From BPA to BPZ: a toxic soup?

How companies switch from a known hazardous chemical to one with similar properties, and how regulators could stop them.
This report was produced by CHEM Trust, a UK-based charity working at UK, EU and International level to protect humans and wildlife from harmful chemicals.

CHEM Trust’s particular concerns are to endocrine disrupting chemicals, the cocktail effect of chemicals and the role of chemical exposures in the early life of wildlife and humans.

CHEM Trust engages with scientific, environmental, medical and policy communities to improve the dialogue concerning the role of adverse effects of chemicals in wildlife and humans and to harness a wide coalition to drive improved chemicals policy and regulation.

For more about our work, including our regularly-updated blog, see www.chemtrust.org

Further copies of this briefing can be downloaded from www.chemtrust.org/toxicsoup

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About the Authors

The main review of the state of science was written by Greg Howard.

Greg Howard is an environmental public health scientist with a broad background in epidemiology, toxicology, and research translation. He holds Doctoral and Master of Public Health degrees in Environmental Health from the Boston University School of Public Health, where his research examined the combination effects of chemical mixtures. He has taught environmental health at Dickinson College, Boston University, Brown University, and Boston College. Dr Howard’s current work focuses on how scientific information can best be used to create effective chemicals policies that protect the environment and public health. He has been a Science & Technology Policy Fellow of the American Association for the Advancement of Science, hosted at the US Environmental Protection Agency, and has extensive experience with European Union’s REACH chemicals policy through collaborations with several EU-based organisations.

The policy recommendations and advice for individuals are written by Dr Michael Warhurst and Dr Ninja Reineke of CHEM Trust, informed by the state of the science, the views of the scientists and CHEM Trust’s experience of following chemicals policy development for more than two decades.
Scientific review

The scientific content of this report has been peer reviewed by two scientists in the field:

- Dr Olwenn V Martin is a Research Fellow in Environmental Health at Brunel University, London. Building on an academic interdisciplinary background in Natural Sciences and Social Sciences, she has expertise in the translation and application of both fundamental and observational research into policy. Her research is focused on ‘emerging’ issues for the risk assessment of contaminants, such as mixtures and endocrine disruptors. She has a continuing interest in methods for evidence integration such as systematic review, meta-analysis, weight-of-evidence as well as socio-economic evaluation.

- Dr Paloma Alonso Magdalena, Associate Professor of Nutrition at Miguel Hernández University of Elche (UMH), Spain. She completed her postdoctoral research in the Department of Bioscience and Nutrition at Karolinska Institutet, Stockholm. Her research is conducted at the Institute of Bioengineering (UMH) and CIBERDEM and is mainly focused on the role that endocrine disruptors play in the etiology of diabetes and obesity. She is particularly interested in understanding how exposure to endocrine disruptors at different periods of life affects maternal and offspring glucose and lipid metabolism.

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# Table of contents

1 Executive summary .............................................................................................................. 2

2 Introduction .......................................................................................................................... 5

3 Out of the frying pan, into the fire ...................................................................................... 6
   3.1 Bisphenol A use and regulation ..................................................................................... 6
   3.2 Bisphenol exposure today .............................................................................................. 8

4 Bisphenols: looking at the evidence .................................................................................. 9
   4.1 The emergence of concerns about BPA .......................................................................... 9
   4.2 Beyond BPA: BPS, BPF, BPAF ..................................................................................... 11
   4.3 The newest head of the Hydra: BPHF .......................................................................... 15
   4.4 Nothing new under the sun ............................................................................................ 16
   4.5 Endocrine activity of bisphenols .................................................................................... 16
   4.6 Bisphenols and human health ....................................................................................... 17

5 An inadequate response ....................................................................................................... 19
   5.1 The sluggish pace of regulation .................................................................................... 19
   5.2 BPA in thermal paper ..................................................................................................... 19
   5.3 What about BPS in thermal paper? ................................................................................ 20
   5.4 What’s EFSA doing? ........................................................................................................ 22
   5.5 An irresponsible approach from parts of industry ......................................................... 22

6 Grouping to speed up regulatory controls ......................................................................... 24
   6.1 Myriad alternatives ....................................................................................................... 24
   6.2 Read-across and grouping .............................................................................................. 24
   6.3 Grouping bisphenols ..................................................................................................... 25
   6.4 Sending a signal ............................................................................................................. 26

7 Conclusions and Recommendations .................................................................................... 27
   7.1 For policy makers and regulators .................................................................................. 27
   7.2 For industry .................................................................................................................... 29
   7.3 For workers ..................................................................................................................... 29
   7.4 For the consumer ............................................................................................................ 30
   7.5 Brexit and EU chemicals regulation .............................................................................. 30

8 Abbreviations ....................................................................................................................... 32

9 References ............................................................................................................................ 34
The story behind bisphenols

Once upon a time...

Then it was discovered...

Linked to:
- Breast cancer
- Infertility
- Early puberty
- Childhood neurological disorders

People started to...

PROTEST

Hooray! Rescued at last!

Wrong!

So...

BPS, BPZ, BPF, BPB, BPAF, BHPF, BP?

And even

Just because a product says it is BPA-free, does not mean there are no health impacts. Companies are replacing BPA with chemicals that are just as worrying. From BPA to BPZ.

It's a TOXIC ALPHABET SOUP

For more details: www.chemtrust.org/toxicsoup
We – and the wider environment – are exposed to many hundreds of man-made chemicals, from everyday products and from pollution. An increasing number of these chemicals have been found to disrupt the sensitive endocrine (hormone) system that plays a crucial role in the development and functioning of our bodies and those of wildlife. These endocrine disrupting chemicals (EDCs) have been shown to cause feminisation of fish and have been associated with neurodevelopmental problems, impaired fertility, certain cancers such as breast cancer, diabetes and obesity and coronary heart disease.

This report focusses on one group of chemicals, the bisphenols; they are all closely related and includes the well-established EDC, bisphenol A (BPA), a chemical that was first found to be an EDC in the late 1930s.

BPA is a component of plastics, food can linings and thermal paper till receipts. It has recently been formally identified as an EDC by the European Chemicals Agency (ECHA), and it is in the process of being banned in till receipts in the EU; its use has already been banned in baby bottles.

**BPA is found in the blood and urine of almost everyone who has been tested, and now scientists are finding the replacements, such as BPS and BHPF, in people too.”**

**Regrettable substitution – from one bisphenol to another**

As BPA has come under pressure from regulators, companies have moved to using other similar bisphenols, such as bisphenol S (BPS), bisphenol F (BPF) and bisphenol HPF (BHPF).

When looking for a new chemical to use in an application, companies will look for one of a similar structure, as it is likely to have similar properties. However, this similarity often extends to toxicity, which is what the scientists are finding with bisphenols.

Back in the 1930s, researchers identified two other bisphenols with endocrine disrupting properties, bisphenol B (BPB) and BPF. Since that time many more bisphenols have been tested, and scientists have found that chemicals similar to BPA will generally have similar endocrine disrupting properties.

BPA is found in the blood and urine of almost everyone who has been tested, and now scientists are finding the replacements, such as BPS and BHPF, in people too.

This report outlines the worrying evidence that companies are moving from one chemical that is proven to be toxic to related chemicals that are likely to be similarly so.

**The role of the regulators**

In the EU, the main management of chemicals is delivered through the REACH Regulation, which is administered by ECHA. However, certain chemical uses are regulated by different systems. For example, chemicals in food contact materials (FCM), like cans or baby bottles, are regulated by the European Food Safety Authority (EFSA).

EFSA and ECHA differ in the way they have addressed bisphenols, and the extent to which they use grouping in their assessment and regulation. Neither has dealt with bisphenols adequately, though ECHA has made more progress than EFSA.
ECHA is doing some work on understanding the use and properties of BPS, but has not put in place any controls on its use. Meanwhile, as far as we are aware, EFSA continues to devote all its attention to BPA.

Despite the EU’s sophisticated chemicals regulatory systems, industry has been permitted to replace one worrying bisphenol with another. This is not an acceptable situation, as the health of future generations is at stake.

Restricting groups of chemicals has to become the rule rather than the exception. When different substances of the same chemical group are likely to be similarly acting and used in the same situation and one is known to be harmful and has been regulated, then regulation should be extended to cover all other similar compounds.

Regulators should not delay action pending further research as ECHA has recently done even with the well-studied BPS.

ECHA has already recognised that it is acceptable for industry to use safety data from similar chemicals (‘read across’) when registering chemicals; the same approach should also be used to restrict groups of chemicals. In the absence of good data to the contrary, chemicals with similar structure should be assumed to have the toxicological properties as harmful as those of the most toxic known substance in the group.

“Despite the EU’s sophisticated chemicals regulatory systems, industry has been permitted to replace one worrying bisphenol with another. This is not an acceptable situation, as the health of future generations is at stake.”

The role of industry
The chemical industry and downstream users have the main responsibility for the continuing use of this group of chemicals, and the movement of the market from one bisphenol to another.

We have uncovered worrying signs of how the chemical industry is selling these other bisphenols to its customers. For example, the majority of companies are claiming, when selling to downstream users, that BPS has no hazards at all. This is a surprising claim when the Risk Assessment Committee (RAC) of ECHA has stated that BPS “is suspected to have many of the same adverse health effects as BPA”. This strongly suggests that industry self-classification of chemicals is not working.

The regulators need to take a grouping approach to chemicals to send a strong signal to the industry that it is not acceptable to replace one hazardous chemical with another with similar properties.
Recommendations

In CHEM Trust’s view, bisphenols should be regulated as a group, not individually. Manufacturers should not be permitted to replace BPA in consumer products with other bisphenols, eg BPS, as is currently the case.

These are our key recommendations:

1. **Regulators should regulate groups of related chemicals**, rather than taking a substance by substance approach. In the absence of good data to the contrary, chemicals with similar structure should be assumed to have the toxicological properties as harmful as those of the most toxic known substance in the group. This approach needs to be used in the main EU chemicals law REACH, and also in other chemical regulations, such as laws on chemicals in food contact materials. ECHA should also investigate the effectiveness of the industry’s self-classification of chemicals, and whether this is being done in accordance with the legal requirements.

2. **Chemical companies must improve their own assessment of the safety of chemicals.** It is not acceptable to claim that a chemical like BPS has no hazards, when a very similar chemical is known to have substantial hazards, including endocrine disruption. Particularly after the regulators have indicated BPS is suspected to have health impacts.

3. **Downstream users of chemicals should not replace one problem chemical with another** similar chemical from the same group.

4. **Workers should ask whether they are being exposed to BPA or other bisphenols**, and ask employers to move to safer non-bisphenol alternatives.

