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REVIEW

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The state of bisphenol research in the lesser developed countries of the EU: a mini-review

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Bisphenol compounds are a class of chemical epoxy resins that are found throughout the world in food packaging, thermal paper products, dental materials, and more. These compounds were deemed to be safe until recently, when some studies noticed adverse effects at very low doses, due to the fact that bisphenol acts as an endocrine disruptor. Over the last ten years, studies have been performed to detect bisphenols (especially BPA) in serum and blood samples throughout the world. Essentially, the majority of the earth's population seems to have significantly measurable levels of bisphenol in their blood plasma or urine. However, the majority of the population is unaware that a potential danger may exist. The purpose of this mini-review is to report upon the state of bisphenol research in the lesser developed member-states of the European Union and to increase awareness of the exposure level and possible adverse health effects of this endocrine disruptor. The results show that only three of the most newly admitted members of the European Union have published research concerning the health effects and/or environmental exposure of EU citizens to bisphenol compounds. Those countries were Slovenia, Poland and the Czech Republic. The rest of the surveyed member-states had little or no published research in relation to bisphenol compounds. Furthermore, even the three nations referred to above still lagged far behind the more advanced EU member-states. The lack of research could translate into a lack of awareness amongst the citizenry of nearly half of the EU, and may be unnecessarily putting those EU citizens at an increased risk of exposure.

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Introduction

Bisphenol is a chemical that has been used as an epoxy resin in many consumer products for several decades. The most common form of bisphenol is known as bisphenol A (BPA), but there are three other compounds currently being used in consumer products that are analogous to BPA. The most widely used are BPS, BPAF and BPF, which are usually found in "BPA-free" products. However, these alternatives are structurally very similar to BPA, and they may have similar adverse health effects. Although there are other forms of bisphenol, these four are the ones mainly encountered by the general public. The monomers are formed by combining phenol with acetone (BPA), hexafluoroacetone (BPAF), formaldehyde (BPF) or sulfur trioxide (BPS). The monomers are then polymerized into an epoxy resin, and used in consumer products. The mechanisms of action are still being investigated, but it is known that BPA is an endocrine disrupting compound. Bisphenol has been used in food packaging and containers, as a lining inside canned foods and beverages, in baby formula packaging, baby bottles, household food containers, dental prosthetics, and even in thermal paper such as sales receipts.[1] It has been determined by the United States Environmental Protection Agency (EPA) that bisphenol (especially BPA) has the third highest priority in terms of its toxic profile.[2] It was originally thought to be safe, due to the fact that at established concentrations for chemical toxicity it has little or no effect. Unfortunately, only within the last ten years it has been shown that bisphenol does not behave as a typical toxin. Instead, bisphenol is an endocrine disrupting compound (EDC), and mimics the action of estrogen *in vivo*. It typically associates with membrane bound estrogen receptors, and is suspected of interacting with several other endocrine pathways as well; such as with thyroid hormone receptors, androgen receptors, and many other signaling pathways of the endocrine system.[3] However, the exact mechanisms of action are not yet known. Several studies have shown that extremely low doses of bisphenol (in the nanogram range) may have significant biological

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effects. A significant amount of work has been done since 2007 in characterizing the epidemiology of this EDC. The exact mechanisms of toxicity are not clear, but much research is being done. The negative health effects seem to be numerous with the most vulnerable groups being developing children and adolescents, as well as pregnant women. Although all age groups seem to experience ill effects, developing children are the most vulnerable.

This xenoestrogen has been potentially associated with an incredible number of diseases and disorders at low does; sometimes very low doses. In adults, it has been indicated in possible problems with both the male and female reproductive system, including abnormal spermatogenesis, sperm motility, and chromosomal irregularities in oocytes. It has also been implicated in altered plasma glucose/insulin levels, a weakened immune system and more than one type of carcinoma. However, the implications for pregnant mothers and developing children are even more numerous. Bisphenol compounds may also have a developmental role in altered brain physiology, behavioral disorders, reduced immune response to carcinogens, increased BMI and childhood obesity, developmental reproductive issues, abnormal meiosis, as well as an altered response to hormones by the mammary glands. The list above is quite long, and bisphenol exposure can be very serious. It has been correlated with increased carcinoma rates in adults, as well as increased rates of diabetes, obesity, metabolic disorders and psychological problems in children. For an excellent review of these low-dose effects, please see the 2013 article by Vandenberg and colleagues.[3] For a European review of the role of BPA on the immune/stress system, please see the collaborative article written by Greek and Swedish researchers.[4] For a perspective on the state of bisphenol regulation in the European Union, the article by researchers at the University of Helsinki is compelling.[5] Most of the studies mentioned above are correlation studies, and there are far fewer mechanistic studies. Since bisphenol toxicity is such a new area of investigation, research about exact mechanisms is not yet available. Therefore, the only known treatment to combat bisphenol exposure is prevention. Using a plastic container to reheat food-stuffs in a microwave oven seems to be the main route of bisphenol exposure. Furthermore, plastic baby-bottles and formula packaging previously used bisphenol polymers, but this has been banned in both the EU and the United States.

