APPENDIX J

HUMAN HEALTH EFFECTS REVIEW ON CHEMICALS OF EMERGING CONCERN

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HEALTH EFFECTS REVIEW ON CHEMICALS OF EMERGING CONCERN

I: Introduction

The purpose of this review is to investigate the state of published scientific knowledge regarding potential risks to human health posed by emerging chemicals of concern (CECs) in the Great Lakes. This report is one component of a larger effort to advise the International Joint Commission on CECs. Great Lakes (GL) contamination from pollution is a well-established issue of ongoing concern. Concerns regarding GL contaminants often warrant fish consumption advisories, apprehension over drinking water quality, and limitations for recreational use of waters. A key problem in the GL is the continued presence, as well as emergence, of toxic substances that may occur at levels above those considered safe for humans and wildlife. In addition to well-known "legacy" toxicants, there also exist chemicals of emerging concern released to the GL and subsequently detected in water, sediments, fish, and wildlife. To protect human and ecosystem health against future threats, researchers and policy makers require a better understanding of such substances with respect to their potential risks.

Considering the vast nature of the topic, this report provides a relatively constrained review of scholarly knowledge regarding chemicals of emerging concern, based on a literature search of 7 categories of CECs. Based upon this review, we provide general suggestions for adapting risk assessment techniques to the growing landscape of pollution exposures in the GL. It was beyond the scope of this report to conduct a full quality assurance/control review of the 271 publications reviewed in preparation for this report. Therefore, this review relies on the established peer-review process of scholarly academic journals to assure quality of the research and resources cited. A recent comprehensive review of CECs in the Great Lakes was conducted by Klecka et al. (Klecka et al. 2010). By comparison, the goals this report to the IJC are: (1) to concisely characterize the diversity and complexity of research under the topic "chemicals of emerging concern", (2) to explore the concepts of risk assessment for CECs, particularly as related to human health risk assessment, and (3) to evaluate whether this review of the literature can provide suggestions to risk assessors and policy-makers for how to proceed in dealing with CECs and human health.

The term "Chemical of Emerging Concern" (CEC) can be used to describe "new and emerging chemicals" (Klecka et al. 2010) but generally refers to a growing awareness of environmental contamination from many chemicals used by society that are unregulated or inadequately regulated. New understanding of such chemicals can initiate new concern over previously unknown effects along with concern over the risk that these chemicals may pose to the health of humans and ecosystems. In addition to this definition, the term CEC is sometimes used to describe any pollutant that is not considered a "legacy" contaminant (Hg, PCBs, Dioxins, etc.). Although we provide a list of CEC categories below, these categories do not encompass all possible "emergent" chemicals that could be present in and contaminate the environment (some of these limitations are listed below). Therefore, this categorization of CECs denotes the complexity of this topic as well as the importance of an increased understanding of these chemicals. To better characterize CECs for the purposes of this review we provide the following as criteria for considering a chemical as a CEC: (1) emerging new chemicals, (2) new effects concerns, and (3) new or unpredicted detections of chemicals in human biological samples that new analytics have made more apparent.

The chemicals of emerging concern reviewed in this paper were originally described in the report, "*Chemicals of emerging concern in the Great Lakes Basin: an analysis of environmental exposures*" (Klecka et al. 2010). The work by Klecka et al. (2010) was conducted to help inform the IJC regarding the peer-reviewed scientific studies and reports since 1997 regarding chemicals of emerging concern that may pose threats to water quality in the Great Lakes watershed. Their work provides a comprehensive review of CEC-related topics, upon which this current paper expands. For this reason, and in order to maintain continuity for the IJC, we have adopted their classification of CECs in our work, with some modifications to fit the scope of this paper. This report, as well as the report put forth by Klecka et al (2010) focused on 15th IJC biennial report categories and did not include nanomaterials, pathogens or genetically altered organisms, nor the legacy chemicals (for example mercury or PCBs). It also focused on point source pollutants to better match the scope of the other two CEC Workgroup efforts on wastewater and ecosystem effects. The legacy chemicals and non-point source contaminants deserve more thorough and ongoing evaluations for human health effects in the Great Lakes region but were beyond the scope of this paper.

Table 1: CEC Categories included in Literature Reviewed

1. Brominated Flame-retardants
    - (BFRs, Polybrominated Diphenyl Ethers (PBDEs))
2. Alkylphenolic Substances
    - Alkylphenol Ethoxylates (APEs or APEOs)
    - APs (alkylphenols)
    - NPs (Nonylphenols)
3. Perfluorinated Compounds
    - PFSAs (perfluorinated sulfonates)
    - PFOS (perflouoroctate sulfonate)
    - PFCAs (perfluorinated carboxylates)
    - PFOA (perfluorooctanoic acid)
4. Current-Use Pesticides
    - (Herbicides, Insecticides, Fungicides)
5. Chlorinated Paraffins (CPs)
    - (CPs, polychlorinated alkanes (PCAs))
6. Synthetic Musks
    - (Fragrances, Personal Care Products)
7. Organic Wastewater Constituents
    - (Pharmaceuticals, Hormones, Disinfectant By-products, etc.)

A search was conducted for each of the above categories using *ISI Web of Science*®, an online academic citation index provided by the Thomson Reuters Company. This index is designed for providing access to multiple databases, cross-disciplinary research, and in-depth exploration of specialized subfields within an academic or scientific discipline. Additionally any cited paper within the cited index is linked to any other literature (book, academic journal, proceedings, etc.), which currently, or in the past, cites this work. Also, journals and/or papers can be selected based upon their citation frequency in the literature, which can be interpreted as a surrogate measure for their impact in a field. In this way, current trends, patterns, and emerging fields of research can be assessed. Web of Science has indexing coverage from the year 1900 to the present. The bibliography included here contains

publications that were queried as of Jan 11th 2011 with several additions as needed for the writing process. Additions included but were not limited to: papers recommended by colleagues and Task Force members, and governmental reports and risk assessments. We also included some references from cited publications that were not found in *ISI Web of Science*® but were located in *pubmed*®.

Topics were queried first through keywords searches relating to the chemical names (e.g."Alkylphenol Ethoxylates" or "Alkylphenolic Substances"). If keyword searching did not yield adequate results, citation indexing was used to acquire related studies. Citation indexing was also used to follow up if particular study showed great relevance (see below).

A subset of peer-reviewed scientific publications from each of the above categories was selected to represent the state of knowledge regarding the occurrence of CECs in the GL and the risks to human health. Particular attention was paid to studies focusing on Great Lakes regions. Additional studies from outside the Great Lakes were also included in an attempt to provide a balanced review on risk for exposure, occurrence in the environment and suites of effects to humans. Some categories yielded hundreds of publications to choose from, whereas the other categories, such as synthetic musks, yielded far fewer hits. One notable issue when researching these chemicals is that, although government agencies have produced comprehensive risk assessments on CEC categories such as synthetic musks (EC 2005a, b, 2008a, b; ECB 2005) these reports did not appear when searching the ISI database. Such issues impede the ability of researchers to cross-reference established knowledge with new investigations that may expand upon these reports. In any case, the criteria for including a given paper were as follows in descending order of priority:

<u>Prioritization Selection Criteria:</u>

1. Relevance to chemical group being searched
2. Relevance to Great Lakes region
3. Topic / Research Description
    a. Risk of exposure
    b. Presence in environment
    c. Effects of chemical on humans and relevant model systems
4. Year of publication (preference to most recent research)

The selection criteria were developed based on discussions with the members of the IJC Health Professionals Task Force (HPTF). In the interest of efficiency, priorities expressed by the HTPF were compiled into the above list and applied to the literature search. It was not necessary to differentially weight the criteria in a selection scheme in order to compile a representative, yet manageable bibliography. Following the above criteria, any papers identified by queries that both described one or more chemicals within the group being searched and were related to the Great Lakes region were selected. Selection of articles describing criteria 3 was not restricted to Great Lakes papers. International papers were selected to round out the desired information. Papers were not selected if they were redundant when compared to more recent studies and showed little relevance to the Great Lakes region. Some categories presented in this review include more publications than others despite, in some cases, yielding similar numbers of hits when queried. This is simply because some categories provided (by our judgment regarding human health) more relevant, less redundant literature than

others. It is possible that greater numbers of relevant studies for a particular chemical group could be interpreted as indirect measures of how well each category is studied, perceived important and/or the extent of research funding available. However, such an analysis was beyond the scope of this project.

II: Brominated Flame Retardants

Description

Brominated flame retardants are a class of additive halogenated flame retardants used in numerous commercial products due to their fire retardant properties. Polybrominated diphenyl ethers (PBDEs), for example, are added to plastics and foam products to make them difficult to burn. The Agency for Toxic Substances and Disease Registry (ATSDR) has published a Toxicological Profile for Polybrominated Biphenyls and Polybrominated Diphenyl Ethers (PBBs and PBDEs) in which they are described as persistent, bioaccumulative and of concern to human health. The ATSDR states that, because PBDEs are added rather than reacted to the product, they could leave the product under ideal conditions and enter the environment. They suggest that this rarely happens (ASTDR 2004). More recent literature reviewed below, however, has observed PBDEs as well as other flame-retardants and their metabolites in sediments, biota, and humans.

This category may include Polybrominated Biphenyls (PBBs) Polybrominated diphenyl ethers or other BFRs (HBCD (hexabromocyclododecane) and TBBPA (Tetrabromobisphenol A)). These chemicals also undergo metabolic transformation in top predators (whales, bears) potentially altering biotransformation and toxcicity (McKinney et al. 2006). PBDE and HBCD metabolites have also been found to bioaccumulate in ringed seals and polar bears (Letcher et al. 2009).

Discussion of Hazards

The potential hazards suggested from our literature search include reproductive and developmental toxicity, immunity toxicity, neurotoxicity and endocrine disruption in humans and wildlife. This has been suggested by epidemiological, laboratory, and field studies (Roze et al. 2009; Saegusa et al. 2009; Talsness et al. 2009; Zhang et al. 2010). The literature pays particular attention to endocrine disruption when studying the effects of BFRs. Alterations to thyroid functions associated with PBDEs and HBCD, such as increased serum levels of thyroxine (T-4) and decreased serum levels of triiodothyronine (T3), have been documented in both human cohorts and exposed lab animals (Saegusa et al. 2009; Talsness et al. 2009; Turyk et al. 2008; Wang et al. 2010; Yang et al. 2009). PBDE metabolites may produce higher endocrine disrupting activity than PBDE parent compounds. Hydroxilated-PBDEs, especially, induce serious endocrine disrupting interactions (Song et al. 2009; Yang et al. 2009).

According to the ATSDR (2004) PBDEs have not been associated definitively with health related outcomes, but are of concern due to their increasing presence and potential for human exposure. Our review identified studies (published after 2004) describing the following health concerns in humans associated with BFR exposure: developmental deficits in children (Roze et al. 2009) male genitourinary (GU) conditions (Small et al. 2009), and alterations of thyroid function (Dallaire et al. 2009; Turyk et al. 2008; Wang et al. 2010). Another study, using NHANES data, found two BFRs; PBB-153 and PBDE-153, which were significantly associated with both diabetes and metabolic syndrome. Dose-response relationships appeared to differ between these two chemicals (Lim et al. 2008). Both Turyk et al. (2008)

and Dallaire et al. (2009) measured PCBs as well as BDE congeners when investigating these associations and, although they made efforts to control for demographics and medical history, it's difficult to rule out the possiblity that the alterations in thyroid function were due soley to PBDEs and PCBs as opposed to other contaminants that may not have been measured. Similar criticisms could be raised regarding the other studies cited above and below.

