Endocrine-disrupting chemicals 2

Endocrine-disrupting chemicals: economic, regulatory, and policy implications

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Endocrine-disrupting chemicals (EDCs) substantially cost society as a result of increases in disease and disability but—unlike other toxicant classes such as carcinogens—have yet to be codified into regulations as a hazard category. This Series paper examines economic, regulatory, and policy approaches to limit human EDC exposures and describes potential improvements. In the EU, general principles for EDCs call for minimisation of human exposure, identification as substances of very high concern, and ban on use in pesticides. In the USA, screening and testing programmes are focused on oestrogenic EDCs exclusively, and regulation is strictly risk-based. Minimisation of human exposure is unlikely without a clear overarching definition for EDCs and relevant pre-marketing test requirements. We call for a multifaceted international programme (eg, modelled on the International Agency for Research in Cancer) to address the effects of EDCs on human health—an approach that would proactively identify hazards for subsequent regulation.

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This is the second in a Series of two papers about endocrine-disrupting chemicals

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Introduction

Endocrine-disrupting chemicals (EDCs) are chemicals capable of interfering with hormone action and which thereby contribute to disease and disability across the lifespan.[1–5] EDCs are found in food and food packaging, water, personal care products, household goods, detergents, fabrics and upholstery, electronics, medical equipment,[6–9] pesticides,[1] and ambient air (table 1).[10] Although many pharmaceuticals are designed to target the endocrine system to promote therapeutic benefits, the release of these drugs into waterways and sewage sludge allows them to contaminate the environment,[11–14] also potentially leading to endocrine disruption.[15,16]

In this Series paper, we examine the approaches that have been taken to quantify economic costs of EDC exposures, describe the regulatory approaches applied to EDCs to date, particularly in the USA and the EU, and detail the strengths and weaknesses of these regulations, showing where consideration of health and economic costs could improve regulations. Finally, we make policy recommendations for the development of methods to identify EDCs, prescribe specific steps to evaluate and restrict exposures, and call for a multifaceted and international programme to harmonise identification, characterisation, and regulation of EDCs in a global context.

Economic implications of EDC exposures

Estimates of the burden of disease and disability, and the costs of environmentally attributable disease, have proven extremely useful to translate findings and inform policy making. These costs are grounded in rigorous methodology first described by the US National Academy of Sciences[17] and leveraged to document the potential economic benefits of policy actions (eg, the phase-out of leaded gasoline, with annual benefits of US$110 billion to 319 billion in the USA[18] and $2·4 trillion globally[19]) when only increases in productivity are counted.

The Global Burden of Disease project uses an approach that calculates disability-adjusted life-year (DALY),[20] where valuations of $50 000 per DALY are used to calculate the costs[21] of clinically significant morbidities such as intellectual disability. DALY estimates currently generated by WHO[22] and Institute for Health Metrics and Evaluation[23] might not be sufficient to evaluate EDCs, which can adversely affect the intellectual capacity of individuals within the normal range of functioning; even decreases in intellectual quotient (IQ) within the normal range are associated with decreased lifetime economic productivity.[24] Economic evaluations relying solely on DALY estimates produce a 200-fold divergence from estimates taking IQ changes into account.[25]

Over the last several years, a series of economic evaluations estimated the burden and disease costs of EDCs on a range of outcomes including neurobehavioural deficits and diseases, male reproductive disorders, obesity and diabetes, and female reproductive disorders.[26–29] The economic burdens (€163 in the EU and $340 billion in the USA, annually) derived from these approaches are

	Representative EDCs
Pharmaceuticals	Trenbolone acetate, ethinylestradiol, dexamethasone, levonorgestrel, rosiglitazone
Cosmetics, personal care products	DBP, benzophenones, parabens, triclosan, DEET
Pesticides, herbicides, fungicides	Chlorpyrifos, glyphosate, pyraclostrobin, DDT, atrazine
Industrial chemicals	BPA, PCBs, triphenyl phosphate, PBDEs
Metals	Lead, cadmium, mercury, arsenic
Synthetic and naturally occurring hormones	Progesterone, testosterone, cortisol, oestrone

Representative EDCs from diverse functional use categories. EDC=endocrine-disrupting chemical. DBP=dibutyl phthalate. DEET=N,N-diethyl-m-toluamide. DDT=dichlorodiphenyltrichloroethane. BPA=bisphenol A. PCB=polychlorinated biphenyl. PBDE=polybrominated diphenyl ether.

Table 1: **List of representative EDCs in use**

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certain to be underestimates as they examined only a small subset of EDCs and health outcomes likely to be affected by EDC exposures.[30–32] These data demonstrate that improved regulations could improve citizens' health via reduction or elimination of exposures and result in huge economic benefits.

Current approaches to regulate EDCs

We review the approaches used for the regulation of EDCs in the EU and the USA, which have the most well developed and far-reaching regulations. We also identify regulatory approaches in other developed and industrialising nations and contrast approaches.