5. Consumers should ask retailers whether products such as plastic bottles, till receipts and food cans are bisphenol-free, and should **ensure that children do not play with till receipts**.
Over the last ten years, CHEM Trust has highlighted the need for improved protection from harmful chemicals in many reports, from the impacts of medicines on the environment,¹ to concerns about impacts of chemicals on the immune system.² Most recently we have shown that children are at risk from being exposed to many chemicals that are capable of impacting the development of the brain.³ In this new report we are interested in looking more deeply into one chemical group, bisphenols, which have been used in a range of products, from certain plastics to food can linings to till receipts.

As this report summarises, the most well-understood member of this group, BPA, has been known to be an EDC for decades, yet EU restrictions on its use remain incomplete (EEA, 2013). The health effects linked with exposure to BPA include: breast cancer, prostate cancer, endometriosis, heart disease, obesity, diabetes, altered immune system and effects on reproduction, brain development and behaviour, including behaviour in children.⁴

This report focuses on a number of chemicals that are very similar to BPA, seem to have similar hazardous properties, yet continue to be routinely used. Despite the EU having some of the most advanced chemicals laws in the world, including the main chemicals law REACH, there are still considerable gaps in the available safety data on these chemicals and many others.

The report then looks at whether it is time to move to a more efficient and protective approach to regulating chemicals, based on action on groups of similar chemicals, rather than the current slow, chemical-by-chemical, approach.

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¹ [http://www.chemtrust.org/pharma](http://www.chemtrust.org/pharma)
² [http://www.chemtrust.org/immune](http://www.chemtrust.org/immune)
The REACH Regulation, now in its tenth year, has been an important tool in reducing EU citizens to toxic exposures. A number of the most hazardous substances have now been restricted. But an overly-narrow application of the REACH text has undermined the system, exposing EU citizens to new chemical threats (EEB, 2017). The problem can be easily summarised: by restricting dangerous substances without taking action on their known replacements, the EU is jumping ‘out of the frying pan, into the fire’. A recent comprehensive study, carried out for the EU Commission in the context of an EU strategy for a non-toxic environment, illustrated several examples of cases of ‘regrettable substitution’, i.e. cases in which chemicals or chemical groups have been substituted with problematic alternatives (EU Commission 2017).

When BPA first came under regulatory scrutiny, manufacturers scrambled to find a replacement, very often settling on BPS, a similar molecule with similar toxicological effects. Any toxicologist aware of BPA’s hazards would also expect that BPS or BPAF, to name only two of BPA’s most common replacements, might have similar activity and health outcomes. Unfortunately, however, regulators too often treat these substitutes as new and entirely unknown molecules that must be studied in depth for years before action can be taken.

3.1 Bisphenol A use and regulation

Many EU consumers have become familiar with the ‘BPA-free’ label found on water bottles, baby bottles, food cans, and till receipts. As a consequence, BPA has become one of the most recognised chemical names in the EU. Most people are also exposed to it; it has been found in the blood and urine of nearly every person tested (Swedish Chemicals Agency, KEMI 2017). A 2008 study in the US showed detectable BPA urine levels in 93% of the 2517 individuals examined (Calafat et al. 2008). In 2009, a study by the German Environment Agency (UBA) found BPA in the urine of 591 out of 599 children aged between 3 and 14 (UBA 2013). A 2015 study detected BPA in over 90% of people from six EU Member States, including 100% of Swedish mothers and children (Covaci et al. 2015). Today, BPA is one of the most closely scrutinised chemicals in the world, yet it is still produced in the millions of tonnes per year in the EU alone.

BPA was first synthesised in 1891, although it was not the first bisphenol in use; that title probably goes to BPS, which was used as a dye as early as 1869 (Glausiusz 2014; Eladak et al. 2015). BPA later found use as a building block for plastics, epoxies, and resins, and these useful materials, in turn, soon found ubiquitous use: plastics, notably polycarbonate, for food packaging and water bottles; BPA-based epoxies used to line cans or bottles; and BPA-derived resins used as sealants in dental fillings. Other uses were found for the BPA molecule itself, including widespread use as a dye developer in thermally-printed papers, including till receipts and many tickets.

In recent years, the EU has moved towards stronger regulation of this widely-used compound, first prohibiting its use in baby bottles in 2011 due to concerns over neurodevelopmental and other toxicological effects (Commission Directive 2011/8/EU). In some cases, as with water and baby bottles, EU and US manufacturers moved to replace BPA before regulation was put into place, but retailers continued to sell BPA-laden bottles produced elsewhere, a clear demonstration of the need for regulatory
action to protect consumers even when some
manufacturers are acting voluntarily
(Hickman 2010).

More recently, the Commission has acted to
restrict the use of BPA in thermal papers like
receipts and train tickets, where it is used
to develop the ink when the paper is heated. This ban will not take effect until 2020
(Commission Regulation 2016/2235/EU).

Since 2016, BPA has been classified in the EU as a substance which is toxic for
reproduction and it has been included in the REACH candidate list for substances of
very high concern (SVHC). A chemical which is classified as an SVHC may then have
its use controlled through REACH’s authorisation procedure, and even before any other
regulatory action the SVHC designation means that many companies will avoid using it.

All manufacturers, importers, or suppliers of BPA must classify and label mixtures
containing BPA as toxic for reproduction category 1B, by 1 March 2018 (Commission
Regulation 2016/1179/EU). The Commission has also just brought in a new regulation
that lowers the permissible level of BPA that can leach from cans, while prohibiting it
from FCM intended for baby foods and formulas (Commission Regulation 2018/213/
EU). This new regulation does not mention BPS.

Despite this patchwork and insufficient approach to regulation, BPA continues to be
produced and used in tremendous volumes. In 2015, its global production was estimated
at 5.4 million tonnes, about a wine bottle’s worth of pure BPA for every person on
the planet (PRWeb 2014). It should be noted that most of that total ends up bound in
plastic or resin. Eliminating BPA involves more than simply leaving it out of products;
in most cases, the chemical role played by BPA in a product still needs to be met, and
BPA is replaced with another substance. It is no surprise that chemical companies and
manufacturers almost always choose molecules very similar in structure to BPA, usually
another bisphenol like BPA’s close cousin BPS, to simplify that transition (Figure 1).

It is also little surprise that those similarly-structured chemicals turn out to have
health and environmental problems comparable to those of BPA. As we shall
see, most of these effects appear to derive from the ability of the bisphenol molecules
to act on the body in the same way as the estrogens, the natural female hormones.

This report focuses on human health
implications of bisphenols, but it is
important to note that BPA has been
found to have a wide variety of impacts
on wildlife, from contributing to
intersex conditions in fish to disrupting
metamorphosis in amphibians (Canesi,
L., & Fabbri, E. 2015). BPS is meanwhile
already ubiquitous in the environment,
and has been shown to affect the
development of Zebrafish larvae (Wu et al.
2018).

In 2015, BPA’s global production was
estimated at 5.4 million tonnes – about
a wine bottle’s worth of pure BPA for
every person on the planet.”
3.2 Bisphenol exposure today

Today, consumers are exposed to BPA, and to a bewildering array of BPA substitutes, through many products and routes of exposure; but neither the consumer, the EU, nor national governments have any way to tell which BPA alternative is being used in any given product, short of performing a sophisticated chemical analysis. This is especially true of imported products: in 2017, Chinese researchers reported finding a previously unknown bisphenol (BHPF) in water bottles purchased from Chinese and non-Chinese suppliers, as well as in the blood of seven out of 100 volunteers from Chinese colleges (Zhang et al. 2017).

Consumer exposures to BPA and its alternatives are both widespread and complex. We might be directly exposed to BPA when we grab a thermally-printed receipt at the shop; when our water bottle is contaminated with the small residual amounts left over from the plastic manufacturing process; from the degradation of plastic food packaging when it is heated; or when the large polymers made from the bisphenol building blocks are broken down through other processes, as by the action of enzymes in saliva on certain dental sealants (Hashimoto and Nakamura 2000).

As we have seen, BPA appears in the urine and blood samples of nearly every person tested, despite recent prohibitions and phase-outs for a number of specific uses. Moreover, because BPA is eliminated quickly from the body, its constant presence in urine and blood “suggests that most of us are continuously exposed to low doses of the substance” (Swedish Chemicals Agency, KEMI 2017). As BPA comes under increasing scrutiny, however, tests in environmental samples and in humans are now identifying BPA alternatives, like BPS and BPF, where previously BPA had been used. A study of 616 samples from US adults, between 2000 - 2014, showed a general decline in BPA detection frequency and concentrations, while BPS exhibited an increasing trend. The levels of BPF showed little change over time, but it was detected in 88% of adults in 2014, with the highest concentrations on a par with BPA (Ye et al. 2015). In 2017, the American environmental health organisation, Silent Spring Institute, found higher levels of BPF than BPA in the 150 volunteers they tested, a finding they called “troubling” (Chemical Watch 2017c).

In order to gain more insights into exposure patterns of the EU population the bisphenols group has been prioritised for the EU-wide European Biomonitoring Initiative HBM4EU 6, which will look at levels of chemicals in EU citizens (Schoeters et al. 2017). CHEM Trust is a stakeholder for this project7, and we have been pushing bisphenols beyond BPA to be included (CHEM Trust Briefing 2017).

Figure 1: Structures of selected bisphenols (estradiol given for reference)
4 Bisphenols: looking at the evidence

4.1 The emergence of concerns about BPA

In the 1990s, researchers at Stanford University, USA, studying the impact of estrogens on yeast cells, were confronted by a strange phenomenon: all their experiments, including the unexposed controls, showed a substantial estrogenic response. They soon tracked down the source of the contamination: an estrogenic substance leaching from the lab’s polycarbonate flasks which they quickly identified as BPA (Krishnan 1993). The following year, another group reported that BPA leached from the lining of food cans, and, when tested in a cell culture, that this BPA-containing leachate had an estrogenic effect similar to that found in the earlier study (Brotons et al. 1995). Researchers quickly demonstrated that BPA also leached from dental sealants (Olea et al. 1996) and polycarbonate bottles, including baby bottles (Biles et al. 1997).

Over the next few years, toxicological studies in rodents showed that BPA could advance the timing of puberty, disrupt oestrous cycles (the rodent equivalent of menstrual cycles), and alter mammary development, a process which might, researchers hypothesised, lead to mammary gland cancer (the rat equivalent of breast cancer) (Markey et al. 2001; Muñoz-de-Toro et al. 2005). Other studies demonstrated effects on the male reproductive system, including impacts on prostate size, sperm production (vom Saal et al. 1998), and susceptibility to prostate cancer (Ho et al. 2006; Prins et al. 2011). BPA has also been shown to have a critical role in the development of metabolic disorders including diabetes and obesity (Alonso-Magdalena et al. 2011; Heindel et al. 2017; Nadal et al. 2017).