Discussion of Evidence for Exposure

As previously reported by Klecka et al (2009) the publications reviewed here indicate Tetrabromodiphenyl Ether (BDE-47), as the most environmentally prominent PBDE found in Great Lakes samples despite discontinuation of Pentabromodiphenyl mixture production in 2004. In contrast to BDE-47, Decabromodiphenyl Ether (BDE-209) still occurs in electronics. BDE-209 finds its way into top predators such as falcons and eagles (Johansson et al. 2009; Park et al. 2009b; Potter et al. 2009; Venier et al. 2010). PBDE levels in falcons were strongly correlated with nest proximity to human populations. Furthermore, BDE -209, while accumulating in these top predators, undergoes metabolic debromination to the banned, lower-brominated PBDEs (Johansson et al. 2009; Park et al. 2009b; Potter et al. 2009). The half-life of BDE 209 in higher organisms appears to be relatively short (Park et al. 2009a).

Both PBDEs and other BFRs (particularly the current-use BFR hexabromocyclododecane or HBCD) accumulate in Great Lakes food webs. For example: Batterman et al. (2007) reported PBDE trends increasing in G.L. fish (*Figure 1*). Additionally, PBDEs and emergent BFRs were reported in the plasma of G.L. bald eagles (Venier et al. 2010).

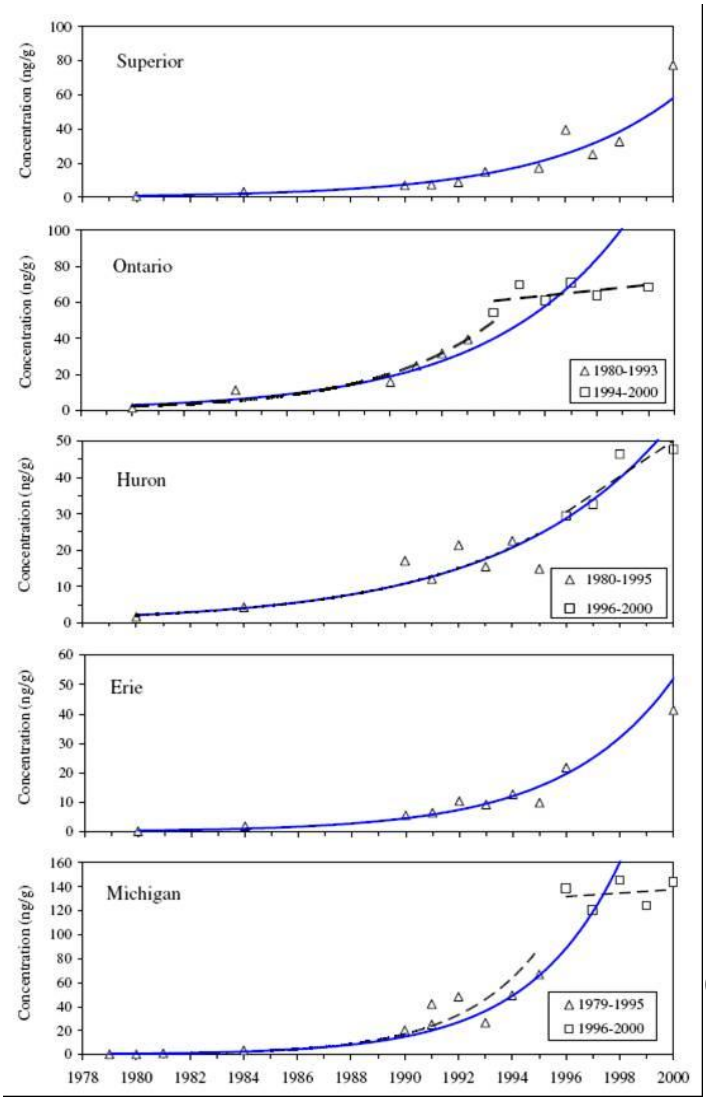

Figure 1. Trends of $\sum_4$BDE (BDE-47, BDE-100, BDE-99, BDE-153) in lake trout (walleye in Lake Erie). Solid line shows exponential model fit to entire record. Dashed line shows bilinear models (exponential and linear) from change-point analysis. For Lake Huron, the exponential portion of the bilinear model (1980–1995) is identical to the exponential model for the entire record (1980–2000). From: (Batterman et al. 2007)

HBCD was recently shown to bioaccumulate in benthic invertebrates of Lake Ontario (*Figure 2*). It has also been shown to accumulate in Great Lakes herring gulls and lake trout (Gauthier et al. 2009; Ismail et al. 2009) as well as other non-Great Lakes food webs (Letcher et al. 2009; Losada et al. 2009).

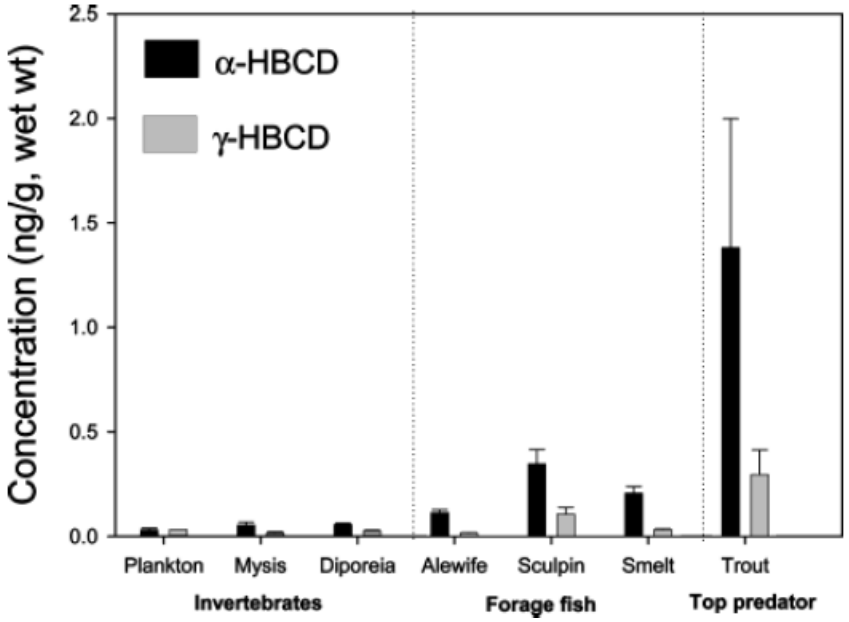

Figure 2. Blank and recovery corrected mean concentrations (ng/g, wet wt) (+ or - standard error) of α- and ɣ-HBCD in a Lake Ontario food web. From: (Tomy et al. 2004)

Human exposure to BFRs is highly probable as contamination increases in the Great Lakes region. It is unclear, however, to what extent human exposure routes stem from Great Lakes sources such as fish consumption. Although BFRs have been shown to accumulate in food webs and sediments of the Great Lakes, it is suggested that PBDE exposure in humans may result from multiple contributors (Anderson et al. 2008; de Wit 2002; Imm et al. 2009; Schecter et al. 2006; Ward et al. 2008). Of particular interest are a variety of inhalation exposure scenarios involving indoor materials such as carpets, car seats, and pillows. Upon comparing blood serum levels to bromine levels of household items measured by portable X-ray fluorescence (XRF) Imm et al. (2009) determined pillows and car seats to be the strongest predictors of lipid adjusted PBDE. Nevertheless, subjects with the highest levels of PBDEs from the study reported consuming more sport caught fish.

Given the increasing levels of BFRs in GL fish it seems probable that fish consumption contributes at least partially to human PBDE and other BFR exposure. As seen on *Table 2*, Anderson et al. (2008) reported weak correlations between PBDE serum concentrations and various exposure routes. It is worth noting that serum PCBs (for which fish consumption is a well-established exposure route) were moderately associated with sport fish ingestion whereas PBDEs showed a much weaker, albeit significant, association. This suggests that although PBDEs and other BFRs accumulate in fish tissues (Batterman et al. 2007; Ismail et al. 2009; Luross et al. 2002; Zhu and Hites 2004) fish consumption is only one of several important exposure routes for PBDEs.

Characteristic	Spearman's correlation coefficient (r)		
	∑PBDEs	∑PCBs	DDE
Age years	0.17[a]	0.50[a]	0.45[a]
BMI kg m^{-2}	0.03	0.01	0.19[a]
Serum lipids mg dl^{-1}	0.00	0.00	−0.10[a]
∑PCB ng g^{-1} lipid	0.17[a]	–	0.69[a]
DDE ng g^{-1} lipid	0.24[a]	0.69[a]	–
Sport fish ingestion years	0.15[a]	0.49[a]	0.35[a]
All fish meals/year	0.02	0.19[a]	0.15[a]
Sport fish meals/year	0.07	0.46[a]	0.29[a]
Great Lakes sport fish meals/year	0.08	0.45[a]	0.26[a]
Shellfish meals/month	0.10[a]	0.06	0.03
Sport fish meals/month	0.04	0.41[a]	0.22[a]
Total fish/shellfish meals/month	0.03	0.30[a]	0.17[a]
Meat or poultry servings/week	−0.04	−0.05	−0.02
Dairy servings/week	−0.06	−0.10[a]	−0.12[a]
Outdoor hours/day	0.10[a]	0.24[a]	0.13[a]
Indoors hours/day	−0.11[a]	−0.27[a]	−0.14[a]
Motor boat hours/day	0.04	0.30[a]	0.16[a]
TV viewing hours/day	0.02	0.10[a]	0.13[a]
Computer use hours/day	0.05	−0.25[a]	−0.19[a]

[a] $p < 0.05$.

Table 2: Associations of PPBDEs, PPCBs, and DDE (ng g_1 lipid) with demographic characteristics and potential exposure routes. Taken from Anderson et al. 2008.

Evidence for additional factors contributing to PBDE exposure is provided by Schecter et al (2006), a market study measuring concentrations of thirteen PBDE congeners in 62 food samples. Additionally, they estimated levels of PBDE intake from food for the U.S. general population by age and sex. In this study, fish exhibited highest levels of PBDEs compared to other foods (*Table 3*), but meat contributed the most to PBDE dietary intake (*Figure 3*). For the first year of life, human milk was the major contributor of PBDEs. Schecter et al. (2006) concluded that diet most likely is not the sole or even major source of PBDE exposure. Furthermore, they point out that although these PBDE levels exceed those found in European and Canadian studies the dietary exposures evaluated in their study fail to explain the 10- to 20-fold higher levels in blood and milk from the U.S. general population.