EU EDC regulations

EU regulations pertaining to chemical substances and environmental hazards are either usage-oriented (eg, biocidal products or cosmetics regulations) or medium-oriented (eg, air or water protection). European environmental policy[33] embraces the precautionary principle, which mandates that exposures should be limited when indications of potentially dangerous effects on the environment, human, animal, or planetary health exist, even in the absence of scientific certainty (table 2).[34,35] In 1999, the EU set in motion steps to prioritise substances for further evaluation as EDCs, monitor EDC exposures and effects, communicate information about EDCs to the public, and develop and validate new testing methods.[36] EU legislative instruments for consumer, health, and environmental protection were progressively amended to account for their EDC effects. In 2018, the EU reaffirmed its application of the precautionary principle and aim to minimise overall EDC exposures, with particular attention to critical windows of development.[37]

Plant protection products and biocides regulation

EDCs are banned from pesticides by the 2009 Plant Protection Products Regulation[38] and the 2012 Biocidal Products Regulation.[39] The hazard-based criteria for EDCs in pesticides are similar to the provisions regarding carcinogens, mutagens, and reproductive toxicants (CMRs).[38,39] Following scientific debate,[40,41] in 2018, the European Food Safety Authority and the European Chemicals Agency published a guidance document proposing how EDCs can be identified in pesticides, either individually or in mixtures, based on test results from the submitting company or the scientific literature.[42] To be considered an EDC, a chemical must produce an adverse effect, alter the functions of the endocrine system, and the adverse effect must be a biologically plausible consequence of the endocrine mode of action. Although these criteria are most aligned with a

	Approach in the EU	Approach in the USA	Argument for change
Overarching approach to chemical regulation	Largely a hazard-based approach—exposures should be limited when indications of potentially dangerous effects exist; no consideration of exposure	Entirely a risk-based approach—regulations must consider both hazards of a chemical and anticipated exposure to that chemical	Risk-based approach does not consider costs of EDCs to chronic disease burden; fails to appropriately capture exposure risks with long latency periods to health outcomes
Pesticides	EDCs banned from pesticides by the 2009 Plant Protection Products Regulation and 2012 Biocidal Products Regulation; EDCs not permitted as active ingredient unless human exposure is negligible; guidance document published on how to identify EDCs in pesticides	EPA mandated under Food Quality Protection Act (1996) to develop screening programme to identify oestrogenic EDCs in pesticide products; final committee report detailed two-tiered panel of assays for oestrogen, androgen, and thyroid-mediated effects; only ~50 pesticides have been screened through tier 1 assays and tier 2 is not yet validated	The approach to screening recommended by the Endocrine Disruptor Screening and Testing Committee was mired in regulatory hurdles and is too limited in testing only disruption of three receptors; need for screening systems that cover all endocrine modalities and that prevent authorisation if screening reveals EDCs
Cosmetics	Neither a general provision nor a definition regarding EDCs; EDCs handled on a case-by-case basis and can involve complete bans, or tolerable limits (eg, triclosan); animal testing is not allowed for substances used in cosmetics	Governed by the FDA Food, Drug, and Cosmetic Act; has no specific provisions to govern EDCs; fragrance loophole allows use of nondescript term fragrance to be used on labels to detail a mixture of chemicals and protect trade secrets	A definition and requirement to consider EDCs across all sectors will vastly simplify the regulatory landscape
Medical devices	EDCs are explicitly permitted above 0·1% in parts that come into contact with the body or bodily fluids only in certain conditions	Governed by the FDA Food, Drug, and Cosmetic Act; has no specific provisions to govern EDCs	A definition and requirement to consider EDCs across all sectors will vastly simplify the regulatory landscape
Drinking water	No specific requirements for testing of EDCs, but movement to add several EDCs to monitoring list	Safe Drinking Water Act explicitly covers oestrogenic EDCs and allows for submission to a screening programme if substantial populations might be exposed	A definition and requirement to consider EDCs across all sectors will vastly simplify the regulatory landscape; regulations must cover more than a single receptor and mode of action
Other sectors	Chemicals not explicitly covered in other specific regulations are covered under REACH; EDCs are regulated under REACH only if demonstrated to be of equivalent concern to CMR or PBT substances; authorisations and restrictions done under a risk-based approach	Chemicals not explicitly covered in other specific regulations are covered under TSCA. EDCs are not specified; authorisations and restrictions done under a risk-based approach	EDC-specific requirements under these overarching agreements would allow for more transparency about regulatory approach to these chemicals and consistent regulations across industries to reduce complexity and costs with standardisation

EDC regulations in the EU and the USA. Overarching approach to chemical regulation and sector or media-specific regulations and the discussion of potential avenues for improving these regulations. EPA=Environment Protection Agency. EDC=endocrine-disrupting chemical. FDA=Food and Drug Administration. REACH=Registration, Evaluation, Authorisation, and Restriction of Chemicals. CMR=carcinogenic, mutagenic, or toxic for reproduction. PBT=persistent, bioaccumulative, and toxic. TSCA=Toxic Substances Control Act.

Table 2: **Regulatory approach differences between the EU and the USA and proposed changes**

hazard-based approach, even when the criteria are met, permission to use the pesticide can still be granted if evidence exists that the adverse effect is irrelevant to humans (and other non-target organisms), or if exposure is negligible.

