is such a large group with many different structures and functions several authors have attempted to identify the compounds that may be of highest interest. Most recently Fick et al. (2010) found that most pharmaceuticals are not considered to be harmful when the average environmental concentration is considered but at the highest levels of environmental contamination some pharmaceuticals are 1000 times greater concentration than that which is estimated to cause harm due to either direct effects or the potential for accumulation. Two classes of pharmaceuticals and their impacts on model species are described as examples.

SSRI's

Selective serotonin reuptake inhibitors (SSRIs) commonly known as antidepressant compounds are widely prescribed in the population in the form of Prozac, Zoloft, Luvox and Paxil. SSRI's inhibit the reuptake of serotonin (5-HT, 5 hydroxytryptamine) and therefore influence signaling mechanisms within the brain. The effects of SSRIs are dose dependent in mammals and lower doses have a stimulatory effect with higher doses impairing the performance of the central nervous system (Dumont et al. 2005). Side effects in mammals include problems with sexual function and appetite. Since neurotransmitters are also involved in regulation of the HPG axis and hormonal control of steroids such as estradiol-17beta and testosterone, SSRI's can affect various biochemical pathways involved in reproduction (Gagne and Blaise 2003,Larson et al. 2003). Limited studies have demonstrated significant physiological effects of exposure to ecological models and several authors have indicated a need for more information on the mechanism of toxicity of fluoxetine in non-target organisms (e.g. Brooks et al. 2003). SSRI compounds have also been shown to impact hormones and reproduction in fish. Japanese medaka (*Oryzias latipes*) plasma estradiol levels in females are significantly increased with exposure to fluoxetine, however reproduction appears unaffected (Foran et al. 2004). SSRI's have also been shown to induce spawning in mussel species (Fong 1998) and influence behavior in several fish species. SSRI's have been shown to decrease aggressive behavior in fish and affect dominance interactions (Perreault et al. 2003). In fish species where sex of an individual fish depends on dominance

interactions, significant effects are seen after exposure. Sex changes in wrasse, *Thalassoma bifasciatum*, have been shown to be associated with the AVT (arginine vasotocin). Fluoxetine-treated males show lower AVT mRNA expression relative to controls (Semsar et al. 2004) which leads to sex reversal (Larson et al. 2003). At concentrations higher than those found in water samples SSRI exposure has been shown to affect feeding behaviors as well (Gaworecki and Klaine 2008).More studies are needed to determine biochemical mechanisms that may be affected by chronic low-level exposures and the nature of any toxic effects of exposure.

Peroxisome Proliferators and Fibrates

A class of drugs called “fibrates” are lipid regulatory compounds including clofibrate (clofibrinic acid, clofibrinic acid), gemfibrozil, ciprofibrate and fenofibrate. A unifying feature of these compounds is that they are thought to stimulate the size and number of peroxisomes (Gonzalez et al., 1998). Thus these compounds are referred to as “Peroxisome Proliferators (PPs).” Peroxisomes are organelles that concentrate potentially harmful molecules in the cell such as hydrogen peroxide and they are also involved in the b-oxidation of long chain fatty acids. It is believed that PPs produce many of their cellular effects by interacting with specific cytoplasmic receptors called peroxisome proliferator activated receptors (PPAR). Their physiological effects can be extensive. This may be a result of their ability to cause oxidative stress, which may also explain how PPs stimulate carcinogenesis in the liver (Moody et al., 1991).

Fibrates are not acutely toxic to algae (*Dunaliella tertiolecta*), a crustacean (*Palaemonetes pugio*), or fish (*Fundulus heteroclitus*) and do not appear to impact protein, lipid, cholesterol, and cytochrome P450 levels in fish (Emblidge and Delorenzo 2006). Research on chronic impacts is limited. Bezafibrate and clofibric acid are some of the most common pharmaceuticals found in the environment. In a chronic study in fathead minnows Weston et al. (2009) found that clofibric acid increased PPAR-regulated fatty acyl-coenzyme-A oxidase (FAO) activity in liver but did not upregulate PPAR-alpha itself. Gemfibrozil, another fibrate, also did not impact PPAR-alpha in rainbow trout but caused a decrease in lipoprotein levels (Prindiville et al. 2011) and gemfibrozil and clofibrate both inhibit yolk reabsorption in zebrafish but not by PPAR induction (Raldua et al. 2008). However it is unclear what impact these exposures would have on other PPAR forms as there are 3 forms of the PPAR: PPARα, PPARβ, PPARγ known in fish. PPARβ was shown to be induced with very high (1500 ug/L) exposures to gemfibrozil in goldfish (Mimeault et al. 2006) in addition to induction of oxidative stress enzymes glutathione-S-transferase and catalase. At environmentally realistic concentrations clofibrate has other impacts as it impairs fish reproduction and impacts androgen production, which has also been noted as a side effect in mammals (Mimeault et al. 2005, Runalls et al. 2007). Gemfibrozil has been shown to strongly inhibit CYP2M, CYP1A and CYP3A

which may contribute to endocrine disruption (Thibaut et al. 2006). More studies are clearly needed.

Phytoestrogens:

Most of the research on the potential impact of phytoestrogens has been gathered in rodent models or tissue cultures. From this data it has been shown that phytoestrogens such as genistein can cause toxic effects to multiple organisms (Kim et al. 2009). In assays using zebrafish this compound has been shown to be estrogenic, teratogenic, and causes other physiological problems in embryos. However these effects are seen at mg/L concentrations, which are up to 100,000 times larger than those seen in the environment. Studies have shown that genistein is not teratogenic at doses up to 1000 mg/kg/day, and the lowest dose where major structural embryonic issues arise is 100 mg/kg/day, comparable to an average human adult consuming 75000 mg (for a 150 lb adult) to have this impact on offspring where the average exposure for a human consuming large quantities of soy is 50 mg/day.