A summary of BPA’s effects can be found in the comprehensive Endocrine Society’s review and scientific statement on EDCs (Gore et al. 2015). In 2017, BPA was officially identified as an endocrine disruptor for human health and the environment by ECHA (see detailed support documents ECHA Member State Committee 2017 a and b).

More information on the potential health effects and special characteristics of endocrine disruptors can be found in Zoeller et al, 2014 and Gore et al, 2015.

The effects of BPA appear to be caused by the disruption of normal hormone signalling pathways (see Box A for more information on hormones and their role in the body). The structure of the BPA molecule is similar enough to that of the body’s natural female sex hormones – the estrogens – so that it can bind and activate the estrogen receptor (ER),8 triggering a cascade of hormone-related events (Figure 2 and Box A) (Wetherill et al. 2007). The fact that BPA can mimic estrogen in this way has been known for decades, but it was initially considered a weak estrogen because of its lower affinity for the estrogen receptors as compared to the major natural estrogen, 17b-estradiol (E2). However, today we know that BPA can promote estrogen-like activities that are similar to or stronger than E2 when it acts through the ‘non-classical’ pathways outside the cell nucleus (Alonso-Magdalena et al. 2012). Furthermore, while BPA can activate the estrogen

8 There are two major classes, and several subtypes, of receptors that are sensitive to the estrogen hormones. For simplicity, in this report we will use the term “ER” to refer to both subtypes of the nuclear estrogen receptor, without differentiating between them. We will occasionally refer separately to the membrane-bound estrogen receptors (mER), sometimes called the “non-genomic” or “extranuclear” estrogen receptors.
Hormones – like estrogen, testosterone, or thyroxine – fit, like a key in a lock, into a precisely-shaped socket in a specific protein called a receptor. Estradiol, for example, the primary estrogen in mammals, fits into the estrogen receptor (ER). The ER then migrates to the nucleus of the cell, where it turns specific genes on or off, thereby affecting nearly every aspect of female reproductive development. Furthermore, the activated ER complex can promote a great variety of cellular responses. In this way, estradiol plays an important role in physiological functions as diverse as cardiovascular function, energy balance, and glucose metabolism. Through processes like these, the hormones and receptors of the endocrine system connect and coordinate critical physiological functions throughout the body.

But it is not just the natural hormones that can trigger these functions: a number of other substances have a molecular shape similar enough to that of a hormone that they too can fit into the receptor’s lock. The molecular structure of BPA, for example, is close enough to that of estrogen that it can bind and activate the estrogen receptor to trigger a cascade of hormone-related events (Figure 2). A molecule that activates the ER is called an ‘agonist’. In other cases, when the fit of a molecule in a receptor is not quite right, the molecules can jam the receptor – just as the wrong key may jam in a lock, preventing the correct keys from turning it. BPA has this effect on the androgen receptor, which it binds to, but does not activate, making it an AR ‘antagonist’ (or an anti-androgen).

Hormones are the messengers of the body, and in tiny amounts can trigger their receptors to cause important effects. Similarly, it takes only miniscule amounts of chemicals with just the right structure – ‘endocrine disruptors’ – to dramatically alter these signalling pathways.

Box A: The key to endocrine disruption

Figure 2: Agonist and antagonist action on a receptor. (Figure courtesy of Leif Saul, www.biologyinmotion.com)
It is important to note that many of the studies referenced here were performed in animals (usually rats or mice) or in cell cultures (in-vitro). As with any animal or cell study, the direct relevance of this research to human populations can sometimes be unclear. Animal studies, for example, have often been performed at doses far higher than typical human exposures. In some cases, the mechanisms of toxicity in animals may not be the same as those in humans. Or, especially when human exposures are uncertain, the studies may not accurately represent the routes by which humans are exposed. Such criticisms are valid, and caution must be used when applying non-human data to human risk assessments. Fortunately, many of these problems can be mitigated by careful study design.

Recent studies of bisphenols have emphasised pathways and endpoints relevant to human health (e.g., with in-vitro studies in human cell lines), and many in-vitro and animal studies are now performed at low, physiologically-relevant doses (Rochester and Bolden 2015). The most compelling reason to rely on non-human data, however, is the simple fact that we usually do not have good data about health effects in people. It is very difficult to identify what chemicals a foetus is exposed to in the womb, for example, or to follow up the health of hundreds of children throughout their lives.

Epidemiologic studies are expensive and time-consuming, and are complicated or confounded by the many other factors that influence our everyday health. Furthermore, an epidemiologic study that demonstrated a significant health effect would, of course, be describing impacts on the human population – precisely the impacts that the regulatory structure is intended to avoid.

Although imperfect, our reliance on non-human data is simply a fact of life for a great many risk assessments, and this will be increasingly true as we study newer substances. It is therefore vital that regulators are able to regulate based on this data, rather than creating a situation where chemicals remain in public use when there is already good evidence that they will be harmful.

### 4.2 Beyond BPA: BPS, BPF, BPAF

The endocrine disrupting effects of BPA finally began to gain greater public attention during the 2000s. After a 2008 report by the US National Toxicology Program noted that “the possibility that BPA may alter human development cannot be dismissed”, calls for BPA’s removal grew stronger (NTP, 2008). In the EU, EFSA’s risk assessment on BPA in 2007 triggered a scientific controversy (Senjen and Azoulay 2008, CHEM Trust 2010, EEA 2013).

Some companies responded to the public concern and soon the ‘BPA-free’ label began to appear widely. However, environmental health advocates did not celebrate the progress made on BPA for long. In 2011, researchers demonstrated that most ‘BPA-free’ water bottles made from many different kinds of plastics still leaked chemicals with estrogenic activity (Yang et al. 2011).

The very close similarity of BPS and BPF to BPA made these chemicals easy substitutes in many uses. Table 1 shows an overview of main uses and exposures of selected bisphenols. It’s worth noting that it is difficult to get much information on many of the bisphenols, so this table is inevitably incomplete. The almost complete lack of regulatory controls on these ‘newer’ bisphenols helps account for their very rapid increase in popularity. Unfortunately, scientists soon confirmed that these molecules, with structures so similar to that of BPA, led as expected to hormonal effects very like those of BPA.
Table 1: Selected bisphenols: examples of uses and exposures

*NB: Based on available data, which is very limited for many bisphenols*

<table>
<thead>
<tr>
<th>Name</th>
<th>CAS</th>
<th>Examples of Uses</th>
<th>Examples of Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BPA</strong> bisphenol A</td>
<td>80-05-7</td>
<td>First synthesised 1891; used as monomer in polycarbonate manufacturing e.g. for electric and electronic products, water pipes, household applications, food packaging; thermal and receipt paper; dental sealant (Eladak 2015; Rochester 2013)</td>
<td>Detectable in the urine of almost all almost humans tested: 98% of German children (UBA 2013); over 90% of people from six EU states (Covaci et al. 2015) and 93% in a study conducted by the US Centers for Disease Control and Prevention (CDC) (Calafat et al. 2008); in serum of pregnant women and breast milk (reviewed in Rochester 2013); ubiquitous in environmental samples: 100% of sewage sludge samples (USA) (Yu 2015)</td>
</tr>
<tr>
<td><strong>BPB</strong> bisphenol B</td>
<td>77-40-7</td>
<td>Used in manufacture of phenolic and polycarbonate resins (US Database TOXNET)</td>
<td>Identified in canned foods (Grumetto 2008) and wastewaters (Česen 2017), as well as human biomonitoring (Cobellis 2009)</td>
</tr>
<tr>
<td><strong>BPF</strong> bisphenol F</td>
<td>620-92-8</td>
<td>Used in epoxy resins and coatings including tank and pipe linings, industrial floors, road and bridge deck toppings, structural adhesives, grouts, coatings, and electrical varnishes, as well as lacquers, varnishes, liners, adhesives, plastics, water pipes, dental sealants, and food packaging (Rochester 2015)</td>
<td>Has been detected in personal care products, paper products (currency, flyers, tickets, mailing envelopes, airplane boarding passes) and food; has been detected in [human] urine at concentrations and frequencies comparable to BPA (Rochester 2015)</td>
</tr>
<tr>
<td><strong>BPS</strong> bisphenol S</td>
<td>80-09-1</td>
<td>First used 1869; used in many industrial applications, “for example, as a wash fastening agent in cleaning products, an electroplating solvent, and a constituent of phenolic resin”; also used as a developer in “BPA-free” thermal paper (Glausiusz 2014; Rochester 2015)</td>
<td>Has been detected in personal care products, paper products (currency, flyers, tickets, mailing envelopes, airplane boarding passes) and food; has been detected in [human] urine at concentrations and frequencies comparable to BPA; ubiquitous in environment (Rochester 2015, Wu et al 2018)</td>
</tr>
<tr>
<td><strong>BPAF</strong> bisphenol AF</td>
<td>1428-01-1</td>
<td>Crosslinking reagent in fluoropolymers &amp; fluoroelastomers (Liao and Kannan 2014)</td>
<td>Detected in 38.7% of personal care products from China; predominant in Taihu Lake, China, suggesting that BPAF was the most widely used substitute of BPA, recently (Lu 2017; Liu et al. 2017)</td>
</tr>
<tr>
<td><strong>BHPF</strong> BHPF</td>
<td>3336-71-3</td>
<td>Used in the synthesis of polymers such as polycarbonate, epoxy resins, polyurethanes, polysters, polyarylates and polyethers; “whether BHPF is also used in materials or containers that come into contact with food — including milk bottles, children’s bottles and sippy cups — and whether humans are exposed to BHPF remains unclear.” (Zhang 2017)</td>
<td>Released from commercial ‘BPA-free’ plastic bottles into drinking water; detected in the blood of 7/100 Chinese college students who regularly drink water from plastic bottles (Zhang 2017)</td>
</tr>
<tr>
<td><strong>BPZ</strong> bisphenol Z</td>
<td>843-55-0</td>
<td>Possible BPA alternative for food contact materials? (Česen 2017)</td>
<td>Identified in wastewaters (Česen 2017); occasional detection in personal care products (PCPs) in China (Lu 2017).</td>
</tr>
</tbody>
</table>
BPS

Researchers reported that receipts collected in the USA, Japan, Korea, and Vietnam had changed from containing BPA to BPS (Liao et al. 2012b). BPS is a very convenient alternative, with a structure and chemical properties so similar to BPA that it can often be used as a ‘drop-in’ replacement, the substitution requiring little or no modification to the manufacturing process. Yet despite nearly a century and a half of use (Table 1), and occasional scientific papers identifying it in niche uses like dental sealants, BPS was still so little known as late as 2012 that the authors of one paper referred to it as “a new bisphenol analogue” (Liao et al. 2012b).