Registration, evaluation, authorisation, and restriction of chemicals (REACH)

REACH is a 2006 European programme that deals with the regulation of chemicals in the EU across multiple sectors, but excluding active substances of plant protection products, biocides, cosmetics, drugs, and chemicals used in medical devices. Annex XIV of REACH stipulates that chemicals that are CMRs, persistent, bioaccumulative, and toxic, and substances that are very persistent and very bioaccumulative, require approval by the European Chemicals Agency for use regardless of the level of human exposure. EDCs require approval by the European Chemicals Agency if demonstrated to be of equivalent concern to CMRs, which can only be achieved after rather lengthy procedures. For products regulated through REACH (including products with likely human exposure), hazards must be identified but authorisations and restrictions of use are decided after assessment of the risk resulting from exposure (ie, aligned with a risk-based rather than purely hazard-based management logic). As of February, 2020, 205 substances were included in the substances of very high concern (SVHC) list (16 for their endocrine-disrupting properties) and are subject to increased regulatory scrutiny and higher reporting standards. 43 substances were placed in annex XIV of REACH (two recognised as EDCs), marking the intent to ban their use once technically and economically suitable alternatives are available.

Compound-specific and country-specific regulations

Several EDCs have specific regulations that apply in all EU countries or in specific countries (table 3). A paramount case is that of bisphenol A (BPA), which in 2017 was listed as an SVHC by the EU due to its endocrine-disrupting properties. BPA was banned from baby bottles in 2011, and later from food containers for infants and young children; France has further banned BPA in all food containers and Sweden has banned its use in epoxies for household water pipes.

US EDC regulations

In the USA, the main chemical regulatory laws on food and food additives, drugs, and cosmetics are administered through the Food and Drug Administration (FDA) and those on pesticides and commercial chemicals not covered elsewhere through the Environmental Protection Agency (EPA).

Toxic Substances Control Act (TSCA)

TSCA, as originally administered in 1976, was intended to regulate all commercial chemical uses not explicitly covered in other sectors. Despite a mandate to proactively assess chemical safety, the EPA reviewed less than 10% of the more than 35 000 chemicals proposed from 1979 to 2004[43] and actively regulated less than ten.[44,45] Approximately 62 000 current-use chemicals were assumed safe at implementation unless the EPA could provide substantial evidence of unreasonable risk to human or environmental health, or both.[43,45] Other reasons for the apparent failure of TSCA to successfully regulate[46,47] include an overly strict standard of judicial review,[46,48] insufficient toxicity information for most chemicals,[46] short timeframes for review, confidential business information provisions,[49] and vague or complicated definitions and exemptions.[50]

A growing appreciation of these limitations led to TSCA reform in 2016.[51] The updated legislation requires the

For **REACH** see https://echa.europa.eu/regulations/reach/understanding-reach

	Country	Approach taken
Pesticides in agriculture	EU and Brazil	Hazard-based exclusion; EU: unless the exclusion applies, unless adverse effect irrelevant to humans (and other non-target organisms), or exposure negligible
EDCs	Australia	Considers the European hazard-based criteria as an indicator, triggering further evaluation in risk assessment of a chemical for ongoing use in products
EDCs	South Korea and Canada	Risk assessment approach identical to other synthetic chemicals
EDCs	Japan	Led some of the earliest initiatives to identify EDCs beginning in 1998, relying heavily on aquatic toxicity tests
EDC pollution	China	Part of its 13th Five-Year Plan of national environmental protection, though the detailed approach to controlling pollution is not made explicit
DEHP, DBP, and BBP	USA, Canada, Israel, Brazil, Hong Kong, Australia, China	Banned or restricted in toys and products for children
BPA	EU, South Africa, India, Canada, Israel, Brazil, USA	Restrictions (EU) or bans (others) for infant baby bottles or food contact materials intended for infants; Brazil: also ban on importation; Sweden: ban on epoxies for household water pipes; USA: not explicit ban, but use in baby products no longer permitted (also further state-specific regulations)
Nonylphenol and ethoxylates	South Korea, Canada, EU	Canada: substantial limits on manufacturing, use, and imports; South Korea: similar, also limits on use of products containing these chemicals; EU: production and use restrictions, both commercial and domestic
Lindane	Banned in 50+ countries	International ban under Stockholm Convention, 2009 (USA not signatory); still permitted as second-line medical treatment in some countries (eg, USA)
Organohalogen flame retardants	USA	US Consumer Product Safety Commission proposed class ban of PBDEs and other groups of organohalogens for all uses in consumer products; PBDEs specifically also voluntarily phased out by manufacturers through negotiations with EPA; PBDEs now banned under Stockholm Convention (USA not signatory)
PFAS	USA, others	PFOS: international ban under Stockholm Convention, 2009 (USA not signatory); PFOA: recent addition with some exemptions; USA: no specific regulations, though a health advisory limit set for drinking water; individual states setting limits below these EPA-mandated levels

Selected endocrine-disrupting chemical regulations in the global context. Selected EDCs chosen to span several diverse chemical classes, and countries or regions participating in regulations for each should not be considered comprehensive. EDC=endocrine-disrupting chemical. DEHP=di(2-ethylhexyl) phthalate. DBP=dibutyl phthalate. BBP=butylbenzyl phthalate. PBDE=polybrominated diphenyl ethers. BPA=biosphenol A. EPA=Environmental Protection Agency. PFAS=perfluoroalkyl and polyfluoroalkyl substances. PFOS=perfluorooctanesulfonic acid. PFOA=perfluorooctanoic acid.

