A CASE STUDY OF CANADIAN REGULATION OF BPA: INSIGHT INTO THE SCIENCE

JAYE ELLIS, ARTURO PAPALUCA, MYRIAM HAMTIAUX, BARBARA F. HALES, AND BERNARD ROBAIRE*

I. INTRODUCTION

In 2010, Canada became the first jurisdiction in the world to prohibit Bisphenol A (BPA) in a range of products including infant feeding bottles.[1] Since that time, the European Union has moved to ban BPA in other materials that come into contact with food and are intended for infants and young children.[2] These jurisdictional differences reflect the ongoing development of scientific knowledge, as well as the controversies that continue to rage within the scientific community, industry, regulatory agencies, and civil society regarding BPA and other substances that act on the endocrine system. These substances mimic naturally produced hormones, and in many cases have been associated with negative health outcomes.[3] Given the great

* Jaye Ellis is Associate Professor at the Faculty of Law, McGill University. Arturo Papaluca is a Study Director in Research and Development at Charles River Pharmaceuticals. Myriam Hamtiaux is an alumna of McGill's Department of Pharmacology and Therapeutics and a medical student at the University of Ottawa. Barbara F. Hales is a James McGill Professor in the Department of Pharmacology and Therapeutics, McGill University. Bernard Robaire is a James McGill Professor in the Departments of Pharmacology and Therapeutics and of Obstetrics and Gynecology, McGill University. The authors are grateful to Tara Barton-Maclaren for her insightful comments on an earlier draft. Any errors are entirely the responsibility of the authors. The authors also wish to acknowledge the financial assistance of the Faculty of Law, McGill University; the Canadian Institutes of Health Research (CIHR) Institute for Population and Public Health team grant (FRN # IP3 150711) and the McGill Sustainability Systems Initiative.

1. Hazardous Products Act (Bisphenol A), 2010 (SOR/2010-53) (Can.). BPA was also prohibited in cosmetics, and a range of information-gathering measures and further regulatory objectives were adopted. For example, certain medical devices that come into contact with patients or patient fluids are surveyed, and targets for the migration of BPA from food packaging linings are under consideration. Government of Canada, *Risk Management Milestones for Bisphenol A*, https://www.canada.ca/en/health-canada/services/chemical-substances/challenge/batch-2/bisphenol-a/risk-management-action-milestones.html, (last visited Feb. 16, 2021).

2. European Commission Press Release IP/11/664, *Bisphenol A: EU Ban on Baby Bottles to Enter into Force Tomorrow* (May 31, 2011).

3. Johanna R. Rochester, *Bisphenol A and Human Health: A Review of the Literature*,

importance of the endocrine system to humans and other species, the presence in organisms and ecosystems of substances that interfere with this system is cause for alarm. However, many such substances are used therapeutically, including vitamins and the birth control pill.[4] The term endocrine disrupting chemical, or EDC, is generally used to refer to chemicals that generate negative health outcomes by interfering with the actions of hormones;[5] this is the meaning that we adopt. We focus on known or suspected EDCs, that is, chemicals whose impact on the endocrine system is or may be harmful.

This paper's objective is to shed light on the science of endocrine disruption, and on the manner in which this scientific knowledge is taken up and acted upon by regulatory agencies. We will proceed through a case study of the Canadian regulation of BPA. We seek to present an accessible yet nuanced and rigorous discussion of the science of endocrine activity in order to promote understanding of the Canadian regulatory decision, and to draw attention to the challenges faced by Environment and Climate Change Canada (ECCC)[6] and Health Canada (HC), as well as regulatory agencies around the world that seek to understand and react to the risks posed by EDCs such as BPA. One dimension of this challenge is the state of scientific knowledge about EDCs. Very little is known about many substances of potential concern, including other bisphenols that have a chemical structure very similar to that of BPA. These knowledge gaps are troubling, not least because structural similarities make these less well-understood chemicals good candidates for replacing those that have been linked to negative health outcomes and have been the object of public concern and regulatory action. The risk thus arises that successive replacement chemicals could in turn be revealed to be EDCs, a phenomenon referred to as regrettable replacement or substitution.[7] In addition to the risks posed to public health, these regrettable replacements affect public confidence in manufacturers and regulators, and possibly in public health science. They are not without risks for manufacturers either, as they must scramble to find

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REPROD. TOXICOL. 42, 132-135 (2013).

4. Katherine E Kelley et al., *Identification of Phthalates in Medications and Dietary Supplement Formulations in the United States and Canada*, ENVIRON. HEALTH PERSPECT. 120, 379-384 (2012).

5. Evanthia Diamanti-Kandarakis et al., *Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement*, ENDOCR. REV. 30, 293-342 (2009).

6. At the time of the BPA regulation, the agency was named Environment Canada.

7. Laura N. Vandenberg et al., *Plastic Bodies in a Plastic World: Multi-Disciplinary Approaches to Study Endocrine Disrupting Chemicals*, J. CLEANER PROD. 140, 373-380 (2017).

alternatives and work to regain the public's trust. A robust chemicals management strategy must provide a solid basis for assessment of alternatives to chemicals that are identified as posing risks, such that the replacement of those chemicals is informed and responsible, avoiding the adoption of replacement substances that are as bad as or worse than those replaced.[8]

This is a crucial moment for the science and politics of endocrine activity and disruption. Canada, Europe, and other jurisdictions are honing in on potential risks posed by EDCs. At the same time, many endocrinologists and toxicologists are raising questions about the means by which regulatory agencies evaluate the hazards and risks posed by endocrine active substances. Scientists are making important advances in potentially ground-breaking methodologies for the study of endocrine disruption in particular and toxicity in general.[9] In that context, this paper aims to contribute to debates about the science, law, and policy of endocrine disruption by articulating an interdisciplinary research agenda which could inform not only future regulatory decisions regarding BPA and other endocrine active substances, but also broader political decisions about the structures and processes through which decisions about the regulation of toxic substances are made.

We begin with a discussion of the phenomenon of endocrine disruption, with a focus on one of the most prominent EDCs: BPA. We also provide a general overview of scientific approaches to identifying EDCs (II). With this general background in place, we proceed to a discussion of the Canadian decision to adopt regulations on the use of BPA in infant feeding bottles and certain other products (III). We then zoom out to provide an overview of the process for assessing risks posed by chemicals. This discussion introduces a controversy surrounding the testing of potential EDCs, with some scientists arguing that conventional toxicity testing methods may not be appropriate means for identifying EDCs. Novel approach methodologies (NAMs) are championed by many scientists and are under examination by regulatory agencies, but they provoke controversies of their own (IV). We then briefly conclude (V).

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8. Joel A. Tickner et al., *The Nexus Between Alternatives Assessment and Green Chemistry: Supporting the Development and Adoption of Safer Chemicals*, GREEN CHEM. LETT. REV. 14, 23-44 (2021); *see also* Joel Tickner et al., *Advancing Alternatives Assessment for Safer Chemical Substitution: A Research and Practice Agenda*, INTEGR. ENVIRON. ASSESS. MANAG. 15, 855-866 (2019).

9. Daniel Krewski et al., *Toxicity Testing in the 21st Century: Progress in the Past Decade and Future Perspectives*, ARCH. TOXICOL. 94, 1-58 (2020).

II. ENDOCRINE DISRUPTION AND BPA

A. Endocrine Disruption

The endocrine system orchestrates the production of hormones that are responsible for our physiological functions from conception onwards. These hormones have essential roles in the regulation of body functions, such as metabolism, growth and development, and sexual function.[10] They are also important for determining the development of embryonic organs.[11] Disruption of hormones can lead to altered human development, and to many disease states such as diabetes, infertility, or cancer.[12]

The potential for certain chemicals to mimic and disrupt the normal functions of hormones was first proposed in 1958.[13] Observations throughout the 1960s of strange behavioural and reproductive patterns in animals suggested that pesticides and other substances might be having such effects.[14] In the 1970s, there was a dramatic demonstration of the serious health hazards that endocrine disrupting substances can cause. Diethylstilbestrol (DES), a drug with estrogenic activity, was prescribed to women to prevent miscarriage, treat hormone imbalance, and combat estrogen deficiency.[15] DES was subsequently linked to the development of clear-cell adenocarcinoma, a rare type of vaginal cancer, in women whose mothers had taken the drug during pregnancy.[16]

In light of these developments, in 1991 a multidisciplinary group of experts held a conference on endocrine disruption. The Wingspread Consensus emerged from the conference, establishing the concept of

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10. ELAINE NICPON MARIEB & KATJA HOEHN, HUMAN ANATOMY & PHYSIOLOGY (Pearson ed., 9th ed. 2013).

11. Vanessa E. Murphy et al., *Endocrine Regulation of Human Fetal Growth: The Role of the Mother, Placenta, and Fetus*, ENDOCR. REV. 27,141-148 (2006).

12. MARIEB & HOEHN, *supra* note 11; Thaddeus T. Schug et al., *Minireview: Endocrine Disruptors: Past Lessons and Future Directions*, MOL. ENDOCRINOL. 30, 833-836 (2016).

13. FX Gassner et al., *Effects of Hormones on Growth, Fattening, and Meat Production Potential of Livestock*, RECENT PROG. HORM. RES. 14, 183-201 (1958).

14. Schug et al., *supra* note 13.

15. Mary Sue Marty et al., *Endocrine Disruption: Historical Perspectives and Its Impact on the Future of Toxicology Testing*, TOXICOL. SCI. 120 Suppl 1, S93-108 (2011).

16. *Id*. Other impacts linked to exposure to DES include higher incidence of a number of reproductive tract abnormalities in sons of women exposed to DES during pregnancy. WB Gill et al., *Association of Diethylstilbestrol Exposure in Utero with Cryptorchidism, Testicular Hypoplasia and Semen Abnormalities*, J. UROL. 122, 36-39 (1979).

endocrine disruption and launching investigations into potential endocrine-disrupting chemicals.[17] In 2002, the World Health Organization (WHO) adopted the following definition of EDCs:

> an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny or (sub)populations.
>
> A potential endocrine disruptor is an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub)populations.[18]

Given the importance of the endocrine system for human health, exposure to EDCs during developmental periods – embryo, infant, and adolescent – can result in long-lasting adverse health effects.[19] The list of health problems associated with exposure to EDCs has grown to include severe reproductive and developmental problems, certain types of cancer, diabetes, cardiovascular and thyroid disease, obesity, and metabolic disorders.[20]

B. BPA

Bisphenol A (BPA) is a chemical widely used in the manufacture of plastics. More specifically, it is found in food containers, water bottles, children's toys, water pipes, polycarbonate eyeglasses and contact lenses, sports equipment, thermal paper receipts, dental products, medical equipment, and electronics.[21] It is the principal component of epoxy resin in the linings of canned foods.[22] Humans are exposed to BPA via numerous routes, including diet, skin contact, inhalation of household dust, and by transfer from mother to foetus (across the placenta) or mother to baby (via lactation).[23] BPA leaches from food containers, leading to exposure as a result of the

17. THEO COLBORN & CORALIE CLEMENT, CHEMICALLY-INDUCED ALTERATIONS IN SEXUAL AND FUNCTIONAL DEVELOPMENT: THE WILDLIFE/HUMAN CONNECTION 364 (Princeton Sci. Publ'g Co. ed. 1992).