There is much controversy concerning what the lowest safe dosage of bisphenol might be.[3,6,7] This is typically referred to as the LOAEL (Lowest-Observed-Adverse-Effect-Level). Some papers also reference the NOAEL (No-Observed-Adverse-Effect-Level). It has been well-established that the acceptable LOAEL before 2007 was far too high, and some researchers have claimed significant negative effects at concentrations well within typical human exposure levels. A CDC (Centers for Disease Control and Prevention) study found 95% of adult human urine samples and 93% of samples in children had detectable levels of bisphenol A.[2] A Europe-wide evaluation of the exposure of mothers and children to BPA was performed and found similar results.[8] Furthermore, the European study correlated socio-economic class with BPA exposure and found that the poorer EU citizens had higher levels of urinary bisphenols, and were perhaps at greater risk. Could this trend also hold true with the lesser developed member-states of the European Union and EDC exposure levels? It is likely.

The state of bisphenol research in the most developed countries of the world really only began in earnest at the beginning of the twenty-first century. This research has mainly occurred in the United States, Japan, Germany and other Western European countries. In the United States, a commission was established to investigate the possible health concerns of bisphenol compounds. This commission released a report known as the Chapel Hill Consensus.[7] The key findings were that bisphenol compounds leech into food products under conditions of normal use, that there are detectable levels of bisphenol in human samples, and that bisphenol compounds do cause a wide range of diverse effects at low doses. Since 2007, interest in the health effects of bisphenol has increased dramatically. It has only been ten years since the first commission report stating that bisphenol compounds (especially BPA) may be hazardous at very low dosages, and only six years ago there were little or no safeguards against the use of bisphenol compounds. Furthermore, lesser developed countries seem to be at greater risk due to a lack of regulations, a lack of resources to find alternatives to EDCs, and mostly they have a lack of awareness of the problem. The lesser developed EU member-states may not be aware that a potential hazard may exist. Therefore, it is a good idea to increase awareness of BPA exposure throughout all the EU member-states.

Methods and materials

The main aim of this work is to evaluate the level and scope of bisphenol research in the lesser developed countries of the European Union. The level of bisphenol research may estimate the level of bisphenol awareness in society. Much research and regulation has been done in the highly developed nations of the world. A good deal of research is currently being conducted in the under-developed world. Of key concern is that under-developed nations may be at a higher risk of exposure to EDCs, and they may have fewer EDC free options. However, between the wealthiest countries of the world and the developing world are the lesser developed countries of the European Union. These are the nations who joined the EU in 2004 or later. These countries do have the advantage of legal regulations established by the EU to protect them more than non-EU countries, but most of these nations are not nearly as developed as the original member-states. Therefore, there may be nearly half of the European Union at risk of needless exposure to bisphenol products (and other EDCs) simply due to a lack of awareness.

In order to determine the amount of research being conducted in a particular EU member-state, the electronic database from the University of Warmia and Mazury was employed.