BPS was identified as being estrogenic at least as early as 2000, as researchers sought alternatives for BPA-derived dental resins (Hashimoto and Nakamura 2000). Receptor-binding studies indicate that BPS’s estrogenic and androgenic potencies are similar to, although probably somewhat less potent than, those of BPA (Kitamura 2005). As was the case with BPA, BPS has also been shown to have effects on non-genomic signalling pathways (in this case, in rat pituitary cells) that are as potent as those of E2 (Viñas and Watson 2013a). These more recently studied pathways are important for basic cell functions including growth, cell differentiation, and death.

The hormonal pathways disrupted by BPS manifest in many different ways in animal studies: in changed uterine growth (Yamasaki et al. 2004); shifts in both male and female sex hormone concentrations; reproductive disruptions including changes to egg production and sperm count (Naderi et al. 2014); as well as statistically significant weight gain and altered hormone metabolic profiles (Ivry Del Moral et al. 2016; Pu et al. 2017). In a recent study, Catanese and Vandenberg (2017) demonstrated that BPS alters maternal behaviour and brain in mice exposed during pregnancy/lactation and their daughters. A summary of BPS effects and hormonal activity can be found in the comprehensive review article by Rochester and Bolden (2015).

Despite these hazards, BPS use boomed after BPA came under scrutiny. A 2017 study found that it is now “ubiquitous” in the environment: “… studies show that BPS is present in water, sediment, sludge, indoor dust and air and consumer products... in all regions of the world, it is present in human urine, indicating that humans are exposed on a daily basis.” (Chemical Watch 2017a, Liu-Hong Wu et al, 2018).

BPF

Another obvious BPA substitute is BPF. Identical to BPA except for the lack of two methyl (CH3) groups at its centre (Figure 1), BPF is used in making epoxy resins, including those for can linings, as well as consumer products like varnishes, adhesives, water pipes, dental sealants, and food packaging (Rochester and Bolden 2015; OEHHA 2012). Recently it was also reported to occur naturally in some types of mustard (Zoller et al, 2016). Although it is the simplest of the class, and known since at least the 1930s, BPF was not thought to be in widespread use until 2012, when it was identified along with BPS as one of the primary BPA replacements (Liao et al. 2012a). Data on BPF exposure is still...
scarce, but a recent biomonitoring snapshot survey by the American NGO, Silent Spring Institute, reported that “participants had lower levels of BPA than the U.S. population, but higher levels of a chemical substitute called BPF” (see one example in Figure 3).\(^9\)

Although less well-studied than BPA or BPS, BPF appears to have similar BPA-like effects. Recent receptor-binding studies indicate that it is about as potent as BPA when acting through at least one of the nuclear ERs (Chen et al. 2016). These studies are complemented by animal tests that show the effects of BPF on uterine growth and testes weights (demonstrating impacts on the estrogen and androgen pathways, respectively) (Yamasaki 2004; Higashihara et al. 2007). BPF, like BPA, also appears to disrupt thyroid pathways (Lee et al. 2017).

\textbf{BPAF}

A third widely-used alternative to BPA is BPAF, in which fluorine atoms replace the hydrogen atoms in the central bridge. BPAF is used as a curing agent in synthetic rubber for in seals and gaskets (Choi and Lee 2017), and as a cross-linking agent in fluoropolymers and fluoroelastomers (Liao and Kannan 2014). Polymers made of BPAF appear to be used in tubing and seals for food and cosmetic products, possibly leading to consumer exposures (NTP 2008). A recent study of personal care products (PCPs) purchased in China found BPAF in 38.7% of samples (Lu et al. 2017), and a study of American and Chinese PCPs detected BPAF in 10.5% (USA) and 6.8% (China) of products tested, including toothpastes, makeup, and body washes (Liao and Kannan 2014). Although no data on BPAF in EU food or cosmetics is available, EU residents may be similarly exposed through either European-made or through imported products.

\textbf{Figure 3: Levels of several bisphenols in a urine sample from an adult American volunteer (2017). Data from the Silent Spring Institute’s Detox Me Action Kit, reproduced with permission from study participant.}

\textbf{https://silentspring.org/blog/results-our-biomonitoring-study-are}
One study of bisphenols in Slovakia identified BPAF (among many other bisphenols) in a number of samples, particularly in the wastewater discharged from food production/processing plants and from textile cleaning facilities, indicating possible routes of exposure for European consumers (Česen et al. 2017).

Unsurprisingly, little toxicity data is available for BPAF, but in-vitro studies indicate that it is a strong ER agonist, perhaps more estrogenic than BPA in certain cellular pathways (Cao et al. 2017), while also acting as an antagonist for the one of the nuclear estrogen receptors (the β subtype) specifically (Li et al. 2012). (See Box A for a description of agonist and antagonist activity.) BPAF also appears to alter reproductive gene expression and testosterone levels (Li et al. 2016).

4.3 The newest head of the Hydra: BPHF

In 2017 another bisphenol entered the public debate. A paper in Nature Communications described the estrogenic activity of an almost unknown bisphenol, fluorene-9-bisphenol, which the authors call BPHF (Zhang et al. 2017). BPHF is only the simplest of a large class of molecules patented in 1987. It is listed as having been produced in the US EPA’s chemical inventory, and it has been registered in REACH. As with many chemicals, the publicly available data is not very helpful: the EU registered substances database reports that BPHF “is manufactured and/or imported in the European Economic Area, but tonnage data is confidential”, and notes that ECHA “has no public registered data indicating whether or in which chemical products the substance might be used”, although it is classified as “very toxic to aquatic life”, and “known to cause eye and skin irritation” (ECHA Database). This lack of knowledge extends to even the most basic information on uses: “Whether BHPF is also used in materials or containers that come into contact with food – including milk bottles, children’s bottles and sippy cups – and whether humans are exposed to BHPF remains unclear”, the recent study reported (Zhang et al. 2017).

The authors started by looking for BHPF in water bottles, and found that the chemical had leached into water from most of the polycarbonate bottles they tested (Zhang et al. 2017). They were also able to detect BHPF in the blood of seven out of 100 students at Chinese colleges who regularly used plastic water bottles, indicating a relatively common human exposure pathway. When tested in a cell culture, BPHF was found not to be estrogenic, but was instead strongly anti-estrogenic, with a potency approaching that of tamoxifen (an anti-estrogenic agent commonly used to treat some forms of breast cancer). Similar effects were seen in mice: although BPHF had little activity on its own, it significantly reduced the activity of estrogen on the uterus, as expected of an anti-estrogen. And BPHF altered the number and body weight of rat pups born to exposed mothers “even at doses lower than those of BPA” (Zhang et al. 2017).

10 Other references sometimes refer to BPHF as BPFL or bisP-FL. It should be noted that the name “fluorene” refers to the three-ring structure found between the two phenols in the BPHF structure; it should not be confused with the element fluorine, which is not present.

11 https://echa.europa.eu/brief-profile/-/briefprofile/100.100.850
Given these findings, and the fact that BPHF is registered under REACH, it is important to clarify the EU uses and exposure levels for this substance.

Although the specific actions of BPHF are somewhat different to those of BPA, it shares the fundamental bisphenol structure of two benzene rings with a hydroxyl group on each end (Figure 1). And, as expected, it acts via one of the nuclear estrogen receptors, a route that we could have anticipated, and avoided, long before BPHF entered commerce.

4.4 Nothing new under the sun
The estrogenic action of the “alternative” bisphenols should not have been a surprise: it was reported more than eighty years ago.

Already in 1936, British researchers, as part of a search for pharmaceutical treatments for hormone-related conditions, published a breakthrough paper in the journal Nature, in which they demonstrated that BPA, BPB, and BPF showed full estrogenic responses in their simple tests on rats (Dodds and Lawson 1936). Two years later, after finding consistently strong results for BPA, BPF, and a variety of other bisphenols, the authors drew the conclusion that “substances containing two phenol groups joined by a carbon chain” — that is, the bisphenols — “are active” — that is, estrogenic. “The number of carbon atoms, the position of double bonds and of substituent groups attached to the carbon chain,” they continued, “all vary the activity” (Dodds and Lawson 1938). Evidently, the basic bisphenol structure — two rings, separated by a short carbon chain, with a hydroxyl group attached at each end — makes a highly effective key to fit the estrogen receptor’s lock (Figure 2).

Despite their strong estrogenicity, bisphenols were soon left behind as researchers developed other estrogens with still higher potency: notably the highly estrogenic pharmaceutical-turned-carcinogen diethylstilbestrol (DES). With the advent of DES, bisphenols had been supplanted in the search for estrogenic drugs. Soon, their endocrine properties forgotten, they found widespread use in plastics, epoxies, and a myriad of other applications. But those early conclusions about the estrogenicity of bisphenols continue to be echoed and refined by researchers today. The authors of one 2002 paper nearly repeated the conclusions of Dodds and Lawson when they wrote, “all or most BPs [bisphenols] have estrogenic activity as a common property. The modification of phenolic rings and bridging carbon or sulphur atoms of BPs seems to influence the estrogen activity…”(Chen et al. 2002).

Interestingly, BPS, which appears not to have been studied during the 1930s estrogenicity experiments, may be the exception that demonstrates the rule. Because it has a sulphur group between its benzene rings, it does not fit the usual bisphenol pattern, and was overlooked in the estrogenicity tests of the 1930s; but its molecular shape mimics BPA very closely, making it an effective key for the ER (Figure 2).

4.5 Endocrine activity of bisphenols
Today, toxicologists are still investigating the details of which atoms and in what positions are necessary for different types of estrogenic and androgenic activity (Perez et al. 1998; Kitamura 2005). But the basic message that bisphenols are generally estrogenic, as described by Dodds and Lawson in 1938, holds true (Table 2). As with Table 1, there is limited information on many bisphenols.