18. World Health Organization (WHO), *International Programme on Chemical Safety, Global Assessment of the State-of-the-Science of Endocrine Disruptors* (2002).

19. ANDREA C. GORE ET AL., INTRODUCTION TO ENDOCRINE DISRUPTING CHEMICALS (EDCs) 15, (Endocrine Society ed., 2014).

20. *Id*.

21. *Id*.; Rochester, *supra* note 3; Laura N. Vandenberg et al., *Human Exposure to Bisphenol A (BPA)*, REPROD TOXICOL 24, 139-137 (2007).

22. Vandenberg et al., *supra* note 21.

23. Joe M. Braun et al., *Impact of Early-Life Bisphenol A Exposure on Behavior and Executive Function in Children*, PEDIATRICS 128, 873-882 (2011); *see also* Gilbert Schönfelder et al., *Parent Bisphenol A Accumulation in the Human Maternal-Fetal-Placental Unit*, ENVIRON. HEALTH PERSPECT. 110, A703- A707 (2002).

consumption of canned foods and beverages.[24] Several environmental and physical factors such as exposure to sunlight and microwaving food in plastic containers enhance the transfer of BPA into the food and beverages we consume.[25] Other routes of exposure also include inhalation of contaminated household dust, and exposure through the skin from handling thermal paper receipts containing BPA.[26] BPA and its metabolites are found in urine[27] and blood[28], in umbilical cord blood and placental tissue[29], in amniotic fluid,[30] in colostrum and breast milk,[31] and in the livers of foetuses.[32]

BPA is quickly metabolised by the body and does not accumulate in tissues.[33] Moreover, it has been shown that changes in consumption practices, such as avoiding the use of canned foods and plastic containers, are sufficient to decrease BPA levels in urine and other body fluids.[34] Increasing the commercial availability of BPA-free products should reduce exposure – that is, if replacement substances pose acceptably low levels of risk.[35] However, even following Canada's 2010 regulatory action on BPA, and the voluntary introduction into Canadian markets of BPA-free products, data from the Report on Human Biomonitoring of Environmental Chemicals in Canada reveal

24. Laura N. Vandenberg et al., *Bisphenol-A and the Great Divide: A Review of Controversies in the Field of Endocrine Disruption*, ENDOCR. REV. 30, 75-95 (2009).

25. GORE et al., *supra* note 19, at 53.

26. Martin Eckardt & Thomas J. Simat, *Bisphenol A and Alternatives in Thermal Paper Receipts - A German Market Analysis from 2015 to 2017*, CHEMOSPHERE 186, 1016-1025 (2017).

27. Braun et al., *supra* note 23.

28. Vandenberg et al., *supra* note 21; *see also* Stephanie M. Engel et al., *Xenobiotic Phenols in Early Pregnancy Amniotic Fluid*, REPROD. TOXICOL. 21, 110-112 (2006).

29. Schönfelder et al., *supra* note 23.

30. Vandenberg et al., *supra* note 21.

31. Vandenberg et al., *supra* note 21, at 144; *see also* Ryoko Kuruto-Niwa et al., *Measurement of Bisphenol A Concentrations in Human Colostrum*, CHEMOSPHERE 66, 1160-1164 (2006); Yen Sun et al., *Determination of Bisphenol A in Human Breast Milk by HPLC with Column switching and Fluorescence Detection*, BIOMED. CHROMATOGR. 18, 501- 507 (2004); Xiaoyun Ye et al., *Measuring Environmental Phenols and Chlorinated Organic Chemicals in Breast Milk Using Automated On-Line Column-Switching–High Performance Liquid Chromatography–Isotope Dilution Tandem Mass Spectrometry*, J. CHROMATOGR. B 831, 110-115 (2005).

32. Muna S. Nahar et al., *Fetal Liver Bisphenol A Concentrations and Biotransformation Gene Expression Reveal Variable Exposure and Altered Capacity for Metabolism in Humans*, J. BIOCHEM. MOL. TOXICOL. 27, 116-123 (2013).

33. Jenny L. Carwile et al., *Polycarbonate Bottle Use and Urinary Bisphenol A Concentrations*, ENVIRON. HEALTH PERSPECT.117, 1368- 372 (2009).

34. Camille A. Martina et al., *Lifestyle Behaviors Associated with Exposures to Endocrine Disruptors*, NEUROTOXICOLOGY 33, 1427-1433 (2012); Carwile et al., *supra* note 33.

35. Chun Z. Yang et al., *Most Plastic Products Release Estrogenic Chemicals: A Potential Health Problem That Can Be Solved*, ENVIRON. HEALTH PERSPECT. 119, 989-996 (2011).

that BPA is still present in the environment.[36] BPA thus remains a relevant issue for the public, industry, and governments.

BPA is one of the most extensively studied EDCs. By binding to estrogen receptors and related proteins, BPA present in the body can potentially mimic or disrupt the functions played by estrogen.[37] Because estrogen plays a pivotal role in several human organs, including the brain, liver, bone, mammary glands, ovaries, uterus, testes and prostate,[38] disruption of estrogenic functions during development could affect reproductive functions later in life.[39] A number of studies have associated BPA exposure with poor reproductive health in both men and women.[40] Some studies have shown that the impact of BPA on reproductive health may be observed in successive generations.[41] Although BPA has also been associated with other female and male fertility disorders, such as endometriosis, miscarriage, premature birth, low birth weight, and reduced sperm quality, more detailed clinical studies are needed to establish whether there are causal links.[42]

The effects of BPA extend to a number of tissues and organs, resulting in negative impacts on the central nervous system, the immune system, and the pancreas.[43] Potential associations between BPA exposure and obesity have been identified.[44] Epidemiological studies tracking these conditions in human populations have also suggested this association. Furthermore, it is thought that exposure to

36. Health Canada, *Fifth Report on Human Biomonitoring of Environmental Chemicals in Canada: Results of the Canadian Health Measures Survey Cycle 5 (2016–17)* (November 2019), https://www.canada.ca/en/health-canada/services/environmental-workplace-health/reports-publications/environmental-contaminants/fifth-report-human-biomonitoring/page-3.html#s9-1 (last visited Aug. 17, 2020).

37. Janet C. Gould et al., *Bisphenol A Interacts with the Estrogen Receptor lpha in a Distinct Manner from Estradiol*, MOL. CELL ENDOCRINOL. 142, 203-214 (1998).

38. Hye-Rim Lee et al., *Functions and Physiological Roles of Two Types of Estrogen Receptors, ER and ER , Identified by Estrogen Receptor Knockout Mouse*, LAB. ANIM. RES. 28, 71-76 (2012).

39. Vandenberg et al., *supra* note 21.

40. Rochester, *supra* note 3; Vandenberg et al., *supra* note 21.

41. Ayelet Ziv-Gal et al., *The Effects of in Utero Bisphenol A Exposure on Reproductive Capacity in Several Generations of Mice*, TOXICOL. APPL. PHARMACOL. 284, 354-362 (2015); Wei Wang et al., *In Utero Bisphenol A Exposure Disrupts Germ Cell Nest Breakdown and Reduces Fertility with Age in the Mouse*, TOXICOL. APPL. PHARMACOL. 276, 157-164 (2014).

42. Rochester, *supra* note 4.

43. Yelena B Wetherill et al., *In Vitro Molecular Mechanisms of Bisphenol A Action*, REPROD. TOXICOL. 24, 178-198 (2007).

44. Samuel Legeay & Sébastien Faure, *Is Bisphenol A an Environmental Obesogen?* FUNDAM. CLIN. PHARMACOL. 31, 594-609 (2017).

BPA during foetal development may be the cause of the increased prevalence of infertility, genital abnormalities, breast cancer, and obesity, all of which are important health problems.[45]

Several regulatory agencies, including the World Health Organization, Health Canada, and the United States National Toxicology Program (NTP), have expressed concerns regarding the potential negative impact of BPA on foetal brain development and behaviour.[46] Evidence from animal studies indicates that exposure to BPA during development triggers anxiety, aggression, and social interaction disorders.[47] Furthermore, scientists have hypothesized that BPA exposure may contribute to behavioural disorders such as attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) in children.[48]

C. Toxicity Testing and EDCs

Any methodology for detecting toxicity and determining the risk of adverse health and environmental impacts as a result of exposure to a toxic substance possesses strengths, weaknesses, limitations, and blind spots. Furthermore, regulatory decisions on toxic substances are inevitably made on the basis of imperfect information. Finally, those decisions cannot, particularly in a democracy, be made on a scientific basis alone. Regulation of a substance has ramifications that go far beyond the economic actors with a stake in that substance, particularly in contexts such as the current one in which little is known about the likely replacements for regulated substances. For these and other reasons, it is important to promote understanding of the scientific study of EDCs and the manner in which this scientific input is incorporated into political and legal decision-making among non-scientists,

45. Monica Muñoz-de-Toro et al., *Perinatal Exposure to Bisphenol-A Alters Peripubertal Mammary Gland Development in Mice*, ENDOCRINOLOGY 146, 4138, 4144–4147 (2005); Niels E Skakkebék et al., *Germ Cell Cancer and Disorders of Spermatogenesis: An Environmental Connection?* APMIS 106, 3-11 (1998).

46. Åke Bergman et al., *State of the Science of Endocrine Disrupting Chemicals 2012: Summary for Decision-Makers*, WORLD HEALTH ORG. (2013). Chloe Welch & Kimberly Mulligan, *Does Bisphenol A Confer Risk of Neurodevelopmental Disorders? What We Have Learned from Developmental Neurotoxicity Studies in Animal Models*. INT'L J. MOLECULAR SCI. 23, 2894 (2022).