This database allowed inquiries to be conducted across the majority of academic databases including, but not limited to: PubMed, EbscoHost, Elsevier, ProQuest, and many more. Articles that were written in the English language between 2006 and 2017 were counted. If a foreign language manuscript contained an abstract in English, it was also included in the count. Articles completely devoid of the English language were excluded from the study. The search phrase was "bisphenol" and "the name of the EU member-state", across all possible search-fields. In order to verify accuracy, a second search phrase of "BPA" and "the name of the EU member-state" was also performed. In each case, the same results were always obtained. However, sometimes the order of relevance varied. Studies that were conducted in collaboration with an academic institution from another nation were included. The nature of these studies will be specifically discussed later. Only articles that investigated the mechanistic, medical, clinical, or environmental effects of bisphenol were counted. Furthermore, articles that studied the various forms of bisphenol (BPA, BPAF, BPF and BPS) were included. Articles detailing the manufacture of bisphenol compounds were also excluded. Many search engines that identify bisphenol by its CAS number, tend to return results that are not relevant to pathology, epidemiology or toxicology. Furthermore, they may miss medically relevant articles that do not identify bisphenol by its CAS number. This is the reason for the methodology described above. The countries that were evaluated are all part of the EU continental mainland, joined the EU in 2004 or later and do not use English as their official language. These countries were Slovenia, the Baltic States of Lithuania, Latvia and Estonia; Poland, the Czech Republic, Slovakia, Hungary, Romania, Bulgaria and Croatia. The countries of Cyprus and Malta were not examined here, in order for this study to focus on continental Europe. All of these countries are generally considered to be lesser-developed than the original members of the European Union in terms of their economy, infrastructure and level of academic research, among other factors.

Results

A glance at the quantitative data is quite revealing. As can be seen in Table 1, the countries of Slovenia, Poland and the Czech Republic have nearly three times the number of publications with regards to bisphenol than all other lesser developed EU member-states combined. Of course, research conducted in advanced countries such as Germany, Japan and the USA far outweigh all of the newer EU countries. However, at least Slovenia, Poland and the Czech Republic are showing some signs of realizing the importance of the issue and publishing research.

As can be seen, there is a large discrepancy in research being done in the region. The Baltic States have the least amount of research occurring in this area, along with Bulgaria. Furthermore, there are conflicting studies with regards to the level of contamination of the Baltic States. For example, an Italian study found that only 10% of European Union river water could be considered as being "very clean", but the river waters of Estonia and Lithuania, along with Sweden, were the cleanest in the entire EU.[9] However, a study funded by the EU SAFE Commission in Brussels warned that the "Baltic states are at higher risk" of bisphenol contamination than other EU member states.[10] With these types of contradictions occurring, even up to the level of the EU parliament, it is imperative that these countries begin to investigate the effects of bisphenol at an academic level. In the next section of this mini-review, the research studies themselves will be examined by country.

Table 1 The distribution of academic research with regards to bisphenol by EU member-state. Source: Database of the University of Warmia and Mazury

Ranking	EU member-state	Number of bisphenol publications	Percentage of research conducted with regards to bisphenol
1	Slovenia	15	27%
2	Poland	13	21%
3	Czech Republic	11	20%
4	Romania	4	7%
5	Croatia	3	5%
6	Hungary	3	5%
7	Slovakia	3	5%
8	Latvia	2	4%
9	Lithuania	2	4%
10	Bulgaria	1	2%
11	Estonia	0	0%
Total	11 member-states	56	100%

Bisphenol research in Slovenia, Poland and the Czech Republic

Slovenia has taken the lead in this particular region in terms of bisphenol research. Slovenia produced fifteen articles between 2011 and 2017. Slovenia seems to be rather advanced in terms of bisphenol research. They have identified it as a hazard, have identified its replacements as a hazard and are constructing ways to remove BPA and its derivatives from the water supply. That is quite impressive for only a six year timespan.

The earliest article from 2011 involves identifying BPA as one of several endocrine disruptors affecting reproductive pathways in a literature survey based review article.[11] The following year, another team used a computer program to quantify the binding energies of bisphenol. They calculated that the metabolically active form of BPA can be a mutagen by binding with the Guanine base of DNA.[12] However, the study only showed that genotoxicity was theoretically possible. However, in the same year a more thorough study of pharmacokinetic models was performed in order to improve the "regulatory risk assessments of BPA".[13] The team used several tissue types and found that the biologically active form of BPA, BPA glucuronide (BPAG), is processed differently in different tissue types. According to their assays, BPAG was formed using Michaelis–Menten kinetics in the kidneys and intestines, but in the liver it followed substrate inhibition kinetics. Furthermore, the liver