Data on whole organism effects relevant to an environmental exposure is minimal. Several fish studies have indicated that genistein and equol induce vitellogenesis in sturgeon (Pelissero et al. 1991), increase 17β-estradiol in Japanese medaka (Zhange et al. 2002), and cause a decline in gametogenesis in trout (Bennetau-Pelissero et al. 2001). Exposure to environmentally relevant levels of equol and genestein has been shown to cause the development of intersex fish and decrease spermatogenesis and oogenesis in medaka and catfish (Kiparisses 2003, Green and Keely 2009).

Higher dose exposure data has indicated that the major mechanisms by which these chemicals may have an impact is through reproduction pathways as phytoestrogens are structurally similar to 17β-estradiol and have been shown to bind to vertebrate estrogen receptors (Kuiper et al., 1997, Morito et al. 2001). Phytoestrogens have been shown to impact reproductive output in laboratory mammals. Studies have shown that genistein fed to rats for their entire life cycle at realistic doses comparable to those found in a normal diet caused decreased sperm counts, reduced sperm motility, decreased litter sizes, and changes in gene expression in the testes that are related to hormones and their receptors (Eustache et al. 2009). Genistein may also impact oocyte development in female mice (Chan 2009) and embryo implantation (Jefferson et al. 2009). Studies suggest that the impacts may be similar to those of ethinyl estradiol, the common birth control hormone but at 1000x less than the potency of EE2 (Declos et al. 2009). Phytoestrogens may also impact the developing nervous system by instigating apoptosis and cell death specifically in the hindbrain and spinal cord (Sassi-Messai et al. 2009). Changes in neurodevelopment at specific time periods and exposure to phytoestrogens has been linked to changes in reproductive behavior indicating neuroendocrine or neurodevelopment may be another mechanism by which these compounds have an effect.

However, the mechanism of response can be tremendously affected by the dose of exposure. For example, genistein has been shown to be both an estrogen agonist and antagonist depending on the concentration of the phytoestrogen and the existing levels of hormones in the cell culture or organism (Bennetau-Pelissero et al. 2001, Zava and Duwe 1997). These compounds may also affect more than pathways that are directly associated with ER binding. Genistein and equol have been shown to inhibit 3β-hydrosteroid dehydrogenase Δ5/Δ4 isomerase and 17β-hydroxysteroid dehydrogenase in human placental microsomes (Le-Bail et al. 2000) and inhibit aromatase activity (Pelissero et al. 1996) and may weakly bind to androgen receptors (Pottinger 1999) or interfere with E2 and testosterone binding to sex steroid binding proteins (Martin et al. 1996).

Fluorinated compounds: Both PFOA and PFOS have been shown to cause cancer, reproductive toxicity, neurotoxicity and hepatoxicity in rodents but at concentrations that are well above environmental exposures (Nakyama et al. 2005, Cui et al. 2009, Kudo and Kawashima 2003). High doses cause damage specifically to liver, kidneys and heart. Prenatal exposure in rodents to perfluorooctane sulfonate (PFOS) delays general growth and development and causes a decrease in overall survival (Thibodeaux et al. 2003). Componds are also neurotoxic but at extremely high doses (Sato et al. 2009). At 30 mg/kg PFOA has multigenerational impacts where maternal exposures cause post-weaning mortality, decreases in body weight, and delayed sexual maturation. But these effects are not seen at lower exposure levels (3 mg/kg-d)(Luebker et al. 2005). Mice appear to be more sensitive where neonatal mortality occurs as low as 0.6 mg/kg-d (Abbott et al. 2007). Other effects at high doses include changes in mammary gland development and lower maternal weight gain. Species appear to vary widely in the toxic effects of PFOA in particular, which may be do to variation in metabolism across species, indicating pharmacokinetics may be particularly important for this compounds (Rodrigues et al. 2009).

PFOS and PFOA have been shown to be peroxisome proliferators and also inhibit glutathione peroxidase and modulate CYP 3A and CyP1A (Yeung et al. 2007, Hagenaars et al. 2008, Krovel et al. 2008). PFOS decreases sperm production and increase the rate of sperm deformity in male rats (Wan et al. 2011). This may be related to oxidative stress pathways as PFOA and PFOS have been shown to impact oxidative stress pathways by increasing superoxide dismutase (SOD), catalase (CAT) and glutathione reductase (GR) and decreasing glutathione peroxidase and glutathione-S-transferase (GST). PFOA exposure also induces DNA damage in cells (Kawamoto et al. 2010).

Fluorinated compounds have not been shown to be acutely toxic to aquatic plants or invertebrates (Li 2009). Information on sublethal impacts on growth and reproduction are limited and mechanistic information is scattered but points to endocrine and oxidative stress impacts. Fluorinated surfactants do cause changes in growth of algae (Liu et al. 2009) and PFOA in particular has been

shown to cause DNA damage in aquatic species such as paramecium at environmentally relevant concentrations (Kawamoto 2010) but not in carp (Kim et al. 2010). Although fluorinated compounds may act through PXR in mammals, in fish PXR pathways are not as clear. PFOA upregulates CYP3A and downregulates CYP1A mRNA in the gills of the minnow (*Gobiocypris rarus*) but these are not correlated with changes in PXR and AhR (Liu et al., 2008). Carcinogenesis in fish species may be linked to this estrogenic activity and CYP inductions rather than PPAR induction (Tilton et al. 2008). These compounds have been shown to be estrogenic in aquatic vertebrates at high doses and induce production of vitellogenin in male minnows (*Gobiocypris rarus*) (Wei et al. 2007). Exposure to PFOA or PFOS may induce both oxidative stress pathways in addition to reproductive pathways but it may be compound dependent. In the carp, *Cyprinus carpio*, PFOA exposure increased vitellogenin and catalase expression where PFOS exposure did not (Kim et al. 2010). In Atlantic salmon PFOS increases the expression of CYP3A, CYP1A1 and GST expression and PFOA and PFOS both caused decreases in plasma estrone, testosterone and cortisol levels (Mortensen et al. 2011). In cormorants PFOS concentration was positively correlated with mRNA levels of glutathione peroxidase 1 and glutathione S-transferase alpha 3 and negatively correlated with levels of heat shock 70-kDa protein 8 and tumor rejection antigen 1 mRNAs (Nakayma et al. 2008). These same patterns of oxidative stress and endocrine disruption are seen in tilapia cell cultures (Liu et al. 2007a, 2007b). They cause oxidative stress and inhibit cholinesterase in planarians but at high concentrations relative to the environment (Li 2009).