Conclusions: BFRs

The information reviewed above suggests that BFRs accumulate in Great Lakes food webs, persist in the environment and disrupt endocrine function. Some degree of human exposure to these chemicals appears likely, if not certain. Potential exposure routes could include inhalation of particles from household items or consumption of various food items including sport caught fish from the Great Lakes. Although the consumption of GL fish may be an important exposure route for some individuals, the reviewed literature suggests it is not the 'major' source. Furthermore, we found no studies or risk assessments that explicitly suggest humans are at risk to PBDE-derived health effects from fish

consumption. However, considering the trends in *figure 1* and *figure 2*, future risk assessments could show otherwise.

We recognize and acknowledge the importance of fish in a healthy diet. Therefore we identify the need for comprehensive risk assessments for BFRs and GL fish consumption to evaluate the degree of 'concern' over this particular pathway for BFRs. Considering the results of Anderson et al. (2008) and Schecter et al. (2006) we suspect that legacy chemicals such as PCBs and Hg remain the dominant hazards of fish consumption, but not enough information exists to make a definitive conclusion.

The literature reviewed here suggests a high potential for exposure to humans, probably through multiple pathways. Despite the lack of definitive health effects associated with BFRs a variety of publications cited here demonstrate common hazards, particularly endocrine disruption. The trends displayed in *figure 1* suggest increasing risk of exposure. Despite the possibility that much of the human exposure to BFRs is not GL related this chemical group should be regarded as high priority. Further clarification of exposure pathways to humans will help to elucidate the degree to which this group of chemicals is a GL priority.

	No. of samples	Lipid-based				Wet weight/whole weight			
		Minimum	Mean	Median	Maximum	Minimum	Mean	Median	Maximum
Human milk[a]	62	6,000	66,000	32,000	419,000	31	1,916	968	21,359
Meat									
Poultry	4	1,708	3,919	3,771	6,423	129	602	498	1,283
Beef	3	581	729	766	840	79	147	105	258
Pork	2	461	744	744	1,028	41	131	131	221
Bacon	3	90	234	298	316	39	103	105	165
Processed meat	5	684	3,408	4,097	5,814	195	918	1,348	1,426
Dairy									
Ice cream	2	859	1,645	1,645	2,431	31.6	101.3	101.3	171
Milk	2	NA	NA	NA	NA	7.9	7.9	7.9	7.9
Cheese	6	577	866	697	883	9.8	185	97.6	683
Eggs	1	NA	739	739	NA	NA	85	85	NA
Fat									
Margarine	1	NA	106	106	NA	NA	88	88	NA
Butter	1	NA	619	619	NA	NA	485	485	NA
Fish	24	1,100	37,319	17,408	480,000	11	1,119	616	3,726

NA, not available.
[a]Data from Schecter AJ (unpublished data) and Schecter et al. (2005b).

Table 3. PBDE concentrations (pg/g wet weight) in the survey items. From Schecter et al 2006.

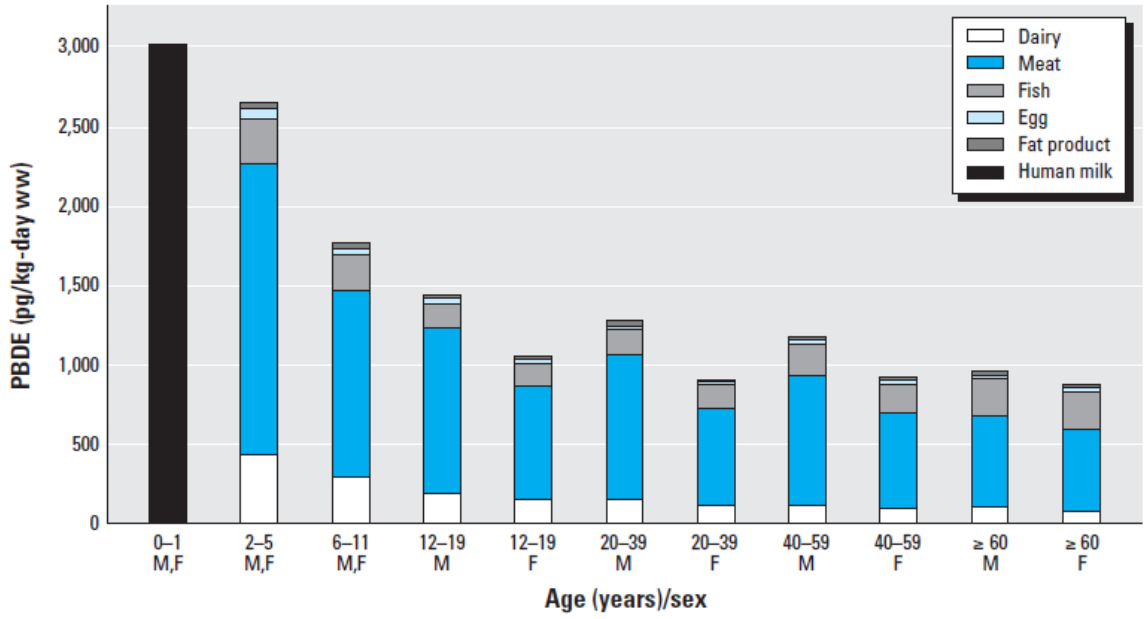

Figure 3. Daily PBDE dietary intake of U.S. population by age and food group (pg/kg body weight) as shown in Table 3. Abbreviations: F, female; M, male. From Schecter et al (2006).

III: Alkylphenolic substances

Description

Alkylphenolic substances (APs) were introduced in the 1940s and are a class of non-ionic surfactants used in detergents, paints, pesticides, personal care products, and plastics. Nonylphenol ethoxylates (NPEs) and their metabolites are a class of the broader group of compounds known as alkylphenol ethoxylates (APEs). Nonylphenol (NP) is the most common 'basic' chemical of the alkylphenol family. NP is typically further reacted to produce NPEs, and other condensation resins. Due to their high performance and cost-effectiveness, NP derivatives have emerged as the preferred ingredient in numerous industrial processes and products. Environment Canada provides a Priority Substances List Assessment Report on Nonylphenol and its Ethoxylates (EC 2001). Alkylphenolics are detected in both biotic and abiotic strata of the Great Lakes (EC 2001; Klecka et al. 2010).

Discussion of Hazards

The literature describes APs as weak endocrine disruptors; certain metabolites such as p-tert-Octylphenol (OP) are known to bind to estrogen receptors (Bechi et al. 2006; Gregory et al. 2009). In a study cited by the EC (2001) risk assessment, NP was 1000–100 000 times less potent than estradiol when stimulating estrogenic activity (Lee and Lee 1996). Effects on sexual development from some of these compounds are documented in both laboratory and field studies using fish and mammals (below).

Egg production by zebrafish, exposed to wastewater effluent contaminated with APEs was reduced up to 89.6%, 84.7% and 76.9% (Zoller 2006). Populations of fish exposed to higher levels of APs and their metabolites show higher prevalence of feminized traits (Balch and Metcalfe 2006; Kortner et al. 2009; Mayer et al. 2007; Vethaak et al. 2005). The prevalence of feminizing effects in male fish is largest in small regional surface waters that receive runoff or wastewater discharges (Vethaak et al. 2005, Mayer et al. 2007). However determining the magnitude of the contributions attributable to APs relative to human hormones in the effluent may require additional studies. For example, Jobin et al. (2009) explored the hypothesis that endocrine disruption in fish is multi-causal, resulting from exposure to mixtures of chemicals with both estrogenic and antiandrogenic properties. Using hierarchical generalized linear and generalized additive statistical modeling they demonstrated that feminizing effects in wild fish could be best modeled as a function of their predicted exposure (based on wastewater effluents) to both anti-androgens and estrogens or to antiandrogens alone (Jobling et al. 2009).

Although limited information exists regarding human effects and exposure, an Italian study estimated dietary intake of NP, OP, and octylphenol ethoxylate (OPE) for adults of about 12, 0.1, and 0.1 mu g day(-1). These estimated intakes of NP and OP were much lower than doses associated with toxic effects in laboratory animals (Ferrara et al. 2005). However, this low risk may not apply to developing fetuses. To investigate the effects of these compounds on human development (Bechi et al. 2006) observed estrogen receptor expression in first trimester human placentas using an in vitro model of chorionic villous explants. Their findings suggest that the human trophoblast may be highly responsive to NPs, which raises concern over maternal exposure in early gestation.

A follow-up study (Bechi et al. 2010) observed effects from extremely low doses of p-NP on the placental release of cytokines. This suggests possible greater risk for maternal exposure to NPs during pregnancy despite previously mentioned weak effects using lab animals. Furthermore, other studies have shown that absorption and distribution of NP in maternal and neonatal rat uteri is extremely rapid, and can easily pass though the placenta during pregnancy (Hong et al. 2004)

Discussion of Evidence for Exposure

The hydrophobic metabolites of APs such as the non-phenols (nonylphenol (NP)) are likely to accumulate in sludge of wastewater treatment plants whereas the water-soluble metabolites are likely to enter the environment when discharged into lakes (Lee et al. 2004). Another study, however, demonstrated accumulation of NP metabolites in aquatic biota of Cootes Paradise in Hamilton, Ontario (Mayer et al. 2007). This study observed a transfer of alkylphenolic substances from sediments to biota and their accumulation in the invertebrate tissue, particularly the highly hydrophobic 4-NP (*figure 4)*. Mayer et al. (2007) suggest ingestion of contaminated sediment as the predominant exposure pathway for these organisms. Since invertebrates serve as an important food source for many wetland organisms, Mayer et al. (2007) suggest that occurrence of these substances in the invertebrate tissue may contribute to high prevalence (83%) of intersex condition observed in white perch collected from Cootes Paradise. Hydrophobic NP metabolites were also detected in osprey eggs from the Chesapeake Bay and fish from the Great Lakes area (Schmitz-Afonso et al. 2003).

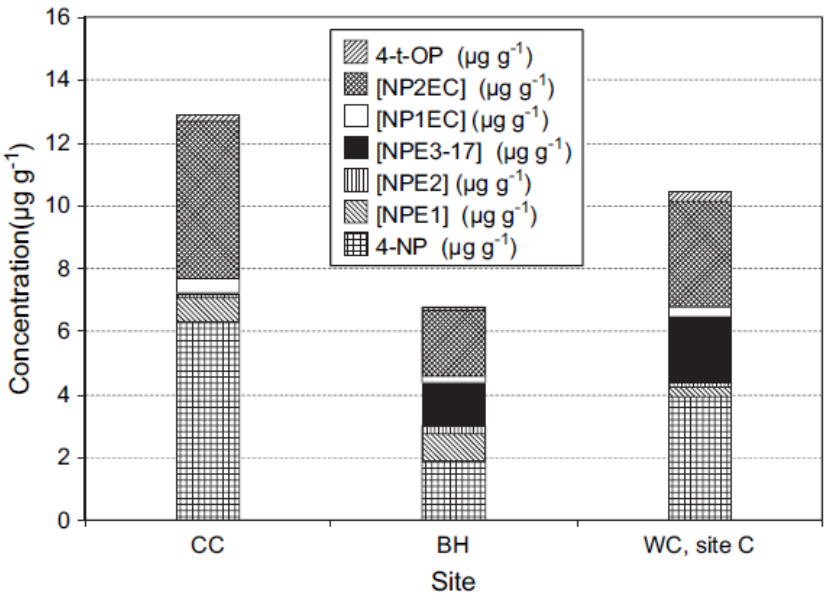

Figure 4: Levels of alkylphenolics (APs) in the tissue of benthic invertebrates collected from three sites (BH, CC, WC) in Cootes Paradise. Invertebrates from Westdale Cut (WC) were collected in the proximity of the site (Mayer et al. 2007).