47. Jennifer T. Wolstenholme et al., *Gestational Exposure to Bisphenol A Produces Transgenerational Changes in Behaviors and Gene Expression*, ENDOCRINOLOGY 153, 3828-3838 (2012).

48. Marijke De Cock et al., *Does Perinatal Exposure to Endocrine Disruptors Induce Autism Spectrum and Attention Deficit Hyperactivity Disorders? Review*, ACTA PAEDIATRICA101, 811-818 (2012).

including those who work in or study the law and policy of environmental and human health protection.

Conventional methods for analysing the toxicity of substances of concern generally involve the administration of high doses of those substances to a small number of laboratory animals. This is a resource-intensive, time-consuming, and potentially ethically problematic approach, which is particularly ill-suited to the evaluation of large numbers of chemical substances for toxic properties. In addition, there is growing evidence that chemicals that act as EDCs, such as BPA, could have adverse health effects after exposure to low doses outside of the range of conventional tests.[49] The Canadian regulatory decision on BPA was based on a "weight of evidence" approach in which all available information was considered.[50] Not only conventional studies using higher doses (measured in mg/kg bodyweight/day) but also less conventional studies, including neurobehavioral studies in which effects were observed at low doses (measured in microgram (µg) per kilogram of body weight per day) were taken into account.[51] This inclusive approach is of great relevance given controversies and emerging understandings in the study of endocrine disruption.

John Peterson Myers and colleagues describe BPA as "a leading high-profile battleground in a scientific revolution currently under way in toxicology,"[52] and argue that "[d]ata emerging from studies of endocrine disrupting chemicals . . . challenge the central assumption that has guided toxicology for centuries, including today's regulatory apparatus for assessing chemical safety."[53] In doing so, they challenge the methods and the adequacy of chemical exposure safety standards.[54]

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49. Sara Edge & John Eyles, *Message in a Bottle: Claims Disputes and the Reconciliation of Precaution and Weight-of-Evidence in the Regulation of Risks from Bisphenol A in Canada*, HEALTH RISK SOC. 15, 432-448 (2013)

50. Government of Canada Press Release: Government of Canada Takes Action on Another Chemical of Concern: Bisphenol A (Apr. 18 2008): https://www.canada.ca/en/news/archive/2008/04/government-canada-takes-action-another-chemical-concern-bisphenol-a.html (last visited 31 Mar. 2022).

51. Vicente Mustieles & Mariana F Fernández. *Bisphenol A Shapes Children's Brain and Behavior: Towards an Integrated Neurotoxicity Assessment including Human Data.* ENVIRON. HEALTH 19:66 (2020); Sarah A Johnson et al. *Effects of developmental exposure to bisphenol A on spatial navigational learning and memory in rats: A CLARITY-BPA study*. HORM. & BEHAV. 80, 139–148 (2016); Shannah K Witchey et al., *Perinatal bisphenol A (BPA) exposure alters brain oxytocin receptor (OTR) expression in a sex- and region- specific manner: A CLARITY-BPA consortium follow-up study*. NEUROTOXICOLOGY 74, 139–148 (2019).

52. John Peterson Myers et al., *A Clash of Old and New Scientific Concepts in Toxicity, with Important Implications for Public Health,* ENVIRON. HEALTH PERSPECT. 117, 1652-1655 (2009).

53. *Id.*

54. *Id.*

While this view is controversial, many scientists believe that the limitations of conventional methodologies for detecting EDCs and informing regulatory agencies of their impacts are serious enough to warrant heavy investment in alternative approaches and methodologies (New Approach Methodologies or NAMs) for toxicology testing.[55] The Canadian BPA risk assessment was completed in 2008, prior to implementation of the recommendations of the US National Academy of Sciences report.[56] Thus, the 2010 Canadian regulation on BPA was based on data that were available prior to the development of NAMs.

D. The Canadian Regulatory Decision on BPA

Environment Canada and Health Canada launched the Challenge Programme in 2006, with the very ambitious goal of screening roughly 200 chemical substances that had been identified as high priorities.[57] BPA was included on this list by reason of its ubiquity, which generates a significant risk of exposure, and due to its identification in 2003 by the European Chemicals Bureau as a potential reproductive toxicant.[58] The Ministers of Health and Environment then conducted a screening assessment, published in October 2008, involving an extensive review of studies of BPA to determine its toxicity pursuant to the Canadian Environmental Protection Act (CEPA).[59] Exposure to BPA was

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55. Stanley T Parish et al, *An Evaluation Framework for New Approach Methodologies (NAMs) for Human Health Safety Assessment,* REGUL. TOXICOL. PHARMACOL. 112, 104592 (2020).

56. Melvin E Andersen & Daniel Krewski, *Toxicity Testing in the 21st Century: Bringing the Vision to Life*, TOXICOL. SCI. 107, 324-330 (2008).

57. *"Challenge" for Chemical Substances That Are a High Priority for Action*, GOV'T OF CANADA, (July 28, 2011), https://www.canada.ca/en/health-canada/services/chemical-substances/challenge.html, (last visited Mar. 31, 2022). The Ministers of Environment and Health are required by s. 73 of CEPA to prepare lists of priority substances for screening on the basis either of high levels of exposure or persistence, bioaccumulation, or toxicity. For an analysis of the debates over BPA among scientists, regulators, and a range of stakeholders, see Sara Edge & John Eyles, *supra* note 50; Steve Maguire & Cynthia Hardy, *Organizing Processes and the Construction of Risk: A Discursive Approach*, 56 ACAD. MANAG. J. 231 (2013).

58. Environment Canada Health Canada, *Screening Assessment for the Challenge: Phenol, 4,4' -(1-Methylethylidene)Bis- (Bisphenol A)*, (Oct. 2008), https://www.ec.gc.ca/ese-ees/3C756383-BEB3-45D5-B8D3-E8C800F35243/batch2_80-05-7_en.pdf., (last visited Apr. 20, 2022); *Updated European Union Risk Assessment Report 4,4'-ISOPROPYLIDENEDIPHENOL (BISPHENOL-A),* EUROPEAN UNION (2008), https://publications.jrc.ec.europa.eu/repository/handle/JRC59988, (last visited Apr. 20, 2022).

59. CEPA provides that a substance is to be considered toxic "if it is entering or may enter the environment in a quantity or concentration or under conditions that
have or may have an immediate or long-term harmful effect on the environment or its biological diversity;

widespread due to the high volume of its use in Canada; slow degradation in oxygen-poor environments; its detection in various environmental media; and high bioavailability (that is, the capacity of the chemical to enter the organism and reach its site of action).[60] In addition to exposure data, evidence of adverse health outcomes was considered:

> Low-level exposure to bisphenol A, particularly at sensitive life cycle stages, may lead to permanent alterations in hormonal, developmental or reproductive capacity. In laboratory testing, these effects have occurred within the range of concentrations measured in Canada, indicating that there is potential for adverse effects in populations, particularly close to point sources.[61]

This evidence, the report states, is "highly uncertain" but "suggestive of potential effects" at doses that correspond to human exposure levels, mainly through diet.[62] When combined with the knowledge that BPA leaches out of plastic bottles into the contents,[63] and evidence of a correlation between prenatal and neonatal exposure to BPA and reproductive and developmental problems,[64] the agencies determined that a case for regulatory action could be made on a precautionary basis.[65] The screening assessment report notes inconsistent results across different studies,[66] and, as indicated above, there is still controversy in scientific and regulatory communities regarding the health impacts of BPA.[67]

On the basis of the BPA screening assessment report, this

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constitute or may constitute a danger to the environment on which life depends; or

constitute or may constitute a danger in Canada to human life or health:" Canadian Environmental Protection Act, S.C. 1999, c.33, §64 (Can.).

The Ministers of Health and Environment are charged with conducting screenings for toxicity in virtue of CEPA. *Id.* at § 74.

60. Tyler Pollock et al., *Trends in Environmental Chemical Concentrations in the Canadian Population: Biomonitoring Data from the Canadian Health Measures Survey 2007-2017.* ENVIRON. INT. 155, 106678 (2021).

61. Environment Canada Health Canada, *supra* note 59.

62. *Id.*

63. *Id.*

64. Reproductive and developmental problems are not the only health impacts discussed in the report; they receive attention here because of their salience to the Canadian regulatory response.

65. CEPA, *supra* note 60, § 76.1.

66. Environment Canada Health Canada, *supra* note 59.

67. Jerrold J. Heindel et al., *Data Integration, Analysis, and Interpretation of Eight Academic CLARITY-BPA Studies*, REPROD. TOXICOL. 98, 29-60 (2020); L. Camacho et al., *A Two-year Toxicology Study of Bisphenol A (BPA) in Sprague-Dawley Rats: CLARITY-BPA Core Study Results*, FOOD CHEM. TOXICOL. 132, 110728 (2019).

substance was added to the List of Toxic Substances.[68] The next step was to develop a risk management approach.[69] The objective identified was to minimise infant exposure "to the greatest extent practicable,"[70] more specifically "to achieve the lowest level of release to infant formula and from polycarbonate baby bottles that was technically and economically feasible."[71] In 2010, after a 60-day consultation period for the proposed risk management plan,[72] the regulations of the Hazardous Products Act[73] were amended to ban BPA in baby bottles. By the time the regulation entered into force, BPA was no longer found in baby bottles. Manufacturers, retailers, and consumers had by then moved to alternatives, which included bottles with plastic linings, glass or metal bottles, and plastic bottles that were BPA-free – and clearly labelled as such, as otherwise they would not sell.[74]

E. The Screening Assessment Report

The BPA screening assessment report is a review of a large number of scientific studies on BPA's chemical properties, the uses to which BPA is put, exposure of members of the population to BPA, and the hazards BPA presents.[75] It is an ambitious review of BPA studies following a range of methodologies and approaches. As will be discussed in further detail below, scientific studies of adverse health effects proceed in different ways depending on the particular research questions on which scientists wish to focus. For example, laboratory

68. CEPA, *supra* note 60, § 90; Order Adding a Toxic Substance to Schedule 1 to the Canadian Environmental Protection Act, S.C. 2021. SOR/2021-86 (Apr. 23, 2021) https://canadagazette.gc.ca/rp-pr/p2/2021/2021-05-12/html/sor-dors86-eng.html, (last visited Apr. 20, 2022).

