Scientific Justification to Address Endocrine Disrupting Chemicals (EDCs): A Roadmap for Action

A Submission to the 2016-2017 Parliamentary Review of the Canadian Environmental Protection Act (CEPA)

Submitted to:
The Honourable Catherine McKenna
Minister of Environment and Climate Change
Email: ec.ministre-minister.ec@canada.ca

The Honourable Jane Philpott
Minister of Health
Email: Hon.Jane.Philpott@Canada.ca

Deborah Schulte
Chair, Parliamentary Standing Committee on Environment and Sustainable Development
Email: ENVI@parl.gc.ca

Submitted by:
Fe de Leon, MPH, Researcher and Paralegal, Canadian Environmental Law Association, Toronto.

Dr. Meg Sears, Prevent Cancer Now, Ottawa.

Dr. James Brophy, Department of Sociology, University of Windsor

Dr. Margaret Keith, Department of Sociology, University of Windsor.

Tom Muir, (Retired economist, Environment Canada) Independent Researcher, Burlington.

Dr. Michael Gilbertson, The Halifax Project, Guelph.

Anne Rochon Ford, National Network on Environments and Women's Health, Toronto.

April 7, 2017

Table of Contents

Summary of Recommendations

Recommendation: Surveillance of Canadians should include focused and increased sampling of at-risk populations, for body burden of environmental toxicants including EDCs and related biological endpoints (biomarkers and disease).

Recommendation: The government should conduct economic cost analyses on EDCs in Canada following the efforts in the EU and the US.

Recommendation: The public health costs for EDCs should be reflected in the overall regulatory analyses (including in CEPA, PCPA and CEAA) in Canada including in the process of identification, assessment and management of EDCs.

Recommendation: The processes of hazard identification and risk assessment should be revisited, with endocrine disruption considered to be an inherently toxic effect.

Recommendation: The Parliamentary Standing Committee on Environment and Sustainable Development should recommend to the Parliament of Canada to review the definition of EDC in CEPA, and to include principles to identify endocrine disrupting properties of chemicals be incorporated into the proposed revisions to CEPA.

Recommendation: The Parliamentary Standing Committee on Environment and Sustainable Development, in its review of the CEPA 1999, should review the government's approach to EDCs and propose amendments to advance the elements of the Roadmap for Action on EDCs in Canada.

Introduction and Context

The body's electrical signalling via nerves is commonly understood, but the earliest signalling (even before nerves develop), that directs growth and remains critical throughout life, is a system of chemical signalling via hormones. The endocrine system encompasses production and interactions of hormones with cells and tissues. At even very low levels (in the parts per billion and parts per trillion range), hormones affect all aspects of development, maturation, reproduction and aging. They affect metabolism (and obesity), intellect and behaviour. Early exposures can have life-long effects, emerging in adolescence, adulthood and old age.

Among today's tens of thousands of chemicals in commerce, many interfere with hormone actions. These endocrine disrupting chemicals (EDCs) now permeate our air, water, land, food and common products; our buildings and natural environments; our bodies, including in the womb; and the natural world. EDCs can contribute to a wide range of chronic diseases, directly costing society billions of dollars plus lost productivity along with substantial social impacts. Despite knowledge of the presence of EDCs, today we see escalating incidence of many endocrine-related conditions ranging from obesity, to metabolic, reproductive and neurological disorders, and various cancers. EDCs are commonplace, as synthetic chemicals in plastics, cleaners and fragrances; anti-stick, anti-stain and flame-retardant chemicals, pesticides and more.

EDCs pose a challenge to regulators because the dose response is complex. Effects at a very low dose may vanish at higher doses, and effects might be very different at different doses or dose timing (one-time versus chronic, or early in life versus in adulthood). Classic chemical assessment underpinned by the assumption that "the dose makes the poison" is simply not valid for EDCs.

While the current regulatory approach has been inadequate to address the unique attributes associated with EDCs, there is an urgency to address all potential contributors to the epidemics of chronic endocrine-related conditions our society is now experiencing. The time is right to recognize that EDCs are toxic on the basis that they interfere with fundamental physiological processes, with life-long impacts.

In this paper, we outline the scientific rationale to act on endocrine disrupting chemicals in Canada and a Roadmap for Action.

Endocrine Disrupting Chemicals – the Scientific Basics

Many chemicals in our environment interfere with natural chemical messengers, in what is known as the endocrine system.[1] Minuscule concentrations of hormones orchestrate life from before conception, to the first differentiation of the nervous system and organs in the embryo, to pregnancy and lactation, child development, sexual maturation, reproduction and healthy aging. Common chemicals mimicking hormones or otherwise disrupting endocrine functions impact metabolism, personality and the ability to learn, and the likelihood of developing chronic diseases such as diabetes, cardiovascular disease and cancer. Indeed, prenatal exposures to

[1] Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, Hauser R, Prins GS, Soto AM, Zoeller RT, Gore AC. 2009. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. Endocr Rev 30:293–342.

EDCs can program offspring for a variety of diseases with long latencies, that only become manifest at puberty, adulthood or in old age.

Over the past several decades, as a by-product of modernity, the human population has become progressively more contaminated with a myriad of chemicals, with endocrine disrupting compounds found in air, water, food and consumer products; even in apparently innocuous house dust. Most people are unaware that their parents and grandparents have accrued these chemicals, or that their children and grandchildren are now conceived and develop in a contaminated womb environment.

Numerous, diverse international reviews lead us to conclude that decades of research continues to identify endocrine disruption associated with chemicals in many animal species, from fish, polar bears, whales and crocodiles, to urban and rural rats and laboratory animals.

Potential links of EDCs to impacts on the environment and human health were highlighted by seminal works over the past several decades. In 1996, the release of *Our Stolen Future* by Theo Colborne et al. brought the issue of hormone disruption to the forefront through a substantial analysis of the scientific literature pertaining to wildlife and humans. Commonly used persistent chemicals including pesticides and flame retardants had been discovered to pose multi-generational harms only after substantial harm had accrued. Colborne et al. highlighted how a "single hit" can be enough to change the trajectory of a life, and concluded,

> As we work to create a future where children can be born free of chemical contamination, our scientific knowledge and technological expertise will be crucial. Nothing, however, will be more important to human well-being and survival than the wisdom to appreciate that however great our knowledge, our ignorance is also vast. In this ignorance we have taken huge risks and inadvertently gambled with survival.

With endocrine disruption in the public eye, a 1998 workshop on breast cancer highlighted how these chemicals contribute to development of the disease, emphasizing the importance of prevention, while suggesting that the public be educated to avoid estrogenic substances.[2] With these findings, the focus on the impacts of EDCs took on a greater importance.

In 2009, the Endocrine Society published its first review on EDCs and documented the evidence concerning effects on human health.[3] In 2012, the World Health Organization reviewed the state of the science in relation to endocrine disrupting chemicals.[4] In 2013, 175 scientists from around the world met in Halifax, Nova Scotia to review evidence of the effects of low dose exposures to environmental chemicals in disrupting cellular control mechanisms and thereby contributing to carcinogenic processes.[5] In 2015, the Endocrine Society published an updated

[2] Bradlow, H. Leon, Devra Davis, Cindy Pearson, Cathy Ragovin, Lea Sekely, Susan M. Sieber, and Ana Soto. "Workshop on Hormones, Hormone Metabolism, the Environment, and Breast Cancer." *JNCI: Journal of the National Cancer Institute* 90, no. 1 (January 7, 1998): 67–67. doi:10.1093/jnci/90.1.67.

[3] Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, Hauser R, Prins GS, Soto AM, Zoeller RT, Gore AC. 2009. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. Endocr Rev 30:293–342.