We really are talking about an A to Z of bisphenols, with initial in-vitro research finding that BPZ is able to activate the estrogen receptor (Mesnage et al. 2017) and it can disrupt the thyroid hormone system (Lee, S. et al 2017).
Table 2: Endocrine activity of selected bisphenols

<table>
<thead>
<tr>
<th>name</th>
<th>estrogenic</th>
<th>anti-estrogenic</th>
<th>androgenic</th>
<th>anti-androgenic</th>
<th>On Swedish Chemicals Agency list of bisphenols likely to be EDCs [13]</th>
<th>On TEDX list of potential endocrine disruptions [14]</th>
</tr>
</thead>
</table>


The bisphenols can be estrogenic or anti-estrogenic, androgenic or anti-androgenic, in different combinations, at different doses, and in different tissues. This can also lead to highly complex interactions between them and the body’s natural hormones. For example, a recent study in a rat cell line reported that BPA, BPS, and estradiol each induced cell proliferation at environmentally relevant concentrations, but that the combination of these greatly suppressed cell proliferation (Viñas and Watson 2013b). The authors cited these “dramatic” disruptive effects, and argued for broad pre-screening of hormonally-active compounds: “Adverse actions from chemicals introduced to the environment should be suspected whenever they can disrupt the actions of a physiologic hormone like E2 [estradiol]” (Viñas and Watson 2013b).

Given the complex soup of chemicals to which we are exposed every day, and our lack of knowledge about most of them, such complexity adds greatly to our concern about the hazards of bisphenols, along with many other known or likely EDCs.

4.6 Bisphenols and human health

The health effects of bisphenols are complex, and may lead to serious and irreversible changes in an organism. Most studies have taken place in rodents, and the evidence for reproductive and metabolic disruption in both males and females is very strong.
Studies of their effects on humans are far more difficult. Bisphenols are especially difficult to study because they are metabolised and eliminated from the body so quickly: most BPA will be excreted in half a day. A urine sample taken today, therefore, can tell us a lot about today’s exposure, but very little about last week’s, or last year’s; this makes it difficult to correlate any recent measurement of BPA exposure in blood or urine with a health effect that might be due to a past BPA exposure. On the other hand, bisphenols are so widely used, and in such a range of applications, that we are being repeatedly, and nearly constantly, exposed (Chevalier and Fénichel 2015). In addition, because of the wide variety of bisphenols in use, any study that looks at exposure to only one of them, most commonly, BPA, will not account for the total exposure to endocrine disrupting bisphenols, likely weakening the study’s results.

Despite these difficulties, the human data available today is largely consistent with the data from animal and other laboratory studies in showing numerous effects of BPA on health (reviewed in Gore et al. 2015; Rochester 2013).

• Since bisphenols can modulate both the estrogen and androgen receptors, it is no surprise that we see evidence for reproductive effects in humans. BPA, which has been studied the most, has been linked to changes in estrogen levels (Meeker et al. 2010), impaired egg cell formation, and reductions in sperm number and quality (Li et al. 2011; Mendiola et al. 2010). A more detailed description of human studies has been summarised by Rochester (2013).

• BPA has been linked to changes in fat tissues, weight gain, and insulin resistance in humans, consistent with its actions on estrogen, thyroid, and other receptors (reviewed in Gore et al. 2015; Rochester 2013), and some scientists have proposed that it contributes to the present epidemic of diabetes and obesity (Alonso-Magdalena et al. 2011; Nadal et al. 2017; vom Saal et al. 2012) as it has been highlighted in the last Scientific Statement of the Endocrine Society (Gore et al, 2015).

• Researchers studying possible neurological effects have found associations of BPA with declines in behavioural scores and increases in attention deficit hyperactivity disorder (ADHD) (Casas et al. 2015; Tewar et al. 2016). A 2016 review of studies in children found that prenatal exposure to maternal BPA was related to higher levels of anxiety, depression, aggression, hyperactivity, inattention and behavioural problems (Ejaredar et al. 2017).

• It has been estimated that about 40% of new cases of cancer are due to hormone-related causes (Maggiolini and Belfiore 2017), and scientists have begun to investigate whether bisphenols play a role. There is little epidemiologic evidence thus far for an association between BPA and breast cancer in humans, but rodent and primate studies indicate that BPA increases susceptibility to mammary cancer (Acevedo et al. 2013; Paulose et al. 2015). One recent study found that BPS modulated levels of estrogen receptor in breast cancer cells (Mesnage et al. 2017). There is also substantial evidence that BPA can increase the risk of prostate, thyroid and other cancers by a complex set of mechanisms including estrogenic and other pathways (Di Donato et al. 2017, Gore et al 2015).

“BPA has been linked to changes in fat tissues, weight gain, and insulin resistance in humans, consistent with its actions on estrogen, thyroid, and other receptors.”
5 An inadequate response

In the EU, the main regulation of chemicals is delivered through the REACH regulatory system, which is administered by the ECHA. However, certain chemical uses are regulated by different systems. For example chemicals in FCMs e.g. cans or baby bottles, are regulated by EFSA, with the overall policy area run by the European Commission Health Directorate General (often called DG Santé).

EFSA and ECHA differ in the way they have addressed bisphenols, and the extent to which they use grouping in their assessment and regulation. Neither has dealt with bisphenols adequately, though ECHA has made more progress than EFSA.

In this section we will ask why ECHA, EFSA and the Commission are knowingly allowing potentially toxic replacements to BPA to be used. We will consider a simple solution: grouping hazardous chemicals by well-defined structural similarities that are directly related to their toxicity and taking according regulatory action. We also acknowledge the work that ECHA does on grouping and avoiding regrettable substitution – for example in the new ‘Strategy to promote substitution to safer chemicals through innovation’,12 while asking why EFSA does not have any similar activities.

5.1 The sluggish pace of regulation

The regulatory response to the health concerns of BPA was very slow. After many years of controversial debate the EU agreed to ban BPA in baby bottles in 2011. This measure was criticised by NGOs as insufficient because it leaves pregnant women and thus the unborn child unprotected, and also does not stop other uses of BPA.13

5.2 BPA in thermal paper

In 2014 France submitted a proposal to restrict the use of BPA in thermal paper.

When ECHA evaluated this restriction proposal, it took an extremely cautious and somewhat defensive approach. ECHA’s Committee for Risk Assessment (RAC) carefully sifted through the existing data in order to calculate specific risk estimates in the affected populations. Although RAC agreed that a number of different endpoints were of concern and needed to be evaluated, the committee concluded that “the available hazard data did not allow for a quantification of the dose-response relationship for effects on the mammary gland, or for the reproductive, immunotoxic, metabolic and neurobehavioural effects” (ECHA 2015). That is, RAC’s uncertainty was not whether these effects are of concern as a result of BPA exposure, but how to quantify the precise level of exposure that is safe.14 After very extensive calculation, RAC’s cautious analysis concluded that risks to workers (specifically, pregnant women working as cashiers and handling receipts) were not controlled, whereas the risks to the general population were low and did not require mitigation.15

14 The estimate of the highest exposure to which a human may safely be exposed is the Derived No-Effect Level (DNEL). Importantly, a calculation of a DNEL assumes that there is some true safe or “threshold” level of the substance in question, whereas for EDCs it remains unclear whether a threshold really exists: “The belief in a dose threshold is therefore derived from the way one imagines that an EDC acts to produce an adverse effect, rather than being evidence-based” (Zoeller et al. 2014).
15 However, we note that RAC’s risk characterisation for exposed members of the general population was as high as 50% to 88% of the level that would have indicated an uncontrolled risk – a very small margin for a quantity so uncertain (ECHA 2015).
The resulting restriction will protect both workers and the general population of the EU as it bans BPA use in thermal papers. However, this ban will not come into effect until 2020 (Commission Regulation 2016/2235/EU).

5.3 What about BPS in thermal paper?

The EU BPA restriction does not address exposures to any of the BPA substitutes – including BPS. This shortcoming was clearly identified during the decision-making process by ECHA’s own committees:

“... the least expensive alternative to BPA is BPS, which is suspected to have many of the same adverse health effects as BPA. A restriction on BPA in thermal paper may thus only ensure that there is a reduction in risk if alternatives other than BPS are chosen by industry as a replacement.” (ECHA 2015)

In fact, ECHA’s Committee for Socio-Economic Analysis (SEAC) explicitly concluded “that preparation of a restriction proposal on BPS should be considered if a restriction on BPA will be implemented”, and RAC similarly “advise[d] against substitution with BPS” (ECHA 2015).

In its final decision, however, the Commission said simply that “the Agency should monitor the use of BPS in thermal paper”, citing the possibility of “an eventual substitution trend towards BPS”, and it asked ECHA to launch a survey to determine whether BPS is being used in thermal paper. The answer to this question – an emphatic “yes” – has been clear since at least 2012, when BPS was first identified in thermal papers (Liao et al. 2012b). A more detailed 2017 study that looked at a large variety of thermal paper types, including “cinema tickets, fruit weight stickers, bus and train tickets, boarding passes and luggage tags”, identified BPS as a major substitute for BPA, accounting for about 30% of this use in Sweden and the Netherlands (Björnsdotter et al. 2017).

As requested by the Commission, ECHA studied the use of BPS in thermal paper and published the first results at the end of 2017 (ECHA, 2017e). This study looked at the use of BPA, BPS and some other developers, and estimated trends from 2014 – 2016:

- BPS use in thermal paper developer increased from 156 to 202 tonnes between 2014 and 2016
- BPA use in thermal paper developer reduced from 2812 to 2743 tonnes in the same period
- Other developers went from 1380 to 1722 tonnes per year.

It is worth noting that the ban on BPA does not actually enter into force until January 2020, and the law is formally dated 12th December 2016 in the EU’s Official Journal. This makes it unclear how much this study really reflects changes in the market as a result of the BPA restriction. The very small decline in BPA use in this period suggests that the market had not yet started moving during the study period.

Interestingly, a 2018 US study found in an analysis of 167 receipts, that BPS was the most prevalent (75% of receipts) followed by BPA (18%), which suggests that at least in the US market the trend has changed. ECHA plans to update the study every year.
While the Commission charged ECHA to monitor BPS use, it also pointed out that, “contrary to BPA, the health risk associated to BPS in thermal paper has not yet been evaluated” (Commission Regulation 2016/2235). In fact, ECHA had already started assessing the EDC hazards of BPS via the separate Substance Evaluation process, and at first there were promising signs that this process might unfold quickly. In 2014, BPS was listed in the Community Rolling Action Plan (CoRAP) of priority substances to be evaluated within three years, by Belgium, due to concerns about possible endocrine disruption and reproductive toxicity (ECHA 2016). (A chlorinated analogue of BPS, 4,4’-dichlorodiphenyl sulfone, is also listed in the CoRAP.

Over two years later, ECHA made its decision on BPS: more research is needed. Specifically, ECHA requested that the registrants perform four more toxicity tests, including two rat studies and a fish test, and set a deadline for these results to be submitted by September 2018 (ECHA 2016). Despite a substantial body of existing literature on BPS, and rather than relying on relevant BPA data, ECHA postponed a real decision for at least two more years, during which time BPS has been, and will continue to be, used in place of BPA.