is responsible for removing this EDC from the biological system. In 2013, another group of researchers investigated further evidence of the mechanisms of bisphenol metabolism. By using liquid chromatography in tandem with mass spectrometry, the team was able to deduce the chemical properties of BPA structural analogs which may occur *in vivo*. They surmise that these BPA analogs are reactive and can form "covalent adducts with nucleophilic macromolecules and/or produce oxidative stress".[14] In 2015, there was a one paragraph abstract from Slovenia describing the use of molecular docking to study the binding of bisphenol AF.[15] The authors conclude that BPAF may promote the progression of cancer cells, because it modulates integrin activation and promotes cell adhesion. In 2016, there were several articles dealing with the mechanisms of bisphenol and its analogs and derivatives. One study investigated the effects of BPS on thyroid hormone activity using yeast cells as a model and was first published as an abstract in a supplemental issue by the same authors in the same year. Effectively, there were two published articles (one supplement and one research manuscript). These both described the use of yeast cells and investigated BPS.[16] Another 2016 article investigated the metabolic activity of bisphenol metabolites, and found they had little or no biological activity with endocrine receptors.[17] There was one purely epidemiological article that investigated the correlation between hormone-related cancer risk and EDC exposure (among several factors). No significant results were obtained.[18] The remaining articles mainly deal with environmental contamination and how to remove bisphenols from the aqueous environment.

The earliest environmental article from Slovenia is from 2013. The article is concerned with methods of removing bisphenols from streams and waterways using catalytic wet air oxidation.[19] An extremely similar article was published by some of the same authors in the following year.[20] In a similar vein, there are two articles from 2016 that discuss various methods of purifying bisphenols and other EDCs from the water supply using various methods.[21,22] Finally, there were two articles that concerned the health effects of bisphenol on aquatic sea-life. The first was a study of the effects of BPA on the water louse[23] and the second was a study of the effects of BPA, BPF and BPAF on various marine organisms.[24] Both studies found significant risks associated with bisphenols at very low doses. The extent of the bisphenol research in Slovenia was the most varied and advanced of the lesser developed member-states of the EU.

Polish research is not too far behind Slovenia. Poland has had 13 publications concerning bisphenol research between 2006 and 2017. This is a longer time span for research than was seen in Slovenia. Eleven of the articles dealt with clinical studies, were concerned with identifying bisphenol as a hazard or were involved with identifying the mechanisms of action for bisphenol compounds. Only two articles were concerned with environmental monitoring of bisphenol compounds, and both studies were from the same university.

The earliest article from 2006 is a literature survey article that examined the research up to that point with regards to carcinomas, genital malformations, cryptoorchidism, decreased fertility and other abnormalities of the male reproductive system that may have been caused by EDC compounds such as bisphenol.[25] Curiously, this paper stood alone as the only Polish work until the next bisphenol research article from the Jagiellonian was published six years later in 2012. The article investigates the mechanisms of BPA in up-regulating the expression of Leptin receptors in human ovarian cancer cells. Although the study was *in vitro*, they did find that Leptin and BPA alone were enough to stimulate ovarian cancer cell proliferation.[26] The study also noted several pathways that were activated by BPA which may also lead to increased ovarian cancer cell activity. The following year, a study was published by the National Institute of Public Health in Warsaw which found that BPA caused mutagenic effects (DNA strand breaks) in lung tissue samples and in the micronuclei of reticulocytes.[27] They compared the mutagenic effects of BPA to the mutagenic effects of X-Ray radiation, and found that X-Rays caused more damage. However, ionizing radiation in combination with BPA exposure may be particularly dangerous; depending on the type of tissue. In the subsequent year, two relevant articles were published from Polish research universities. The first 2014 study came from the same research team at the Jagiellonian. In this study, the team investigated the role of BPA in the cell migration of ovarian cancer cells. The previously mentioned 2012 study showed that BPA helped promote cancer cell proliferation through various pathways, and this 2014 study showed that BPA uses the same mechanism of action to promote the "reduction of adhesion and the initiation of metastasis".[28] Although the study was *in vitro*, it does give a mechanistic insight into how bisphenol compounds may promote or induce a hormonally-sensitive cancer. In the same year, a purely clinical trial was published. The team examined a possible correlation between BPA exposure and post-menopausal breast cancer using logistic regression techniques. The levels of urinary BPA metabolite were compared with breast cancer incidence.[29] No significant results were obtained. The greatest amount of bisphenol literature was published in Poland in 2015. One was a clinical research article, another was a review article and the third was a position statement from Polish Academia. The clinical article focused upon cryptoorchidism in new born males. The study found a statistically significant correlation between cryptoorchidism and serum BPA levels (both conjugated and total BPA levels), as well as a positive correlation between problems with conception and serum BPA levels.[30] The most frightening aspect of this research is that all participants lived in a region that has extremely low levels of industrialization, and is nearly free of environmental pollution. The review article mainly focused on estrogen dependent breast and uterine cancers and the evidence that bisphenols and other EDCs may contribute to their prevalence in the population.[31] The final Polish publication from 2015 is a position statement calling for more research to be done with regards to EDCs and especially