[4] World Health Organization, United Nations Environment Program. 2012. State of the science of endocrine disrupting chemicals [Internet]. Available from: http://www.who.int/ceh/publications/endocrine/en/index.html

[5] Goodson WH 3rd, Lowe L, Carpenter DO, Gilbertson M, Manaf Ali A, Lopez de Cerain Salsamendi A. 2015. Assessing the carcinogenic potential of low-dose exposures to chemical mixtures in the environment: the challenge ahead. Carcinogenesis. 2015 Jun;36 Suppl 1:S254-96.

review of the research findings with particular reference to the science published since the 2009 statement.[6]

Biomonitoring has increasingly linked EDCs to the following range of human health problems, many of which result from earlier exposures, particularly during "windows of development" or "vulnerability" that occur from the period *in utero* through adolescence.

These human health effects include:

- Hormonally-linked cancers including breast,[7] prostate,[8] testicular,[9] and thyroid;[10]
- Adverse reproductive outcomes including defects in the structure and function of reproductive organs,[11] and infertility;[12]
- Impaired lactation;[13]
- Immune dysfunction, particularly with prenatal exposure;[14]
- Altered metabolism and obesity;[15]
- Neuro-developmental effects leading to behavioural and intellectual deficits,[16]
- Autoimmune/inflammatory conditions including allergies, autoimmune disease and endometriosis;[17]
- Cardiovascular disease;[18]
- Impaired thyroid function;[19]
- Compromised bone health;[20]

---

[6] EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals.
Gore AC, Chappell VA, Fenton SE, Flaws JA, Nadal A, Prins GS, Toppari J, Zoeller RT.
Endocr Rev. 2015 Dec;36(6):E1-E150.

[7] Gray J, Evans N, Taylor B, Rizzo J, Walker M. State of the Evidence: The Connection Between Breast Cancer and the Environment. International Journal of Occupational and Environmental Health. 2009;15(1):43–78.

[8] Koutros S, Freeman LEB, Lubin JH, Heltshe SL, Andreotti G, Barry KH, et al. Risk of Total and Aggressive Prostate Cancer and Pesticide Use in the Agricultural Health Study. Am. J. Epidemiol. 2013 Jan 1;177(1):59–74.

[9] Vega A, Baptissart M, Caira F, Brugnon F, Lobaccaro J-MA, Volle DH. Epigenetic: a molecular link between testicular cancer and environmental exposures. Front Endocrinol (Lausanne) [Internet]. 2012 Nov 29 [cited 2013 Apr 7];3. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3515880/

[10] Zoeller TR. Environmental chemicals targeting thyroid. Hormones (Athens). 2010 Mar;9(1):28–40.

[11] McLachlan JA, Simpson E, Martin M. Endocrine disrupters and female reproductive health. Best Practice & Research Clinical Endocrinology & Metabolism. 2006 Mar;20(1):63–75.

[12] Woodruff TJ, Carlson A, Schwartz JM, Giudice LC. Proceedings of the Summit on Environmental Challenges to Reproductive Health and Fertility: executive summary. Fertility and Sterility. 2008;89(2):281–300.

[13] Konkel, L. Mother's milk and the environment: Might chemical exposures impair lactation? Environmental Health Perspectives. 2017 January. 125 (1). https://ehp.niehs.nih.gov/125-a17/

[14] Rogers JA, Metz L, Yong VW. Review: Endocrine disrupting chemicals and immune responses: A focus on bisphenol-A and its potential mechanisms. Molecular Immunology. 2013 Apr;53(4):421–30.

[15] Janesick A, Blumberg B. Obesogens, stem cells and the developmental programming of obesity. International Journal of Andrology. 2012;35(3):437–48.

[16] Stewart PW, Lonky E, Reihman J, Pagano J, Gump BB, Darvill T. The Relationship between Prenatal PCB Exposure and Intelligence (IQ) in 9-Year-Old Children. Environ Health Perspect. 2008 Oct;116(10):1416–22.

[17] Kuo C-H, Yang S-N, Kuo P-L, Hung C-H. Immunomodulatory effects of environmental endocrine disrupting chemicals. Kaohsiung J Med Sci. 2012 Jul;28(7):S37–S42.

[18] Belcher SM, Chen Y, Yan S, Wang H-S. Rapid Estrogen Receptor-Mediated Mechanisms Determine the Sexually Dimorphic Sensitivity of Ventricular Myocytes to 17?-Estradiol and the Environmental Endocrine Disruptor Bisphenol A. Endocrinol. 2012 Feb;153(2):712–20.

[19] Fortenberry GZ, Hu H, Turyk M, Barr DB, Meeker JD. Association between urinary 3, 5, 6-trichloro-2-pyridinol, a metabolite of chlorpyrifos and chlorpyrifos-methyl, and serum T4 and TSH in NHANES 1999-2002. Sci Total Environ. 2012 May 1; 424:351–5.

[20] Glynn AW, Michaelsson K, Lind PM, Wolk A, Aune M, Atuma S, Darnerud PO, Mallmin H (2000). Organochlorines and bone mineral density in Swedish men from the general population. Osteoporosis International, 11(12):1036-1042.

- Transgenerational epigenetic alterations of gene expression.[21]

Principles Defining EDCs

In 2012, the Endocrine Society, which represents scientists worldwide involved in research on hormones, noted that, "[h]ormones play direct and essential roles in many aspects of development and in adult physiology. Hormones represent the means by which biological development progresses in an orderly and coordinated manner and by which major physiological processes are coordinated." In other words, there may be no safe level of exposure to endocrine disruptors for some vulnerable populations such as fetuses, newborns, the developing child and adolescent, and those living in areas of high exposure to EDCs.

In its effort to identify principles for evaluation of EDCs, the authors from the Endocrine Society asserted that "[e]nvironmental chemicals that interfere with any aspect of hormone action should be presumed to produce adverse effects." [22] Thus they developed a broader definition of EDCs based on detection of molecular effects in cell cultures rather than whole organisms to overcome these limitations as follows: A hormone disruptive substance is an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action. Of note, there is no reference to "adverse" effect. "Endocrine disruption" should be considered formally and explicitly as a facet of "inherent toxicity," because EDCs have pervasive, irreversible, serious adverse effects on public health.

The Endocrine Society developed a list of the following principles of hormone action that distinguish the characteristics of endocrine disrupting chemicals. These principles should be used in undertaking research and decisions to designate EDCs.

- Hormones act on receptors and, as a consequence of responses within tissues, hormone receptor distribution and abundance represent important characteristics defining hormone action.
- An EDC can interfere with hormone action on the receptor by affecting any number of steps in a biochemical pathway. This includes affecting the amount of hormones produced and interfering with the ability of a hormone to reach the right receptor at the right time and right location.
- Hormone-receptor systems are "tuned" such that very low doses of hormones effectively alter development, and ultimately adult physiology. Accordingly, chemicals can interfere with hormone action in very low doses, producing irreversible effects on development and critical physiological systems.
- Some hormones exert their actions through more than one receptor. Therefore, different elements of the spectrum of effects produced by those hormones are attributable to the different individual receptors.
- Likewise, chemicals that interact with only a subset of the endogenous hormone's receptors will produce a mosaic of effects that does not reproduce an endocrine disease but may be detrimental nonetheless.

[21] Anway MD, Skinner MK. Epigenetic Transgenerational Actions of Endocrine Disruptors. Endocrinology. 2006 Jun 1;147(6):s43–s49.

[22] Zoeller RT, Brown TR, Doan LL, Gore AC, Skakkebaek NE, Soto AM, Woodruff TJ, Vom Saal FS. 2012. Endocrine-disrupting chemicals and public health protection: a statement of principles from The Endocrine Society. Endocrinology. 153(9):4097-110.

- EDC exposures during development can have effects on hormone action that cannot be corrected, leaving permanent adverse impacts on cognitive function and other health parameters.
- People are exposed to multiple EDCs at the same time, and these mixtures can have a greater effect on the hormone system than any single EDC alone.