Table 3: **Selected chemical-specific approaches to addressing EDCs**

EPA to conduct a risk-based review of all chemicals in commerce, prioritise chemicals to facilitate risk-based review, consider vulnerable populations, and determine safety before allowing marketing. Although the new TSCA also provides authority for the EPA to regulate chemicals, request additional safety testing, and gather additional data as needed,[48,52] endocrine disruption testing is not mentioned. Even if such testing was required, resources and protocols are insufficient to prioritise, evaluate, and rigorously assess newly proposed chemicals or those already in use. Although the EPA states that it has completed approximately 2600 new chemical reviews (as of February, 2020) since enactment of the revised legislation, only eight chemicals were halted pending more information; none have been prohibited.[53] The long-standing gaps in toxicity testing for chemicals are unlikely to have been addressed in such a short period of time.

For **Strategic Alliance for International Chemicals Management** see http://www.saicm.org

Food, Drug, and Cosmetic Act (FDCA)

The FDCA of 1938 requires that manufacturers produce food products that are safe, pure, wholesome, and labelled without deception, giving the FDA broad regulatory authority over products that fail to meet the requirements of the Act.[54] The Food Additives Amendment of 1958 addressed concerns applicable to food additives, but also exempted food additives from regulation if they were generally recognised as safe (GRAS).[54,55] No requirements exist to submit information regarding GRAS determination to the FDA,[56,57] and a comprehensive review of GRAS substances initiated in the 1970s was never completed.[57] A 1997 amendment established the principle of food contact substances and set out regulatory guidance for these chemicals, exempting materials contributing to dietary concentrations below 0·5 µg/kg (with the exception of likely or known carcinogens).[58] These issues have contributed to the FDA failing to reconsider the status of any GRAS substance since 1982, and resulted in more than 10 000 GRAS substances allowable in US food products today.[56] Notably, the FDA has no specific requirements for EDC testing nor action following their identification.[59] As such, EDCs such as nonylphenol, BPA, tributyltin, triclosan, and several phthalates are legally and intentionally used in food contact materials. These materials also contain polymerisation byproducts, impurities, and breakdown compounds known as non-intentionally added substances, many of which migrate into food.[60]

State regulatory authority

Several US states have regulations relevant to specific EDCs (table 3). California passed Proposition 65 in 1986, requiring the state to maintain a list of chemicals known to cause cancer or reproductive toxicity. This regulation requires product documentation detailing a potential risk to consumers beyond the so-called safe levels, although it does not specifically require listing of EDCs. Despite this limitation, the Proposition has inspired new legislation for deliberation in New York, where, if passed, the Consumer Chemical Awareness Act would give consumers information about consumer and personal care products that contain a carcinogen, mutagen, EDC, or other chemical of concern.

EDC regulations beyond the USA and the EU

EDCs have been identified as an emerging policy issue by the UN Environment Programme (UNEP), which oversees global policy through Strategic Alliance for International Chemicals Management. In 2015, the alliance welcomed the 2012 WHO and UNEP State of the Science report on EDCs, noting scientific dissent only from the chemical and pesticide industries.[61] Although the report identified efforts by the USA, the EU, Japan, and the Organisation for Economic Cooperation and Development to develop testing guidelines for EDCs, these tests focus exclusively on the oestrogen, androgen, and thyroid pathways,[62] and ignore not only other receptors (48 known human nuclear receptors exist), but also many other potential mechanisms of action.[5]

A 2017 report commissioned by UNEP and authored by the International Panel on Chemical Pollution, identified 28 policy actions, by governments worldwide, that substantially vary in the scope of EDCs addressed and emphasise evaluation of industrial chemicals (select examples included in table 3). The highly variable approaches to address and limit hazardous EDCs are especially concerning as synthetic chemical manufacturing and use are increasing rapidly in developing countries and economies in transition.[63]

Model regulations and harmonisation across the globe would go far, especially in the context of limited regulatory resources for oversight. Current efforts largely focus on monitoring adherence to existing international conventions (Stockholm, Basel, Rotterdam, etc) which are notable because they limit a subset of persistent organic pollutants (many EDCs), through binding international agreements (table 3). However, the USA has not ratified these agreements and continues to produce and export certain chemicals (chlordane, several flame retardants, etc) that these conventions have banned.

Consideration of economic costs: current approaches to EDC regulations

Balanced analyses should evaluate the costs of regulations and compare them with the costs—health care, economic, and otherwise—of failing to regulate. The costs associated with regulating a chemical (or class) would include the actual burden of implementing new laws and policies, as well as possible lost economic activity. There could also be benefits for another industry making similar products posing lower environmental and human health risk. The costs associated with inaction would include the economic burden to health and the environment incurred by exposure to the

unregulated compounds. From a societal perspective, a proper approach would be to weigh the costs of developing safer alternatives (which are initially borne by producers but ultimately passed to the consumer) against the economic benefits of reduced disease and disability. The real costs of replacing EDCs are often lower than initial estimates as innovation and technological developments, as well as consumer demand, address the need to identify substitutes in products. Still agencies in the EU and the USA tasked with protecting public and environmental health fail to take these costs into account when making regulatory decisions. Two examples presented here illustrate how regulatory failures in the USA and the EU have allowed EDC exposures to continue, contributing to morbidity and serious economic burdens.