69. Environment Canada Health Canada, *Proposed Risk Management Approach for Phenol, 4,4'-(1-Methylethylidene) Bis (Bisphenol A),* GOV'T OF CANADA, 1, 4 (Oct. 2008) https://www.ec.gc.ca/ese-ees/6FA54372-A09E-45CD-8A5F-39EBDD55D13A/batch2_80-05-7_rm_en.pdf, (last visited Apr. 20. 2022).

70. *Id.* at 12.

71. *Id*. at 13.

72. *Id* at 16. Consolidated comments from that process are presented in *Summary of Public Comments Received on the Government of Canada's Proposed Risk Management Approach Document on Phenol, 4,4' -(1-Methylethylidene)Bis- (CAS RN 80-05-7)*, GOV'T OF CANADA, (Oct. 2010) https://www.ec.gc.ca/ese-ees/FFCB9B55-44CA-40F5-A53F-355FB1769546/batch2_80-05-7_rm_pc_EN.pdf, (last visited Apr. 20, 2022). Not surprisingly, comments ranged from complaints that the government had gone too far on a flimsy scientific basis to complaints that it had not gone far enough by not slating BPA for elimination. *Id*.

73. Hazardous Products Act; Hazardous Products Regulation; Order Amending Schedule I to the Hazardous Products Act (bisphenol A) 2010 (Canada Gazette, Part II).

74. Maguire & Hardy, *supra* note 58.

75. Environment Canada Health Canada, *supra* note 59.

studies often involve the exposure of a relatively small number of animals, generally rodents, to high levels of the chemical of interest over a fixed period of time. In contrast, large human populations may be exposed to lower levels of the chemical of interest for a longer time. Such cases present a natural experiment that epidemiologists can analyse to learn more about the impacts of chemicals on humans. For example, a population may be exposed to a large amount of a substance over a short period of time (acute exposure) as a result of a major chemical leak. Epidemiological methods may also be employed when a group of employees in a factory are exposed to small amounts of a substance over the course of their professional lives (chronic exposure). Epidemiologists also examine associations between everyday exposures to a wide array of chemicals and health outcomes.

As a general rule, epidemiological studies provide evidence of association between an exposure and an effect but can rarely be used for establishing causality. Laboratory studies typically focus on a relatively narrow range of some of the more serious health risks, namely organ toxicity, carcinogenicity, mutagenicity, immunotoxicity, and reproductive and developmental toxicity. Such studies can use a relatively small number of animals because laboratory animals have highly controlled genetic and environmental conditions. This means a single variable can be tested, i.e., exposure to a specific chemical. Exposures may be acute (single dose or over a short time) or chronic (repeated doses over a longer time). If scientists are interested in honing in on the impacts of a chemical on a particular organ, function, or process, it may be feasible to use *in vitro* laboratory techniques in which cells or organs are cultured and then exposed to a substance or mixture. This is a very short list of the myriad approaches that scientists may take to study various dimensions of a substance's toxicity. Each presents its own strengths, weaknesses, and limitations. Scientists and regulatory authorities are able, by looking at large numbers of studies carried out using a variety of approaches and methods, to develop a more complete picture of the risks posed by exposure to substances such as BPA.

The approach taken in the screening assessment report prepared by Environment and Health Canada was to look at a wide range of scientific studies and data on BPA. The report's authors used a weighted approach,[76] meaning that they did not treat all studies and data as equally worthy of confidence and therefore equally reliable. A

76. Environment Canada Health Canada, *supra* note 59, at 2.

study whose results generate a lower level of confidence may nevertheless provide valuable information and insight and therefore be worth taking into consideration, even if there are good reasons not to depend heavily on its results. For example, it may involve only a small sample or use novel methodologies or experimental designs. A weighted approach allows assessors to consider a broad and deep body of evidence while at the same time taking account of the different degrees of confidence that various studies generate.

Weighted reviews of a wide range of scientific literature and other data constitute a well-accepted approach to informing regulatory decisions regarding toxic substances, but they are not without controversy. Regulatory authorities seek to ensure that the procedures followed for generating the scientific data that inform regulatory decisions are described carefully and adhered to scrupulously in order to promote transparency, consistency, rigour, and objectivity. It is widely acknowledged that weighting scientific evidence for consideration in a risk assessment depends on professional judgment; this means that, quite inevitably, different professionals may not reach precisely the same conclusion. However, the exercise of this discretion need not be arbitrary or subjective if a robust methodology is adopted for weighting studies and other pieces of evidence, along with transparency regarding that methodology and the manner in which it was applied.[77]

F. Regulatory Responses by other Jurisdictions

The varied responses of different jurisdictions[78] to the evolving

77. The research teams responsible for two consecutive reports on EDCs prepared for the World Health Organization and the United Nations Environment Program traded criticisms of one another's methodologies following the publication of the second of these reports. James C. Lamb IV et al., *Critical Comments on the WHO-UNEP State of the Science of Endocrine Disrupting Chemicals–2012*, REGUL. TOXICOL. PHARM. 69, 22-40 (2014); Åke Bergman et al., *Manufacturing Doubt about Endocrine Disrupter Science–A Rebuttal of Industry-Sponsored Critical Comments on the UNEP/WHO Report "State of the Science of Endocrine Disrupting Chemicals 2012,* REGUL. TOXICOL. PHARMACOL. 73, 1007-1017 (2015) (comparing International Programme on Chemical Safety, *Global Assessment of the State-of-the-Science of Endocrine Disruptors*, WHO (2002) https://www.who.int/ipcs/publications/en/toc.pdf?ua=1; A. Bergman et al., *State of the Science of Endocrine Disrupting Chemicals*, WHO (2012) https://apps.who.int/iris/bitstream/handle/10665/78102/WHO_HSE_PHE_IHE_2013.1_eng.pdf, (last visited Apr. 20, 2022).

78. As noted above, Canada's ban was prompted in part by risk assessments in Europe. Following Canada's regulatory action, the European Union banned BPA in baby bottles in 2011. *Commission Directive 2011/8/EU*, OFF. J. EUR. UNION (Jan. 28, 2011) (regarding the restriction of use of Bisphenol A in plastic infant feeding bottles 2011). For an overview and analysis of earlier European initiatives on BPA, *see* Tessa Fox et al., *Regulating the Use of Bisphenol A in*

scientific understanding of BPA and other bisphenols indicate that regulatory authorities are unclear on how to react to these emerging scientific insights. Varied responses across jurisdictions may be due to timing with respect to the information available at the time of the assessment (2008 versus 2017) or legislative differences between jurisdictions such as Canada and Europe. In Canada, under CEPA, risk is assessed on the basis of exposure and hazard, whereas in Europe, evaluation of risks posed by EDCs is largely based on hazard.[79] Companies whose products are traded internationally may need to comply with more stringent requirements than those imposed in their own jurisdictions. The actions taken by Canada in 2010 may appear modest now, a decade later, but at the time were a world first. Regarding the modesty of the Canadian measures, one interesting observation is that manufacturers of infant formula have not waited for Canadian regulators to address that issue. There is some indication that the Canadian regulation is being treated by many constituencies as a floor rather than a ceiling, and manufacturers are responding to scientific insights and consumer concerns rather than waiting for

Baby and Children's Products in the European Union: Current Developments and Scenarios for the Regulatory Future, EUR. J. RISK REGUL. 2, 21-35 (2011). Denmark, Belgium, and Sweden have taken additional actions against BPA in food contact materials intended for infants and young children; and France has banned the substance in all food contact materials. European Parliamentary Research Service, *New Rules on Bisphenol A in Food Contact Materials*, EUR. PARLIAMENT, (Feb. 2018) https://www.europarl.europa.eu/RegData/etudes/ATAG/2018/614705/EPRS_ATA(2018)614705_EN.pdf, (last visited Apr. 20, 2022). Among some of the other steps taken by European agencies, four are worthy of particular note: the decision by the Member State Committee of the European Chemicals Agency (ECHA) to identify BPA as a Substance of Very High Concern (SVHC), European Chemicals Agency, *Agreement of the Member State Committee on the Identification of 4,4'-Isopropylidenediphenol (Bisphenol A) as a Substance of Very High Concern* (Dec. 14, 2017) https://echa.europa.eu/documents/10162/81862f4e-92bc-6f64-9a01-42565b526022, (last visited Apr. 20, 2022); the extension by the European Parliament of the BPA ban to all food contact materials intended for infants and young children, *Commission Regulation EU 2018/213*, OFF. J. EUR. UNION (Feb. 12, 2018) https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32018R0213&from=EL, (last visited Apr. 20, 2022) (regarding the use of that substance in Plastic Food Contact Materials 2018); the European Commission decision to ban BPA in thermal paper, such as that used in receipts, *Commission Regulation EU 2016/2235*, OFF. J. EUR. UNION (Dec. 12, 2016) https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016R2235&from=EN, (last visited Apr. 20, 2022) (introduced in 2016, the ban will take effect in 2020); and the most recent action, a resolution of the European Parliament calling on the European Commission to take further steps to regulate endocrine disrupting substances, treating them in a similar manner to substances with carcinogenic or mutagenic substances, or substances that are toxic for reproduction, Resolution on a Comprehensive European Union Framework on Endocrine Disruptors, EUR. PARL. DOC. P8_TA-PROV(2019) 0441.

79. Christopher D Kassotis et al., *Endocrine-Disrupting Chemicals: Economic, Regulatory, and Policy Implications*, LANCET DIABETES ENDOCRINOL. 8, 719-730 (2020).

regulatory agencies to impose further restrictions on this substance. This desire to get ahead of the regulatory curve is not particularly surprising. Manufacturers and retailers are reacting not only to scientific insights into bisphenols, but also to public discomfort with those substances and, in some cases at least, the availability of alternatives that may permit the avoidance of bisphenols altogether. The fact that bisphenols are receiving increased scrutiny by scientists and regulators creates incentives to look elsewhere when designing products.

The screening assessment report was prepared, and the regulatory decision taken, against a backdrop of uncertainty and controversy. There were also rapid developments in scientific approaches to studying toxicity that many commentators have argued presage a paradigm shift.[80] These developments have important implications for regulatory agencies, and therefore stakeholders. In what follows, this broader context will be further explored to shed additional light on the Canadian regulatory decision on BPA, on the process leading up to it, and on emerging approaches and methodologies that promise to put additional tools at the disposal of agencies responsible for the regulation of toxic substances.