Canadian Examples of Vulnerable Populations at Risk

There is a growing body of Canadian evidence that our air, water, food, consumer products and general environment are contaminated with EDCs, and that current exposure levels are associated with serious, wide-ranging harms to human health and wildlife. All Canadians face health risks from chronic exposure to EDCs that have been linked to reproductive and developmental effects.[23]

Of particular concern are early life stages, especially in the womb, and women at vulnerable ages who live in highly contaminated locations, or are exposed to high levels of chemicals including EDCs at work.

Populations that are not being protected include some industrial workers, some racial and socioeconomically marginalized groups, and some communities impacted by chemical industries. Some examples illustrating the variety of populations being exposed to chemicals and experiencing effects, some of which may be attributable to EDCs include:

a. Thyroid hormone levels and neurological development are affected by polychlorinated biphenyls (PCBs) and toxic metals in fish eaters in the Great Lakes basin, Quebec, and internationally;[24,25]
b. Women working with a variety of EDCs such as plastics in the automotive industry, bisphenol A (BPA) in the plastic lining of cans in canneries, and agricultural chemicals were found to be more than twice as likely to develop breast cancer.[26]
c. Sarnia and the Aamjiwnaang First Nation are surrounded by the largest concentration of petrochemical industrial facilities in Ontario.[27] Residents are exposed to multiple

[23] Cooper K, Marshall L, Vanderlinden L, Ursitti F. Early Exposures to Hazardous Pollutants/Chemicals and Associations with Chronic Disease - A Scoping Review [Internet]. Canadian Environmental Law Association, Ontario College of Family Physicians, and the Environmental Health Institute of Canada, for the Canadian Partnership for Children's Health and Environment; 2011 Jun. Available from: http://www.healthyenvironmentforkids.ca/resources/EE-andCD-scoping-review

[24] National Research Council (US) Committee on Hormonally Active Agents in the Environment. "Neurological Effects." In *Neurologic Effects*. National Academies Press (US), 1999. https://www.ncbi.nlm.nih.gov/books/NBK230224/.

[25] Abdelouahab N, Mergler D, Takser L, Vanier C, St-Jean M, Baldwin M, et al. Gender differences in the effects of organochlorines, mercury, and lead on thyroid hormone levels in lakeside communities of Quebec (Canada). Environmental Research. 2008 Jul;107(3):380–92.

[26] Brophy JT, Keith MM, Watterson A, Park R, Gilbertson M, Maticka-Tyndale E, et al. Breast cancer risk in relation to occupations with exposure to carcinogens and endocrine disruptors: a Canadian case--control study. Environmental Health. 2012 Nov 19;11(1):87.

DeMatteo R, Keith MM, Brophy JT, Wordsworth A, Watterson AE, Beck M, et al. Chemical Exposures of Women Workers in the Plastics Industry with Particular Reference to Breast Cancer and Reproductive Hazards. NEW SOLUTIONS: A Journal of Environmental and Occupational Health Policy. 2012 Jan 1;22(4):427–48.

Brophy J, Keith M, Watterson A, Gilbertson M, Beck M. Farm work in Ontario and breast cancer risk. Rural Women's Health. University of Toronto Press; 2012. p. 101–21.

environmental toxins, and have experienced elevated incidences of cancer, and reproductive and developmental disorders. The community has experienced a skewed sex ratio, with a significant and substantial decline in the proportion of male live births.[28]

d. Potential for harm exists downstream of tar sands, as exposed water carries pollutants including endocrine disrupting chemicals. For example, an increased rate of biliary cancer has been found in residents of Fort Chipewyan, on the Athabasca River;[29]
e. The Supreme Court of Canada recently upheld a workers' compensation award to three hospital laboratory workers who developed breast cancer, and who were exposed to a variety of chemical reagents and to poor air quality from the hospital incinerator.[30]

Recommendation: Surveillance of Canadians should include focused and increased sampling of at-risk populations, for body burden of environmental toxicants including EDCs and related biological endpoints (biomarkers and disease).

Examples of EDCs and their Management: Canadian Context

Several EDCs have been addressed in recent years under *CEPA (1999)*; the final example below is yet to be addressed as a concern by the government. There are many lessons to be learned from the following examples of delayed and limited actions:

a. ***Persistent flame retardants and perfluorinated compounds used as non-stick and permanent press chemicals*** have been detected in Canadians' blood, fat, breast milk and in marine mammals for decades. They can affect endocrine function and early child development, and contribute to the development of cancers. Many have been banned in other jurisdictions, their efficacy is questionable, and less risky, more sustainable alternative options exist. Some flame retardants that have been banned in Scandinavia since the 1990s are recently subject to phase-out in Canada. Substitutes are in place for some chemicals, while some key applications for flame retardants are not covered by regulations.[31] Needs and efficacy assessments reveal that options exist (e.g. metal instead of plastic casings or less flammable natural fabric substitutions) that require no flame retardants, and are indeed preferable, more durable and more easily recycled.
b. ***Bisphenol A (BPA)*** is an endocrine disruptor that is ubiquitous in food can linings, drink

[27] MacDonald E, Rang S. Exposing Canada's Chemical Valley. An Investigation of Cumulative Air Pollution Emissions in the Sarnia, Ontario Area [Internet]. Ecojustice; 2007. Available from: http://www.ecojustice.ca/publications/reports/report-exposing-canadas-chemical-valley/attachment

[28] Mackenzie CA, Lockridge A, Keith M. Declining Sex Ratio in a First Nation Community. Environ Health Perspect. 2005 Oct; 113(10):1295–8.

[29] Pereira AS, Bhattacharjee S, Martin JW. Characterization of Oil Sands Process-Affected Waters by Liquid Chromatography Orbitrap Mass Spectrometry. Environ. Sci. Technol. 2013 May 21;47(10):5504–13.
Alberta Health Services. March 24, 2014. Cancer incidence in Fort Chipewyan follow-up report http://www.albertahealthservices.ca/assets/healthinfo/poph/hi-poph-surv-cancer-overview-fort-chip-2014-03-24.pdf

[30] Supreme Court of Canada 2016. British Columbia (Workers' Compensation Appeal Tribunal) v. Fraser Health Authority, 2016 SCC 25.

[31] Government of Canada PW and GSC. Canada Gazette – GOVERNMENT NOTICES. Flame retardants screening assessments [Internet]. 2016 [cited 2016 Nov 2]. Available from: http://gazette.gc.ca/rp-pr/p1/2016/2016-10-08/html/notice-avis-eng.php#na1

containers, myriad hard plastic products and thermo-paper such as cash register receipts.[32] The Canadian Health Measures Survey indicates that BPA is found in the blood of virtually every Canadian; and findings are mirrored in Maternal-Infant Research on Environmental Chemicals (MIREC).[33] A Canadian ban of BPA was restricted to polycarbonate baby bottles and has been targeted for prohibition in cosmetic products using the Cosmetic Ingredient Hotlist;[34] however, the growing body of evidence regarding BPA in particular led to unfortunate substitution with substances from the same chemical family in some applications. The substitutes are comparable, if not worse, in terms of endocrine disruption.[35]

c. ***Triclosan*** is an anti-bacterial chemical that exerts many biological effects including endocrine disruption affecting thyroid functions. Triclosan can react in surface water to form toxic dioxins. ***Triclocarban*** is a related phenol with some similar properties and applications. These chlorinated chemicals have some medical applications, but are widely used in cleaning and personal care products, and are added to plastics, clothing and myriad items. Along with metabolites, they contaminate humans including the fetus,[36] water, wildlife, sewage sludge and land as these chlorinated chemicals are not adequately removed in sewage treatment plants.