bisphenol compounds in relation to human health.[32] A Polish study from 2016 investigated bisphenol compounds for their detrimental effects on erythrocytes. They found that the bisphenol compound BPAF increased calcium ion concentrations in the cytosol and increased phosphatidylserine exposure to the point where the erythrocyte was destroyed through the process of eryptosis.[33] Although the study was *in vitro*, it is alarming since BPAF is marketed as a safe alternative to BPA products. The final two studies are very recent, from 2017. The same group from the Jagiellonian report that the same ovarian cancer cell line that was previously shown to proliferate and migrate in the presence of BPA, can also be upregulated by derivatives of BPA.[34] Another group from a different Polish university showed that BPA causes liver damage in developing large animal models (pigs) at legally acceptable levels with even more significant damage occurring at higher levels. Furthermore, several neuronal markers showed upregulation in the parasympathetic nervous system after BPA exposure.[35] The remaining two articles deal with environmental contamination in the Gulf of Gdańsk.

The two environmental articles from Poland come from the same research team at the University of Gdańsk. The first is from 2015, and the latest is from 2017. The first article identifies bisphenol as one of several EDCs that are contaminating the aquatic life in the bay of Gdańsk.[36] The second article specifically investigates bisphenol accumulation, as well as two other classes of EDCs, in mussels from the bay of Gdańsk.[37] Poland seems to be ahead in terms of mechanistic and clinical research of bisphenols, but seems to lag behind in environmental monitoring.

Research in the Czech Republic is not too far behind Slovenia and Poland. The Czech Republic has had 11 publications concerning bisphenol research between 2004 and 2017. This is a longer time span for research than was seen in Slovenia or Poland, but there are quite a few large time gaps between publications. Eight of the articles dealt with clinical studies, were concerned with identifying bisphenol as a hazard or were involved with identifying the mechanisms of action for bisphenol compounds. Three articles were concerned with environmental monitoring of bisphenol compounds.

The first studies are from 2004 and 2006. They concern the leeching of bisphenols into foods from food storage containers.[38] Another article concerned the leeching of bisphenol from wine corks.[39] The earlier study claims that leeching is minimal, but they do not consider the hazards of low dose effects; perhaps due to the very early nature of this study. In a similar vein, the wine cork study also showed that detectable amounts of BPA can be leeched from certain types of artificial wine corks, but any potential adverse health effects are downplayed. The following year, a similar study was performed on common food-stuffs available in grocery stores throughout the Czech Republic. The study did find detectable (and in some cases relatively high) levels of bisphenols in many foods.[40] This is the first study in the region to investigate BPA derivatives along with BPA itself, and they suggest that these may potentially pose health risks. After this manuscript was published, there was a five-year hiatus in bisphenol research within the Czech Republic. Then in 2012, there were two articles published by the same research team concerning the hazardous effects of bisphenol compounds on goldfish.[41,42] The same lead author was listed in both articles from the same year. The first article described a decrease in sperm motility as a consequence of BPA exposure, while the second article described decreased sperm quality as a consequence of BPA exposure. These two articles were most likely produced from the same set of experiments. A productive year in terms of bisphenol research for the Czech Republic was 2015. Two articles were published that dealt with measuring the concentration of BPA in various body fluids and a mechanistic study of how bisphenol compounds interact with nuclear receptors in biological pathways. The first article from 2015 determined the BPA levels of various bodily fluids.[43] The researchers developed an assay and validated it by measuring human plasma and seminal fluid. The second article of the year is more mechanistic in its approach, and shows a higher level of investigative skill. This group examined several different compounds, including BPA, for their involvement with nuclear receptors in human hepatocytes.[44] They found that BPA, along with parathion, activates arylhydrocarbon receptor (AhR), and therefore may play a role in many biological processes. There was only a single review article in 2016, and it concerned the replacement of BPA with BPS. The article concluded that it was ill-advised to substitute one bisphenol compound with another bisphenol compound without knowing the health risks of the replacement.[45]