Several authors have indicated the general need for more toxicity data on PFCs other than PFOS and PFOA (Lau et al. 2007; Giesy et al. 2010).

Synthetic musks:

The synthetic musks in general are not considered to be acutely toxic as the LC_{50} values in many studies are orders of magnitude greater than concentrations found in the environment (Balk et al. 1999) for example acute toxicity in copepods is 0.6-1.9 mg/L and environmental concentrations are in the ng-ug/L range (Breitholz et al. 2003, Wollenberger 2003). In vivo mammalian models do not indicate any acute impact of these chemicals when taken orally as a single chemical dose. Sublethal effects for some species are present within the range of environmentally relevant concentrations with the greatest sensitivity in most assays to AHTN versus HHCB. Aquatic invertebrates are the most sensitive in chronic sublethal toxicity assays (Breitholz et al. 2003, Wollenberger et al 2003). and larval development is a more sensitive endpoint than acute toxicity. In the copepod *Nitocra spinipes* developmental effects are seen at 100 fold lower concentrations than other endpoints such as mortality (as low as 20 µg HHCB/L) (Breitholtz et al. 2003). In the copepod *Acartia tonsa* larval development is impacted at 26 µg AHTN/L and 59 µg HHCB/L (Wollenberger et al. 2003). Chronic effects in *Xenopus laevis and Danio rerio* occur in the range from 250 to

450 µg/L (Chou and Dietrich 1999).

The mechanism of action data that do exist for synthetic musks both polycyclic and nitro musks indicate several mechanisms that may be disrupted by exposures. Several studies have indicated that they are not genotoxic at even high doses (Kevekordes et al. 1997, Mersch-Sunderman et al. 1998). Both nitro musks and polycyclic musks have been shown to inhibit the activity of multidrug efflux transporters in the mussel *Mytilus californians*, a standard toxicity model but an uncommon endpoint to monitor (Luchenback and Epel 2004,2005). These transporters are a major method of ridding an organisms tissues of xenobiotics and musks inhibit their action as low as 0.09 uM exposures and activity does not return to normal after 48 hours. Although the population level ramifications of this inhibition have not been demonstrated the authors indicate that in the environment where there are multiple xenobiotics present this could enhance the impacts of other chemicals.

There is a potential for synthetic musks to be anti-estrogenic although the mechanism by which this may take place is unknown and results are variable among assays (review by Witorsch and Thomas 2010). In addition, these impacts are only seen at relatively higher than environmental doses relevant to humans and only in vitro. Cell culture assay of *Drosophila melanogaster* indicate that there are no steroidal impacts at environmental concentrations (Breitholz et al. 2003). However, estrogen antagonist effects have been seen in zebrafish (Schreurs et al. 2005) and developmental impacts have been seen in mussels and fish at environmentally relevant concentrations (Gooding et al. 2006 and Carlsson and Norrgren 2004 respectively) indicating these compounds may have a greater impact on aquatic organisms than humans.

For some emerging contaminants the parent compounds are the greatest concern but the amino metabolites of musk ketones and xylenes have been found in significant quantities in the environment with potentially greater effect. These amino byproducts of the treatment of musks in the sewage treatment plant process have been shown to be present at up to forty times the concentration of parent compounds (Rimkus et al. 1999). This is of concern as the toxicity of these compounds in *Daphnia magna* has been found to be 100x greater than the parent compounds (Behechti et al. 1998). The toxicity to other organisms is unknown but needs to be investigated to provide the complete environmental risk of the release of musks.

Chlorinated paraffins:

Reviews by the U.S. NIH National Toxicology Program and the European Union have concluded that the acute toxicity of chlorinated paraffins is low to non-existent for most organisms. For example the LC50 values for acute (48-96 hour) exposures to short chain (SCCP's, 10-13) and medium chain or long chain chlorinated parafins (MCCP's or LCCP's, C14-20+) were greater than 300 mg/L

for a study of rainbow trout and bluegill (Howard et al. 1975). Most studies find no acute impact except in the highest dose exposures (600+ mg/kg) in soil invertebrates (Bezchlebova et al. 2007), fish (Linden et al. 1979, Madeley and Maddock 1983a,b,c,d,e as cited in Environment Canada 2008) birds (Linden et al. 1979, Madeley and Birtley 1980) and mammals (Howard et al., 1975, Birtley et al.1980, Serrone et al. 1987). Invertebrates, both pelagic and sediment or soil dwelling are the most sensitive species with regards to chlorinated paraffins. Daphnia are the most sensitive with a 21-day chronic LOEC of 8.9 ug/L and an estimated NOEC of 5 ug/L (Thompson and Madley 1983). In worm species the NOEC estimates are well within the range of CP's found in mussel and fish tissues within the Great Lakes (Bezchlebova et al. 2007).

Chronic studies demonstrate evidence that SCCP's are carcinogenic. The NIH National Toxicology Program studies estimated that for 2-year chronic rat and mouse studies there was clear evidence of the potential for SCCP's to cause carcinogenicity. These studies found increases in hepatocellular neoplasms adenomas or adenocarcinomas in kidney tubular cells and follicular cell adenomas or carcinomas of the thyroid gland in female rats. male and female mice and increased incidences of adenomas and carcinomas of thyroid gland follicular cells in dosed female mice (NTP 308 1986). MCCP's did not cause the same impacts.