   The US Food and Drug Administration (FDA) is banning antibacterial personal care products because the commercial sector failed to produce evidence of efficacy – that use reduces rates of infections in the community, as claimed or implied in advertising.[37] Triclosan is not only ubiquitous and does not prevent infections in the community, it may contribute to anti-microbial resistance.[38] At a high level World Health Organization meeting on September 21 2016, antimicrobial stewardship was again recognized to be an urgent priority.[39] Canada's proposal on triclosan focuses on development of pollution prevention plans under CEPA 1999. No regulations on triclosan has been proposed, while triclocarban awaits assessment under CEPA, 1999.

d. ***Atrazine*** is a herbicide commonly used on corn. It is clearly an endocrine disruptor, most famously causing functional feminization of frogs.[40] Its current status is again uncertain, as

---

[32] Government of Canada EC. Environment Canada - Proposed Risk Management Approach for Phenol, 4,4'-(1-methylethylidene) bis (Bisphenol A) [Internet]. 2010 [cited 2013 Feb 4]. Available from: http://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=6FA54372-1

Vandenberg LN. Exposure to bisphenol A in Canada: invoking the precautionary principle. CMAJ. 2011 Aug 9;183(11):1265–70.

[33] Arbuckle, Tye E., Lorelle Weiss, Mandy Fisher, Russ Hauser, Pierre Dumas, René Bérubé, Angelica Neisa, et al. "Maternal and Infant Exposure to Environmental Phenols as Measured in Multiple Biological Matrices." *Science of The Total Environment* 508 (March 1, 2015): 575–84. doi:10.1016/j.scitotenv.2014.10.107.

[34] Notes: Additional management initiatives on BPA include measures such as Codes of Practice, Performance Agreements and Pollution Prevention Plans.

[35] Mesnage, Robin, Alexia Phedonos, Matthew Arno, Sucharitha Balu, J. Christopher Corton, and Michael N Antoniou. "Transcriptome Profiling Reveals Bisphenol A Alternatives Activate Estrogen Receptor Alpha in Human Breast Cancer Cells." *bioRxiv*, 2017. doi:10.1101/112862.

[36] Arbuckle TE, Weiss L, Fisher M, Hauser R, Dumas P, Bérubé R, et al. Maternal and infant exposure to environmental phenols as measured in multiple biological matrices. Sci Total Environ. 2015 Mar 1;508:575–84.

[37] US Food and Drug Administration. Press Announcements - FDA issues final rule on safety and effectiveness of antibacterial soaps [Internet]. [cited 2016 Sep 28]. Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm517478.htm

[38] Carey DE, McNamara PJ. The impact of triclosan on the spread of antibiotic resistance in the environment. Front Microbiol [Internet]. 2015 Jan 15 [cited 2016 Sep 28];5. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4295542/

[39] WHO | Antimicrobial resistance [Internet]. WHO. [cited 2016 Sep 28]. Available from: http://www.who.int/antimicrobial-resistance/en/

[40] Hayes, Tyrone B., Vicky Khoury, Anne Narayan, Mariam Nazir, Andrew Park, Travis Brown, Lillian Adame, et al. "Atrazine

on March 13, 2017, the PMRA issued a decision with the note that endocrine disruption was accommodated with an additional uncertainty factor,[41] and then the same day a re-initiation of the review in light of additional data.[42]

e. ***Organic ultraviolet (UV) filters in sunscreens*** is a group of EDCs yet to be addressed. Many chemicals with multiple ring structures absorb UV frequencies, and they are generally used in combinations for broad spectrum coverage. These chemical structures have a high potential to be endocrine disruptors; for example, the sunscreen ingredient 3-benzylidene camphor was banned in the European Union [43] due to insufficient margin of safety, noting estrogenic, anti-estrogenic and anti-androgenic activities at levels below the no-adverse-effect level that had been used to determine the margin of safety.[44] This is typical with non-monotonic dose responses. Recent screening identified that 13 of 29 UV filters in use mimicked the hormone progesterone, and impaired sperm function at biologically relevant concentrations.[45] In other research, levels in surface water interfered with endocrine function, stress biomarkers and development of midges,[46] and mixtures of UV filters acted additively.[47] With hundreds if not thousands of possible chemicals that absorb UV light, it is an intractable problem to examine endocrine effects of various chemicals alone and in mixtures. Fortunately, it is unnecessary to use (and to assess) numerous possible mixtures of UV absorbing organic chemicals because zinc and titanium oxides, also in sunscreens, block UV light across the entire spectrum. Among these mineral sunscreens, larger particles would appear to be safer as they result in lower levels of systemic absorption and, although evidence is mixed, the risk of penetration of nanoparticles through the skin is not encountered with larger particles.[48] Potentially harmful photocatalytic reactions are lower with larger particles, with zinc compared with titanium oxides, and recently with particle coatings.

Induces Complete Feminization and Chemical Castration in Male African Clawed Frogs (Xenopus Laevis)." *Proceedings of the National Academy of Sciences* 107, no. 10 (March 9, 2010): 4612–17. doi:10.1073/pnas.0909519107.

[41] Government of Canada, Health Canada. "Re-Evaluation Note REV2017-09, Special Review Decision: Atrazine, March 29, 2017) [Health Canada, Pest Management Regulatory Agency]." Decision, March 24, 2017. http://www.hc-sc.gc.ca/cps-spc/pubs/pest/_decisions/rev2017-09/index-eng.php.

[42] Government of Canada, Health Canada. "Re-Evaluation Note REV2017-10, Special Review Initiation: Atrazine (March 31, 2017) [Health Canada, Pest Management Regulatory Agency]." Decision. Accessed April 4, 2017. http://www.hc-sc.gc.ca/cps-spc/pubs/pest/_decisions/rev2017-10/index-eng.php.

[43] EUR-Lex. COMMISSION REGULATION (EU) 2015/1298 of 28 July 2015 amending Annexes II and VI to Regulation (EC) No 1223/2009 of the European Parliament and of the Council on cosmetic products [Internet]. 2015 [cited 2016 Sep 30]. Available from: http://eur-lex.europa.eu/legal- content/EN/TXT/?uri=uriserv%3AOJ.L_.2015.199.01.0022.01.ENG

[44] Scientific Committee on Consumer Safety. Opinion of the Scientific Committee on Consumer Safety on 3-Benzylidene camphor [Internet]. European Commission; 2013. Available from: http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_134.pdf

[45] Anders Rehfeld, Dorte Louise Egeberg, Steen Dissing, Niels Erik Skakkebaek. Organic Ultraviolet Filters Mimic the Action of Progesterone on Human Sperm and Interfere with Sperm Functions. In: Endocrine Disrupting Chemicals and Gene Regulation and Development (posters) [Internet]. Endocrine Society; 2016 [cited 2016 Oct 7]. p. FRI-121-FRI-121. (Meeting Abstracts). Available from: http://press.endocrine.org/doi/abs/10.1210/endo-meetings.2016.ED.1.FRI-121

[46] Ozáez I, Morcillo G, Martínez-Guitarte J-L. Ultraviolet filters differentially impact the expression of key endocrine and stress genes in embryos and larvae of Chironomus riparius. Sci Total Environ. 2016 Jul 1;557–558:240–7.

[47] Ozáez I, Morcillo G, Martínez-Guitarte J-L. The effects of binary UV filter mixtures on the midge Chironomus riparius. Sci Total Environ. 2016 Jun 15;556:154–62.

[48] Australian Government Department of Health Therapeutic Goods Administration. Literature review on the safety of titanium dioxide and zinc oxide nanoparticles in sunscreens [Internet]. Therapeutic Goods Administration (TGA). 2013 [cited 2016 Sep 29]. Available from: https://www.tga.gov.au/literature-review-safety-titanium-dioxide-and-zinc-oxide-nanoparticles-sunscreens

These examples illustrate that Canada's management approach focuses on establishing adverse effects for substances affecting endocrine systems, and in the process opens the door to a large number of substitutes that may be just as harmful. Furthermore, current management measures on substances linked to endocrine disruption are targeted at "control" rather than elimination or preventative measures.