III. THE RISK ASSESSMENT PROCESS

Toxicity testing methodologies have been developed and refined over the course of decades, and there is a high degree of consensus among scientists and regulators as to their appropriateness and reliability. However, this consensus is beginning to break down as far as EDCs are concerned. Even among observers who maintain a high degree of confidence in conventional methodologies, there are concerns about the time and resources they require, as well as the ethical problems that the use of laboratory animals poses.

A. Clarity

As noted above, the endocrine disrupting potential of BPA is an extremely well-studied phenomenon – yet it also remains highly controversial. In an attempt to address knowledge gaps, uncertainties, and disagreement among scientists, the Consortium Linking Academic and Regulatory Insights on Bisphenol A Toxicity (CLARITY-BPA) was created in the United States by the National Institute of

80. Hongmao Sun et al., *Paradigm Shift in Toxicity Testing and Modelling*, AAPS J 14, 473-480 (2012).

Environmental Health Sciences (NIEHS) and the National Center for Toxicological Research (NCTR) of the Food and Drug Administration (FDA).[81] CLARITY involved a further round of studies on BPA that were designed to generate consensus regarding its status as an EDC.[82] Key to attaining this objective was the assembly of scientists from regulatory agencies, academia, and industry. This was in acknowledgement of the fact that scientific studies tend to be structured differently depending on their aims, which in turn are influenced by the intended audience: academia, regulatory agency, or industry. Many of the BPA studies in which endocrine disruption has been observed were academic studies, seeking to expand the boundaries of knowledge and often employing novel methodologies. These studies were often not conducted using the standardised experimental protocols referred to as good laboratory practices (GLP). [83] Regulatory agencies have generally placed a great deal of emphasis on strict adherence to GLP standards, in order to generate a high degree of reproducibility and thus to promote consistency and even-handedness.[84] The CLARITY-BPA study sought "to bridge guideline-compliant research conducted at the FDA," that is, in conformity with such standardised protocols, "with hypothesis-based research investigations conducted by academia on the toxicity of BPA."[85] The aim was to reduce differences between studies and to understand the full range of potential adverse health effects from exposure to BPA.[86] However, due to the differences in the parameters that were measured (i.e., standard study designs and endpoints assessed under GLP guidelines for regulatory purposes in industry or government labs versus specific, more focussed study designs and measures (not GLP) in academic research laboratories), CLARITY did not resolve the

81. Thaddeus T Schug et al. *A New Approach to Synergize Academic and Guideline-compliant Research: The CLARITY-BPA Research Program.* REPROD TOXICOL 40, 35-40 (2013); Heindel et al., *supra* note 68.

82. L. Camacho et al., *supra* note 68.

83. John Peterson Myers et al., Why Public Health Agencies Cannot Depend on Good Laboratory Practices as a Criterion for Selecting Data: The Case of Bisphenol A, ENVIRON. HEALTH PERSPSECT . 117, 309-315 (2009).

84. *See Id*. at 309–10 (noting why regulatory agencies established GLP).

85. NAT'L TOXICOLOGY PROGRAM U.S. DEP'T OF HEALTH AND HUMAN SERV., NTP RESEARCH REPORT ON THE CLARITY-BPA CORE STUDY: A PERINATAL AND CHRONIC EXTENDED-DOSE- RANGE STUDY OF BISPHENOL A IN RATS, ii (2018).

86. Gail S. Prins et al., *CLARITY BPA Academic Laboratory Studies Identify Consistent Low dose Bisphenol A Effects on Multiple Organ Systems*, BASIC CLIN PHARMACOL. TOXICOL. 125, 14-31 (2019).

controversies. In fact, it added to them.[87] An important dimension of this controversy turns on the issue of effects at different doses: the presumption that effects will increase in frequency and severity at higher doses is central to conventional approaches to toxicology, and was an important point of contention between scientists conducting GLP studies and those using alternative or novel methods.[88] To better understand this controversy and the uncertainty that it generates for regulatory agencies and stakeholders, we take a closer look at the evaluation of risks posed by toxic substances.

B. Exposure and Hazard

While it can seem counterintuitive for a regulatory agency not to proceed with prohibitions or strict regulation of a substance as soon as it has been classified as toxic, it is crucial to bear in mind that hazard is only one element of risk. The other element is exposure. This is exemplified by the epidemiological and toxicological mantra that "the dose makes the poison:" many substances that have a neutral or positive impact on human health and well-being at certain levels of exposure become problematic only once exposure begins to reach higher levels.[89] It is when individuals in a population are exposed to a substance of concern at a level that is correlated with a negative impact on health outcomes that they are deemed to be at risk. The terms risk and hazard are distinct for the purposes of toxicology.[90] Risk refers to the probability of harm based on both hazard and exposure, and exists only in situations where exposure to the hazardous chemical has occurred, or will occur, at levels that cause harm.[91]

The level, frequency, route, and duration of exposure to a chemical (exposure assessment) and the relationship between dose and effect (dose-response relationship) are evaluated in the risk assessment process.[92] Chemical risk assessments are based on a very large number

87. Patricia A. Hunt et al., *The Bisphenol A Experience: A Primer for the Analysis of Environmental Effects on Mammalian Reproduction*, BIOL. REPROD. 81, 807-813 (2009).

88. L. Camacho et al., *supra* note 68; Heindel et al., *supra* note 68 (describing how several independent lab studies observed non-linear dose-response functions).

89. *Die dritte Defension wegen des Schreibens der neuen Rezepte,* SEPTEM DEFENSIONES 1538. Werke Bd. 2, Darmstadt 1965, 510.

90. National Research Council (US) Committee on the Institutional Means for Assessment of Risks to Public Health. Risk Assessment in the Federal Government: Managing the Process. Washington (DC): National Academies Press (US); 1983. PMID: 25032414.

91. C.J. VAN. LEEUWEN & T.G. VERMEIRE, RISK ASSESSMENT OF CHEMICALS: AN INTRODUCTION (2nd ed. 2007).

92. Maged Younes, *Toxicological Risk Assessment*, in REGUL. TOXICOL. PHARM. 65, 67 (Franz-Xaver Reichl & Michael Schwenk eds.) (2014); CURTIS D. KLAASSEN & JOHN B.

of scientific studies that are carried out using methodologies and protocols that have been developed over the course of decades, subjected to rigorous validation, and, in many cases, approved by domestic regulatory agencies and international organisations such as the Organization for Economic Cooperation and Development (OECD).[93] Reliance on the use of these well-described, validated guideline protocols to evaluate the adverse health effects of chemicals provides assurance to international regulatory agencies, governments, and stakeholders that conclusions are based on sound data. Furthermore, the basis on which decisions are made can be explained to a broad audience, including manufacturers and consumers, and assurance is provided that all chemical risks are handled in the same manner, reducing disparities, arbitrariness, and subjective risk assessments.

Consideration of the interrelationship between hazard and exposure, which together permit an assessment of risk, sheds light on the Canadian government's decision to regulate BPA in baby bottles and similar items, but not to go further. It is important to acknowledge the hybrid nature of the category of "CEPA toxicity", that is, meeting the criteria in CEPA for listing as a toxic substance. Heavily informed by science, the concept encompasses more considerations than the inherent qualities of the substance itself.[94] The hybrid nature of the concept of CEPA toxicity is also made clear from the role played by precaution in the decision-making process. The health risks posed by BPA were not deemed to have been conclusively established by the data generated in toxicity tests, but a potential risk was nevertheless identified on a precautionary basis.[95] Recall as well that the issue of exposure loomed large: BPA is ubiquitous in our environment; Canadians (and people in the developed world in particular) are exposed to the substance through contact with a wide variety of products and pathways; and the substance is found, albeit at low concentrations, in a number of human body fluids and tissues. While it is eliminated from the body very quickly, its endocrine disrupting properties may make humans particularly vulnerable to its effects at certain developmental stages, including *in utero*, infancy, and puberty.

WATKINS III, CASARETT & DOULL'S ESSENTIALS OF TOXICOLOGY (Third ed., McGraw-Hill Medical 2015).

93. Daniel Krewski et al., *Toxicity Testing in the 21st Century: A Vision and a Strategy*, J. TOXICOL. ENVIRON. HEALTH B CRIT. REV., 13, 51–138 (2010).

94. Canadian Environmental Protection Act, S.C. 1999, c.33, §64 (Can.).

95. BUREAU OF CHEM. SAFETY, HEALTH RISK ASSESSMENT OF BISPHENOL A FROM FOOD PACKAGING APPLICATIONS, 10 (2008) (Can.).

As a result, a conclusion was reached that for most Canadians in most circumstances, the potential risk was acceptable.

BPA has received an enormous amount of attention from scientists, yet its health risks remain only partially understood. Part of the reason for this incomplete information and uncertainty may lie with certain characteristics of endocrine disrupting substances, namely their capacity to induce changes (not necessarily harmful ones) at low doses. As noted, many experts question whether conventional toxicity testing using high doses is appropriate for suspected EDCs. Since hormones play a critical role in maintaining homeostasis throughout the body, the small changes in hormones that result from exposure to an EDC may have long-lasting and significant effects, especially at sensitive life stages.

C. Dose-Response Relationships

One of the major challenges faced by scientists in regulatory agencies, government, industry, and academic labs is to understand the relationship between an exposure, or dose, and an adverse health effect, or toxicity. In a conventional toxicology approach, it is predicted that increasing the dose will increase the response, rendering adverse outcomes more frequent or more severe.[96] This type of dose-response relationship is termed monotonic.[97] In the design of such an experiment, a group of animals serves as the control, not being exposed to the chemical under investigation. Other groups are treated with different doses of the chemical of interest. The lowest dose at which there is no response is identified as the No Observed Adverse Effect Level (NOAEL).[98] The lowest dose which produces a response is identified as the Lowest Observed Adverse Effect Level (LOAEL).[99] The LOAEL serves as the "point of departure" to be used as a basis for making the extrapolations needed for assessing risks.[100] Information garnered from experimental results will often be

96. Michael A. Dorato & Jeffery A. Engelhardt, *The No-Observed-Adverse-Effect-Level in Drug Safety Evaluations: Use, Issues, and Definition(s)*, REGUL. TOXICOL. PHARM. 42, 265-274 (2005).

97. Rory B. Connolly & Werner K. Lutz, *Nonmonotonic Dose-Response Relationships: Mechanistic Basis, Kinetic Modeling, and Implications for Risk Assessment*, TOXICOL. SCI. 77, 151-157 (2004).