A neurotoxic EDC continues to escape regulation in the USA

Chlorpyrifos, an EDC known to disrupt thyroid hormone action,[26] represents a clear regulatory failure by the US EPA.[64] Chlorpyrifos was voluntarily withdrawn by manufacturers (under agreement with the EPA) in 2000 for indoor pesticide use (with some exceptions), following evidence of neurotoxic effects.[65–67] In 2015, the EPA proposed to revoke all permissible uses in food products in response to a petition;[64,68,69] however, the EPA administrator reversed this decision in 2017, suggesting that there was insufficient animal evidence of adverse health impacts and improper dependence on epidemiological data. Following extended court challenges, the revocation was fully reversed in July, 2019,[70] allowing this pesticide to continue to be used on food crops. In February, 2020, a major manufacturer, Corteva, announced its intention to cease production in the USA, due to decreasing demand from agricultural users.[71]

Allowing the continued use of chlorpyrifos does not consider the ensuing economic burden. Based on its well documented associations with reduced IQ, estimated annual costs of $44 billion are expected in the USA[64] if exposures continue at current levels. These estimates do not account for other potential health effect costs beyond IQ loss, nor do they account for potential damage to the environment, including possible effects on pollinator species.[72] Furthermore, the failure to regulate chlorpyrifos has negative economic consequences for industries marketing safer alternatives.

By contrast, the European Food Safety Authority released a human health assessment for the renewal of approval for chlorpyrifos, which expired in January 2020.[73] The authority determined that given neurodevelopmental effects at the lowest doses examined in toxicological studies, and support for these findings in the epidemiological literature, no safe exposure level could be set for chlorpyrifos, and thus a risk assessment for use could not be completed. Because the approval criteria could not be met, EU approval has not been renewed.

An EDC is labelled an SVHC in the EU but given a clean bill of health in the USA

More than a hundred studies in humans suggest that exposures to BPA can contribute to endocrine diseases including obesity, diabetes, and neurodevelopmental disorders.[74] This literature is supported by more than 1000 studies from controlled laboratory experiments documenting the endocrine-disrupting properties of this chemical, and its effects on the health of rodents, aquatic animals, and non-human primates.[1,75,76] An extensive scientific literature on the associations between BPA and human diseases indicates that the procedures used to determine whether current human exposures are safe are insufficient and flawed.[77,78]

In response to concerns raised by health advocates and scientists, the National Institute of Environmental Health Sciences and National Toxicology Program developed a collaborative research study, CLARITY, to determine if the methods used for hazard assessments are sufficient for EDCs like BPA.[79,80] Exposures and standard toxicological endpoint examinations were done at the FDA, and masked organs, tissues, or animals were then transported to academic labs for additional mechanistic testing. Although the FDA continues to claim their results suggest BPA is safe at current levels of exposure, work from the academic partners shows that BPA affects the brain, prostate, ovary, and other organs at levels currently deemed safe.[81]

In the meantime, regulatory agencies in the EU have used these and other academic studies to conclude that BPA disrupts the mammary gland and cognitive function, and alters metabolism and reproduction.[82–84] The French environmental health agency, for example, has described in detail why BPA meets the legal criteria to be labelled an EDC. The substance was then recognised as an SVHC by the European Chemicals Agency.[85,86] Still, the agency concedes that this labelling is unlikely to sufficiently protect human health, noting that "authorisation is the most binding measure that can be associated with the SVHC status and it does not apply to monomers and intermediates. A significant amount of BPA is placed on the European market as a monomer and intermediate".[85]

Like chlorpyrifos, the failure to efficiently regulate BPA does not consider the economic costs of continued use of this chemical in consumer products. Estimates of BPA contributions to the costs associated with childhood obesity alone amount to $2 billion in the EU and $2·4 billion in the USA.[31] To date, there are no estimates of the economic contribution of BPA to other adverse health outcomes (eg, attention-deficit hyperactivity disorder, cancer, or infertility).

A path forward: policy recommendations

We next recommend actions centred on identification and mechanistic assessment of EDCs, strategies to monitor and reduce exposures, and regulatory actions that could better protect human and environmental health (table 4).