Economic Costs

There has been a growing appreciation of the need in medicine for broad "translational research" to integrate and communicate evidence from a variety of sources, including economics, not only to improve clinical practice but also to improve public health.[49] The increasing integration of scientific evidence has documented that EDCs contribute substantially to disease and disability with associated economic costs. Increasing trends in numerous disease categories, such as breast cancer, testicular cancer, obesity, hypospadias, cryptorchidism, declining sperm count and quality, diabetes, autism prevalence, Attention Deficit Hyperactivity Disorder, loss of IQ and intellectual capacity, asthma, immune-related and autoimmune disease, and both male and female reproductive disorders and infertility, have been measured in the US, Canada, Europe, Scandinavia, and Asia.

In an effort to quantify a range of health and economic costs that can reasonably be attributed to EDC exposures in the European Union (EU), the United States, and Scandinavia, expert panels integrated scientific evidence, including mechanistic and experimental toxicology, and epidemiology in a weight-of-evidence framework. Consensus by these panels on probable causation in the EU produced a median cost of €157 billion (or $209 billion US), corresponding to 1.23% of EU gross domestic product annually.[50] Notably, using the lowest end of the probability range of causation produced a median range of €109 billion that differed modestly from base case probable causation.

In a 2016 analysis restricted to effects of two EDCs on female reproductive disorders (diphenyldichloroethene-attributable fibroids, and phthalate-attributable endometriosis), across the EU, attributable cases were estimated to be 56 700 and 145 000 women, respectively, with total combined economic and health care costs estimated to reach €163 million and €1.25 billion.[51]

From a similar expert panel using a weight-of evidence methodology, it was found that the disease costs of EDCs were much higher in the USA than in Europe ($340 billion [2·33% of GDP] *vs* $217 billion [1·28%]). The difference was driven mainly by loss of intelligence quotient (IQ) points and by intellectual disability.[52]

---

[49] Ogilvie D, Craig P, Griffin S, Macintyre S, Wareham NJ. 2009. A translational framework for public health research. BMC Public Health. 2009 Apr 28;9:116.

[50] Leonardo Trasande R. Thomas Zoeller Ulla Hass Andreas Kortenkamp Philippe Grandjean John Peterson Myers Joseph DiGangi Martine Bellanger Russ Hauser Juliette Legler Niels E. Skakkebaek Jerrold J. Heindel. 2015. Estimating Burden and Disease Costs of Exposure to Endocrine-Disrupting Chemicals in the European Union
Journal of Clinical Endocrinology and Metabolism. 100(4): 1245-1255.

[51] Hunt PA, Sathyanarayana S, Fowler PA, Trasande L. Female Reproductive Disorders, Diseases, and Costs of Exposure to Endocrine Disrupting Chemicals in the European Union. J Clin Endocrinol Metab. 2016. doi:10.1210/jc.2015-2873.
http://www.endocrinologyadvisor.com/androgen-and-reproductive-disorders/edc-associated-health-care-costs-up-in-europe/article/485310/

[52] Teresa M Attina, Russ Hauser, Sheela Sathyanarayana, Patricia a Hunt, Jean-Pierre Bourguignon, John Peterson Myers, Joseph Digangi, R Thomas Zoeller, Leonardo Trasande. 2016. Exposure to endocrine-disrupting chemicals in the USA: a population-

Other studies in Scandinavia showed annual costs of effects on human male reproduction, at a middle estimate of etiological fraction, of €77 million ($102 million US @1.33). The range of estimates was €7.7 million to €154 million EUR annually.[53]

It was concluded that EDC exposures in the EU, the US and Scandinavia, are likely to contribute substantially to disease and dysfunction across the life course, with costs in the hundreds of billions of Euros and dollars per year. These estimates represent only those EDCs with sufficient epidemiologic studies, and those with the highest discerned probability of causation.

There is a priority need to incorporate evidence on endocrine disruption into translational medical research to improve population health. This evidence should include linkage of evidence from different levels of biological organization, not only clinical and epidemiological evidence of endocrine action and associated etiologies but also evidence related to genes and macromolecules, cells, circuits, and signalling pathways.

Recommendation: The government should conduct economic cost analyses on EDCs in Canada following the efforts in the EU and the US.

Recommendation: The public health costs for EDCs should be reflected in the overall regulatory analyses (including in CEPA, PCPA and CEAA) in Canada including in the process of identification, assessment and management of EDCs.

Significant International work on EDCs

World Health Organization

In 2012, the United Nations Environment Program and World Health Organization (WHO) published an extensive review of anthropogenic chemicals that disrupt the endocrine system, and a summary for decision-makers. They concluded that:

> Worldwide, there has been a failure to adequately address the underlying environmental causes of trends in endocrine diseases and disorders.
>
> Health-care systems do not have mechanisms in place to address the contribution of environmental risk factors to endocrine disorders. The benefits that can be reaped by adopting primary preventive measures for dealing with these diseases and disorders have remained largely unrealized.[54]

WHO goes further to states that:

based disease burden and cost analysis. The Lancet Diabetes & Endocrinology, Volume 4, No. 12, p 996–1003, December 2016 DOI: 10.1016/S2213-8587(16)30275-3. http://www.thelancet.com/journals/landia/article/PIIS2213-8587(16)30275-3/abstract

[53] Ing-Marie Olsson (24 November 2014). "The Cost of Inaction: A Socioeconomic analysis of costs linked to effects of endocrine disrupting substances on male reproductive health". TemaNord 2014:557. Nordic Council of Ministers. http://dx.doi.org/10.6027/TN2014-557 ISSN 0908-6692.

[54] World Health Organization. 2012. State of the Science of Endocrine Disrupting Chemicals 2012: Summary for Decision-Makers. http://apps.who.int/iris/bitstream/10665/78102/1/WHO_HSE_PHE_IHE_2013.1_eng.pdf?ua=1

> EDCs have the capacity to interfere with tissue and organ development and function, and therefore they may alter susceptibility to different types of disease throughout life. This is a global threat that needs to be resolved.[55]

European Union

The European Parliament has passed a series of regulations concerning commercial chemicals called The Registration, Evaluation, Authorization and Restriction of Chemicals.[56] Further, there was a legal requirement for the European Commission to set criteria for the identification of endocrine disrupting chemicals by December 2013. The Commission failed to meets its deadline in 2013 prompting a legal challenge by Sweden. The European Union General Court ruled in Sweden's favour in December.[57,58]

In 2013, amidst the contestation, an international group of scientists, convened by the European Commission in Brussels, produced the Berlaymont Declaration.[59] They stated that they "are concerned that the prevalence of endocrine-related diseases continues to increase in the European Union and globally [and that t]his is not well recognised by the public and largely ignored by policy makers." A consensus on the scientific principles for identifying endocrine disrupting chemicals was only reached in 2016.[60]

Organization for Economic Cooperation and Development (OECD)

The Organization for Economic Cooperation and Development (OECD) has been advancing development of a conceptual framework, screening and testing methods, and guidelines for EDCs.[61] Canada has been actively engaged in the OECD scientific processes and chemicals methods development and validation.[62,63]

---

[55] World Health Organization. 2012. State of the Science of Endocrine Disrupting Chemicals 2012: Summary for Decision-Makers. http://apps.who.int/iris/bitstream/10665/78102/1/WHO_HSE_PHE_IHE_2013.1_eng.pdf?ua=1

[56] Regulation (EC) 1907/2006 (Registration, Evaluation, Authorisation and Restriction of Chemicals; Regulation (EC) 1223/2009 Cosmetics; (Directive 2000/60/EC) Water Framework Directive; (EC) 1107/2009 Regulation Plant protection products; (EU) No 528/2012 Biocidal products.