A study from Taiwan observed concentrations of 4-NP and 4-OP in 59 human milk samples and suggested food consumption behaviours could contribute to NP and OP exposure (Chen et al. 2010). OP concentration was significantly associated with the consumption of cooking oil (beta = 0.62, $P < 0.01$)

and fish oil capsules (beta = 0.39, P < 0.01) after adjustment for age and body mass index (BMI). NP concentration was also significantly associated with the consumption of fish oil capsules (beta = 0.38, P < 0.01) and processed fish products (beta = 0.59, P< 0.01). The food pattern of cooking oil and processed meat products from factor analysis was strongly associated with OP concentration in human milk (P < 0.05).

Chen et al. (2010) observe that food consumption (particularly the use of cooking oil) is an important exposure route for Alkylphenols. Interestingly, the mean NP concentration in human milk from the Taiwanese participants (4.47 lg/kg) was much higher than those reported in studies from other nations (Ademollo et al. 2008; Cheng et al. 2006). The authors suggest this may be due to the elevated levels of Alkylphenol concentrations in Taiwanese rivers and sediments compared to countries such as Italy, Japan and Germany (Cheng et al. 2006). Additionally, the Italian study (Ademollo et al. 2008) demonstrated a positive correlation between NP in breast milk and fish consumption (assessed within the cohort via questionnaire). NPs have also been observed in cow's milk as well as human breast milk in Chinese and Italian studies (Dorea 2009; Lin et al. 2009).

Conclusions: APs

The EC (2001) report on NP and NPEs concluded that these substances are "toxic" as defined in Section 64 of CEPA 1999 and that options to reduce exposure should be investigated. EC (2001) also cautions that other APEs such as OP and OPEs (also covered above) have many of the same physical/chemical properties, which make them likely candidates as replacement or alternative products for NP and NPEs. However, they also possess similar toxicological properties and greater estrogenic properties. Exposure to humans is particularly concerning when one considers the presence of NPs in breast milk and the vulnerability of developing infants. Not enough information exists to comment specifically on the potential for exposure to humans living in the Great Lakes Regions.

Given the spatial distribution of AP contamination (e.g. near wastewater treatment effluents) one may expect moderate risk of exposure to humans, particularly from GL related sources. However, the above studies suggested bioaccumulation of AP metabolites and identified AP metabolites in human breast milk. Although weakly estrogenic, the potential for exposure to developing infants who may be susceptible to APs (and perhaps APs mixed with other estrogen-mimickers) warrants precaution. Based on our review, we consider these of moderate to high priority in GLs exposure and human health respectively. Further information on synergistic effects of endocrine disruptors and environmental AP occurrence would alter the above recommendation.

IV: Perfluorinated Compounds

Description

Perfluorinated Compounds (PFCs) are used as surfactants in a variety of industrial processes and are ubiquitous in the environment. This is due to widespread use over the past 50 years in a broad range of applications, including use as surface treatments for carpets, fabric, and leathers for stain resistance, as well as coatings on various paper products (Klecka et al. 2010). Health Canada (HC) provides a risk assessment for perfluorooctane sulfate (PFOS), its salts and its precursors, which are forms of PFCs. Since PFOS is likely the ultimate perfluorinated degradation or metabolic product of the group of the substances considered in their report, HC suggested that levels of this compound in human tissue provide a useful indicator of exposure to this group of substances from all potential sources (HC 2006). The complex structure of perfluorinated surfactants makes it difficult to predict their environmental behaviour from an understanding of their physical-chemical properties. (Klecka et al. 2010).

Discussion of Hazards

Endpoints considered in the Canadian PFOS human health risk assessment included histopathological effects in the liver, carcinogenicity as well as hematological and hormonal parameters in humans (HC 2006). Potential human health outcomes due to PFC exposures suggested in recent literature vary from reproductive and endocrine disruptive effects to immunotoxicity of lab animals. Many publications simply cite prevalence in human blood and environment as cause for investigation, rather than invoking concern over any specific effect. Nevertheless, PFCs seem to affect reproductive and endocrine function in laboratory animals and human cohorts.

Some studies documented endocrine disruption in fish as alteration of thyroid status. For example, PFC exposure was found to alter gene expression in the hypothalamic-pituitary-thyroid axis of dosed zebrafish (Shi et al. 2008; Shi et al. 2009). Additional studies using fish revealed reproductive deficits including alterations to ovary development as well as offspring deformation and mortality (Ankley et al. 2005; Du et al. 2009).

Studies from the literature search suggesting hazards to human health mostly involved endocrine function, reproduction, and development. PFCs were shown to easily pass the placental barrier in mother-neonate pairs raising concern over fetal development (Midasch et al. 2007). A hospital-based cross-sectional epidemiologic study of singleton deliveries in Baltimore, Maryland observed small negative associations between low levels of both PFOS and PFOA concentrations and birth weight, ponderal index (mass/height index), and head circumference (Apelberg et al. 2007). A similar study from Japan indicated a negative correlation between in utero exposure to low levels of PFOS and birth weight (Washino et al. 2009). Finally, PFCs were associated with fewer normal sperm in a cohort of Danish men (Joensen et al. 2009). Efforts to identify developmental deficits and no adverse effect levels have yielded suggestive – but limited – results (Bjork et al. 2008; Butenhoff et al. 2009a; Butenhoff et al. 2009b; Chengelis et al. 2009a; Chengelis et al. 2009b; Das et al. 2008)

Discussion of Evidence for Exposure

PFCs are known to accumulate in Great Lakes biota including lake trout, blue gill and birds. The predominant perfluorinated compounds detected in fish were PFOS (Delinsky et al. 2009; Furdui et al. 2007; Sinclair et al. 2006; Ye et al. 2008). Furdui et al. 2007 recently reported the spatial distribution of various PFC contaminants in lake trout from the Great Lakes. Fish from Lake Superior contained the lowest total concentrations, while the highest levels were found in samples from Lake Erie. Fish from Lakes Ontario and Huron showed similar total concentrations, respectively, while samples from Lake Michigan were lower (*Figure 5*).

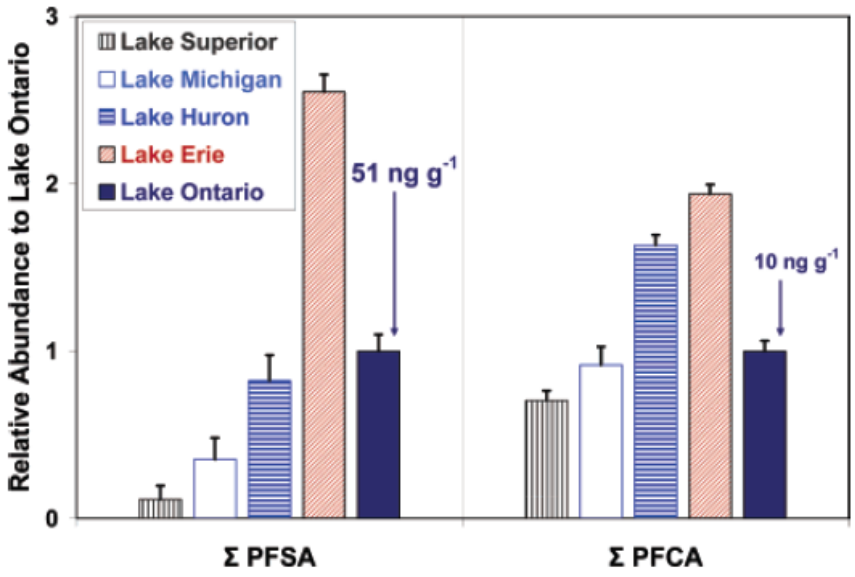

Figure 5: The relative abundance of total perfluorinated sulfonates and carboxylates in lake trout from the Great Lakes. All concentrations determined with internal standardization were compared with the values from Lake Ontario (absolute values indicated by arrows). As reported by (Furdui et al. 2007).

Furdui et al. (2007) also reported significant correlations between PFOS concentration and trout body weight (*figure 6*). This suggests that PFCs bioaccumulate and biomagnify in food chains like other persistent bioaccumulative toxics such as Hg and PCBs. This is further confirmed by (Ye et al. 2008) who found median PFOS levels significantly elevated in piscivorous fish (88.0 ng/g) when compared with non-piscivorous fish (15.9 ng/g) in whole fish homogenates from the Ohio, Missouri, and Upper Mississippi Rivers.

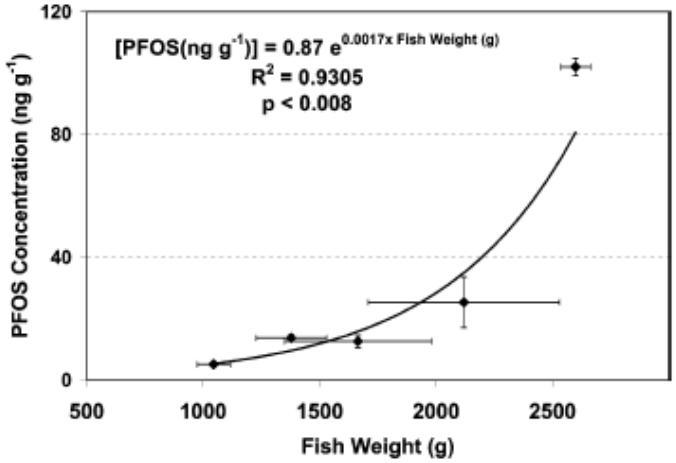

Figure 6: Correlation between the level of PFOS and the body weight of lake trout from the Great Lakes (r) 0.05). The values represent averages of the concentrations determined with the standard addition method for each lake (error bars = SEM). Taken from Furdui et al. (2007).

Fish contamination of PFCs occurs inland within the Great Lakes region as well. A study by Sinclair et al. (2006) revealed elevated levels of PFCs (PFOS were the most prevalent PFC) in Minnesota samples of blue gill, with median concentrations of 47.0-102 ng/g at locations along the Mississippi River, 2.08 ng/g in the St. Croix River, and 275 ng/g in Lake Calhoun. These results suggest that PFC contamination in freshwater fish is not limited to areas with known historical PFC inputs.

Food, breast milk and water ingestion are thought to be important PFC exposure routes for humans (Berger et al. 2009; Trudel et al. 2008; von Ehrenstein et al. 2009). In a comprehensive assessment of consumer exposure to PFOS and PFOA Trudel et al. (2008) investigated PFC contributions from gender- and age-specific exposure scenarios. The study found that North American and European consumers are likely to experience ubiquitous and long-term uptake doses of PFOS and PFOA in the range of 3 to 220 ng per kg body weight per day (ng/kg(bw)/day) and 1 to 130 ng/kg(bw)/day, respectively. The greatest portion of the chronic exposure to PFOS and PFOA is likely to result from the intake of contaminated foods and drinking water (*figures 7 and 8*).