Sublethal effects from chlorinated paraffins can include behavioral issues and a reduction in growth. Water exposures of 40 ng/L or more of short chain (10-14) CP's caused a loss of motor function in bleaks (*Alburnus alburnus*) and rainbow trout (*Onchorycus mykiss*)(Howard et al. 1975, Svanberg 1978, Bengtsson and Ofstad 1982, Swigert and Bowman, 1986) and chronic studies indicated reduced growth of fingerling rainbow trout at 10 ppm (Lombardo et al. 1975). Longer chain CP's with lower chlorine content appear to have lesser effects than their shorter chain counterparts (e.g. Madeley and Birtley 1980, Fisk et al. 1996, Cooley et al. 2001). No effects were seen in adult rainbow trout exposed to CP's with 20-30 carbons and 42% chlorine up to 385 ppm in feed (Madeley and Birtley, 1980).

Necrosis has been suggested as the major mechanisms of acute toxicity for chlorinated paraffins (Tomy et al. 1998). High chronic exposures caused death in mammalian models, inflammation of tissues, malignant lymphomas and adenocarcinomas (National Toxicology Program 1986a, 1986b, Bucher et al. 1987). Short and intermediate have also been shown to inhibit gap junction intercellular communication which may be the mechanism of carcinogenicity (Kato and Kenne 1996). Again, most of these studies were high dose exposures compared to environmental concentrations - up to 1000mg/kg (vs 43 mg/kg as highest concentration in environmental measures of potential food items for mammals). High dose exposures in mammals have also indicated CP's may affect peroxisome proliferation and interfere with thyroid mechanisms (Wyatt et al. 1993). For sublethal chronic exposures in fish that are at more realistic dose levels narcosis has been suggested as a mechanism of action as behavioral

endpoints seem to be affected.

One of the concerns with these compounds is their high potential for bioaccumulation. Persistent and bioaccumulative substances such as chlorinated paraffins may take decades to reach a maximum steady state in the environment and masijmum steady state concentrations in tissues of organisms. Therefore toxicity assays based even on 30 day studies may underestimate potential effects to natural populations of longer-lived species as noted by Environment Canada (2008). Levels of polychlorinated parafins that have been found in zebra mussels, yellow perch and carp tissues in the tributaries of the Great Lakes and other locations (Tomy et al., 1997, Muir et al. 2000, Houde et al. 2008), have been shown to cause changes in behaviors and formation of lesions in livers of trout (Cooley et al. 2001). In addition PCA caused inflammation and alterations in lipid metabolism (Cooley et al 2001). Chlorinated alkanes are also bio-transformed with unknown breakdown products persisting in tissues that may cause additional impacts not seen in traditional studies (Fisk et al. 2006).

Phthalates

Phthalates, specifically di(2-ethylhexyl) phthalate (DEHP), di-n-butyl phthalate (DBP), and butyl benzyl phthalate (BBP) have been demonstrated to be endocrine disruptors and impact the development of offspring in mammalian models at levels that are comparable to those found in individuals that are at the higher end of the exposures documented in humans and wildlife (Lyche et al. 2009 and Swan 2008 for review). Animal studies show the biggest change in males that were exposed at critical development windows and have altered secondary sex characteristics. There is little information on impacts on bird species.

EU ERA reports on different phthalates (e.g. 2004, 2006, 2008) indicates that there is no risk to the aquatic environment from these compounds and therefore no need for further concern or study. The results of this report have been questioned in the literature as this assessment is based on estimations of exposures that underestimate what is present in water and sediment, the level of bioaccumulation, and the elimination from the analysis of studies showing sublethal impacts (Oehlmann et al. 2008). Nonetheless phthalates have been shown to have low acute toxicity to many ecological toxicology species. Acute LC50 values for soil species are 1064-3335 mg/kg in annelids (Neuhauser et al. 1986) but some have suggested that this is due to lack of uptake or microbial or metabolic degredation over the 14 day exposure and not due to properties of the chemicals themselves (Albro et al. 1993). Aquatic species also appear to have a high tolerance for acute exposures (*Chironomus tentans* ,*Lumbriculus variegatus, Hyalella azteca,* not toxic up to 70 ug/L (Call et al. 2001a, 2001b, Wilson et al. 2002). Phthalates do impact fish behavior. At high concentrations that are not related to environmental concentrations (100 ug/L) feeding and reproduction related shoaling behavior are decreased in stickleback (Wibe et al.

2002, 2004). High sediment concentrations decrease egg hatching in frogs (Larsson and Thuren 1987) and cause increased mortality in Xenopus (Lee et al. 2005) but again at concentrations that are an order of magnitude greater than what has been shown in the environment. Realistic concentrations appear to have little effect on reproduction, growth, surivival etc. in Japanese medaka (Metcalfe et al. 2001, Patyna et al. 2006, Oehlmann et al. 2008).