The Czech Republic had three articles investigating the contamination of water. Two concerned contaminated drinking water, while the third discussed the pollution of the natural environment. The oldest article from 2010 elaborates on a method of detecting BPA in drinking water,[46] while the most recent article concerns the contamination of drinking water due to old pipes with an aging inner coating of epoxy resins.[47] The team did find that aging pipes with epoxy resin do add BPA to the water supply. The final study involves aquatic life and examines many different potential contaminants that accumulate in the muscles of fish.[48] The team found the levels of pollutants to be lower than what was reported in previous studies. Although the Czech Republic is in the top three countries of the region in terms of bisphenol related research, only one article displayed a grasp of the mechanisms at the molecular level, while most articles simply found ways of measuring bisphenol compounds in wine, canned food and water pipes.

Bisphenol research in the rest of the lesser developed EU member states

The remaining eight countries of the EU region being examined had a combined total of 18 publications concerning bisphenol research. This is only three more than the output of Slovenia. Romania had four publications between 2007 and 2017. Two were biologically relevant, and used *in vivo* hydroxyl

radical production in rat models to investigate oxidative stress induction in rats after exposure to bisphenol A and two other EDCs.[49,50] Unfortunately, there have been no new studies from this team since 2014. Two articles used exotic techniques to remove bisphenols, with one article being a Finnish collaboration and the other being a collaboration with Harvard University.[51,52] One Romanian paper listed BPA as a key word, but never investigated it. That study was excluded.

Croatia, Hungary, and Slovakia had three publications each. Croatia had three articles with one being a collaborative effort with a team in Italy. Two articles were both environmental as well as biologically relevant. The first analyzed the effects of BPA on earthworms, and noted oxidative stress and behavioral changes at low cutaneous doses.[53] The second article involved the cytotoxic effects of bisphenol on sea urchin embryos.[54] This particular study did analyze gene expression in relation to BPA and found a specific glycoprotein that aids against the cytotoxic effects of BPA. There was also one article strictly about environmental contamination.[55] The study found bisphenol contamination in the water and soil sediments of Kaštela Bay on the Adriatic Sea. The level of research for Croatia was not bad, given that it is the newest member of the European Union. The same cannot be said for Hungary. There were three articles published, but two were collaborations with Yale University where most of the laboratory work seems to have been done. There was also one environmental sampling article. Both publications that were biologically relevant involved the interference of BPA with synaptogenesis.[56,57] The experimental work was done in rat and non-human primate cell cultures. The environmental article measured the levels of EDCs in a lake in Western Hungary.[58] Slovakia had three very good articles that investigated the mechanisms of bisphenol activity. The first article was published in 2005 and was followed up by the same team in 2009. Their research focused on hormonal production in ovarian cells in the presence of BPA and its derivatives.[59,60] They also investigated bisphenol effects on meiosis in porcine oocytes. Unfortunately, there has been no further research published from this team. The most recent article from Slovakia is from 2013. The team evaluated T-type calcium channel inhibition by bisphenol.[61] Unfortunately, this is the only article from this research group. Although Slovakia had a handful of solid bisphenol research publications, they have not consistently been able to produce quality bisphenol research.

From the Baltic states, only Lithuania had a single biologically relevant publication. That article exposed mussels to low-doses of BPA for 3 weeks and noted the induction of micronuclei in the gills.[62] There was an EU study performed in both Lithuania and Latvia that sampled bisphenol levels and found both countries to be at "high risk".[14] However, there is no mention that any researchers from those two countries participated. There has also been a recent German study that found the coastal waters of Latvia to be contaminated with bisphenol and several other compounds.[63] Again that study was based in Germany. There are two EU member states that have no published articles concerning bisphenol research. Those two countries are Bulgaria and Estonia. Bulgaria has a single collaborative article with Portugal, but it is an article about techniques to extract certain chemicals from water samples and how efficient the techniques are. The article uses bisphenol in the title, but bisphenol was never mentioned at all in the text. Therefore, that article was excluded as not being relevant. Meanwhile Estonia has no academic research whatsoever pertaining to bisphenol in biological systems or in the environment.