It is understandable that ECHA and the Commission prefer not to make a decision quickly, whether on substance evaluation or restriction, especially in the face of industry resistance, and that they desire as much data as possible before restricting BPS use. But the implicit decision they are making is that it is acceptable to expose EU citizens to BPS while the years-long risk assessment and restriction processes play out. The implication is that we do not have enough evidence to make a decision, but we are willing to allow its use to continue and grow, in clear contravention to REACH’s “no data, no market” principle. Essentially, the regulator is giving the benefit of the doubt to the BPS manufacturers, and continuing the essentially involuntary exposure of the EU population.

It should be noted that several non-bisphenol alternatives are readily available: the 2017 study described earlier (Björnsdotter et al. 2017) found one non-bisphenol alternative used in about 60% of samples from Norway, and no samples had BPS as the main developer. The same study found that nearly 90% of thermal papers collected in Spain still relied on BPA, with only 8% of samples using BPS. EU regulation should be ensuring that the Spanish market does not transition to BPS as BPA is phased out.

As we have discussed above (Section 2.1), it is important to be cautious when interpreting animal and cell culture data for application to humans. On the other hand, ECHA’s emphasis on scientific certainty, as exemplified by the drawn-out BPS substance evaluation process, means that its regulatory actions fail to protect consumers to ongoing or emerging exposures. ECHA’s need for scientific certainty also puts it in the difficult position of being unable to keep up with the pace of scientific discovery, which is indeed very rapid: a quick PubMed search identifies over 500 studies on bisphenols in 2017 alone. As a result, however, ECHA and the Commission are asking questions that have in some cases already been answered by independent scientists, as in the Commission’s request for information about BPS use. As of the end of 2017, ECHA’s “Hot Topics” webpage still refers to BPS as “one potential replacement that is being considered by industry” (ECHA 2017a).
The slow progress of regulation guarantees EU citizens and workers many more years of exposure to BPA and BPS, in thermal paper and many other uses. Once BPA and BPS are regulated exposure will move to other bisphenol alternatives, unless the regulators become more active. The data on these other bisphenols is much scarcer than the data on BPA or BPS, however, and in some cases, little or no study has been made of their effects on humans or animals, as we saw with BHPF. Given ECHA’s demand for scientific certainty, this raises the possibility that regulation of these alternatives may be many years away. By contrast, a ‘grouping’ approach to regulating this class of molecules would allow us to use the data now available on BPA as an excellent starting point for assessing and controlling the use of its close relatives.

5.4 What’s EFSA doing?
There is little sign that EFSA, responsible for regulation of chemicals in FCMs, is engaging with the issue of bisphenols beyond BPA. EFSA is currently re-assessing the toxicity of BPA, but this process is not planned to address BPS or other bisphenols. BPS is approved for use in food contact plastics, and a search of the EFSA web site finds no sign of any re-evaluation of this approval. The EU currently has no harmonised approval process for chemicals used in food contact coatings (e.g. can linings), or paper and card FCMs, so it is very hard to know which bisphenols are being used in these products. CHEM Trust has strongly criticised these gaps in EU regulation and the Commission has said that it will review the laws on chemicals in FCMs in 2018.

5.5 An irresponsible approach from parts of industry
Faced with an opportunity to reduce consumer exposures to known hazards, some manufacturers appear to have taken the easy way out, substituting BPA with similarly structured bisphenols. But worse still, industry has capitalised on the public’s concern, and its lack of scientific expertise, to advertise products that are ‘BPA-free’. Although this phrase may sound reassuring to consumers, many of these products may be no safer. By 2011, researchers were already reporting that most ‘BPA-free’ water bottles still leached chemicals with estrogenic activity (Yang et al. 2011). In some cases, these products might actually be worse, if the replacements like bisphenol C (BPC) or BPAF are used (Chen et al. 2016).

Because manufacturers and importers are not required to disclose the details of a product’s chemical composition, we have virtually no systematic data about which bisphenols are used in which applications.

Industry appears to be substituting new and poorly-studied bisphenols at a pace that simply cannot be matched by researchers or regulators. Environmental monitoring is now turning up more new bisphenols in more places. A study from the USA and China identified bisphenol AP (BPAP) in about 10% of personal care products, including nearly half of toothpastes tested (Liao and Kannan 2014). Tests of wastewater in Slovakia found BPZ, and identified BPC in wastewater for the first time (Česen et al. 2017). A survey of sewage sludge from the USA as far back as 2006/2007 identified BPP, BPB and BPZ.

“Given that RAC has said that BPS “may have a toxicological profile similar to BPA”, how is it tenable for the majority of companies selling BPS to tell their customers that it has no hazards, and why do none of them say that it may be a reproductive toxicant?”
along with the well-known bisphenols (Yu et al. 2015). While not all of these studies are directly relevant to exposures in the EU, they indicate the widespread use of virtually unstudied bisphenols that appear to have been introduced into the global marketplace.

Despite this data, and despite the ongoing pattern of substitutions, ECHA maintains that the “alternative” bisphenols “are used in small volumes and in niche applications where exposure is likely to be limited” (Chemical Watch 2017d). The widespread demand for BPA substitutes, and the increasing detection of these chemicals in samples around the globe, belies that claim.

*Companies selling BPS label it as non-hazardous*

When companies sell chemicals in the EU, and in most other countries, they must label them to show their hazards. In some case these hazards will have been agreed by the EU regulator, this is known as harmonised classification and labelling, CLH. 20 If there is no harmonised classification, then companies must decide themselves how to classify the chemical. In this latter case, the company must still submit their classification to ECHA, where it is entered into the Classification and Labelling Inventory. 21

**BPA** has a harmonised EU classification 22:

- May cause an allergic skin reaction
- Causes serious eye damage
- May cause respiratory irritation
- May damage fertility or the unborn child (Reproductive toxin class 1b)
- “Additionally, the classification provided by companies to ECHA in REACH registrations identifies that this substance is toxic to aquatic life with long lasting effects.”

**BPS** does not have a harmonised classification, so it is up to individual companies to say how hazardous it is; here’s the result (as of 6th Feb 2018)23:

- 240 say that BPS has no hazards
- 68 say it is “Harmful to aquatic life with long lasting effects”
- 17 say it “Causes serious eye irritation”
- 4 say it “Causes skin irritation”, “Causes serious eye irritation”, “May cause respiratory irritation.”

The majority of companies selling BPS claim that it has no hazards, and none of the companies selling BPS suggest that it may be a reproductive toxicant, despite the fact that it is agreed that BPA “may damage fertility or the unborn child”.

The ECHA RAC concluded in 2015, while examining BPA, that “BPS, the most likely substitute according to the Dossier Submitter, may have a toxicological profile similar to BPA and thus RAC advises against substitution with BPS”. 24

Given that RAC has said that BPS “may have a toxicological profile similar to BPA”, how is it tenable for the majority of companies selling BPS to tell their customers that it has no hazards, and why do none of them say that it may be a reproductive toxicant?

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6 Grouping to speed up regulatory controls

6.1 Myriad alternatives
When a substance like BPA or BPS is found to be harmful to health, industry is often able to ‘drop in’ a replacement substance with similar chemical and physical properties, requiring only minor changes to the industrial process. There appears to be no shortage of possible bisphenol substitutes: in 2014, a US EPA assessment identified twenty possible substitutes for BPA in thermal paper, including the bisphenols BPF, BPC, BPAP, BisOPP-A, and MBHA, as well as two ‘proprietary’ chemicals that EPA evaluated but did not publicly identify (US EPA 2015).

Researchers and regulators, however, end up playing catch-up with the industry. First they must identify which chemicals are used in which products, and whether and how consumers are exposed. Then begins the year-long process of testing each chemical for safety and trying to characterise the level of risk begins. The result is a ponderous game of Whack-A-Mole, as regulators try to understand how to manage one chemical even as industry has moved on to the next. Unfortunately, this ‘game’ may have large impacts on human health and the environment.

Yet it is critical that we address chemicals that might be viable substitutes for BPA. Despite the need to register chemicals in REACH and the fact that not all bisphenols have been registered yet, it is quite likely that many of the alternative bisphenols are used in products imported into the EU.

If the regulatory decisions around BPA and BPS are difficult, the decisions about other bisphenols will be much more so. A regulatory decision on any ‘alternative’ bisphenol cannot be based on a traditional risk assessment, because we simply do not have enough data, and will not have enough for many years. It is neither realistic nor protective to argue that the health effects of these newer bisphenols are essentially unknown, and then to call for more research, as ECHA has now done even with the relatively well-studied BPS. Dodds and Lawson’s 1938 paper, and the great deal of evidence accumulated in the eighty years since, makes a strong case that bisphenols, as a chemical class, are typically estrogenic. Instead, “when evaluating the safety of compounds for consumer use,” as one recent review suggests, “it may be prudent to consider entire classes instead of individual compounds” (Rochester and Bolden 2015). We now know enough about the molecular mechanisms of bisphenols that we can identify which specific parts of the molecule contribute to estrogenic or androgenic activity (Kitamura 2005). This gives us a convenient way to define a class of bisphenols for research and regulation.

6.2 Read-across and grouping
One method that is used to fill gaps in toxicity data is ‘read-across’. This refers to the idea that data on a relevant toxicological or environmental fate endpoint of a poorly-known substance can be derived from information about a closely related, better-studied substance (ECHA 2017c).

Read-across is a relatively common process, used primarily to fill gaps in substance registration data. Although the concept behind read-across is a simple one, its implementation requires substantial expertise; ECHA’s Read-Across Assessment Framework provides guidance on evaluating the scientific suitability of a read-across proposal (ECHA 2017c). Read-across is grounded in the idea that we may group related substances which have similar physical, chemical, and ecotoxicological properties as a result of structural similarity (this may include similarity of precursors, or of likely metabolic or degradation products).
The grouping approach is not new, and the REACH legislative text emphasises its use in assembling the safety data for registering chemicals. Annex XI of the REACH text gives specific guidance on use of grouping and read-across, while Annexes VII, VIII, IX, and X explicitly call for the evaluation of read-across data from ‘structurally related substances’ before new tests are carried out. This approach can be helpful in reducing unnecessary testing, especially on animals.

ECHA has previously used grouping based on structural similarity or similarity of hazard for screening purposes, for classification and identification of SVHCs, e.g. for chromium and cadmium compounds. Of the sixteen risk management option analyses (RMOAs) produced in 2016, for example, four were for groups of substances (ECHA 2017b). Other groupings already in use include several groups of perfluorinated compounds, of which the perfluorooctanoic acid-related substances and salts have already been restricted, while other perfluorocarbon acids, their salts and precursors are still under consideration. Attention on the perfluorinated compounds has now shifted to the short-chained PFASs, where, ECHA hopes, “work on a handful of substances will be used to address tens, if not hundreds of precursors” (ECHA 2017b), demonstrating the potential strength of the grouping approach.