	Existing evidence	EDC change proposed	Argument for change
Consensus on EDC identification	Differing definitions of EDCs are currently used by nearly every agency and sector, no consensus; most require adverse effects in animal models	Legally valid definition of EDCs applicable in all sectors that does not require evidence of adverse effect in whole organism models	Different definitions are problematic for regulators and industry; requiring adverse effects as proof of harm necessitates a comprehensive understanding of all disease states and mechanisms of action
Consensus on methods to evaluate EDCs	Most US regulations require oestrogenic EDC testing only; most EU regulations for pesticides require oestrogen, androgen, and thyroid hormone axis	Two-tiered testing plan: tier 1 screening approach to evaluate all nuclear receptor-related and non-nuclear receptor mechanisms, some functional outcomes; tier 2 inclusive of diverse disease-state models in diverse species	Testing a single receptor for a single mechanism of action is insufficient; broad testing of known endocrine endpoints is needed to more thoroughly evaluate potential endocrine-mediated disruption and to prioritise for higher-order testing in animal models
Establishment of global biomonitoring programmes	Biomonitoring programmes are currently limited to very developed nations and monitor at most several hundred chemicals	Expansion of testing particularly to countries that do not have the resources to monitor these exposures is critical; expansion of testing to greater number of substances of high concern	A clear environmental justice issue; low-income and middle-income countries cannot afford a national biomonitoring programme and yet often are disproportionately exposed to products and waste deemed too contaminated from the wealthiest nations
Mandatory provision of chemical composition for marketed substances	Few requirements exist for provision of chemical compositions, often product suppliers do not appreciate chemical production chain for their own products; trade secret exemptions are considerable	Requirement for full disclosure of all chemical constituents and additives used in all consumer products; clear consequences for incorrect information	Far too much federal funding is going to simply identifying chemical constituents in consumer products rather than assessing potential health consequences from exposure; this expenditure is avoidable with regulations on industry disclosure and labelling
Inclusion of economic costs associated with EDC-related morbidities in cost	Economic costs related to EDC exposures are not included in relevant cost–benefit analyses	Requirement for regulations to consider the EDC-related morbidity costs and for WHO and Institute for Health Metrics and Evaluation to include these effects in estimates of the global burden of disease	Inclusion of these costs would have benefits on health outcomes, human suffering, health expenditures, and environmental justice concerns surrounding exposure inequalities; rapid increase in direct human evidence of adverse effects via EDCs
Hazard-based approach to regulation of EDCs	Used in part across EU regulations; USA uses a risk-based approach, using cost–benefit analyses	Shift to a hazard-based approach to regulating EDCs across all countries and sectors rather than using risk-based approaches	Delay to gather paramount human health studies, particularly with long latency disease outcomes; is not protective of human health; ignores potential impacts on health and biodiversity
Establishment of International Agency for Research on EDCs	Equivalent agency for the evaluation of chemical carcinogens has successfully operated for >50 years	An international agency under WHO to transparently evaluate potential EDCs	These consensus statements would be used by regulatory agencies around the world to limit exposures to EDCs and consolidate weight of evidence approaches

Key proposed policy changes needed to promote effective regulatory environment to protect human health from exposure to EDCs. EDC=endocrine-disrupting chemical.

Table 4: **Proposed policy changes to EDC regulations**

Testing and identifying EDCs

Our first recommendation centres on the identification of EDCs, as effective screening programmes are essential to subsequent actions. Unfortunately, the currently available or validated tests used to determine if a chemical is an EDC do not cover all endocrine modes of action. In the USA, regulations require testing for oestrogen agonist activity only for pesticides and drinking water contaminants, while the recommendations from the Endocrine Disruptor Screening and Testing Advisory Committee[87] promote evaluation of oestrogen, androgen, and thyroid receptor disruption. In the EU, the European Chemicals Agency and the European Food Safety Authority guidance document on the identification of EDCs in pesticides also recommends gathering information on oestrogenic, androgenic, thyroidal, and steroidogenic modalities.[88] Of these, disruption of the thyroid axis has particularly poor coverage, and other pathways (eg, metabolic, glucocorticoid, etc) are not covered at all. Further still, for the better covered modalities (eg, oestrogen and androgen signalling), the validated tests appear too insensitive for some EDCs, working best for endogenous hormones. For example, the uterotrophic assay measures oestrogen-dependent changes in uterine weight, though relatively high concentrations of oestrogenic EDCs must be administered to alter uterine weight,[89] and disruption of oestrogen signalling can occur without organ weight effects.[90] Sensitive assays exist to test a broader number of nuclear receptors, and other receptor types, and to assess some of the more diverse mechanisms of action for EDCs.[5] Assays to examine these mechanisms, such as receptor expression, hormone transport, hormone synthesis, and epigenetic alterations, should soon be validated for inclusion in regulatory requirements. In contrast, the Organisation for Economic Cooperation and Development guidance provides comprehensive documents pertaining to the development and validation of test guidelines for a variety of endocrine activities, including standardised protocols, mechanistic insights, and evaluation of new assays for potential inclusion, covering more diverse pathways than those formally required under US or EU regulations.

We propose that a two-tiered system be employed to identify suspected EDCs and known EDCs, similar to what others have suggested previously.[91] In the first tier, high-throughput screening methods are used to evaluate

substances for a wide range of endocrine modalities.[92,93] These assays should assess both agonist and antagonist activities of a broad range of receptors (not limited to nuclear types), and receptor-independent mechanisms, for comprehensive coverage across endpoints.[5] Work is needed to ensure appropriate validation and rigour in testing (including positive and negative controls, technical and biological replicates, quality assurance and control), to determine how results will be interpreted, how conflicting results from different screening assays targeting the same endpoint will be reconciled,[94] and how chemicals will be prioritised for additional higher-order testing. This high-throughput approach can support the testing of all receptor systems conducive to in-vitro screens, rather than focusing on a select few. Efforts to address this through high-throughput testing of diverse chemicals in diverse mechanism assays are underway through the ToxCast and Tox21 programmes,[95,96] though questions remain as to interpretation and quality control of these efforts.[94,97,98] These first-order tests should be coupled with more functional in-vitro assays to assess outcomes such as adipocyte development, steroidogenesis, and spermatogenesis, among others, to cover a broader biological base of potential EDC-induced disruption.