[57] Åke Bergman, Anna-Maria Andersson, Georg Becher, Martin van den Berg, Bruce Blumberg, Poul Bjerregaard, Carl-Gustaf Bornehag, Riana Bornman, Ingvar Brandt, Jayne V Brian, Stephanie C Casey, Paul A Fowler, Heloise Frouin, Linda C Giudice, Taisen Iguchi, Ulla Hass, Susan Jobling, Anders Juul, Karen A Kidd, Andreas Kortenkamp, Monica Lind, Olwenn V Martin, Derek Muir, Roseline Ochieng, Nicolas Olea, Leif Norrgren, Erik Ropstad, Peter S Ross, Christina Rudén, Martin Scheringer, Niels Erik Skakkebaek, Olle Söder, Carlos Sonnenschein, Ana Soto, Shanna Swan, Jorma Toppari, Charles R Tyler, Laura N Vandenberg, Anne Marie Vinggaard, Karin Wiberg and R Thomas Zoeller. 2013. Science and policy on endocrine disrupters must not be mixed: a reply to a "common sense" intervention by toxicology journal editors. Environmental Health. 12:69. http://ehjournal.biomedcentral.com/articles/10.1186/1476-069X-12-69

[58] European Commission. 2016. Defining criteria for identifying endocrine disruptors in the context of the implementation of the plant protection products regulation and biocidal products regulation. Commission Staff Working Document Impact Assessment. Brussels SWD(2016) 211 final.

[59] The 2013 Berlaymont Declaration on Endocrine Disrupters.
http://www.brunel.ac.uk/__data/assets/pdf_file/0005/300200/The_Berlaymont_Declaration_on_Endocrine_Disrupters.pdf

[60] Roland Solecki, Andreas Kortenkamp, Åke Bergman, Ibrahim Chahoud, Gisela H. Degen, Daniel Dietrich et al. 2016. Scientific principles for the identification of endocrine-disrupting chemicals: a consensus statement Arch Toxicol DOI 10.1007/s00204-016-1866-9

[61] OECD Work Related to Endocrine Disruptors.
http://www.oecd.org/env/ehs/testing/oecdworkrelatedtoendocrinedisrupters.htm

[62] Organization for Economic Cooperation and Development. Series on Testing and Assessment: Testing for Endocrine Disrupters. Accessed April 4, 2017.
http://www.oecd.org/chemicalsafety/testing/seriesontestingandassessmenttestingforendocrinedisrupters.htm.

[63] Draft Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption. April 2012.

Strategic Approach of International Chemicals Management (SAICM)

The Strategic Approach of International Chemicals Management (SAICM), coordinated under the United Nations Environment Program, is a policy framework established in 2002 with an overall objective to achieve the sound management of chemicals throughout their life cycle so that by the year 2020, chemicals are produced and used in ways that minimize significant adverse impacts on the environment and human health and chemical safety around the world. Along with over 100 countries, Canada is an active participant in SAICM.

As part of its implementation of SAICM, participating countries and stakeholders identified several key emerging policy issues including on endocrine disrupting substances. In October 2012 at the third meeting of the International Conference on Chemicals Management (ICCM), a resolution on EDCs was achieved. The participating organizations and stakeholders under SAICM:

> Decides to implement cooperative actions on endocrine-disrupting chemicals with the overall objective of increasing awareness and understanding among policymakers and other stakeholders;[64]

The work on EDCs was reaffirmed at the forth meeting of ICCM by "Recognizing that continued actions on endocrine-disrupting chemicals by all stakeholders will be needed in order to attain the objectives of the Strategic Approach." Discussions under the ICCM and SAICM framework on EDCs continues, with some UN regions such as Latin America developing resolutions that aim to support the implementation of SAICM and further investigate the impacts of EDCs on human health, consideration of vulnerable populations, particularly women and children, analysis of policy and regulations promoting the reductions in EDCs and best practices in substitution.[65,66]

Limitations of Risk based approach to Identify, Assess and Manage EDCs

A number of limitations within the risk based approach for chemicals assessment and management that are applied by many countries including Canada that prevent an effective approach to identify, assess and manage many chemicals, particularly EDCs.

With Canada's international involvement, and the numerous shortcomings detailed above, it is time to act upon lessons learned, to focus and to commit to fully utilize the products of this work. These actions will be most evident in the modernization of assessment and management applied to chemicals and pesticide products in Canada.

Regulatory regimes for chemicals under CEPA and for pesticides under the *Pest Control Products Act* (PCPA) rely on traditional toxicological testing, assessment and risk management.

---

[64] United Nations Environment Programme and World Health Organization. International Conference on Chemicals Management: Third session, Nairobi, 17–21 September 2012. Document SAICM/ICCM.3/24 - Emerging policy issues.

[65] United Nations Environment Programme and World Health Organization. International Conference on Chemicals Management: Fourth session, Geneva, 28 September–2 October 2015.
Document: SAICM/ICCM.4/15 - Report of the International Conference on Chemicals Management on the work of its fourth session

[66] See: United Nations Environment Programme and World Health Organization. Fourth Latin American and Caribbean Regional Meeting on the Strategic Approach to International Chemicals Management
Mexico City, Mexico, 22 August 2013. Document: SAICM/RM/LAC.4/11 - ANNEX II: Summary of the workshop on Endocrine Disrupting Chemicals (EDCs)

This framework is not amenable to reliably detect and respond to scientific evidence related to the long-term health effects of exposures to EDCs. Special techniques and decision-making framework are needed for EDCs because:

a. Low dose, environmentally relevant exposures can cause harms not identified in high dose experiments;
b. The timing and levels of exposure are critically important. Early life exposures, even at low doses, can have life-long consequences that may even extend to the following generations;
c. "Endocrine disruption" should be considered formally and explicitly as a facet of "inherent toxicity," because EDCs have pervasive adverse effects on public health. When substances are grouped for risk assessment because of their similar mode of action (usually based on structural similarities), unmeasured different endocrine effects may not be accounted for (e.g. a focus on androgen activity may miss estrogen mimicry by a similar but different chemical), so precautionary and risk management measures must account for the possibility that similar chemicals may have different endocrine effects.
d. There may be no safe level of exposure to endocrine disruptors for some vulnerable populations such as fetuses, newborns, the developing child and adolescent, and those living in areas of high exposure to EDCs. Flagging of chemicals using rapid screening approaches may be of great utility, but rapid screening should not be used to "close the book" on endocrine disruption or reduce other requirements for testing.
e. Multiple exposures over time to various chemicals (e.g. daily exposures in the workplace in addition to exposures from food, water, etc. at other times) may cause greater cumulative or synergistic effects, particularly for EDCs[67] Practices of determination of "margins of exposure" for various populations including children and women, and among populations with high level and other deleterious exposures (e.g. workers, and members of communities in polluted areas) require re-evaluation;
f. Regulatory restriction of exposure to a chemical occurs after demonstration not only of an effect, but also substantial harm demonstrating that the effect is "adverse." Significant effects in animal test systems are commonly dismissed as not sufficiently adverse to engender actions, although implications for developing humans may be life-changing. Chemical assessment assumes that observations of "no adverse effect" when a chemical is tested at levels above environmental levels (possibly 100 to 3000-fold or higher concentrations) means that the chemical is "safe" at lower concentrations. Thus, environmentally relevant testing may not occur, despite knowledge that EDCs can cause effects at low doses or concentrations, that do not manifest at higher levels. Experimental dose-response relationships, must include environmentally relevant exposures below current standards such as for air, water, soil, food and products, "daily intake" values and occupational exposure limits;
g. Disincentives to test at lower doses testing include the above, as well as the fact that should any (adverse) effect be observed, it will reduce potential for the required extrapolation factor (sometimes called "uncertainty" or "safety" factor) or margin of exposure necessary to permit registration and use of the chemical; and
h. Evidence of "adverse effect" required for EDCs. Chemicals with biological effects that have been established using molecular testing systems continue to be marketed because the