The above findings support the notion that GL fish consumption could play an important role in human exposure to PFCs (especially PFOS). Studies from other regions have suggested this exposure route. A study from Sweden analyzed PFC levels in fish muscle tissue from edible species caught in the second largest freshwater lake in Sweden, Lake Vattern, and in the brackish water Baltic Sea (Berger et al. 2009). The authors calculated human exposure to PFOS via fish intake for three study groups, based on consumption data from literature. The results showed that PFOS intake strongly depended on individual fish consumption as well as the fish catchment area. Comparing these findings to the results from Trudel et al. (2008), suggests that Great Lakes fish consumption is a PFC exposure route that deems serious consideration.

Conclusions PFCs

Our review presents relatively strong evidence for human exposure to PFCs. This exposure is likely due to oral exposure routes including food and water consumption. These chemicals are accumulating in Great Lakes fish and therefore could contribute to human exposure via fish consumption. The evidence for human health hazards from PFCs is inadequate for definitive risk assessment or even identification of specific hazards. We classify this chemical group as high exposure priority and moderate human health priority in the Great Lakes.

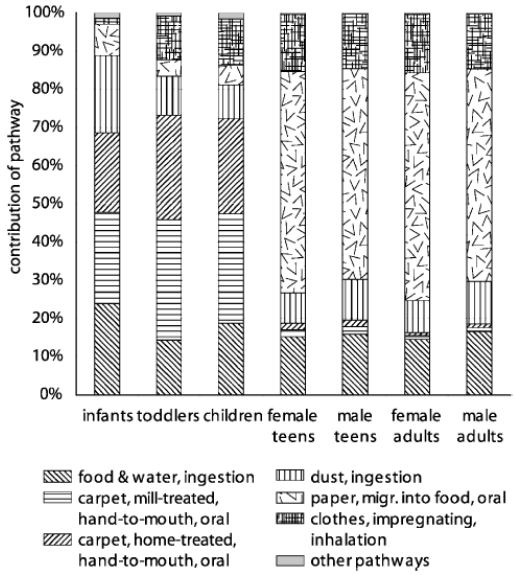

Figure 7: contribution of different PFOA exposure pathways to PFOA results for high-exposure scenarios in North America (Trudel et al. 2008).

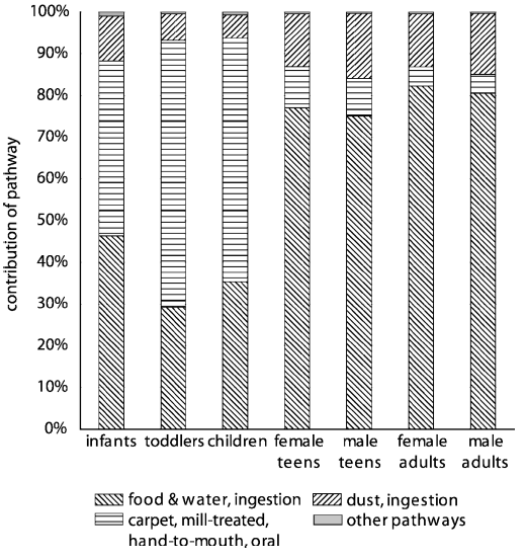

Figure 8: contribution of exposure pathways to PFOS in North America for the high-exposure scenario (Trudel et al. 2008).

V: Current-use Pesticides

Description

Klecka et al. (2009) reported that pesticides are often observed in surface waters, sediments, groundwater, and sometimes atmosphere. Most studies from our review focused on surface, ground or drinking water, particularly when investigating human health risk (Ochoa-Acuna et al. 2009; Waller et al. 2010). The pesticides most frequently detected in stream water include five agricultural herbicides (atrazine, metolachlor, cyanazine, alachlor and acetochlor), five urban use herbicides (simazine, prometon, tebuthiuron, 2,4-D, and diuron), and three widely used insecticides (diazinon, chlorpyrifos and carbaryl) (Klecka et al. 2009). Although herbicides and insecticides likely have different modes of action, the category "pesticides" often encompasses these two categories with other chemicals. In this review "pesticides" were treated as one broad category. This was done to keep the volume of literature manageable for review, but it also served to conceptualize the issue of "agrichemicals" as a common risk category. Many studies included multiple chemicals in their reports. Some reports group them as "agricultural contaminants" or "agrichemicals" the environmental source of which is generally thought to be agricultural or urban runoff.

Discussion of Hazards

A disadvantage of grouping pesticides, or any diverse group of chemicals, is the increased challenge of identify specific hazards associated with the group. A study from Indiana found that atrazine, and perhaps other co-occurring herbicides in drinking water, is associated with an increased prevalence of small-for-gestational-age infants (Ochoa-Acuna et al. 2009). Furthermore, a retrospective, case-controlled study using Washington State Birth Certificate and US Geological Survey databases found an association between maternal exposure to surface water atrazine and fetal gastroschisis (congenital fissure of the ventral abdominal wall), particularly in spring conceptions (Waller et al. 2010). Studies like these support the notion that developing infants may be susceptible to pesticide-contaminated drinking water. Both of these retrospective cohort studies controlled for socio-economic and behavioural factors such as drinking and smoking. However, confounding stressors (air pollution, water quality, and other contaminants) are not well accounted-for. This is a common problem with studies associating human health effects with CECs.

The above associations are, however, supported by laboratory studies showing cellular and hormonal alterations to exposed human tissues. Orton et al. (2009) tested 11 pesticides (isoproturon, diuron, linuron, 4-chloro-2-methylphenoxy acetic acid (MCPA), mecoprop, atrazine, simazine, PCP, trifluralin, chlorpropham, and bentazone) for endocrine disruption. Common effects from this study were antiestrogenic/antiandrogenic activity in a yeast screen, and inhibition of ovulation, accompanied by decreased testosterone production. Changes to in vitro human chorionic gonadotropin (hCG) stimulated hormone production in ovarian follicles was also observed (Orton et al. 2009). Another study exposed human MCF-7 cells to environmentally relevant concentrations of atrazine. The doses altered protein expression in the cells. Affected proteins included those regulating oxidative stress such as superoxide dismutase and structural proteins such as actin or tropomyosin (Lasserre et al. 2009).

It is also worth noting that pesticides negatively affect amphibian and fish reproduction according to several papers and reviews (Jin et al. 2010; Langlois et al. 2010; Rohr and McCoy 2010). Many studies outline negative effects of atrazine and other herbicides on amphibian reproductive health such as sex ratios and gonadal function (Langlois et al. 2010; Rohr and McCoy 2010). Similar effects were found in laboratory exposed rats (Abarikwu et al. 2010) and zebrafish (Jin et al. 2010). This suggests that amphibians could serve as important sentinels of human health especially when considering agricultural runoff and drinking water exposure. We discuss later in this report the potential advantages and limitations when attempting such extrapolations of risk.

Discussion of Evidence for Exposure

Atrazine and other agricultural contaminants are suspected to negatively affect human birth outcomes via drinking water exposure. The Indiana study cited above calculated monthly concentrations during 1996-2002 of nitrates, atrazine and other pesticides using United States Geological Survey's National Water Quality and compared them to monthly United States birth defect rates for live births from 1996 to 2002 using United States Centers for Disease Control and Prevention natality data sets. Elevated concentrations of agrichemicals in surface water from April-July coincided with higher risk of birth defects in live births with maternal last menstrual period occurring in the same period (April-July) (Winchester et al. 2009). These patterns, and those observed by Ochoa-Acuna et al. (2009) suggest a relationship between agricultural application/runoff and human exposure (*figure 9*).

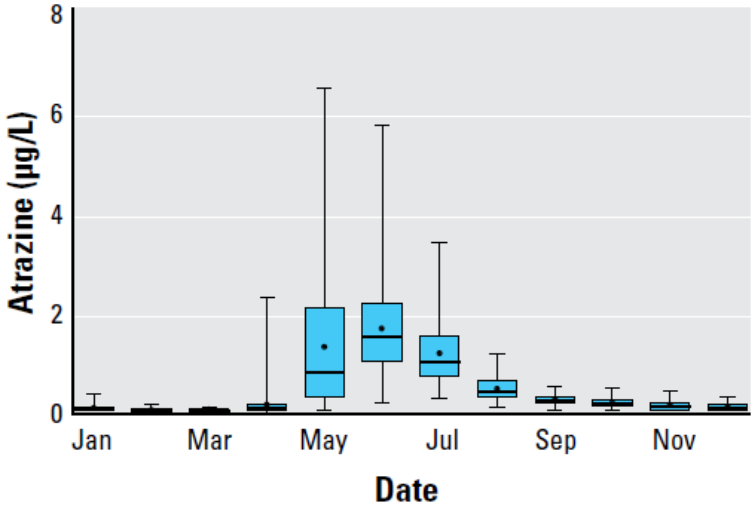

Figure 9. Seasonal pattern of atrazine concentrations in finished drinking water in Ft. Wayne, Indiana, USA. Dots indicate mean, lines median, boxes the interquartile range (25th–75th percentiles), and bars the 5th–95th percentiles (Ochoa-Acuna et al. 2009).

Agricultural runoff is suspected to contribute greatly to the presence of these chemicals in the aquatic environment as well as soils (Echols et al. 2008; Pham et al. 2000; Riederer et al. 2010). Additionally, many pesticides travel further in water than they do in air (Matthies et al. 2009).

Conclusions: Pesticides (Agrichemicals)

As previously mentioned, many studies investigate health concerns related to agricultural runoff but not necessarily specific agrichemicals. Nevertheless, evidence of cellular stress and endocrine disruption raise human health concerns. Since pesticides appear to occur primarily in surface and ground waters, the potential exists for human exposure via drinking water. Even water treatment can result in disinfectant by-products which may raise health concerns. Antibiotic resistance of pathogens is another cause for concern.

Many veterinary pharmaceuticals (sometimes referred to as agripharmaceuticals) occur in the environment presumably from agricultural runoff and the lack of treatment for animal waste. These chemicals could include pharmaceuticals (amprolium, carbadox, monensin, and tylosin) as well as natural and synthetic steroid hormones (Snow et al. 2010; Song et al. 2010). Chemicals such as pesticides and veterinary pharmaceuticals are manufactured with specific modes of action (i.e. specifically designed to be biologically and physiologically active). In this way, and because they are associated with agricultural runoff, veterinary pharmaceuticals and pesticides should be considered as an important group of agrichemicals which warrant serious consideration.

Human exposure data for these chemicals are well covered in the CDC Fourth National Report on Human Exposure to Environmental Chemicals (CDC 2009). From this report, it is clear that humans in the United States are exposed to several pesticides as evidenced by their presence in urine samples from the National Health and Nutrition Examination Survey (NHANES). The risks from these chemicals could include but are not limited to: reproductive, genotoxic, carcinogenic, neurotoxic, and respiratory.