In the second tier, testing using more sensitive assays should be conducted, with a focus on endpoints relevant to human diseases, and targeting relevant critical windows to identify likely adverse impacts.[91] Because current regulations require that a chemical induces adverse effects to be recognised as an EDC, and adverse effects can only be observed in vivo, second tier assays will need to use vertebrate animals or epidemiological evidence until the regulatory definition of an EDC is significantly altered. The EPA has proposed restrictions and plans to eventually ban the use of mammals for regulatory testing, though there are no guidelines yet in place for how in-vitro assays will be used to fill this gap. EU authorities, in contrast, have legislation in place proposing the replacement, reduction, and refinement of vertebrate animal testing, like the Organisation for Economic Cooperation and Development guidelines. Until the EDC definition is updated and guidelines are available to use in-vitro data for regulatory purposes, in-vivo assays must continue to provide crucial toxicological data. Non-mammalian vertebrate models such as fish (zebrafish, medaka) and amphibians (*Xenopus*)—particularly larval stages that would obviate the EU restrictions—and invertebrate models have great potential to also fill this research gap. Hormone receptors are highly conserved across vertebrates,[99] the ease of breeding and short developmental timing allow for comprehensive mixture testing, and functional conservation in areas such as adipose biology, lipid metabolism, and glucose signalling provides robust utility in modelling human disease states.[100] These and more typical mammalian models (eg, rodents) should be used to help ensure rigorous validation of in-vitro assays and to examine more complex organismal responses. Where possible, linkages should be assessed between first-order mechanistic testing and higher-order in-vivo outcomes to elucidate potential pathways underlying effects; importantly, however, adverse endocrine outcomes should not be discounted for lacking this mechanistic information. A determination of adverse effect should be sufficient for identification as an EDC and subsequent regulation.

As chemicals are identified as EDCs and regulated based on these tests, care must also be taken to limit regrettable substitutions. Polybrominated diphenyl ethers were replaced with organophosphate ester flame retardants that have their own health concerns,[101] and BPA has been replaced in some products with other bisphenols that have similar or worse effects for particular endpoints.[102,103] Regulations that support development of safer alternatives and require testing before allowing alternatives onto the market should help prevent regrettable substitutions. These pre-market tests should encompass the defined in-vitro and in-vivo endpoints we have discussed; chemicals intended for commerce should receive the same attention given to chemicals already present on the market.

Evaluating exposures to EDCs

Our second recommendation encompasses evaluating exposures to EDCs. In a hazard-based regulatory environment, chemicals identified as EDCs would simply be removed from use, at least for products entailing possible human exposure. A risk-based regulatory approach currently prevails in which the effects are evaluated on the basis of degree of exposure. It is therefore essential that decision makers know how chemicals are being used, can access robust biomonitoring data so that exposures can be characterised, and can implement exposure mitigation programmes as needed. Although some developed nations have highly informative biomonitoring programmes, more of such efforts must be developed worldwide (eg, to capture the dynamic complexity of exposures). Human exposure data should be accessible to researchers and organisations to foster analyses of global trends and factors influencing exposures. These factors can also power global and local educational campaigns to inform the broader public about safe and simple steps to reduce EDC exposures, accompanied by regulations that make it compulsory to provide information on the chemical composition of marketed products and their hazards. A type of measure that has long proven to have a high impact in decreasing human exposure to EDCs is to withdraw from the market a product or set of consumer products causing such exposure.

Limiting exposures to EDCs through regulations

Our third major recommendation centres on improving regulations governing EDCs. We suggest three main avenues to bolster regulatory approaches to these chemicals: a legally valid definition of EDCs applicable in all sectors of the economy and jurisdictions of the world,

inclusion of economic costs of EDC-related health effects in global disease estimates, and a hazard-based approach to EDC regulation, at least when human exposures occur. The Endocrine Society has defined an EDC as "any chemical or mixture of chemicals that interferes with any aspect of hormone action" whereas other definitions, such as that from WHO, specifically require that an adverse effect is documented.[1,104,105] Requiring an adverse effect to define an EDC is problematic because regulatory agencies often disagree on which outcomes are adverse.[106] This notion is especially true in the context of in-vitro high-throughput assays that have been proposed for use in regulations; these assays would determine activity based on receptor binding, reporter gene activation or inhibition, or functional outcomes such as altered steroidogenesis or differentiation. As such, moving away from definitions that require the observation of adverse effects in vivo, and adopting the Endocrine Society definition, provides a relevant path forward, especially in the context of the limitation of animal testing. Such an approach should be adopted across all sectors to ensure consistent treatment of EDCs regardless of product source.

Our second proposed strategy to bolster the regulatory approach to EDCs is to include EDCs in estimates of the global burden of disease, particularly important considering the substantial human and economic costs due to EDC-related morbidities.[107] The European Commission considers the aim of minimising human and environmental exposure to EDCs as scientifically justified. In parallel, in countries and sectors where risk-based approaches remain the paradigm, reductions in EDC exposures are warranted based on direct human evidence of adverse effects, as described in paper 1 of this Series. Where implemented, such policies will have positive impacts not only on health outcomes, but also on health expenditures and other indirect costs. In the USA, EDC exposures are often higher in ethnic minorities[108] and contribute to inequalities in diseases and disability, including neurocognitive outcomes.[29] EDC policies are justified on economic grounds and to further environmental justice.