98. Dorato & Engelhardt, *supra* note 96.

99. Laura N. Vandenberg, *Low-Dose Effects of Hormones and Endocrine Disruptors*, VITAM. HORM. 94, 129-165 (2014).

100. Hoda Izadi et al., *Evaluation of a Benchmark Dose for Point of Departure Determination for a Variety of Chemical Classes in Applied Regulatory Settings*, RISK ANAL. 32, 830-835 (1998).

supplemented through mathematical modelling: for example, scientists may use experimental results to calculate the dose associated with a specific change, perhaps a 10% increase in the incidence of an adverse effect, as compared to control. This dose is then defined as the benchmark dose for this chemical and endpoint.[101]

Once the NOAEL, LOAEL and/or the benchmark dose for a response are determined in a toxicology study, risk assessors may apply uncertainty factors to adjust for knowledge gaps associated with these data. Uncertainty factors are used to address the extrapolation of data from animal studies to effects on humans; for different impacts within individuals in a population; and for differences in doses in laboratory experiments as opposed to real-world exposures, among other things.[102] Chemicals may affect pathways or targets in animals but not humans, or be handled differently in animals and humans. Human responses may vary since individuals are unique.[103] It may be difficult to extrapolate from a short-duration animal study to a lifetime of human exposure. There is uncertainty in estimating a no-effect level from a dose where effects are observed. Finally, the most subtle adverse effect may not have been evaluated. Uncertainty factors are applied to account for these knowledge gaps and sources of variability.[104]

One of the important questions in toxicology is whether chemicals have toxic effects only when the exposure is above a certain level or threshold. The threshold is defined as the dose below which no adverse effects are observed after exposure to a chemical.[105] The failure to observe effects could result from different factors. Perhaps exposure to only a few molecules is not sufficient to produce significant changes in

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101. Miwako Dakeishi et al., *Relation between Benchmark Dose and No observed adverse effect Level in Clinical Research: Effects of Daily Alcohol Intake on Blood Pressure in Japanese Salesmen,* RISK ANAL. 26, 115-123 (2006).

102. Peter M. Chapman et al., *A Critical Evaluation of Safety (Uncertainty) Factors for Ecological Risk Assessment*, ENVIRON. TOXICOL. CHEM. 17, 99-108 (2009).

103. HEALTH CANADA, SCIENCE POLICY NOTE*:* THE APPLICATION OF UNCERTAINTY FACTORS AND THE PEST CONTROL PRODUCTS ACT FACTOR IN THE HUMAN HEALTH RISK ASSESSMENT OF PESTICIDES 6 (2008) (Can.).

104. Health Canada describes the use of uncertainty factors as follows:

> The term "uncertainty factor" is used to denote factors associated with interspecies extrapolation, intraspecies variation, extrapolation from a LOAEL to a NOAEL where no NOAEL is available, extrapolation for duration of dosing and database deficiencies. HEALTH CANADA, SCIENCE POLICY NOTE: THE APPLICATION OF UNCERTAINTY FACTORS AND THE PEST CONTROL PRODUCTS ACT FACTOR IN THE HUMAN HEALTH RISK ASSESSMENT OF PESTICIDES 5 (2008) (Can.).

105. *Conducting a Human Health Risk Assessment*, U.S. ENV'T PROT. AGENCY, https://www.epa.gov/risk/conducting-human-health-risk-assessment (last visited Jan. 27, 2022).

an organism, which might mean that the organism is able to repair any damage that might be caused. However, it might also mean that no effects are observed because the numbers of animals tested were too low to determine, with confidence, the effects of exposure at a low dose. Toxicologists have generally accepted that there is no threshold for chemicals that act as mutagens, by damaging DNA or changing the DNA reading sequence. In other words, it is assumed that any level of exposure to these chemicals may cause harm. Ingredients in cigarette smoke serve as an example. Many of the chemicals found in cigarette smoke do cause DNA damage; human epidemiology studies have associated even passive smoking (exposure to second-hand smoke) with adverse health effects.[106] Based on this evidence, many scientists and regulatory agencies conclude that there is no safe level of exposure to these chemicals—in other words, no threshold. This has led many jurisdictions to seek to reduce exposure as much as possible, for example by banning smoking cigarettes indoors, in cars, and near building entrances.

The question that many scientists and regulatory authorities are facing is how to assess the risk associated with exposure to chemicals for which the relationship between dose and health effects is not monotonic—that is, does not follow the pattern whereby a greater dose leads to a greater effect. Some studies of EDCs, including a number with BPA, have reported effects at low doses that were not observed at higher doses.[107] This phenomenon is known as a non-monotonic dose-response relationship (NMDR).[108] A review of the scientific literature on BPA reveals that the detection of NMDRs varies according to both the endpoints being measured and the number of doses evaluated in individual studies. There is an increase in the detection of NMDRs in studies with higher numbers of doses.[109] NMDRs may be U-shaped, meaning that the highest response for the endpoint that is measured occurs in the lowest and highest dose ranges, or have an inverted U-shape, in which the highest response occurs in

106. NATIONAL RESEARCH COUNCIL, ENVIRONMENTAL TOBACCO SMOKE: MEASURING EXPOSURES AND ASSESSING HEALTH EFFECTS 8–12 (1986).

107. Laura N Vandenberg et al., *Hormones and Endocrine-Disrupting Chemicals: Low-Dose Effects and Nonmonotonic Dose Responses,* ENDOCR. REV. 33, 378-455 (2012); Fabien Lagarde et al., *Non-Monotonic Dose-Response Relationships and Endocrine Disruptors: A Qualitative Method of Assessment* ENVIRON. HEALTH 14, 13 (2015).

108. Lagarde et al., supra note 74.

109. Corinne E Hill et al., *Nonmonotonic Dose–Response Curves occur in Dose Ranges that are Relevant to Regulatory Decision-Making,* DOSE-RESPONSE 16, 1559325818798282 (2018).

the intermediate dose range.[110]

Health effects at low, environmentally relevant doses[111] have been observed in human population studies.[112] Human epidemiological studies may follow a cohort, or a large group of subjects, for many years, or they may be based on natural experiments such as chemical spills or workplace exposure to a substance that is later identified as toxic. There are concerns that these effects may not be observed in the conventional toxicology testing used to inform regulatory decisions and may therefore be excluded from the risk assessment process. However, the data from epidemiological experiments are often available only after the fact, once a chemical is found in the environment at levels that have raised concern, which means that these insights are too sporadic and arrive too late to play a role in preventing exposures that may be associated with adverse health effects.

Concern about the ability of toxicity tests to detect NMDRs associated with low-dose effects and exposure to some EDCs, such as BPA, led the United States Environmental Protection Agency (EPA) to ask the National Academies of Sciences, Engineering, and Medicine to form a committee to develop a strategy to evaluate the evidence for endocrine-related low-dose effects.[113] Based on a review of both animal and human studies for two EDCs, phthalate plasticisers and brominated flame retardants, the Committee observed that there were similar outcomes in animals and humans and that even though dose ranges differed, the magnitude of changes (effect estimates) were similar.[114] The integration of these approaches can increase confidence in the data.

IV. INTRODUCTION OF NEW APPROACHES TO TOXICITY TESTING

In a ground-breaking report entitled *Toxicity Testing in the 21st*

110. Vandenberg *supra* note 70, at 138.

111. An environmentally relevant dose is a dose that is or could be observed in real-world conditions.

112. Andrea C. Gore et al., *Implications of Prenatal Steroid Perturbations for Neurodevelopment, Behavior, and Autism,* ENDOCR. REV. 35, 961-991 (2014); Åke Bergman et al., *The Impact of Endocrine Disruption: A Consensus Statement on the State of the Science,* ENVIRON. HEALTH PERSPECT. 121, A104-106 (2013); Vandenberg *supra* note 74.

113. NATIONAL ACADEMIES OF SCIENCES, ENGINEERING, AND MEDICINE, APPLICATION OF SYSTEMATIC REVIEW METHODS IN AN OVERALL STRATEGY FOR EVALUATING LOW-DOSE TOXICITY FROM ENDOCRINE ACTIVE CHEMICALS 1 (2017).

114. NATIONAL ACADEMIES OF SCIENCE, ENGINEERING, AND MEDICINE, *supra* note 115, at 159.

Century: A Vision and Strategy, published in 2007, the United States National Research Council (NRC) referred to "a revolution" in biology building on

> progress being made in the elucidation of cellular-response networks. Those networks are 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.[115]

The Toxicity Testing in the 21st Century report (TT21C) was born of an initiative by the EPA and the US National Institute of Environmental Health Sciences (NIEHS) to develop guidance for new approaches to toxicity testing.[116] The NRC's objectives for such new approaches were identified as follows:

- 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.[117]

One of the problems identified by the NRC consisted of "major gaps in current toxicity-testing approaches," while emerging technologies are deemed to hold "great promise for screening chemicals more rapidly."[118] In addition to considerations arising from the drive to refine, reduce and replace animal use (3Rs),[119] the NRC noted that "the relevance of . . . animal studies [involving high doses] for the assessment of risks to heterogeneous human populations exposed at much lower concentrations has been questioned."[120]

The TT21C report proposes "a transformative paradigm shift" involving *in vitro* (cell or organ cultures, lower species animal models,

115. NATIONAL RESEARCH COUNCIL (NRC), Toxicity Testing in the 21st Century: A Vision and a Strategy 36 (2007).

116. *Id.* at 1–2.

117. *Id.* at 42–3.

118. *Id.* at 28.

119. W.M.S. Russell and R.L. Burch, *The Removal of Inhumanity: The Three R's*, THE PRINCIPLES OF HUMANE EXPERIMENTAL TECHNIQUE (spec. l ed., Universities Federation for Animal Welfare 1992) https://caat.jhsph.edu/principles/chap4d.

120. NATIONAL RESEARCH COUNCIL, *supra* note 116 at 35.

or *in silico* computer modelling) methodologies to predict toxicity, rather than relying on *in vivo* experiments with rodents or other mammalian species.[121] Realising this vision would require extensive development of test procedures and of approaches and methodologies for interpreting and extrapolating the results to human populations.[122] The reason why the report's authors describe the proposed approach as transformative is that it involves a different approach to identifying health outcomes than that at the heart of traditional toxicology with its dependence on *in vivo* testing. Rather than looking for "apical end points," that is, major changes observed in test subjects, an approach that relies heavily on *in vitro* and *in silico* methods instead focuses on "important biologic perturbations in key toxicity pathways."[123] Such perturbations indicate a potential to cause adverse health outcomes without demonstrating the actual health outcomes experimentally.