Our mandate to focus on point source pollutants restricted our review of this category and prevents us from drawing conclusions regarding exposure and health risk. The review conducted here does not allow for a representative perspective of the literature on the various chemicals that may be included in the pesticide category. Upon completion of this review (which primarily relied on the *ISI Web of Science*® database) it became clear that a full ascertainment of the literature on pesticides did not fall within the scope of the current report. Pesticides are certainly an important group of chemicals which warrant a separate review dedicated solely to literature concerning pesticides and agrichemicals within the Great Lakes.

VI: Chlorinated Parrafins

Description

Chlorinated paraffins (CPs), technical mixtures of polychlorinated alkanes (PCAs), occur ubiquitously in the environment (Bayen et al. 2006). CPs are used as lubricants and coolants in metal cutting and metal forming operations and as secondary plasticizers and flame retardants in plastics. Polychorinated alkanes represent a difficult analytical problem because of the complexity inherent in industrial mixtures. The total number of possible congeners is unknown, but far exceeds 10,000 (Eljarrat and Barcelo 2006). CPs seem to behave similarly to persistent organic pollutants (POPs), leading several countries to impose regulations on the use of CPs. The U.S. Environmental Protection Agency identified Short-Chain Chlorinated Paraffins (SCCPs), for action plan development based on their presence in humans; persistent, bioaccumulative, and toxic (PBT) characteristics; use in consumer products; production volume; or other similar factors (EPA 2009).

Discussion of Hazards

According to the EPA action plan acute toxicity of SCCPs (C_{10-13}) is very low. There was no evidence of developmental effects in prenatal developmental toxicity studies in rats and rabbits (EC 1999; EPA 2009; UNEP. 2009).

The liver, kidney and thyroid are major target organs in repeated-dose studies with rats and mice. When administered by gavage, chlorinated paraffins (C_{12}, 60 percent chlorine) are carcinogenic in rats and mice of both sexes (NTP 1986, 2005). The underlying mechanisms for the carcinogenicity of SCCP in rats and mice are not clearly known.

According to our literature review, updates to the state of knowledge on CPs are limited. PCAs show sub lethal developmental deficits in laboratory frogs as well as trout (Buryskova et al. 2006; Cooley et al. 2001). Trout exposed to the PCAs (whole fish concentrations 0.22-5.5 microg g(-1)) showed a diminished or no startle response, loss of equilibrium, and developed a dark coloration. Dark coloration, however, is an indicator of stress and may not be pathologically relevant. Histopathological lesions were also observed in the livers of trout from each exposure group. Cooley et al. (2001) suggested that PCA toxicity is inversely related to carbon chain length, as has been observed in similar studies investigating mammals. The concentrations in the fish from this experiment were at levels that have been reported in invertebrates and fish from contaminated sites in the Great Lakes.

Discussion of Evidence for Exposure

According to the EPA action plan the primary non-occupational routes of exposure to SCCPs include ingestion, both directly and through contaminated food, and dermal contact with products. Chlorinated paraffins have been isolated from human liver, kidneys, adipose tissue and breast milk. SCCP exposure could occur from sources far from their use and release due to their potential for environmental transport (EPA 2009). For example, SCCPs have been found in breast milk samples taken from Inuit women (UNEP 2009).

SCCPs and Medium Chain Chlorinated Paraffins (MCCPs) were found to biomagnify from prey and predators in both Lake Michigan and Lake Ontario. Trophic magnification factors for the invertebrates-forage fish-lake trout food webs ranged from 0.41 to 2.4 for SCCPs and from 0.06 to 0.36 for MCCPs (Houde et al. 2008). Klecka et al. (2010) reported on several studies that detected CPs in sediment and water within the Great Lakes but the information is limited and our literature search failed to uncover new information on the occurrence of these chemicals in the environment.

Bayen et al. (2006) offered the following future research priorities for CPs: improvements in analytical methodologies (reducing the complexity of the analysis, producing reference materials and performing interlaboratory studies); determining background levels of chlorinated paraffins in the environment and human populations (this question should be answered using quality assured analytical tools allowing the intercomparison of data); and investigating the sources of CPs to the environment and to humans.

Conclusions

Information we found relevant to risk assessment on CPs was relatively sparse. The above information suggests a moderate concern for human exposure in the GL. Even fewer studies were found regarding human health effects. Based on the literature search for this review, the database remains inconclusive regarding the potential for human health hazards of CPS. Further research, perhaps following the priorities set forth by Bayen et al. (2006) could allow for stronger statements regarding concern over GL CP contamination.

VII: Synthetic Musks

Description

Synthetic musks are used extensively in perfumes, cosmetics, detergents, cleaning products, and other personal care products. As such, they have found their way into the surface water, sediment, and biota of the Great Lakes basin particularly near wastewater effluents (Guo et al. 2009; Sumner et al. 2010). Unlike their natural counterparts, synthetic musks have physical-chemical properties similar to other hydrophobic and semi-volatile organics that are known to bioaccumulate and biomagnify in aquatic organisms (Klecka et al 2010).

Discussion of Hazards

The European Commission (EC) has recently compiled risk assessments for the following synthetic musks: musk xylene (EC 2005a), musk ketone (EC 2005b), 1-(5,6,7,8-tetrahydro-3,5,5,6,8,8-hexamethyl-2-naphthyl)ethan-1-one (AHTN) (EC 2008a), and 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-2-benzopyran (HHCB)(EC 2008b) in which predicted no effect concentrations (PNEC) were developed (*Table 4)*. These risk assessments generally extrapolate human health risk from rodent models.

	Musk xylene	Musk ketone	AHTN	HHCB
PNEC water (ug/L)	1.1	6.3	2.8	4.4
PNEC sediment (mg/kg dw)	0.3	0.5	1.72	2.0
PNEC 2^o consumer (mg/kg food)	1.0	0.3	1.1	3.3

Table 4: predicted no effect concentrations (PNEC) from the EC risk assessments (EC 2005a, b, 2008a, b).

Laboratory studies suggest that synthetic musks influence endocrine function. These compounds show weak estrogenic activity (Bitsch et al. 2002b; Schreurs et al. 2004; Schreurs et al. 2002). One study tested a variety of musk fragrances using the E-screen assay which demonstrated estrogenic activity. A statistically significant increase in proliferation rate of human MCF-7 breast cancer cells was detected for two nitro musks (musk xylene, musk ketone), a major metabolite of musk xylene (p-amino-musk xylene), and the polycyclic musk fragrance AHTN (Bitsch et al. 2002a). Other studies show developmental toxicity of mussels (Gooding et al. 2006; Luckenbach et al. 2004) and fish (Carlsson and Norrgren 2004a). The zebrafish model has suggested both endocrine disruption and reproductive effects in response to synthetic musks (Carlsson and Norrgren 2004b; Schreurs et al. 2004; Schreurs et al. 2002). One study suggested that certain polycyclic musks, including AHTN and HHCB, induce the expression levels of hepatic estrogen receptor alpha and vitellogenin mRNA/protein and modulate expression levels of CYP3A4 mRNA in the livers of male medaka (Yamauchi et al. 2008). The actual health consequences to humans from synthetic musk exposure remain unclear based on our review.

Discussion of Evidence for Exposure

Concentrations of polycyclic, but not nitro musks, were detected in freshwater fish from two urbanized areas in the lower Great Lakes: Hamilton Harbour in western Lake Ontario, and the Detroit River and nearby western Lake Erie (O'Toole and Metcalfe 2006). Although Klecka et al. (2009) report that musks occur most frequently in biota (as compared to water or sediment) there exists little other information regarding their occurrence in humans or human exposure. One study observed low levels of musks in human breast milk (Kang et al. 2010). Their presence in Great Lakes biota, however, suggests a potential for exposure via fish consumption.

Two studies have evaluated serum levels of synthetic musks related to cosmetic use but no dominant source of nitro musk uptake was observed. Although their relationship to body surface area indicates cosmetic products applied to the skin as the likely origin of plasma concentrations (Hutter et al. 2010; Hutter et al. 2009). Based on the residue patterns and accumulation features, another study concluded that the exposure characteristics for synthetic musks are different from those of POPs, and that the major source of exposure to synthetic musks is probably via dermal absorption or inhalation (Reiner et al. 2007). However, as their use increases and they enter the environment (for example, near wastewater treatment facilities) the potential for exposure via drinking water or food web accumulation could increase.

Conclusions: Synthetic Musks

As with CPs the literature on synthetic musks provided sparse evidence for both exposure and health effects within the GL. Based on the current information we characterize the risk to human health and potential for exposure in the GL as low. It should be noted, however, that additive effects of mild estrogen mimickers such as synthetic musks and APs could alter such recommendations.

VIII: Organic Wastewater Constituents/Pharmaceuticals

Description

For reasons of efficiency and operational synthesis, we consolidated pharmaceuticals and Organic Wastewater Constituents (OWCs) into one group for this review. These are two very diverse groups of chemicals and they often overlap one another in the literature. These categories are so diverse that keyword searches proved impractical. The most successful method employed for searching OCWs and Pharmaceuticals was to meta-search the papers that cited papers such as Kolpin et al. (2002). This method of searching yielded papers that studied both OWCs and pharmaceuticals, often together. The reason for overlap is that pharmaceuticals generally enter the environment through wastewater from human excretion or simply flushing pills down the toilet.

OWCs can include anything from human hormone metabolites, to APEs (already covered as a separate chemical group) to a variety of pharmaceuticals. Often times CECs from different categories (drugs, APs, hormones, synthetic musks) appear together in the same paper. Therefore, they are included together in this review as they generally appeared within the literature. Two exceptions to this, APs and synthetic musks, are covered separately above. These two chemical groups seemed distinct enough to warrant their own literature searches. Overall, most papers focused on the following drugs and OCWs: coprostanol (fecal steroid), cholesterol (plant and animal steroid), N,N-diethyltoluamide (insect repellant), caffeine (stimulant), triclosan (antimicrobial disinfectant), tri(2-chloroethyl)phosphate (flame retardant), and 4-nonylphenol (nonionic detergent metabolite already covered in the APs section).

Discussion of OWCs and Pharmaceuticals

Perhaps the most "popular" OWC of study was Triclosan. Seven of the 29 OWC studies we reviewed focused on the effects and occurrence of Triclosan in the environment. Triclosan has broad-spectrum anti-microbial activity against most gram-negative and gram-positive bacteria. It is widely used in personal care products, household items, medical devices, and clinical settings. Due to its extensive use, there is potential for humans in all age groups to receive lifetime exposures to triclosan, and, indeed, triclosan has been detected in human tissues and the environment (Fang et al. 2010). Triclosan is suspected to disrupt endocrine function as shown in laboratory studies using wistar rats of both sexes (Kolpin et al. 2002; Stoker et al. 2010).

Most of the published studies suggest low appreciable risk to human health from current environmental exposures of pharmaceuticals. However, (Kumar et al. 2010) identified the following shortcomings in determining risk to human health from environmental exposure to pharmaceuticals: (1) Use of measured versus predicted pharmaceutical concentration, (2) Identification of pharmaceuticals-of-concern and compounds needing special considerations, (3) Use of source water versus finished drinking water-related exposure scenarios, (4) Selection of representative exposure routes, (5) Valuation of uncertainty factors, and (6) Risk assessment for mixture of chemicals.