Our third proposed strategy is to focus on a hazard-based approach to the regulation of EDCs. With risk-based approaches, a regulatory response is only triggered if exposure levels reach some critical level (eg, a reference level or value assumed to trigger a response of a given amplitude, or an insufficient margin between exposures and doses that are anticipated to cause hazards).[109] In contrast, a hazard-based approach finds the hazardous properties of a chemical as sufficient for regulation and marketing prohibition, independent of exposure risks and cost–benefit analyses. For many EDCs, data are lacking to support using risk-based approaches, hampering other regulatory actions.[110] The lag from identifying new exposures to completing human studies of effects, especially for disease outcomes with longer latencies such as diabetes or cancers, is the most serious and intrinsic flaw of the risk-based regulatory paradigm. To delay regulating chemical hazards until sufficient data are available to inform risk assessment is costly in human health as well as economic terms. A shift in the paradigm towards hazard-based regulation, as has been embraced by the EU pesticides regulation, is thus warranted.

We argue that such hazard-based regulations should be used for regulating EDCs across all sectors (or at least for those with potential human or ecological exposures) in all countries. Because non-monotonic exposure–response relationships exist for many synthetic chemicals including EDCs,[5,111] doses that cause harm cannot be used to extrapolate to lower doses that are safe.[112] Although some risk-based approaches attempt to account for age-related vulnerability, they falsely presume that the population sensitivity can be quantified a priori. As such, we suggest the inclusion of EDCs as a specific hazard category for regulatory purposes across countries, of similar concern to other hazards such as carcinogens. A first step would be for endocrine disruption to be part of the international Globally Harmonised System of classification and labelling of chemicals and of the area-specific corresponding regulations such as the EU 2008 regulation on the classification, labelling and packaging of substances and mixtures.[113] We propose a defined testing paradigm to evaluate all chemicals in commerce, hazard-based approaches to regulation, and clear timelines and actions required following EDC identification.

An International Agency for Research on EDCs (IARE)

To foster the development of some of these recommendations, we suggest the establishment of a new international agency, or a broadening of the International Agency for Research on Cancer (IARC)'s scientific charge, to include endocrine disruption. When the IARC was established in 1965, it was tasked with evaluating the evidence of carcinogenesis due to environmental hazards.[114] Since that time, the IARC has evaluated hundreds of environmental chemicals and agents in a transparent and reproducible manner.[115] We propose that an IARE should be created within WHO and funded in a similar manner to protect against undue influence from industry or other stakeholders, and managed with a parallel structure to allow expert working groups to evaluate chemicals that are suspected to be EDCs, adapting the approach applied by the IARC.[116,117] Such an independent body will promote more efficient procedures for identifying EDCs globally. Like the operation of the IARC, monographs published as a result of the efforts from IARE working groups would describe the state of the evidence using three streams of evidence (eg, mechanistic, animal, and epidemiological studies) and principles similar to those used in systematic reviews.[118] One of the key reasons cited for the success of the IARC is that it explicitly does not make policy recommendations; thus, the body of work that would be created by the IARE would be used by regulatory agencies

Search strategy and selection criteria

This Series paper relied on the collective expertise and experience of the authors; thus, a comprehensive literature search was not done before initiating the study. Authors have previously published extensively on the economic costs of various environmental contaminants including endocrine-disrupting chemicals. Regulatory context was examined via direct evaluation of legislation and through targeted evaluation of regulatory critiques published previously to compare and contrast hazard and risk-based regulations globally, though focusing on the EU and the USA.

around the world to limit, or hopefully eliminate, EDC exposures, with the IARE staying expressly apolitical.[117] A January, 2020, consensus on the key characteristics of EDCs, provides a framework, with ten mechanisms of action and assays that are available to probe some of these, that could be used to identify EDCs.[5] This approach follows a similar framework describing key characteristics of carcinogens that has been used by IARC expert panels.[119] We propose that an autonomous body that can bring together diverse experts for international collaborative reports on EDCs would foster global movement on regulations.[115,116] As noted with the creation of the IARC, an international organisation is likely to be freer of non-scientific constraints in suggesting regulatory actions than national organisations,[117] a point that is easily demonstrated by the recent US and EU regulatory failures discussed in preceding sections.

Conclusions

In the past decades, regulatory efforts and policies to decrease human exposure to EDCs have been insufficient to minimise exposure to the vast majority of EDCs.[120,121] Given the overwhelming scientific evidence of EDCs as a human health hazard and the economic costs of inaction, it is clear that improved regulations are needed. As we have described, the current approach to limiting exposure to EDCs in humans is dangerously slow and insufficient. Simply too few chemicals used in commerce have been thoroughly tested for endocrine-disrupting properties, with an ever-expanding list of chemicals requiring evaluation; other serious weaknesses persist in testing approaches. Although the EU has taken positive steps toward regulating EDCs, the approach taken in the USA (and other countries) is limited or altogether absent. Regulatory bodies that have applied risk-based evaluations of regulatory options have failed to consider the full cost of EDC-related health impacts to adequately protect health. To this end, we suggest expanded and comprehensive testing strategies to conclusively identify EDCs, and a shift from a flawed, risk-based paradigm to one that proactively excludes chemicals with some evidence of hazardous properties until further detailed reassuring testing data become available. An international initiative on EDCs, which would be supported by UN, could address the weaknesses related to hazard identification and provide much-needed guidance for policies globally.

Contributors

LT conceptualised the Series paper, and contributed equally to the US policy section with CDK and LNV. RS, BAD, and MP equally contributed to the EU policy section, relying on a published report prepared by BAD and RS for the EU Parliament, while LNV and CDK developed the proposal for the International Agency for Research on Endocrine Disruption with LT and RS. LT had final editorial oversight.

Declaration of interests

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