Discussion

As can be seen, the state of bisphenol research by the academic community varies greatly between the newer members of the European Union. Sixty-eight percent of bisphenol research in these countries has been conducted in the three countries of Slovenia, Poland and the Czech Republic. That is more than two-thirds of the research from the region being concentrated within the academic institutions of only three nations. Some member-states have done no independent research whatsoever, and are possibly not even aware that they may have significant amounts of bisphenols in their environment and in their human population.

Although Slovenia, Poland and the Czech Republic need to conduct further advanced bisphenol research, those countries have produced advanced research. That research involved an analysis of the mechanisms involved and the pathways used by bisphenol compounds in biological systems. These countries have at least done some environmental sampling in an effort to define the amount of pollution. All three countries have also progressed in their research from the early stages of identifying that BPA may be a problem, then investigating the mechanisms of how it may be causing the problem, and finally expanding research to include not only BPA but also the other significant forms of bisphenol.

It is extremely likely that these lesser developed nations of the EU have much smaller national research budgets than scientific leaders such as Germany, Japan and the USA; but that is a sign of decreased awareness of the effects of EDCs. Less academic research funding will translate into fewer articles published investigating the possible health consequences of BPA and its derivatives. As previously referenced, Covaci *et al.*[8] found that the lower socio-economic classes were at higher risk of BPA exposure, and this may also hold true when describing the newer and lesser developed nations of the EU. The result will be fewer bisphenol health-related articles published. From an epidemiological point of view, this may be an indicator of decreased awareness of the problem for a particular region. This particular region happens to be half of the European Union.

This mini-review recommends that more collaboration should occur between academic institutions from the developed countries of the EU to help academics in these newer member-states. Not only will this help the lesser developed states to mature in their level of scientific research, but it will

also increase the rate of published research into this particular problem, since more laboratories working across the entire European Union will bring more scientists together from diverse backgrounds.

Conclusions

A proposal may be that the amount of academic research pertaining to bisphenol is indicative of the level of awareness in that country of the possible health risks associated with this particular EDC. The awareness of scientists and medical researchers about the effects of bisphenols should translate into a more general awareness of possible adverse health effects within the public inside the country. The reasoning is that scientists and medical personnel involved in academic research are highly regarded in their respective communities. Those academic researchers mainly read and publish work in English, but will also communicate in their native language with members of the media, the government and the public in general. Therefore, there may be a correlation between the amount of bisphenol research published in the English language from a particular country, and the level of awareness of the potential dangers of bisphenol in the general population. This is most likely not the only factor influencing the level of awareness, but it could be a reasonable indicator that may help direct further research.

The more that the general public is aware of the potential risks of bisphenol, the more likely they will be to avoid bisphenol compounds in their daily lives. For example, at the consumer level more people may choose BPA free products, choose not to reheat foodstuffs in plastic containers, or be sure to wash their hands after handling thermal paper products. At the government level, there may be more efforts made to monitor drinking water, curb Bispheol exposure in the environment and further regulate local manufacturers of endocrine disrupting compounds. However, if the general public of a specific geographical area is unaware of the potential hazards, they may be unnecessarily at risk of exposure. Far fewer scientific articles with regards to BPA or BPA alternatives were published in the English language from research institutions located in central Europe. This state of affairs may be remedied with increased cooperation between research universities from Japan, Germany and Western Europe and research institutions from Central/Eastern Europe. The environmental health effects of bisphenol A and its alternatives are a very new branch of research; however, the entire world should be made more aware of the issue.

Abbreviations

AhR	Arylhydrocarbon receptor
BPA	Bisphenol A
BPAF	Bisphenol AF
BPF	Bisphenol F
BPS	Bisphenol S
CDC	(United States) Centers for Disease Control
EDC	Endocrine disrupting compound
LOAEL	Lowest-observed-adverse-effect-level
NOAEL	No-observed-adverse-effect-level

Conflicts of interest

The authors have no conflicts of interest to declare.

Authors' contributions

MT performed the review and wrote the article. LR participated in the study design. JW conceived of the study and helped to draft the manuscript. All authors read and approved the final manuscript.

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