However, defining groups of substances is not an easy process. While read-across under REACH must be based on structural similarity, ECHA is at pains to point out that “structural similarity alone is not sufficient to justify” read-across (ECHA 2017c). A read-across hypothesis must be provided which explains why the structural similarity is expected to allow predictions of environmental fate or ecotoxicological properties.

Identifying the health effects of new, heretofore unstudied compounds, often with more subtle health impacts like endocrine disruption, is challenging. Yet at the same time, EU citizens are being exposed to unregulated but predictable chemicals, especially those used as substitutes for substances moving through the regulatory process. For example, new bisphenols like BPB are found in human and environmental monitoring studies in Europe. Similarly, of seven long-chained perfluorocarboxylic acids already identified as SVHCs, none are registered under REACH, yet all of these appear on the EU market and in the EU environment (ECHA 2017b).

6.3 Grouping bisphenols

ECHA has not, to our knowledge, considered grouping bisphenols, but has followed a one-by-one approach. The idea of grouping bisphenols has been proposed before, including by CHEM Trust, during a consultation on restrictions on BPA in food packaging material. In this consultation we argued that EFSA and the European Commission’s DG Health should expand the restriction to apply to other bisphenols as well, since they are likely substitutes (Chemical Watch 2017b). The Commission did not react to our suggestion and stayed focused on BPA.

The class of bisphenols appears to provide an ideal set of candidates for a group:

- The structural similarity of bisphenols is well defined, with alkyl and aromatic substitutions, sometimes chlorinated or fluorinated, analogous to those of the diisocyanates; obviously, this group should also include variations on this structural theme, for example, BPS and thiodiphenol. Polymers of bisphenols which might contain or degrade into monomers (like BPA-based polycarbonate) should also be included. This grouping is well-defined on structural grounds, and is far less complex than other groups.

“In CHEM Trust’s view, the evidence that a grouping approach to bisphenols is needed is now indisputable.”
• Our read-across hypothesis is very clear: the binding of the bisphenols to estrogen and other receptors is well understood, and the expected downstream endocrine disruptive effects of this binding are well characterised for a number of these compounds. Indeed, this hypothesis can be thought of as deriving directly from Dodd and Lawson’s early work. The default position should be that all bisphenols are viewed as being part of this group, unless there is substantial evidence that a particular bisphenol does not have endocrine properties.

• Bisphenols, like BPS, are often used as ‘drop-in’ substitutes. This attests to the similarly of their basic physiochemical and bulk properties, and reinforces the idea of grouping.

A read-across hypothesis along these lines would be an appropriate screening tool for endocrine disrupting effects of bisphenols. Moreover, this hypothesis is also fairly specific, and could allow us to predict the likelihood or absence of effects for various possible substitutes using combinations of molecular modelling and receptor-binding assays.

In fact, the Swedish Chemicals Agency has already begun to investigate a grouping approach for bisphenols. Using computer models called ‘Quantitative structure-activity relationship’ models, or QSAR, they were able to assess each molecule’s likely fit into the estrogen receptors and, therefore, able to make an educated guess about its health effects. Through this process, they identified 37 bisphenols as both likely to be estrogen-active and used in applications where consumers will be exposed (KEMI 2017).

In CHEM Trust’s view, the evidence that a grouping approach to bisphenols is needed is now indisputable.

6.4 Sending a signal
In addition to its scientific and regulatory value, a grouping approach to regulation would send a signal to manufacturers, even outside of the EU, that bisphenol alternatives should not be assumed to be viable long-term replacements. This applies not just for thermal paper, but for any consumer-facing use where BPA is substituted. Even the nomination of such a ‘candidate group’ would send a message about the presumptions used when regulating.

The evidence shows that bisphenols can be expected to have the potential for endocrine-active effects which might require regulation. Future use and registration of bisphenols would be subject to a requirement to show that this endpoint is not being triggered. This approach is fairly likely to be effective: there is evidence that SVHC identification alone is enough to have caused many users to transition away from a substance. Moreover, the identification of a substance as a carcinogen, mutagen, or reproductive toxicant (CMR) gives the Commission the authority to fast-track a restriction under Article 68(2).

It is also notable that some companies and scientists are starting to investigate bisphenols that may not have endocrine disrupting properties (Soto et al 2017).
7 Conclusions and Recommendations

It is not acceptable that the EU’s regulatory systems currently allow the replacement of one bisphenol with proven toxicity with another which has similar properties. Our report concludes that the current approach is a risky gamble, and when impacts may be linked to reproductive failure, impaired brain development of children and certain types of cancer, it is clear that the health of future generations is at stake. This is why grouping in regulatory risk management must be adopted, and regulators must become more determined in controlling the use of chemicals from problematic groups.

A more extensive use of grouping has been backed by a detailed study produced for the European Commission as part of the development of a new strategy for a non-toxic environment, which is part of the EU’s 7th Environmental Action programme (7thEAP). The final study (EU Commission, 2017) concludes that “the use of grouping strategies for assessing chemicals with structural similarities needs to be scaled up” to increase regulatory efficiency and effectiveness. Among the proposed recommendations for relevant elements for a strategy for a non-toxic environment, the study mentions a “move from the current chemical-by-chemical to groupings of chemicals approaches in risk assessment and management”.

CHEM Trust makes the following recommendations in order to implement a more effective and protective chemicals regulatory system.

7.1 For policy makers and regulators

This report shows that bisphenols are a group of substances which generate concern because of their widespread use in many consumer products and endocrine disrupting properties.

Regulating chemical groups must become the rule rather than the exception. This report illustrates that the current approach of controlling harmful chemicals individually leads to long delays for environment and health protection, causes an immense workload for regulators and can lead to regrettable substitution and unsustainable business decisions.

Acting on whole chemical classes will be more protective, more efficient and give a clearer steer to industry, instead of jumping from the frying pan into the fire. Not restricting the group will lead to many years of one-by-one substitution and testing. Without more stringent regulation and swifter replacement with non-regrettable substitutes, current and future generations will continue to suffer impacts from harmful chemicals.

As a point of principle, when substances of the same chemical group are likely to be similarly acting, and used in the same situation as that of a known harmful chemical in that group which has been regulated for use, regulation should be extended to cover that and all other similar compounds. In the absence of data to the contrary, chemicals with similar structure should be assumed to have the toxicological properties as harmful as those of the most toxic known substance in the group.
Grouping for REACH and CLP
Different grouping approaches have been successfully used for classification and labelling, assessing chemicals and in some cases for proposing restrictions (ECHA 2017d). In CHEM Trust’s view it is high time to tackle bisphenols as a group in all ongoing assessment and restriction discussions.

• The EU Commission has already asked ECHA to investigate whether the BPA restriction would need to be extended to BPS. It would make sense to include other bisphenols in that exercise.

• ECHA’s ongoing work on grouping, in collaboration with several Member States, is very promising and 4 out of 16 proposed RMOAs cover groups (ECHA 2017b). We would like to encourage an even more systematic use of grouping in the context of REACH restrictions and authorisations.

• Substance evaluation should also give more heed to the known toxic properties of other members of that group, and draw conclusions accordingly. If there are already good indications that a similar structured substance has similar actions, then it really does not make sense to require the same amount of information to be generated. Requiring ‘almost duplicate’ information will not only lead to an unnecessary time delay, but also lead to an unnecessary use of laboratory animals in such further testing. A case in point is the evaluation of BPS, where more tests have been requested; it will be the end of 2018 before the results become available.

• Industry also should be obliged to use information from groups when classifying and labelling chemicals. The Classification and Labelling Inventory entry for BPS shows that the majority of notifiers do not classify BPS as hazardous, despite the joint RAC and SEAC opinion highlighting in 2015 that BPS is suspected to have similar effects as BPA (see 5.3 above).

Grouping for food contact materials
EU laws covering chemicals in FCMs such as packaging and pipes are separate from REACH and take a different approach. There is a substance-by-substance approval process for chemicals used in plastic FCM, but this only considers individual substances rather than similar chemicals in the group.

In addition, for other FCM like paper, inks and coatings there is not even an EU-harmonised list of approved chemicals. Controls can be put in place on individual chemicals such as BPA, but these do not cover related chemicals such as BPS.

Specific recommendations for FCM regulation:
• The Commission’s review of FCM legislation, which has just started, should add group-based restrictions as a solution to tackle harmful chemicals much more efficiently.

• When the Commission puts in place controls on BPA, such as their recent proposal for a reduced migration limit in coatings, the controls should also cover BPS and other bisphenols.

• EFSA’s revision of its hazard assessment of BPA should include other bisphenols and include cumulative exposures, in order to increase protection and speed of action.

“Without more stringent regulation and swifter replacement with non-regrettable substitutes, current and future generations will continue to suffer impacts from harmful chemicals.”

“It is not acceptable that the EU’s regulatory systems currently allow the replacement of one bisphenol with proven toxicity with another which has similar properties.”
Grouping for cumulative risk assessment

• This report makes the argument that more group restrictions based on structural similarity and similar hazard profile are needed and that the bisphenols group is a case in point. The reality of cumulative exposure to multiple, similarly acting, bisphenols, should also be considered in risk assessments.

• It is right to assess groups of chemicals together, as indeed EFSA has done when conducting cumulative risk assessment of pesticides impacting the nervous system and thyroid system (EFSA 2013).

• In addition to the grouping of chemicals for a risk assessment, there is a need to extend the approach to form broader substance groups for restricting chemicals.

7.2 For industry

Examples of regrettable substitution in past years and decades have shown that those companies who move to chemicals from the same group may only have a very short-term business advantage and could put their reputation at significant risk. Others have instead started to develop safer alternatives, for example see the case study on BPA in thermal paper in recent ChemSec brochure “Look ahead”.26

In general, companies should become more aware of the need to move out of groups of harmful substances and be more proactive.

• Don’t find alternatives within chemical substance groups: stay away from replacing chemicals with similar substances which may later on be found to be just as problematic. This report illustrates the case of bisphenols, but many other examples can be found e.g. flame retardants and perfluorinated chemicals.

• Use ChemSec’s SIN list and SINIMILARITY tool:
  http://chemsec.org/business-tool/sin-list/
  http://chemsec.org/business-tool/sinimilarity/

• Take responsibility for self-classification under the CLP Regulation and for the dossier updates in REACH and start considering information from the whole substance group. For example, regarding BPS, most notifiers in the current Classification and Labelling Inventory do not provide any classification for BPS. In contrast, the joint RAC and SEAC opinion noted back in 2015 that BPS is suspected to have similar effects as BPA. This information should be provided to suppliers and consumers and not to do so is not in line with the obligation under REACH to ensure safe use and to update dossiers in light of new information.