Initiatives such as this hold great promise for uncovering more information and insight, more rapidly, into BPA and other known or potential EDCs. Despite the immense investment of time and resources into studying BPA, significant uncertainties remain about its health effects. These uncertainties are partly due to the complexity of human organisms and the multifaceted roles played by the endocrine system. However, they also have to do with certain inherent limitations of high-quality toxicology studies following conventional methodologies and approaches, as well as the difficulties of extrapolating from those studies to human organisms in light of the kinds of exposures to which people are subject in the real world. When one considers that BPA is not the only bisphenol, let alone chemical, whose endocrine-disrupting properties are insufficiently understood, the immensity of the challenge facing scientists and regulatory agencies is more apparent. Thousands of new chemicals enter into commerce annually, some of which are produced in high volumes and which, therefore, may lead to high levels of exposure. Conventional *in vivo* toxicity tests and risk assessments for all these chemicals would require immense resources and take a good deal of time. The Canadian government has sought to address this issue by requiring the submission of data on new substances prior to their entry into the Canadian market.[124] Nevertheless, the need for rapid production of

121. *Id.* at 46–47.

122. *Id.* at 48.

123. *Id.*

124. Chemicals Management Plan Science Committee, *Advancing Consideration of Endocrine-disrupting Chemicals under the Canadian Environmental Protection Act, 1999*,

information remains pressing. This has led to tremendous interest among researchers in academia, government, and industry in the development of new approach methods (NAMs) to screen and prioritise chemicals for their potentially adverse biological effects. Government regulatory agencies and international organisations such as the OECD are evaluating these new approaches and seeking to determine how they contribute to priority setting and risk assessment. One of the major attributes of NAMs is that they promote the 3 Rs by *reducing* the number of animals used, *replacing* animal testing, and use of *refined* methodology to decrease animal pain, distress and/or suffering.[125]

A. In silico Methodology

In silico, or computer-based, toxicology can be used to analyse, simulate, visualize, and predict the toxicity of a substance. This methodology was developed for pharmacology, using information from computational methods to screen chemicals for potential beneficial or adverse effects to develop therapeutic drugs.[126] The most common *in silico* methods are quantitative structure-activity relationship (QSAR) models.[127] QSAR models employ algorithms to predict toxicity based on the characteristics of chemicals.[128] Large datasets composed of previously-established biological information regarding a particular molecule (the parent molecule) are used to predict the biological activity of molecules with similar structures.[129] The QSAR models can then be used to make predictions about the biological effects of other chemicals that possess a given structural feature.[130] In addition, they may be used to enhance the robustness of

CANADA.CA (July 18-19, 2018) https://www.canada.ca/en/health-canada/services/chemical-substances/chemicals-management-plan/science-committee/meeting-records-reports/committee-report-july-18-19-2018.html (Can.).

125. Thomas Hartung, *From Alternative Methods to a New Toxicology,* EUR. J. PHAR. BIOPHARM. 77, 338-349 (2011).

126. Luis G. Valerio Jr., *In Silico Toxicology for the Pharmaceutical Sciences*, TOXICOL. APPL. PHARMACOL. 241, 356-370 (2009).

127. Arwa B Raies & Vladimir B Bajic, *In Silico Toxicology: Computational Methods for the Prediction of Chemical Toxicity*, WILEY INTERDISC. REVS COMPUT. MOL. SCI. 6, 147-172 (2016); Glenn J Myatt et al., *In Silico Toxicology Protocols*, REGUL TOXICOL PHARM 96, 1-17 (2018).

128. ALOK DHAWAN & SEOK KWON, IN VITRO TOXICOLOGY (2017); Giuseppina Gini, *QSAR Methods*, *in* SILICO METHODS FOR PREDICTING DRUG TOXICITY (2016).

129. Dhawan & Kwon, *supra* note 128; Bas J. Blaauboer et al., *The Integrated Use of Alternative Methods in Toxicological Risk Evaluation - ECVAM Integrated Testing Strategies Task Force Report 1*, ALTERN. LAB. ANIM. 27, 229-237 (1999).

130. This is a very well-accepted view among toxicologists but by no means a unanimous one: see, e.g., Bas J. Blaauboer & Melvin E. Andersen, *The Need for a New Toxicity Testing and Risk*

in vitro and *in vivo* methods by making predictions regarding ideal experimental conditions, thus improving the design of research protocols.[131] The OECD has developed a QSAR Toolbox, designed to help users to fill data gaps, that is being used in a number of regulatory programmes.[132]

Other *in silico* programmes are also being used to provide rapid exposure estimates for thousands of chemicals.[133] Targeted analyses are used to detect chemicals that scientists expect to find in a sample.[134] Non-targeted analyses, requiring sophisticated technologies and data processing capacity, can be used to identify both known and unknown chemicals in our environment.[135] Finally, software packages have been developed to estimate chemical concentrations in humans following exposure.[136] Many of the tools and resources that can be used to estimate chemical exposures are available on the website of the US EPA.[137] Using these models and approaches, it is possible to make useful predictions about exposure.

Despite certain limitations, the predictive capacity of *in silico* models renders them a robust and economical complement to *in vitro* and *in vivo* methods.[138] Many regulatory agencies, including Health Canada, are looking closely at these methodologies, but their

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Analysis Paradigm to Implement REACH or Any Other Large Scale Testing Initiative, ARCH. TOXICOL. 81, 385-387 (2007). Huanxiang Liu et al., *QSAR Prediction of Estrogen Activity for a Large Set of Diverse Chemicals under the Guidance of OECD Principles*, CHEM. RES. TOXICOL. 19, 1540-1548 (2006).

131. Blaauboer & Andersen, *supra* note 131, at 386.

132. *OECD QSAR Toolbox: Frequently Asked Questions*, OECD, https://www.oecd.org/env/ehs/risk-assessment/oecdqsartoolboxfrequentlyaskedquestions.htm (last visited July 21, 2020).

133. *Rapid Chemical Exposure and Dose Research (ExpoCast)*: https://www.epa.gov/chemical-research/rapid-chemical-exposure-and-dose-research, U.S. EPA (last visited July 21, 2020).

134. Heidelore Fiedler et al., *A Critical Review of a Recommended Analytical and Classification Approach for Organic Fluorinated Compounds with an Emphasis on Per- and Polyfluoroalkyl Substances,* INTEGR. ENVIRON. ASSESS. MANAG. 17, 331-351 (2021).

135. Jon R Sobus et al., *Integrating Tools for Non-targeted Analysis Research and Chemical Safety Evaluations at the US EPA,* J. EXPO. SCI. ENV. EPID. 28, 411-426 (2018).

136. Katie Paul Friedman et al., *Utility of In Vitro Bioactivity as a Lower Bound Estimate of In Vivo Adverse Effect Levels and in Risk-Based Prioritization,* TOXICOL. SCI. 173, 202-225 (2020).

137. United States Environmental Protection Agency (EPA), *Rapid Chemical Exposure and Dose Research* https://www.epa.gov/chemical-research/rapid-chemical-exposure-and-dose-research#1, (last visited Mar. 31, 2022).

138. OECD, GUIDELINES FOR THE TESTING OF CHEMICALS, https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-1-physical-chemical-properties_20745753 (last visited May 18, 2020).

widespread adoption to support regulatory decision-making depends on a strong consensus among toxicologists that these methods are robust and reliable.

B. In vitro Methods

In vitro toxicology may contribute important information on the mechanism of action of a chemical – that is, *how* it produces or contributes to particular health outcomes.[139] Another advantage of *in vitro* methods is their efficiency, resulting in savings in labour, cost, and time.[140] It is relatively easy to generate *in vitro* studies on a sufficiently large number of chemicals over a wide range of concentrations to produce confidence in the results. The caveat is that isolated cells cannot capture everything that may occur in an intact tissue, organ, animal, or person: the laboratory environment in which cell cultures are maintained is dramatically different from the environment of a living organism.[141] Nevertheless, data derived from these *in vitro* methods can be used to screen large batteries of chemicals, generating large data sets and important insights into the effects of chemicals. These screening techniques, known as high throughput and high content screening (HTS, HCS) cell culture-based approaches, have been used to assess the biological activity of thousands of chemicals.[142] This initiative, known as Tox 21, proposes "a transformative paradigm shift" from reliance on *in vivo* methods to the use of *in silico* and *in vitro* methodologies.[143]

C. Organoids and Lower Species Animal Models

While analyses of the effects of a chemical in cell culture systems provide valuable information, it is also important to understand how cells interact. During *in utero* development, embryonic stem cells differentiate to form all the organs in the body. Each organ is composed of many distinct cell types, and their interactions are crucial. Allowing cells in culture to grow either on their own, or in combination with other cells derived from the same tissue, into a three dimensional

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139. VA Baker, *Endocrine Disrupters: Testing Strategies to assess Human Hazard,* TOXICOL IN VITRO, 15, 413-419 (2001); Marcel Leist et al., *Adverse Outcome Pathways: Opportunities, Limitations and Open Questions,* ARCH. TOXICOL. 91, 3477-3505 (2017).

140. *Id.*

141. *Id.*

142. Abishankari Rajkumar et al., *Elucidation of the Effects of Bisphenol A and Structural Analogs on Germ and Steroidogenic Cells Using Single Cell High-Content Imaging.* TOXICOL. SCI. 180, 224-238 (2021).

143. *See* NAT'L RSCH. COUNCIL (NRC), *supra* note 115, at 46–47.

structure known as an organoid, is leading to greater understanding of importance of cell-cell communication in determining the effects of exposure to a chemical. To capture the intricacy of these interactions and their impact on organ functions, the US National Center for Advancing Translational Sciences (NCATS) and collaborators are focusing on the development of "tissues on a chip" to model the structure and function of human organs.[144] There is interest in the use of these tissue chips known as organoids for toxicity testing and prediction of drug safety.[145]

There is also interest in the possibility that toxicity testing in simpler species provides valuable information that will bridge the gap between *in vitro* and more traditional *in vivo* approaches. One of the model species that is of interest to researchers and industry is *Caenorhabditis elegans*, a worm that has many different organs yet is small, easy to culture in a lab, and has a short life cycle.[146] These characteristics make *C. elegans* amenable to high-throughput technologies. The zebrafish (*Danio rerio*) has also become very popular as an experimental model, in part because its embryos are transparent, facilitating the study of effects on development.[147]

D. Validation of NAMs

Tremendous international collaborative efforts are underway to incorporate NAMs into regulatory decision-making.[148] A range of international and national organisations and agencies are in the process of validating alternative methods.[149] The validation process ensures

144. *Tissue Chip Initiatives and Projects*, NAT'L CTR. FOR ADVANCING TRANSLATIONAL SCI., https://ncats.nih.gov/tissuechip/projects#:~:text=NCATS%2Dsupported%20researchers%20are%20testing,and%20genetic%20changes%20in%20space (last visited Aug. 17, 2020).