[67] Committee on Toxicity Testing and Assessment of Environmental Agents, National Research Council. Toxicity Testing in the 21st Century: A Vision and a Strategy. Washington, D.C.: The National Academies Press; 2007.

known effects have been argued not to be harmful. Harms may be difficult to detect due to complexities of exposures, mechanisms and subtle developmental and delayed effects. For these reasons, the Endocrine Society and others insist that endocrine disruption demonstrated *in vitro* should be considered a marker of toxicity of a chemical (similar to persistence, bioaccumulation potential and carcinogenicity).

i. Other challenges for the identification, assessment and management of EDCs exist. There is potential for large-scale approaches to "tease out" and support addressing EDCs. Strengthened, increased access to data and funding for independent research, including infrastructure for environmental health information to assemble environmental and health data, to facilitate analysis and rapid answering of research questions using existing scientific and medical information for public and occupational health.

Recommendation: The processes of hazard identification and risk assessment should be revisited, with endocrine disruption considered to be an inherently toxic effect.

Systematic Scientific Review for Chemicals Assessment and Management

Chemical assessments would benefit from systematic scientific review approaches, for greater transparency and scientific auditing. Currently the claims of "weight of evidence" decision-making are backed up with neither the evidence (research included and relevant data), the expert grading of the contributory research, nor the detailed weighing to reach decisions.

Systematic, transparent scientific methodology used to carry out chemical assessment, with full public access to relevant documentation, is necessary for informed consultations. This is essential for accountability in the complexities of weight of evidence determinations. Transparency is also essential when weighing severe, irreversible outcomes such as developmental toxicity and cancer, as "acceptable risk" may have different interpretations across Canadian society. Although industry-supplied data for pesticides may be viewed in the Reading Room, this is only available after the decision has been finalized (not during consultation) and there is no independent, transparent, public recourse following viewing of the data (objections are dealt with in-house and are not public).

Systematic Review is a highly prescribed methodology in clinical medicine, that has been demonstrated to produce more reliable, credible and actionable conclusions. Systematic Review is now formulated for application to environmental health questions, to provide the same benefits to public health.[68].

Systematic Review methodology is used to address specific key questions with all available evidence, and the process entails:

- systematic searching for all relevant scientific research;
- screening for relevance and streaming per key questions;
- data extraction, compilation, analyses and meta-analyses;

[68] Rooney, A. A., Boyles, A. L., Wolfe, M. S., Bucher, J. R. & Thayer, K. A. Systematic Review and Evidence Integration for Literature-Based Environmental Health Science Assessments. Environ. Health Perspect. 122, 711–718 (2014)]

- grading of studies according to study quality and indicators of reliability (e.g. size of study, exposure ascertainment, controls, quality of reporting, funding sources, etc.);
- application of the grading to the extracted evidence (sometimes termed "weighing"); and
- drawing of conclusions regarding key questions.

Systematic searches may identify thousands of peer-reviewed references, and a review may include data from more than a hundred studies for each key question. A strong systematic review would cover the entire relevant timeframe. An updated review should only be carried out to build upon a previous, demonstrably rigorous systematic review – a rare entity in environmental health. Systematic Review is generally supported by software, so that entire searches, lists of included and excluded studies (with reasons for exclusion), extracted data, etc. are all readily exported and shared.

Canada's commitment on EDCs under the *Canadian Environmental Protection Act, 1999*

Section 44(4) of the Canadian Environmental Protection Act, 1999 (CEPA1999) states that the Ministers:

> shall conduct research or studies relating to hormone disrupting substances, methods related to their detection, methods to determine their actual or likely short-term or long-term effect on the environment and human health, and preventive, control and abatement measures to deal with those substances to protect the environment and human health.[69]

Section 43 of the Act defines hormone disrupting substance as:

> … a substance having the ability to disrupt the synthesis, secretion, transport, binding, action or elimination of natural hormones in an organism, or its progeny, that are responsible for the maintenance of homeostasis, reproduction, development or behaviour of the organism. (substance hormonoperturbante)[70]

Canada's approach to chemical assessment under CEPA and the *Pest Control Products Act* is to ensure "acceptable risks" for any life stage (there are misconceptions that regulators ensure "safety" (i.e. freedom from danger, or hazard or injury.) The distinction between hazard and risk, and the regulatory approach to manage to the point of "acceptable risk" versus elimination of hazard is documented in the government response to a petition to the Office of the Auditor General on endocrine disrupting substances by the Canadian Environmental Law Association and Ecojustice in July 2012.[71] The response to the petition by the government indicated that:

> The assessment process takes into account the quality and quantity of available scientific evidence, the adequacy and limitations of studies, critical toxicological endpoints and exposure routes, sources and pathways, as well as assessments

[69] Canadian Environmental Protection Act, 1999, S.C. 1999, c. 33
[70] Canadian Environmental Protection Act, 1999, S.C. 1999, c. 33
[71] Ecojustice, Canadian Environmental Law Association. "Federal Research on Hormone Disrupting Substances as Required under the Canadian Environmental Protection Act, 1999," December 14, 2012. http://www.oag-bvg.gc.ca/internet/English/pet_340_e_37607.html

> and conclusions of other jurisdictions. This approach considers multiple lines of evidence, including endocrine-related research available at the time of the assessment, in determining whether a substance may pose a risk…..Endocrine disruption is one of many potential mechanisms by which adverse effects may be induced.[72]

In response to the definition of endocrine disrupting substances, the government response indicated that

> A substance is considered to be a disruptor when the function(s) of the endocrine system is altered beyond the range of normal variability consequently causing adverse biological effects. Therefore, hormone disruption is but one potential mechanism by which adverse effects may be induced. …***A key consideration is that, although a substance has the potential to interact with a particular component of the endocrine system, it should not be interpreted as evidence that the substance causes adverse health/ecological effects.***[73] (emphasis added)

Since CEPA was revised in 1999, there has been extensive research, monitoring and evaluation of EDCs. Canada has also contributed to these discussions including in June 2015, where Canada's Mission to the European Union participated in an EU conference held in Brussels on the criteria for identification of endocrine disruptors and the related impacts.[74] In that conference Canada took the policy position that in the assessment of the "safety" of pesticides, it takes a "risk-based rather than hazard-based approach." [75]

Canada's position that endocrine disruptors may induce effects that are not necessarily adverse is problematic, as early life exposure to endocrine disruptors may have delayed adverse effects that are not necessarily endpoints in traditional toxicological testing. The approach is based on the an assumption that "safe" levels based on "thresholds" can be calculated, and that EDCs can be managed by maintaining exposures below these levels,[76] but endocrine disruptors' non-monotonic dose response invalidates assumptions of threshold effects. In practice, traditional toxicology does not test for effects below the calculated threshold and therefore undetected and irreversible effects may occur at lower levels. As well, the application of extrapolation or uncertainty factors has the effect of dissuading industries from toxicological testing at environmentally relevant levels, as any adverse effects would preclude access to the Canadian market.