Mechanisms associated with sublethal impacts include steroid pathways disruption through PPARs, estrogenic and antiandrogenic impacts and oxidative stress. Phthalates have been shown to bind to peroxisome proliferator activated receptors and impact steroid hormone metabolism through this pathway which is unlike their impact in humans (Fan et al. 2004). In vitro tests have shown phthalates weakly bind to estrogen receptors in both fish cells and yeast assays (Jobling et al. 1995, Harris et al. 1997) and have antiandrogenic activity (Sohoni and Sumpter 1998). In vivo phthalates impact a vitellogenin like protein in *Mytilus edulis* at 50 ug/L (Cajaraville and Ortiz-Zarragoitia 2006). Chronic studies with fathead minnows and carp have shown the production of vitellogenin in males demonstrating an estrogenic impact as low as 100 ug/L and 1 mg/L respectively (Harries et al. 2000, Barse et al. 2007). In female Japanese medaka 1 ug/L reduces vitellogenin and the production of oocytes (Kim et al. 2002). Freshwater mussels exposed to relatively high exposures (500 ug/L) They have been shown to impact antioxidant pathways by instigating catalase and acyl-CoA oxidase and inhibiting superoxide and manganate superoxide dismutase in *Mytilus galloprovincialis* (Orbea et al. 2002). Phthalates cause genotoxicity in Mytilus at much lower doses (50 ug/L, Barsiene et al. 2006). They also disrupt general metabolism in liver and muscle at concentrations in the ug/L range (Barse et al. 2007).

Bisphenol A

Bisphenol A exposures that are relevant to those seen during fetal development in humans have been shown to cause early puberty, affect prostate tissue development and mammary gland development, change the morphology and functioning of the reproductive tissues in female mice, and affect sexual differentiation in the brain, and alter behavior of offspring (see Wolstenholme et al. 2010 for review). It has several endocrine system targets and studies suggest the possibility of epigenetic effects, meaning changes in the expression of genes in a tissues without changes in the actual DNA sequence of the organism. BPA has been suggested to impact the methylation of DNA impacting which genes turn on when and therefore impacting the function of certain tissues within an organism. This mechanism may also indicate that exposure of the parents to BPA can then have an impact on the next generation even without an exposure. A scientific panel organized by NIH to examine the data relative to BPA found that there is a lack of reproducibility in effects seen in low-dose experiments (those most approximating exposures) and therefore the panel found that they had minimal concern for reproductive effects of BPA but had the greatest

concern for neural and behavioral effects of this compound (Chapin et al. 2008).

BPA has also been shown to affect reproduction in invertebrates, amphibians, and fish (Oehlmann et al. 2009 for review). Metabolites of this compound may also be biologically active (Ishibashi et al. 2005). There is still a need for more chronic studies of more sensitive organisms and documentation of effects seen in natural populations in the field.

The most dramatic effects of BPA in wildlife occur in invertebrates. Acute toxicity in Daphnia and copepods (*Acartia spp*., *Tigriopus japonicaus*) occur in as low as 240 ug/L (Chen et al. 2002, Hirano et al. 2004, Park and Choi 2007). Chronic studies show changes in reproduction and development in Crustacea as low as 0.1 ug/L (Andersen et al. 2001, Marcial et al. 2003) and changes in reproduction as low as 300 ug/L. Results are concentration dependent where low doses (10-60 ug/L) stimulate growth rates in A. tonsa and 100 ug/L or higher inhibit growth and development (Oehlmann et al. 2008). In Chironomids development is delayed at levels of 78 ng/L (Watts et al. 2001).

Sublethal BPA exposure in invertebrates also appears to impact endocrine systems and secondary sex structures. BPA creates superfemales in Ramshorn snails (*Marisa cornuarietis*) with gross changes in secondary sex characteristics at concentrations as low as 0.1 ug/L tested (NOEC was estimated to be 14.9 ng/L) (Schulte-Oehlmann et al. 2001). Acute exposure to BPA has been shown to induce metamorphoss in *Capitella capitata* (polychaete) at 11.4 ug/L (Biggers and Laufer 2004). Low concentrations of BPA also stimulate embryo production in mud snails as low as 5 ug/L (Jobling et al. 2004). In birds BPA exposure is negatively correlated with the weights of secondary sex structures such as the combs and testes of male chickens as well as sperm counts in exposures as low as 2 ug/g (Furuya et al. 2003, Furuya et al 2006).

BPA has been shown to be estrogenic in vertebrates such as fish and has been shown to bind and activate ER (Harris et al. 1997) and induce vitellogenin and zona radiate synthesis in several fish model species as low as 50 ug/L and alter hormone levels in plasma as low as 1 ug/L (Lindholst et al. 2001, Sohoni et al. 2001, Brian et al. 2005, Ishibashi et al. 2005, Labadie and Budzinski 2006, Larsen et al. 2006, Mandich et al. 2007). But the mechanisms of BPA's effect may be much more than the estrogenic processes for which it was originally developed. BPA has been shown to affect heat shock protein expression, oxidative stress pathways as well as hormone systems. In *Mytilus* species BPA in the uM range has been shown to increase phosphoproteins, alter the MAP-kinase pathway, downregulate metalotheionein expression, and alter oxidative stress pathways (Canesi et a. 2007). Similarly in birds BPA exposure is negatively correlated with the production of antioxidant enzymes, glutathione peroxidase 3 and glutathione S-transferase (Nakayama et a. 2006). Again, most studies of mechanisms demonstrate effects at concentrations above environmental levels.

Nanomaterials: Compared to other chemicals there is significantly less information regarding potential impacts of engineered nanomaterials and specifically the potential for environmental exposures, the rates of uptake and release of these chemicals and their potential environmental risks. The field of nanotoxicology is in its infancy and requires a different set of tools to evaluate impacts than traditional chemicals (Oberdorster et al. 2005). The data that do exist indicate that if a manufactured nanomaterial does reach certain tissues (e.g. inhaled into lungs) it may cause similar damage to asbestos and other fine particulates. Much of the toxicity depends on the chemistry of the nanomaterial as they can be composed of carbon structures or metals with various side groups and both the core structure and the side groups can contribute to toxicity (Klaper et al. 2009, Klaine et al. 2008). One of the main problems in this field is not knowing what may enter the environment or what organisms may come in contact with through various routes. So even though studies may find a particle to be acutely toxic it is unknown whether the dose is relevant to a realistic exposure scenario.