IX: Discussion

Impediments in Assessing Health Hazards Associated with IJC Categories of CECs

This review discusses seven CEC categories; with each category containing multiple metabolites congeners, species, or related chemicals. Grouping the CECs in this way allows us to more easily

construct an organized discussion of the topic, but also has the potential to over simplify what is truly a complex field of research.

A recent report to the EPA identified emerging contaminants and persistent, bioaccumulative, and toxic (PBT) chemicals that were not being considered in current Great Lakes contaminant measurement programs (Muir et al. 2009). They evaluated 22,043 chemicals of interest. Of these, Muir et al. (2009) identified 610 probable PBT substances that should be considered for further study and measurement in the Great Lakes region. Furthermore, they estimated that 101 of the 610 chemicals have been measured in the Great Lakes region (as parent compound or degradation products) and about 47 (legacy organochlorines, PBDEs and perfluorinated alkyl acids) are on routine monitoring lists. This leaves hundreds of un-measured, poorly studied candidates that warrant "concern". It's important to consider that this list could be longer if more information existed on the other 21,000 chemicals originally considered. It may seem that the term Chemical of Emerging Concern implies "new chemicals"; however, this term appears to more adequately define chemicals that we do not yet understand well enough to assess risk. For this reason, we simply define these chemicals as "concerning".

The goals of risk assessment are clear. Researchers and policy makers around the world use risk assessment to characterize the nature and magnitude of health risks to humans and ecological receptors from chemical contaminants and other stressors that may exist in the environment. This information is then used to assist in determining strategies for protecting humans and the environment from stressors or contaminants (EPA 2008). The steps used in this process outline a clear, logical path for how modern societies have agreed to deal with pollution: Hazard Identification, Exposure Assessment, Dose-Response Assessment, and Risk Characterization. Currently, this process is carried out considering one chemical at a time in the forms of risk quotients and toxicological reports such as those cited above (ASTDR 2004; EC 1999, 2001, 2005a, b, 2008a, b, c; ECB 2005; EPA 2008, 2009; NTP 1986, 2005).

Limitations to 'Traditional' Approaches

The above description generally outlines the process by which researchers and policy-makers guide causal research, aid in decision-making, as well as justify policy and management decisions. The chemical-specific nature in which this process is traditionally carried out limits our ability to address: (1) the enormous and growing lists of chemicals, (2) uncertainty regarding the effects of chemical mixtures, (3) the impacts of mixed and confounding stressors and (4) residual unknown or unmeasured risk factors. Uncertainty is a well-accepted concept in risk assessment. However, as the list of CECs grows, so grows the uncertainty as to whether or not risk assessments are accurately or operationally capturing and managing the actual risks. This begs the question: "Do all risk assessments need to be chemical-specific?" Historically, and from a legislative standpoint, the answer has been "yes". For example: The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) of 1996 states that all pesticides distributed or sold in the United States must be registered (licensed) by EPA. Such licensed chemicals must be proven not to elicit any unreasonable adverse effects on the environment and humans. The chemical-

specific nature of risk assessment is also required by Section 408 The Federal Food, Drug, and Cosmetic Act (FFDCA), which authorizes EPA to set tolerances, or maximum residue limits, for pesticide residues on foods. The Clean Air and Clean Water Acts establish similar provisions which are typically met by setting limits to specific contaminants

The chemical-specific nature of traditional risk assessment is meant to reduce uncertainty with regard to cause-effect interpretations as well as accommodate federal regulations as exemplified above. The simplification of focusing on chemicals one-at-a time makes risk calculations more interpretable and remedial actions more identifiable. Unfortunately, this specificity may only increase uncertainty that risks from cumulative, additive, and synergistic effects are not being identified. Furthermore, it can be difficult to accept that observed effects from observational cohort studies associating human health risk to chemical stressors are from the chemicals measured and not other uncharacterized variables. A number of the observational studies cited above include such limitations.

As described above, evaluating the risks of potentially toxic substances employs a largely empirical, exposure-based approach through monitoring of selected chemicals in various media and biological receptors. This has resulted in an extensive knowledge base regarding the spatial and temporal status of selected chemicals in aquatic ecosystems such as the Great Lakes. The current review indicates that many CECs are present in ecosystems in and around the Great Lakes. However, the continued lack of effects data on those chemicals represents an obstacle to assessing risk, thereby limiting the ability of Regions, States, and Tribes to make sound risk and remediation decisions.

Reducing the uncertainties regarding adverse effects associated with exposures to potentially toxic chemicals is a high priority issue. Chemicals of emerging concern, in particular, require a more predictive approach due to the lack of existing effects data. Researchers may begin to fulfill this need by increasing efforts to use effects-based information to predict and evaluate toxicity of chemicals. This effects-based information could be derived from approaches that enhance knowledge of biological systems, use sub-organismal endpoints as indicators of toxicological activity, and predictive toxicological methods, which used together, enhance the ability to link chemical exposures to adverse effects relevant to risk assessment endpoints. The adoption, and acceptance of such techniques, may require a paradigm shift in both regulatory and research approaches.

Uses and limitations of Effect-Directed Analysis

An increasingly popular method for assessing risk to stream ecosystems from multiple toxicants is Effect Directed Analyses (EDA). In contrast to evaluating individual chemicals, EDA provides the advantage of assessing complex mixtures as they exist in the environment. This analysis employs laboratory bioassays indicating effects on cellular, organism or population level, which are intended to link measureable effects of complex environmental samples to distinct toxicants. Many ecological risk assessments from the European Union employ EDA to bridge the gap between chemical contamination and ecological status (Brack et al. 2007). EDA is a form of toxicity testing similar to toxicity screening; similar (sometimes the same) assays are used. Generally speaking, toxicity testing and EDA are methods used to quantify toxic response of biological pathways (either whole organism, or at cellular, molecular and genetic levels). Toxicity tests such as EDA uses assays that focus on biological responses suspected or known to be caused by toxic stressors (e.g. teratogenicity, genotoxicity, endocrine disruption, etc.).

EDA assays are relatively rapid and inexpensive compared to other toxicity tests such as those seeking to evaluate observable outcomes using mammalian models.

EDA was employed by (Keiter et al. 2009) to investigate the potential role of toxic substances in fishery declines within the Danube River. They applied bioassays to sediment samples, which evaluated cytotoxicity, toxicity to bacteria, endocrine disruption, zebrafish embryo toxicity and mutagenicity. The results of the study indicated toxic substances as a likely candidate for fish decline in the river. Keiter et al. (2009) were able to associate the afore-mentioned toxic effects with suspended particulate matter as well as effluents from pulp mills and sewage treatment plants. The zebrafish test was particularly telling as embryos exposed to sediments from the upper Danube revealed significantly higher embryo toxicity. This study uses EDA in a unique fashion: tests normally used for screening were treated as risk variables (ecotoxicological hazard potential) to test the hypothesis that Danube fisheries were at risk due to the presence of toxic chemicals. We propose that measures of ecotoxicological hazard potential could allow researchers to conduct predictive risk assessments without relying on resource-intensive chemical screening techniques.

EDA techniques such as the zebrafish sediment contact assay developed by Hollert et al. (2003) and employed by Keiter et al. (2009) provide a comprehensive method to investigate native sediments and particulate matter without employing extraction procedures. These sediment contact assays can be used to estimate bioavailability of particle-bound lipophilic substances and their toxicity to vertebrate development. Tools such as these would provide a quantitative measure of sediment or water contamination for use in risk investigations.

In isolation, EDA tests tell little of which specific chemical contaminants induce the measured effects (e.g. which chemicals in the Danube induced fish teratogenicity). However, in conjunction with local knowledge and further research, including targeted chemical analysis and risk propagation modeling, EDA can help prioritize remedial action and hypothesis testing. The integration of EDA tools could augment the effectiveness of monitoring, and reduce the dependence on chemical screening and chemical profiling. These tools would thereby delay expensive chemical identification until such time as causal hypothesis testing is indicated.

Priority Area: Collect relevant human health data for environmental studies

In addition to developing new risk assessment tools it is necessary to increase the availability of relevant human health data for the purposes of epidemiological study and Human Health Risk Assessment (HHRA). Such programs would regularly collect relevant human-health data to facilitate study of human health/environment interactions and compile the information into (relatively) easily accessible databases. Some examples of current efforts on this front include: the Wisconsin Pediatric Cardiac Registry (WPCR) Database, National Children's Study (NCS), and Exposure Profiling (Malecki et al. 2006). Such databases would more easily allow for epidemiological studies on defined populations at risk.

A major impediment in the study of environmentally-linked diseases is an inability to reliably detect, quantify, and characterize the risk from chemical mixtures and multiple environmental stressors (Assmuth et al. 2010; EPA 2003; Sexton and Hattis 2006; Wigle et al. 2008). There exists no clear

agreement on the appropriate tools required for accurate measurement of these risks. The challenge of deciding how and what to measure is further complicated for studies where logistical and cost constraints preclude the collection of all possible measurements. The motivation for the National Children's Study (NCS) (a large-scale longitudinal study that will enroll 100,000 women from stratified, probability based sample locations and follow them from before conception to early adulthood) was to have sufficient power to evaluate multiple interacting environmental exposures (Branum et al. 2003). The success of studies such as the NCS will greatly depend on the accurate, cost-effective, characterization of environmental exposures thought to be related to the health outcomes of interest (Strauss et al. 2010).

The Commission for Environmental Cooperation (CEC; set up under the North American Agreement on Environmental Cooperation) has recently called for an increased effort in measuring indicators of children's' health. In a report titled "Children's Health and the Environment in North America: a First Report on Available Indicators and Measures", the CEC describes cooperative work on children's health and the environment undertaken by the NAFTA-participating countries in three defined priority areas (CEC 2006). These priority areas include asthma and respiratory disease, lead and other chemicals, and waterborne diseases. The report presents thirteen indicators that fall within these priority areas. The indicators of interest include, but were not limited to: air quality parameters, asthma prevalence's, pollutant release and transfer register data (such as the U.S. toxic release inventories), lead blood levels, pesticide residues on foods, and water quality parameters. CEC (2006) reported that efforts by the three countries to compile these indicators revealed a number of data gaps and opportunities for improvement.

In 2002, the U.S. Congress allocated funding to the Centers for Disease Control and Prevention (CDC) to develop the National Environmental Public Health Tracking Program. The Council of State and Territorial Epidemiologists and CDC identified specific areas and indicators that should be evaluated to address the lack of understanding of environmentally related diseases. Future evaluations of these indicators should consider how well the indicator predicts human health and environmental conditions, and the adequacy of available data. In addition, the evaluators should also consider how best to standardize data collection and define the indicators (CDC 2011). Programs such as these are essential tools in the pursuit of more inclusive, accurate and integrated risk assessments.