---

[72] Response Federal research on hormone disrupting substances as required under the Canadian Environmental Protection Act, 1999 (Petition 340). http://www.oag-bvg.gc.ca/internet/English/pet_340_e_37607.html

[73] Response Federal research on hormone disrupting substances as required under the Canadian Environmental Protection Act, 1999 (Petition 340). http://www.oag-bvg.gc.ca/internet/English/pet_340_e_37607.html

[74] EU Conference "Endocrine disruptors: criteria for identification and related impacts" Brussels, 01 June 2015 http://ec.europa.eu/health/endocrine_disruptors/events/ev_20150416_en

[75] Consultation on Regulations Identifying Criteria for Endocrine Disruptors: Potential Trade Impacts: Canada. https://ec.europa.eu/health/sites/health/files/endocrine_disruptors/docs/ev_20150601_co04_03_en.pdf Consultation on Regulations Identifying Criteria for Endocrine Disruptors: Potential Trade Impacts: Canada

[76] Consultation on Regulations Identifying Criteria for Endocrine Disruptors: Potential Trade Impacts: Canada https://ec.europa.eu/health/sites/health/files/endocrine_disruptors/docs/ev_20150601_co04_03_en.pdf Consultation on Regulations Identifying Criteria for Endocrine Disruptors: Potential Trade Impacts: Canada

Recommendation: The Parliamentary Standing Committee on Environment and Sustainable Development should recommend to the Parliament of Canada to review the definition of EDC in CEPA, and to include principles to identify endocrine disrupting properties of chemicals be incorporated into the proposed revisions to CEPA.

Opportunities for Policy and Law Reform in Canada: A Roadmap for Systematic Scientific Assessment and Management of EDCs

Over the course of a generation, scientific evidence initially in wildlife has solidified that many chemicals also affect the human endocrine system, at levels currently experienced in our air, water, food, homes, workplaces and public spaces. Effects seen at high doses are unrelated to effects at low doses, and numerous common EDCs have persisted in commerce as well as the environment under the current regulatory systems for chemicals in commerce, including pesticides.

Recognizing the importance of disease prevention and the impact of environmental and occupational exposures to EDCs on human health, we urge the Canadian government to develop hazard assessment procedures and policies that are more responsive to the disproportionate exposures and burdens, particularly for at-risk populations, and that function effectively to prevent toxic exposures in the environment, workplaces and consumer goods.

We, the undersigned, call upon the government to undertake key steps to address EDCs in Canada:

STEP 1: Identification and evaluation of endocrine disruption as an adverse effect

Develop chemical testing and assessment criteria with greater emphasis on hazard associated with endocrine disruption, rather than a regulatory focus solely on presumed monotonic potency and potential exposure:

a. Screen chemicals based on primary indicators of harm using molecular biological techniques to identify hormone disruption or epigenetic changes, in order to recognize chemicals that might contribute to risk of illness, rather than relying only on traditional disease endpoints (e.g. tumours);[77]

b. Screen pharmacological properties (entry, absorption, metabolism and elimination) of both new substances and those already in circulation. These include nanotechnologies and biological technologies;

c. Mandate assessments that consider timing of exposure, cumulative or synergistic exposures, high- and low-dose effects, and underlying susceptibility factors (age, occupation, race, socio-economic status, gender, and other social determinants of health).

d. Review EDC potential of existing and new substances (including nanomaterials) in the Canadian market. This would be similar to categorization requirements in CEPA 1999 focused

[77] Committee on Toxicity Testing and Assessment of Environmental Agents, National Research Council. Toxicity Testing in the 21st Century: A Vision and a Strategy. Washington, D.C.: The National Academies Press; 2007.

on persistence, bioaccumulation and inherent toxicity and potential exposure of substances under the Domestic Substances List.

Step 2: Precautionary Principle, Pollution Prevention and Elimination goals should guide management of EDCs

Apply the precautionary principle and the substitution principle in all government decisions related to chemical assessment, management and regulation, especially with respect to EDCs:

a. Identify potential EDCs in Canada;

b. Identify populations at heightened risk of exposure to EDCs;

c. Require all ingredient and contaminant identification for materials and goods;

d. Take protective actions by requiring inherently safer substitutes (including consideration of the null alternative), and elimination of potentially hazardous ED substances. These actions should be undertaken when there is an association and plausible link with harm, rather than awaiting the extensive human disease and associated research necessary to achieve (if ever) absolute proof of harm;

e. Establish a registration program (EDC inventory) process for chemicals known or suspected of being EDCs; and

f. Include explicit language to identify endocrine disrupting chemicals through hazard assessment and their regulation through virtual elimination.

g. Collect and report on EDC levels according to existing inventories including the National Pollutants Release Inventory and Environmental Emergency Plans.

Step 3: Adopt Informed Substitution to achieve Prevention and Elimination of EDCs

Adopt a regulatory focus that shifts from chemical-by-chemical management, to comprehensive pollution prevention strategies by allocating significant resources to the elimination or significant reduction of exposures to toxic chemicals via:

a. Assess need and best practices to achieve identified ends;

b. Green chemistry research and development;[78]

c. Best innovative practices, alternatives assessment and informed chemical substitution;

d. Toxic use reduction programs;

e. Primary pollution prevention in all endeavours subject to federal assessment and oversight (e.g. transporting upgraded petrochemical products rather than dilbit);

[78] Schug TT, Abagyan R, Blumberg B, Collins TJ, Crews D, DeFur PL, et al. Designing endocrine disruption out of the next generation of chemicals. Green Chem. 2012 Dec 19;15(1):181–98

f. Prohibited substance regulation, remediation and enforcement; and

g. Improving federal-provincial jurisdictional arrangements for regulatory control of chemicals.

Step 4: Achieving Transparency, Accountability and Effective Public Engagement on EDCs Identification, Assessment and Management (Systematic Scientific Assessment)

Increase scientific rigour, validity and transparency, and public engagement and participation (particularly for populations at elevated risks) in health and safety assessment, and chemicals management processes by all levels of government and academia:

a. Employing Systematic Scientific Review processes and reporting, to improve rigour of chemical assessments, and to increase transparency and accessibility of information on chemical substances and government actions;

b. Provide information and meaningful public engagement on the significant parameters of decision-making;

c. Provide financial and technical support for groups to engage effectively to address chemical hazard primary prevention as well as risk management;

d. Address elevated risk associated with vulnerable populations (e.g. vulnerabilities due to life stage, socio-economic situation, occupational exposure, morbidities) in chemical assessment and management including but not restricted to CEPA 1999 and *Pest Control Products Act*;

e. Apply the precautionary principle and substitution principle within all phases of the assessment and management of EDCs (including under CEPA and Pest Control Products Act); and

f. Include high-risk groups and representatives in advisory and technical roles related to assessment and management of chemicals.

Recommendation: The Parliamentary Standing Committee on Environment and Sustainable Development, in its review of the CEPA 1999, should review the government's approach to EDCs and propose amendments to advance the elements of the Roadmap for Action on EDCs in Canada.

In the coming weeks, we expect to further the above Roadmap by developing and proposing amendments to CEPA to attempt to facilitate government action on EDCs.

Respectfully submitted by:

Fe de Leon MPH
Researcher and Paralegal
Canadian Environmental Law Association
Toronto, ON
Email: deleonf@cela.ca;
Telephone: 416-960-2284 ext 7223

Meg Sears PhD
Chair
Prevent Cancer Now
Dunrobin, ON
Email: meg@preventcancernow.ca;
Telephone: 613-832-2806; Cell: 613-297-6042

James Brophy PhD
Department of Sociology, University of Windsor
Emeryville, ON
Email: jimbrophy@yahoo.com;
Telephone: 519-735-2944

Tom Muir,
(Retired economist, Environment Canada),
Independent Researcher
Burlington, ON
Email: betty.muir@sympatico.ca

Margaret Keith PhD,
Department of Sociology, University of Windsor
Emeryville, ON
Email: margkeith@yahoo.com;
Telephone: 519-735-2944

Anne Rochon Ford
National Network on Environments and Women's Health
Toronto, ON
Email: annerf@sympatico.ca;
Telephone: 416-712-9459

Michael Gilbertson PhD
The Halifax Project
Guelph, ON
Email: michael.gilbertson23@gmail.com