There is a significant body of literature on the cellular impacts of various nanomaterials. The direct cellular toxicity of various nanomaterials as measured for example, by DNA intercalating probes (e.g., YOPRO 1 and propidium iodide), metabolic assays (e.g., lactate dehydrogenase activity), and mitochondrial activity assays (e.g, MTT), has recently been assessed in vitro in a number of mammalian cells including fibroblasts (Sayes et al. 2004, Ding et al. 2005, Kirchner et al. 2005, Sayes et al. 2005), cancer cells (Bosi et al. 2004, Tsoli et al. 2005); hepatocytes (Derfus et al. 2004, Hussain et al. 2005); keratinocytes (Monteiro-Riviere et al. 2005); kidney cells (Cui et al. 2005); endothelial cells (Yamawaki and Iwai 2006); macrophages and lymphocytes (Uo et al. 2005, Shvedova et al. 2005, Muller et al. 2005, Bottoni et al. 2006). From these studies, it is clear that nanomaterials can be toxic to cells and result in both necrosis and apoptosis.

Few studies have been conducted to determine the impact of nanomaterials at a larger scale, from an organism level to population level response. Fullerene nanomaterials have been suggested to cause oxidative stress and brain damage in fish at exposure levels of only 1 ppm (Oberdorster 2004, Zhu et al. 2006). Our own research has found fullerene nanoparticles to be toxic to *Daphnia* at similar concentrations (Lovern and Klaper 2006) and that even smaller doses have impacts on physiology and behavior of Daphnia (Lovern et al. 2007). Product formulation of the nanomaterial has been shown to have an impact on the toxicity (Heinlaan et al. 2008) and the method by which nanoparticles are introduced to an aquatic medium (Lovern and Klaper 2006). Effects of exposure can also be long lasting. After an initial thirteen week inhalation exposure to titanium dioxide nanoparticles, rats continued to exhibit adverse effects one year later (Warheit and Everitt 2004). A subset of metal oxide nanoparticles cause developmental abnormalities in zebrafish but this is dependent on the type of metal oxide. Zinc

oxide delays zebrafish embryo and larva development, decreases survival and hatching rates, and causes tissue damage but titanium dioxide and aluminum oxides do not (Zhu et al. 2008). Fullerenes also impact zebrafish development and cause pericardial edema (Zhu et al. 2007). However, the toxicity is significantly impacted by the composition of the nanomaterial. For example, fullerenes that are made more water-soluble by functionalization (Sayes et al. 2004, Sayes et al. 2005) and CdSe quantum dots that are coated (Derfus et al. 2004) are significantly less toxic to cells. In a study examining the effects of variously charged side-chains, it was shown that fullerenes with cationic side-chains were more toxic and hemolytic to red blood cells than fullerenes with anionic or neutral side-chains (Bosi et al. 2004). Hydroxylation of fullerenes has been shown to lower toxicity to zebrafish embryos (Zhu et al. 2007).

While general toxic effects have been reported, there has been significantly less research on the mechanism underlying this toxicity. A study utilizing a focused gene array of cell cycle/death-related genes, demonstrated that a number of key apoptotic genes and genes associated with arrest in the G1 phase of the cell cycle were induced with toxic levels of single-walled carbon nanotubes (SWNTs) (Cui et al. 2007). Studies have suggested that carbon nanotubes (CNTs) and carbon particles stimulate oxygen radical formation and this may also be responsible for cellular toxicity (Oberdorster 2004, Jia et al. 2005). Research has primarily focused on the toxic effects of fairly high concentrations (e.g., 10-400 ug/ml) of nanomaterials. In contrast, studies on the chronic effect of exposures to sublethal nanomaterial levels on pivotal physiological systems have just begun.

B. Community and Ecosystem Endpoints

Most studies on contaminants, particularly emerging contaminants, has focused on single organism studies with model species. Although the studies listed above provide a wealth of information on the potential effects of exposures ecological risk is often assessed as a population, community or ecosystem endpoint. There are few studies that examine changes in community structure or ecosystem function with respect to ECs. These may not be entirely related to the individual organism responses as not all organisms will respond to a given chemical or mixture in the same way and the removal of one organism from a system, while important, may not results in larger scale effects as another may take its functional place. In addition the few studies that do exist demonstrate that conservative NOEC estimates in a single organism test do not necessarily predict toxicity in a more complicated experimental design.

Microcosm experiments that have examined two or more organisms and their response to emerging contaminants demonstrate that organisms do not uniformly respond to EC's and these differences in response can change a community structure. For example Hanson et al. (2005) examined the toxicity of PFOS to the aquatic macrophytes *Myriophyllum sibiricum* and *M. spicatum* in outdoor microcosms. *M. sibiricum* was found to be more sensitive to PFOS than *M.*

spicatum and their NOEC concentrations differed by an order of magnitude changing the structure of the mesocosm. Contaminants exposures have been found to simplify community structure, particularly in bacterial communities. Phthalates in soil microcosms substantially affects the bacterial community structure by decreasing diversity(Chao and Cheng 2007, Kaponen et al. 2007). Exposures can also change the population dynamics between two competitors or predators. Sanderson et al. (2003) found that mesocosms that began with diverse zooplankton communties became simplified when exposed PFOS and PFOA partly due to a rotifer species, which increased in abundance as the community changed and competition and predation shifts occurred. Laboratory studies do not always predict results in mesocosm studies. Daphnia exposed to DEHP in a zooplankton mesocosm study had lower LOEC values than their companion laboratory chronic assays.

Mesocosms provide other useful information as well such as the bioaccumulation or bioconcentration in different segments of the ecosystem, the comparmentalization of each chemical, degredation with light and community exposures, etc. There is a clear need for more of these types of studies.