145. *Id.*

146. Maxwell CK Leung et al., *Caenorhabditis elegans: An Emerging Model in Biomedical and Environmental Toxicology,* TOXICOL SCI 106, 5-28 (2008).

147. Keng Po Lai et al., *Zebrafish as the Toxicant Screening Model: Transgenic and Omics Approaches.* AQUAT TOXICOL 234,105813 (2021).

148. Reza Farmahin et al., *Recommended Approaches in the Application of Toxicogenomics to derive Points of Departure for Chemical Risk Assessment*, ARCH TOXICOL 91, 2045-2065 (2017); Robert J. Kavlock et al., *Accelerating the Pace of Chemical Risk Assessment*, CHEM RES TOXICOL 31, 287-290 (2018); Krewski et al., *supra* note 10.

149. European Centre for the Validation of Alternative Methods (EVCAM). Inter-Agency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). Japanese Centre for the Validation of Alternative Methods (JaCVAM). Annamaria A Bottini et al., *Optimisation of the Post-Validation Process: The Report and Recommendations of ECVAM Workshop 67*, ATLA-ALTERN. LAB. ANIM. 36, 353-366 (2008) (discussing the three initiatives and some of their activities).

that the alternative methods developed by researchers will be accepted by regulatory agencies for safety testing and assessment purposes, product approval, or classification.[150] Test method validation refers to a scientifically rigorous process of determining the reliability and relevance of a particular test method and the extent to which a procedure (or assay) using this method accurately measures or predicts a biological effect.[151] The correlation between the data obtained *in vivo*, *in vitro,* and *in silico* should be consistent, reproducible, and easy to access.[152] Of course, the inherent limitation of the data obtained using any of these approaches is that they may not be applicable to humans due to potential differences in the molecules that are targeted and the manner in which the chemicals are handled in humans, as opposed to laboratory conditions or computer models.[153] For instance, the molecules or pathways that are targeted in humans may not be present in animals or cells. Further, the way the chemical is handled in the body may increase or decrease its toxicity, since metabolism may render the substance harmless or increase its activity. In addition, different means of eliminating chemicals will affect the body's response. Perhaps it is not surprising that the effects produced by a chemical, such as BPA, may depend on the test system (*in silico, in vitro*, or *in vivo)* and that this will need to be considered in interpreting the data. In addition, BPA exposure may produce various integrated biological outcomes at different periods of life. This is not unique to BPA. The development of pathways, known as Adverse Outcome Pathways,[154] that "describe a logical sequence of causally linked events at different levels of biological organisation, which follows exposure to a chemical and leads to an adverse health effect in humans or wildlife" is one of the goals of the OECD.[155] It is anticipated that this type of "chemical risk assessment based on mechanistic reasoning" will be very useful in allowing researchers and regulators to connect the findings from different test systems with health outcomes.[156]

150. Helena Kandárová & Silvia Letašiová, *Alternative Methods in Toxicology: Pre-Validated and Validated Methods*, INTERDISCIP. TOXICOL. 4, 107-113 (2011).

151. *Id.*

152. *Id.*

153. Coady KK. et al., *Current Limitations and Recommendations to improve Testing for the Environmental Assessment of Endocrine Active Substances*. INTEGR. ENVIRON. ASSESS. MANAG. 13, 302-316 (2017).

154. Matthieu Mondou et al., *Envisioning an International Validation Process for New Approach Methodologies in Chemical Hazard and Risk Assessment*, ENVIRON. ADVANCES 4, 100061 (2021).

155. *Id.*

156. USERS' HANDBOOK SUPPLEMENT TO THE GUIDANCE DOCUMENT FOR DEVELOPING

The acceptance of new approaches and methodologies by scientists can be a slow and sometimes difficult process. Scientists must have grounds for confidence in those methodologies; this requires having extensive experience with their accuracy and prediction value. Only then can a substantial body of evidence be developed that is sufficiently robust, reliable, and relevant to generate confidence. Once a certain degree of consensus around a novel approach or methodology has been arrived at by scientists, the truly hard work begins: namely, the post-validation process, involving acceptance of scientifically approved methodologies by regulatory agencies.[157] As Annamaria Bottini and colleagues note, regulatory agencies often take a conservative approach to studying chemical risk, with the result that accepted methods for determining hazard and risk can come to be "frozen in time."[158] One very important reason for this conservatism is that public safety depends on the scientific inputs that contribute to regulatory decision-making, inputs that depend heavily on methodology.[159] In addition, regulators are themselves not always particularly knowledgeable about methodological developments.[160]

The universal validity of scientific knowledge should militate in favour of take-up of scientific progress on methodology across the globe, at roughly the same rate from one region or state to another. But this does not necessarily happen,[161] in part because of different cultural, social, economic, and political factors in different states. Some important differences include varying levels of risk aversion, different degrees of aversion to different types of risk, varying levels of confidence of political authorities and members of the public in science, and different understandings of what constitutes an appropriate division of labour among scientific experts and other participants in decision-making. Be that as it may, a degree of global consensus on methodologies and approaches for toxicity testing is necessary to avoid patchworks of standards that impede trade flows, as well as lack of confidence in regulatory authorities beyond one's

AND ASSESSING ADVERSE OUTCOME PATHWAYS, OECD, https://www.oecd-ilibrary.org/environment/users-handbook-supplement-to-the-guidance-document-for-developing-and-assessing-adverse-outcome-pathways_5jlv1m9d1g32-en (last visited July 21, 2020).

157. Bottini et al., *supra* note 149, at 353.

158. Annamaria A. Bottini et al., *Food for Thought. . . on Globalisation of Alternative Methods*, ALTEX 24, 255-269 (2007).

159. *Id.*; Bottini et al., *supra* note 149, at 361.

160. *Id.*

161. Bottini et al., *supra* note 158, at 255.

borders. For these and other reasons, various international organisations and interjurisdictional bodies and processes have been tasked with harmonising, or at least coordinating, the scientific validation of testing methodologies as a means of promoting the widespread take-up of a common suite of approaches and methods across the globe. Chief among these organisations is the OECD. Regional and national bodies have also been created explicitly to promote the validation of alternative methods in Canada,[162] Europe,[163] the United States,[164] and Japan.[165]

In vetting new methodologies, regulatory agencies look to the usefulness and limitations of the test method. They seek to determine the method's reliance, meaning the reproducibility of results from a test within and across laboratories and over time, when performed using the same standardized protocol, and relevance, meaning the usefulness of results in light of the purposes and objectives pursued by testing.[166] Recently, several alternative methods (the direct peptide reactivity assay, Keratinases, and the human cell line activation tests) have been validated for use in predicting the ability of chemicals to elicit an allergic reaction in skin.[167]

V. CONCLUDING REMARKS

The challenges that known and suspected EDCs pose to political authorities are significant. Many of the health effects that these substances produce, or are suspected to produce, are serious. Gaining insights into their impact is arduous, time-consuming, and resource-intensive. Even for substances such as BPA that have received an enormous amount of scientific and regulatory scrutiny, knowledge gaps and scientific controversies remain significant. NAMs hold immense promise, but many of these methodologies remain to be

162. CANADIAN CENTRE FOR ALTERNATIVES TO ANIMAL MODELS (CCAAM); CANADIAN CENTRE FOR THE VALIDATION OF ALTERNATIVE METHODS (CaCVAM).

163. EUROPEAN CENTRE FOR THE VALIDATION OF ALTERNATIVE METHODS (EVCAM).

164. INTER-AGENCY COORDINATING COMMITTEE ON THE VALIDATION OF ALTERNATIVE METHODS (ICCVAM).

165. JAPANESE CENTRE FOR THE VALIDATION OF ALTERNATIVE METHODS (JaCVAM) (discussing these three initiatives and some of their activities); *see also* Bottini et al., *supra* note 149.

166. Niladri Basu et al., *EcoToxChip: A Next generation Toxicogenomics Tool for Chemical Prioritization and Environmental Management*, ENVIRON. TOXICOL. CHEM. 38, 279-288 (2019); Leon H. Bruner et al., *Validation of Alternative Methods for Toxicity Testing*, TOXICOL. IN VITRO, 10, 479-501 (1996).

167. Joyce VB. Borba et al., *Pred-Skin: A Web Portal for Accurate Prediction of Human Skin Sensitizers*, CHEM. RES. TOXICOL. 34, 258-267 (2021).

validated. Regulators interested in exploring and expanding reliance on NAMs face risks. Moving from well-understood toxicological methodologies, with which scientists, regulators, and industry have many decades of experience, to much newer and less familiar methodologies is a difficult process involving complex communications between science and policy to foster confidence and trust, and further confidence-building work with stakeholders, including industry and civil society.

As we have seen, the regulation of BPA by Canada and other states takes place against a backdrop of scientific uncertainty and controversy. It is clearly not up to government agencies to arbitrate these controversies, but at the same time they cannot simply wait for them to be resolved. It may be that increasing experience with NAMs will promote their broader acceptance within scientific communities, and that regulatory authorities and stakeholders will themselves learn to trust in the capacity of these methodologies to relay relevant and reliable information on risk. However, as Cynthia Hardy and Steve Maguire note, the shift from one approach for generating insight into risks posed by chemicals to another approach itself generates an array of different types of risks for regulatory agencies, industry, civil society organisations and many other actors that either make representations regarding safety on the basis of particular bodies of knowledge or rely on those representations in pursuing their own activities.[168]

The Canadian regulatory decision on BPA was made at a particularly turbulent time in the science of endocrine disruption. Regulatory agencies in Canada and other jurisdictions must navigate a context which is rendered more complex with ongoing developments in toxicology and endocrinology. Our aim in this paper has been to shed light on the regulatory decision-making process and the broader scientific context in which it is embedded, and to draw attention to ongoing scientific developments of great relevance to the regulation of EDCs.

168. Maguire & Hardy, *supra* note 57.