Priority Area: Expand role of screening assays in risk assessment process

A recent paper (Ankley et al. 2010) proposes that ecological risk assessors face increasing demands to assess more chemicals, with greater speed and accuracy, and to do so using fewer resources and experimental animals. Furthermore, new approaches in biological and computational sciences should be applied to meet these challenges (Ankley et al. 2010). Ankley et al. (2010) propose the adverse outcome pathway (AOP) framework (a conceptual construct that portrays existing knowledge concerning the linkage between a direct molecular initiating event and an adverse outcome at a biological level of organization relevant to risk assessment) as a method for increasing the effectiveness of modern ecological risk assessment (ERA). We concur with these suggestions and propose that approaches such as AOP and EDA could serve to strengthen not just ERA but HHRA.

The National Research Council recently produced a report titled: "Toxicity Testing in the 21st Century: A Vision and a Strategy" (NRC 2007). The purpose of this report was to outline a vision for new approaches in toxicity testing using recent scientific advances. NRC (2007) cites substantial progress in the elucidation of cellular-response networks—interconnected pathways composed of complex biochemical interactions of genes, proteins, and small molecules that maintain normal cellular function, control communication between cells, and allow cells to adapt to changes in their environment. These advances could transform toxicity testing from a system based on whole-animal testing to one founded primarily on in vitro methods that evaluate changes in biological processes. NRC (2007) outlines the following objectives for improving toxicity testing to accommodate current limitations:

- Provide broader coverage of chemicals and their mixtures, end points, and life-stage vulnerabilities.
- Reduce the cost and time of testing, increase efficiency and flexibility, and make it possible to reach a decision more quickly.
- Use fewer animals and cause minimal suffering to animals that are used.
- Develop a more robust scientific basis of risk assessment by providing detailed mechanistic and dosimetry information and by encouraging the integration of toxicologic and population based data.

The opportunities presented by recent advances are important; however, the NRC (2007) points out that much refinement, development, funding, and years of research will be required before a new and efficient system of toxicity testing can be established. It is important to understand that shifting the paradigms in which assessors and researchers employ techniques to identify hazards and assess risk may also allow us to enhance these fields using relatively simple models such as zebrafish. Researchers can make these shifts now to form the first steps in establishing this much needed novel and efficient framework. To do this, the support of policy makers and funders will be required. In researching this topic, we find a common theme: novel approaches are needed if we hope to assess the toxicity and manage risk from the enormous and growing list of chemical contaminants in the environment.

The development of techniques such as EDA for use in HHRA could help these protocols to accommodate for complex mixtures of poorly monitored and poorly understood chemicals (i.e. real-life conditions). The next step in this process would be to calibrate promising *in-vitro*, *in-vivo*, and *in-situ* assays to respond to "real-life conditions". In this way, EDA would have the potential to serve the same purposes as 'Hazard Identification' if properly applied. Also, EDA measures could serve as risk-reduction goals, benchmarks, or standards for regulatory purposes relating to human health (similar to the concept of 'biotic integrity' (Karr 1991, 1986) used for ecological risk assessments and compliance with water quality standards for the Clean Water Act). In certain cases this would require the acceptance of non-apical measures as valid toxicity endpoints. Depending on the situation, it may not be necessary to run specific chemical analysis for all risk assessments. Well-understood EDA responses combined with local knowledge (industry, geography, ecosystem and historical events) might be sufficient to make policy and management decisions and test hypotheses for human health responses

Well-established screening assays exist in the literature and are used for various applications. Some examples include fish teratogenicity (Hollert et al. 2003; Keiter et al. 2009; Keiter et al. 2010) and endocrine disrupting assays from the EPA Tier 1 screening list for Endocrine Disrupter Screening

Program (EPA 2011). We recommend studies that investigate applicability of certain EDA assays to HHRA in conjunction with studies that investigate the ability of certain assays to respond to specific CECs in both laboratory and natural settings. We strongly support such an approach, as it will form an important framework for meeting the future challenges of both ERA and HHRA.

This report essentially identifies four priorities: (1) to update toxicity testing for better integrated ecosystem and human health risk assessments, (2) to develop better risk assessment strategies for mixtures of CECs (which may occur at very low concentrations), (3) to develop new methods to better manage contaminants with poorly understood or unknown mechanisms leading to human health effects, and (4) move away from the legalistic cause: effect focus to better defining concern through a probabilistic approach that recognizes increased risk.

Conclusions and Recommendations

In addition to the literature cited above, the exposures to North Americans from many of the chemicals reviewed here are presented in the Fourth National Report on Human Exposure to Environmental Chemicals (CDC 2009). Additionally, governmental risk assessments from Canada, U.S. and the E.U. have investigated many of the reviewed chemicals at length. Although these works are useful, they do not provide a sufficient framework for making the requested recommendations. We therefore find that the current exposure information and risk assessment methodologies do not provide a basis, as yet, for recommendations with respect to the growing list of chemical contaminants in the Great Lakes basin. The CDC stated that the human health effects of most CECs at low environmental doses or at biomonitored levels from low environmental exposures are unknown (CDC 2009). This produces a dilemma in identifying Chemicals of Emerging Concern to human health. We therefore recommend that serious consideration be given as to how concern will be defined and interpreted in this context.

We note that current use pesticides which are primarily non-point source exposures warrant a separate and more complete review. Also it must be noted that pharmaceuticals in the wastewater do not adequately address non-point source pollution from the agriculture and other “run-off” sources. In general the findings from the contractors’ report is in agreement with the SOLEC Biological Markers of Human Exposure to Persistent Chemicals Indicator #4177 which concludes that for the Great Lakes, human health assessment was/is “undetermined” and “not assessed”.

This topic (Chemicals of Emerging Concern) reemphasizes the 2006 recommendations to the governments on the Great Lakes Water Quality Agreement (GLWQA) from the IJC: “It is now time for a new Agreement with the requisite resources to produce significant results more rapidly so that the Great Lakes, as well as their tributaries, bays and connecting channels, are drinkable, swimmable and fishable for this generation and those to come (IJC 2006).” The extent to which CEC contamination threatens these goals (in addition to other important stressors such as: urbanization, climate change, invasive species, nutrient loading/eutrophication, microbial contamination, and sediment loading) remains unclear despite recent risk assessment efforts.

This review paper outlines the need for action to adapt risk assessment, research, and policy to better inform the public regarding the concern for chemical contaminants in humans and the environment. Without these new directions in risk assessment, and the support of policy makers, risks to human health in the GL can neither be adequately precisely determined nor managed.

We agree with the 15th Biennial report and furthermore conclude that the methodologies, especially those regarding assessment of health effects, do not provide a complete framework for making recommendations on this topic and must be adapted to more closely match the methods evolving in the ecosystem effects work of the CEC Workgroup.

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XI. Glossary of Key Terms

Acetochlor	A herbicide used for pre-emergence control of weeds (EPA- registered use only for field corn)
AHTN	1-(5,6,7,8-tetrahydro-3,5,5,6,8,8-hexamethyl-2-naphthyl)ethan-1-one (a synthetic musk)
Alachlor	A herbicide for control of annual grasses and broadleaf weeds in crops, primarily on corn, sorghum and soybeans
Amprolium	A veterinary drug mainly used to treat coccidiosis in poultry and other birds
Antiandrogenic	A hormone receptor antagonist compounds that are capable of preventing or inhibiting the biologic effects of androgens, male sex hormones
APEs	Alkylphenol ethoxylates
APs	Alkylphenolic substances
Atrazine	A Triazine herbicide currently registered for use against broadleaf and some grassy weeds
BDE -209	Decabromodiphenyl Ether (brominated flame retardant)
BDE-47	Tetrabromodiphenyl Ether (brominated flame retardant)
BFR	Brominated Flame Retardants
Bioaccumulate	The accumulation of substances (particularly pollutants) in an organism
Carbadox	Antimicrobial product to prevent and treat disease in swine and to maintain weight gain during periods of stress, such as weaning Banned in Canada but not U S
Carbaryl	An insecticide used in agricultural and residential settings for pest treatment
CEC	Chemical of Emerging Concern
Chlorpyrifos	Organophosphate insecticide used for agriculture
Chorionic Cillous Explants	Explants of placental cell cultures

Congeners	Chemistry term that refers to one of many variants or configurations of a common chemical structure
CP	Chlorinated Parrafin
Cyanazine	Pre- and post-emergent herbicide used to control annual grasses and broadleaf weeds
CYP3A4	Cytochrome P450 3A enzyme, involved in the metabolism of xenobiotics in the body
Cytokines	Cell signaling protein
Diazinon	Organophosphorus insecticide used to control pest insects in soil, on ornamental plants, and on fruit and vegetable field crops
Diuron	A herbicide used to control weeds and mosses on non-crop areas and among many agricultural crops such as fruit, cotton, sugar cane and legumes
Gavage	Force-feeding by means of a small plastic tube passed through the nose or mouth into the stomach
HBCD	Hexabromocyclododecane (brominated flame retardant)
HHCB	1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-2-benzopyran (a synthetic musk)
Histopathological	Branch of pathology concerned with the tissue changes characteristic of disease
Human Chorionic Gonadotropin (hCG)	Glycoprotein hormone produced during pregnancy that is made by the developing embryo after conception and later by the syncytiotrophoblast (part of the placenta)
MCCP	Medium Chain Chlorinated Paraffin
MCF-7	A breast cancer cell line isolated in 1970 from a 69-year-old woman
Metolachlor	A broad spectrum herbicide for general weed control
Monensin	Antibiotic that increases the rate of weight gain and enhances feed efficiency in ruminants
NP	Nonylphenol (alkylphenolic substance)
NPE	Nonylphenol Ethoxylates (alkylphenolic substance)

OP	p-tert-Octylphenol (alkylphenolic substance)
OPE	Octylphenol Ethoxylate (alkylphenolic substance)
OWC	Organic Wastewater Constituents
PBB	Polybrominated Biphenyls (brominated flame retardant)
PBDE	Polybrominated Diphenyl Ethers (brominated flame retardant)
PBT	Persistent, Bioaccumulative, and Toxic (substance)
PCA	Polychlorinated alkanes
Pentabromodiphenyl mixture	pentaBDE, liquid mixture of tri- to hepta- bromodiphenyl ethers (brominated flame retardant)
PFC	Perfluorinated Compounds
PFCA	Perfluorinated Carboxylates (perfluorinated compound)
PFOS	Perfluorooctane Sulfate (perfluorinated compound)
PFSA	Perfluorinated Sulfonates (perfluorinated compound)
Piscivorous	An organism that eats fish
POP	Persistent Organic Pollutants
Prometon	A non-selective herbicide that is part of the triazine group of herbicides
SCCP	Short-Chain Chlorinated Paraffins
Simazine	A chlorinated triazine herbicide, a class of herbicides that also includes the pesticides atrazine and propazine
TBBPA	Tetrabromobisphenol A (brominated flame retardant)

Tebuthiuron, 2,4-D,	A nonselective broad spectrum herbicide
Trophoblast	Specialized cells of the placenta that play an important role in embryo implantation
Tylosin	An antibiotic used in veterinary medicine and to promote growth in livestock
Vitellogen	A precursor protein of egg yolk normally in the blood or hemolymph only of females that is used as a biomarker in vertebrates of exposure to environmental estrogens which stimulate elevated levels in males as well as females