III. Combinations of emerging contaminants

The greatest threat may be that organisms are exposed to a multitude of chemicals at the same time, some of which may have similar mechanisms of action. When considered in combination the concentration may be at a level that does cause an effect and some data suggest that the combination of these chemicals can cause a greater impact than any chemical considered singly. There is now evidence that combinations of emerging contaminants similar to what is present in the environment may have a greater than additive impact on toxicity (Schell et al. 2009). This may particularly apply to chemicals that act on similar biochemical pathways in an organism to the extent that multiple low-dose exposures will collectively cause an alteration where each individual exposure does not (e.g. Petersen and Tollefsen 2010; Rider et al. 2010). For example Jacobsen et al. (2010) in a study that combined five fungicides at their no effective concentration levels found that in combination they caused an increase in mortality and a change in the secondary sex characteristics of rodents. Brietholz et al. (2008) found that combining six brominated flame retardants with differing chemical structures at their respective no effective concentration levels caused a significant increase in mortality in the copepod *Nitocra spinipes* and at five times the NOEC level complete mortality.

A number of studies have suggested two chemicals with the same mechanisms of action may have an additive effect where the combination is predicted by determining dose-response curves for each of the chemicals individually (Brian et al. 2005; Correia et al. 2007; Zhang et al. 2009). Other studies have found that the predicted expression profile of a pathway from exposure to an individual chemical is not always present or statistically relevant when assayed in the

mixture (Filby et al.2007; Finne et al., 2007). These contrary results may be due to the concentrations used in each assay providing a different mechanistic response or alternatively a compensatory response by the organism may alter the impact of the mixture. As an example, Ankley et al. (2009) in studying the effect of anti-androgen compounds on the hypothalamic-pituitary-gonadal axis in fathead minnows (FHM)(*Pimephales promelas*) found male FHM either: 1) showed no change in T levels as compared to the control (Martinović et al. 2008), or 2) had low T but increased mRNA transcript levels of genes involved in steroidogenesis (Ankley et al. 2007, 2009b).

This has also been found to extend to chemicals with different mechanisms of action but the same target (Rider et al. 2010). Overall this points to a concern that even if a single chemical has not been shown to cause a significant human or environmental health impact it effect as part of a mixture may be significant. Sewage effluent, which contains a mixture of low levels of various emerging contaminants causes changes in the timing of metamorphisis and male sexual development in R. pipiens but had no effect on any endpoints in the fathead minnow (Parrott and Bennie 2009, Sowers et al 2009a, 2009b). This type of research indicates a clear need for more studies that examine the impacts of combinations of chemicals at environmentally realistic concentrations to elucidate real world exposure scenarios.

IV. Evidence for Effects in the Great Lakes

To date the evidence for the effects of emerging contaminants in the Great Lakes is limited. There have been many studies on persistent organics that have shown reproductive impacts in fish and birds with increasing tissue concentrations of pollutants. There may have been some of the emerging contaminants that could have been accumulated in the same fashion and be a contributing cause to the effects seen. Current studies by the EPA and Environment Canada examining accumulation of these compounds in biota across the Great Lakes should be connected to comparable studies of organism endpoints and reproductive impacts to begin to link these contaminants to potential effects in natural populations.

V. Future Needs for Evaluating the Effects of Emerging Contaminants

Ecologicl effects research for ECs has largely been acute exposures of single chemicals with a small number of model organisms in the laboratory and few comparable studies of natural populations of organisms. Studies are often based on mortality in acute exposures with a single compound. For studies examining mechanisms of action there has been a concerted focus on a minimal number of pathways, mainly related to reproductive hormones and oxidative stress. Some of these are carried out at concentrations that are well above environmentally realistic exposures and therefore may not provide an accurate picture of the mechanisms that may be truly impacted. The lack of information on chronic

exposures and sublethal impacts is evident and there is a **need for sublethal chronic impacts of these chemicals at low and environmentally realistic exposures and mechanism of action at these more realistic exposure levels.** At the very least this information is needed for proper risk assessment but also for any potential modeling efforts to determine the effects of compounds with limited information. In all fields of toxicology there is a desire to develop models to indicate the potential impacts of a compound to eliminate the need for extensive testing across multiple taxonomic groups and time periods and this includes the potential impact of a given chemical or classes or chemical on the environment. These models can also be used as an initial screening tool to determine which chemicals may be the most important to study further. Current ecological models are often based on narcosis or death as an endpoint and therefore have been found to be limited in their predictive capabilities (Sanderson and Thomsen 2007, Reuschenback et al. 2008, Jager et al 2009). In order to populate models **data is needed on mechanisms of action in addition to sublethal endpoints such as reproduction, growth, and metabolism especially in low dose and chronic exposure scenarios where responses may not be linear but hormetic.**

Many chemicals may act on the same pathway and individual exposures will not provide a complete picture of what is happening in the environment. Some have proposed examining the impact of emerging contaminants using a mechanism of action approach to try to account for this possibility (Daughton 2004). Assays of pathways of importance to apical endpoints (survival, cancer, reproduction, immune function, stress, energetics) and the impact of multiple chemicals on these pathways may provide more information than a chemical-by-chemical approach. **We need more information on impacts of mixtures of these chemicals with traditional pollutants and a way to measure effects in the field**

These studies have by in large been for primary products. There are also a multitude of breakdown products associated with these compounds that have not been measured and in some cases have not been identified. In addition there are thousands of chemicals in production that have not been monitored. Howard and Muir (2010) recently completed a survey of chemicals in commerce and identified 610 out of 23,000 that are potential additions for monitoring efforts due to their high-production volume and use in the Great Lakes and their potential for persistence in the environment. **More data is needed on the impacts of byproducts or metabolites as they may be more toxic than the parent compounds in addition to the impacts of mixtures of chemicals.**

There is a need for investigating the impacts at the levels of populations, communities and ecosystems rather than just the individual organism level. Most studies to date have been of single organism effects. Microcosm

studies using mixtures of species and mixtures of chemicals would provide more detailed information not only on individual effects but larger system effects and the effects of the system on the chemicals.

The research needs regarding the fate, transport, transformation and effects of emerging contaminants was the topic of a May 2010 Wingspread conference in Racine, Wisconsin. This was a follow up to a series of Wingspread conferences in the 1990's to address one class of emerging contaminant, endocrine disruptor. One of the reasons for this follow up was the recognition that research needs even just within endocrine disruptors had not been met and there were still many unanswered questions regarding their distribution and effects on humans and wildlife. In addition, we now know that emerging contaminants can disrupt more than just endocrine pathways and the 2010 meeting broadened the scope of concern. The meeting involved a dozen scientists representing academia, government, and industry. Conclusions coming from this conference included the overall conclusion that despite the fact that the last two decades had produced a number of studies on emerging contaminants, as a whole these were disconnected and left many gaps that leave assessment of the impact of these chemicals largely unknown (Novak et al. 2011). The major recommendation coming from this conference was the need for establishing a formal national research program on emerging contaminants to coordinate studies on fate, exposures, and impacts on humans and other parts of ecosystems. Currently the research efforts that do exist are fragmented among agencies with the most formal effort coming from the U.S. Geological Survey who monitors for the presence of these contaminants in various freshwater systems around the country, including some in the tributaries of the Great Lakes. Presence in the Lakes themselves, in food, in wildlife, in humans, and all effects research is relatively minimal and scattered throughout the federal agencies leaving major gaps in our knowledge. Research gaps identified in this conference included:

- A need to understand which compounds are of greatest importance.
- An understanding of the relationships between source and exposure, and the spatial and temporal variability and distribution of the release of emerging contaminants.
- An understanding of how chronic low-dose exposures impact organisms.
- Linking effects seen in the lab to field populations and human populations
- More information on effects of contaminants on other pathways besides endocrine system and the effects of CEC transformation products on biota and humans.
- A better understanding of which routes of exposure are most important for a given organism or organ system, and the effects of exposure, often at low or temporally variable concentrations, is of critical importance.

- Larger level impacts such as those on ecosystem structure and function .

These topics are not unique to this one meeting but have been proposed in the literature and other meetings regarding emerging contaminants. An organized federal research agenda would provide a framework to organize research in these areas and hopefully funding to accomplish these research goals. Currently the only group of emerging contaminants with such a program are the nanomaterials which are covered under the National Nanotechnology Initiative, an interagency organization of nanomaterials research. Even under this program the amount of funding for human health and environmental effects research is minimal compared to expenditures on the science of new nanomaterial development.

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Table 1.

Ecological acute toxicity

Drug	Organism	Toxic concen.	Exposure time	Citation
Acetaminophen	V. fischeri	15 min = 567.5 mg/L	5 and 15 min	Kim, Y. et al. 2007
	D. magna	96h = 26.6	96h	Kim, Y. et al. 2007
	Japanese medaka	96h = >160mg/L	96h	Kim, Y. et al. 2007
Caffeine	mussel	.08mM	48h	Martin-Diaz, Gagne, Blaise 2009
	rainbow trout	100mg/L	48h	Gagne, Blaise, Andre 2006
	Chironomus	1,230mg/L	48hrs-7days	
	Ceriodaphnia	60mg/L	48hrs-7days	
Carbamazepine	mussel	.4mM	48h	Martin-Diaz, Gagne, Blaise 2009
	V. fischeri	15 min = 52.2	5 and 15 min	Kim, Y. et al. 2007
	D. magna	96h EC50 = 76.3mg/L	96h	Kim, Y. et al. 2007
	Japanese medaka	96h = 35.4	96h	Kim, Y. et al. 2007
Carisoprodol	Swiss mice	750mg/kg for reproductive		Heindel, George, fail. Feb. 1997
	rat fetuses	<300mg/kg for general	24 hr	Blicharski, Burdan, Malkiewicz et al 2002
Statins	Rainbow Trout	11.2ng/g	4-24 hours	Estey, Chen, Moon. 30 Oct. 2007
Triclosan	zebrafish	0.42mg/L Embryo and 0.34 mg/L Adult at 96hrs	96hr-6days	Oliveira, Domingues, Grisolia et al. 2008

Table 2.

Single Organism Studies: Effects at Relevant Concentrations

Chemical	Mortality	Repro	Devo	Growth	Behavior	Carcin.	Metabolism	Genetic Epigen.	Immune
Flame Retardants	crustacea frogs	X	X	X	X	X	X		X
Triclosan/ triclocarban	bacteria, algae	X	X						
Pharmaceutical									
SSRI's		X			X				
PP's		X					X		
Phytoestrogens		X	X		X				
PFOA, PFOS		X	X	algae		X	X	X	
Synthetic musks	Crustacea	X	X						
metabolites	D. magna								
Chlorinated paraffins	inverts/ Daphnia			X	X	X			
Phthalates		X	X		X		X	X	
Bisphenol A	Crustacea	X	X					X	
Nanomaterials	Daphnia, fish, cells		X		X	Don't know exposure			

Table 3.

Single Organism Studies: MOA													
Chemical	**ER**	**AR**	**EROD**	**Thyroid**	**Hormone**	**Vt**	**CYP 1A, 3A, 2M**	**Ox. stress**	**PPAR**	**DNA damage**	**Neurot.**	**Necrosis**	**Other**
Flame retardant	X	X	X				X	X		X	X		
Triclosan	X	X		X	X	X							
Pharmaceut.													
SSRI					X						X		
Clofibrate								X	Fish?				
Phytoestrog	X				X		X		X				
PFOA,PFOS							X	X		X			
Synthetic musks	X												Multidrug ET
Chlorinated paraffins				X					X	X		X	cell commun., lipids
Phthalates	X	X				X		X	X	X			
Bisphenol A	X				X	X		X					HSP, MT, MAPK
Nanomat								X				X	apoptosis