• Industry and trade associations should develop better guidance for different sectors and downstream uses with regards to how to avoid regrettable substitution.

• Use advice and recommendations available from ECHA, including the report from July 2017 Approaches for Accelerating Substitution under REACH and beyond: Strategic Options Assessment (ECHA 2017f).

7.3 For workers

• Ask your organisation whether you are handling any products containing bisphenols.

• If your organisation is using BPA, ask it to move away from all bisphenols, don’t just swap from BPA to another bisphenol.

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26 http://chemsec.org/publication/investors/look-ahead/
7.4 For the consumer

To protect the public from exposure to harmful chemical groups such as bisphenols, proper policy measures are required, as laid out in the previous chapter of this report. As an individual, you can help ensure that governments and the EU make these vital improvements by contacting your government and the politicians that represent you, including Members of the European Parliament, if you live in the EU. For details see:

- http://www.chemtrust.org.uk/takeaction-citizen/

However, in the meantime, you can reduce your own exposure to some extent. Here are some ideas:

- Minimise your handling of till receipts or other thermal paper. The EU has agreed to ban this chemical, but this will take time to come into force, and there are concerns that similar chemicals will be used to replace BPA.

- Don’t let children play with receipts!

- Food packaging uses a wide range of chemicals, and the regulation of packaging materials is not as good as it should be. In particular, current EU laws do not properly control the chemicals used in paper, card, inks, glues and coatings. To reduce your exposure, try to reduce your use of packaged food and instead buy more fresh products. Store cereals, rice etc in glass jars.

- House dust has been found to have quite high levels of a range of problematic chemicals, including phthalates, brominated flame retardants and BPA. It’s generally a good idea to make sure you clean your home frequently in order to reduce the build-up of dust.

Other sources of advice about avoiding hazardous chemicals:

- CHEM Trust report ‘No Brainer’, www.chemtrust.org/brain

- Breast Cancer UK has a set of pages explaining how you can reduce your exposure to hazardous chemicals: http://www.breastcanceruk.org.uk/reduce-your-risk

- Project Nesting from Women in Europe for a Common Future, particularly aimed at those who are pregnant: http://www.projectnesting.org/start

7.5 Brexit and EU chemicals regulation

This report is critical of a number of aspects of the EU regulatory system for chemicals, however this system is the most advanced and protective in the world. We do believe that more efforts have to be invested to improve its speed and effectiveness in addressing groups of chemicals, but this is best done within the current REACH system. REACH has a database of chemical properties and uses, which will help facilitate this group-based approach to regulation. This database is the most advanced chemical database in the world, though much work still needs to be done to fill in data gaps.
The EU’s system for regulating chemicals in FCMs is not as effective as REACH, but it is at least being reviewed at the moment.

The UK has voted to leave the EU, and the Brexit process threatens to take the UK out of the EU’s regulatory processes on chemicals and other environmental and product policy.

If the UK does not stay within REACH, the UK government will lose access to the REACH databases and other REACH processes. This means that UK regulators will have much more limited information on chemical safety, which will make it much more difficult for them to protect public and worker health and the environment.

The UK could replicate the decisions taken in REACH, but any delay in banning chemicals is likely to lead to dumping of products in the UK in the gap between the EU and UK regulations coming into force. Any deregulation of the REACH authorisation process will lead to use of chemicals of very high concern in the UK even if this use is banned in the EU.

In CHEM Trust’s view the UK should stay within the REACH system after Brexit. This will require the UK to accept decisions made by the EU (the UK will no longer have a vote), but the UK should be able to participate in these decisions, as Norway does. See CHEM Trust’s Brexit and Chemicals page for more details: http://www.chemtrust.org/brexit/

### Timeline of BPA

- **Late 19th Century**: BPA and BPS start to be produced and used
- **1936**: Dodds and Lawson report estrogenicity of BPA, BPB and BPF
- **Mid 90’s**: Concerns over potential endocrine disrupting effects following BPA exposure from consumer products and food contact materials
- **2006**: EU bans BPA-based polycarbonate baby bottles
- **2010**: ECHA Risk Assessment Committee concludes that ‘BPS may have a toxicological profile similar to BPA’ and advises against substitution with BPS
- **2011**: France bans BPA in all food contact materials
- **2015**: France and Denmark introduce restrictions on BPA in baby bottles
- **2016**: EU classifies BPA as “toxic for reproduction” and adds it to the REACH candidate list of substances of very high concern
- **2017**: EU agrees BPA is an endocrine disrupter for human health and for the environment
- **2018**: EU agrees to bans BPA use in thermal paper (to take effect 2020)
- **2019**: Sweden Chemicals Agency identifies 37 bisphenols with estrogenic properties and likely consumer exposure
8  Glossary and Abbreviations

ADHD: Attention Deficit Hyperactivity Disorder – a group of behavioural symptoms including inattentiveness, hyperactivity, and impulsiveness
AR: Androgen Receptor
BisOPP-A: (4,4’-Isopropyllidenebis(2-phenylphenol) CAS:24038-68-4) – alternative to bisphenol A
BPs: bisphenols – a group of chemicals
BPA: bisphenol A – a chemical used in the manufacture of clear polycarbonate plastic, and to manufacture other plastics, including the lining inside many food and drink cans. Known to have endocrine disrupting properties
BPAF: bisphenol AF (4-[1,1,1,3,3,3-Hexafluoro-2-(4-hydroxyphenyl)propan-2-yl]phenol, CAS:1478-61-1) – alternative to bisphenol A
BPAP: bisphenol AP (4,4’-(1-Phenylethyldiene) bisphenol, CAS:1571-75-1)) – alternative to bisphenol A
BPB: bisphenol B (2,2-Bis(4-hydroxyphenyl)butane, CAS:77-40-7) – alternative to bisphenol A
BPC: bisphenol C (2,2-Bis(4-hydroxy-3-methylphenyl)propane, CAS:79-97-0) – alternative to bisphenol A
BPF: bisphenol F (Bis(4-hydroxyphenyl)methane, CAS:620-92-8) – alternative to bisphenol A
BHPF: fluorene-9-bisphenol, CAS:3236-71-3 – alternative to bisphenol A
BPPH: bisphenol PH (2,2-Bis(2-hydroxy-5-biphenyl)propane, CAS:24038-68-4) – alternative to bisphenol A
BPS: bisphenol S (4-Hydroxyphenyl sulfone, CAS:80-09-1) – alternative to bisphenol A
BPZ: bisphenol Z (4,4’-Cyclohexylidenebisphenol, CAS:843-55-0) – alternative to bisphenol A
CLP: The EU Regulation (EC) No 1272/2008 on the Classification, Labelling and Packaging of substances and mixtures
CMR: Carcinogen, Mutagen or Reproductive toxicant
CoRAP: Community Rolling Action Plan, a program of the REACH regulation which indentifies substances for evaluation by the Member States in the next three years. Under REACH, chemicals must be registered by producers. If there are initial concerns that the manufacture and/or use of these substances could pose a risk to human health or the environment (e.g. endocrine disrupting properties, CMR properties), these substances are evaluated by a Member State.
DES: diethylstilbestrol – a synthetic form of the female hormone estrogen, prescribed to pregnant women between 1940 and 1970’ to prevent miscarriage among others
DG Health: Directorate-General for Health and Food Safety of the European Commission
DNEL: Derived No-Effect Level – the estimate of the highest exposure to which a human may safely be exposed to a chemical
E2: 17b-estradiol – the major female sex hormone
ECHA: European Chemicals Agency
EDCs: endocrine disrupting chemicals – also known as hormone disrupting chemicals. A chemical that can interfere with the endocrine or hormone system – the body’s own sensitive chemical messaging system

EFSA: European Food Safety Authority
ER: Estrogen Receptor
EU: European Union
FCM: Food Contact Material (e.g. food packaging)
KEMI: The Swedish Chemicals Agency – the Swedish Government’s agency for chemicals regulation
MBHA: (Methyl bis(4-hydroxyphenyl)acetate CAS:5129-00-0) – alternative to bisphenol A.

NGO: Non Governmental Organisation
NTP: US National Toxicology Program
OEHHA: Office of Environmental Health Hazard Assessment in California
PBT/ED: Persistent, Bioaccumulative, Toxic / Endocrine Disrupting (properties of a substance)
PCPs: Personal Care Products
PFASs: Per- and polyfluoroalkyl substances – a group of very persistent chemicals commonly used as grease and stain repellents in consumer items
QSAR: Quantitative structure-activity relationship models – computational tool for assessing chemicals
RAC: Committee for Risk Assessment – this ECHA committee assesses the risks of substances related to human health and the environment. RAC produces opinions in the framework of the Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances and mixtures (CLP Regulation), and in the authorisation and restriction processes of REACH
REACH: Registration, Evaluation, Authorisation and Restriction of Chemicals regulation (Regulation (EC) No 1907/2006) – the main EU regulation covering industrial chemicals
RMOAs: Risk Management Option Analyses, an initiative carried out by a Member State or ECHA aimed at identifying whether further regulatory risk management activities are needed for a substance and to identify the most appropriate instrument to address the concern
SEAC: Committee for Socio-Economic Analysis – this ECHA committee assesses the socio-economic impact of possible legislative action on chemicals through the REACH Authorisation or Restriction processes
SIN List: Substitute it Now! List, a list of chemicals (produced by the NGO ChemSec) which are likely to be banned or restricted in a near future under REACH, encouraging substitution of problematic chemicals with safe alternatives
SINIMILARITY: ChemSec tool indicating substances structurally similar to a substance on the SIN List, with the aim of avoiding the substitution of one problematic chemical with another
SVHC: Substances of Very High Concern – in the REACH chemicals regulation system
TEDX: The Endocrine Disruption Exchange
UBA: Umweltbundesamt – German Environment Agency
US EPA: United States Environmental Protection Agency
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Keep in touch with CHEM Trust’s work through our blog at www.chemtrust.org; all our reports can also be downloaded from this site.

Previous publications include:

i. No Brainer: The impact of chemicals on children’s brain development: a cause for concern and a need for action, report by CHEM Trust (2017)

ii. Chemicals in food contact materials: A gap in the internal market, a failure in public protection, briefing by CHEM Trust (2016)

iii. Circular Economy and Chemicals: Creating a clean and sustainable circle, briefing by CHEM Trust (2015)

iv. Fracking pollution: How toxic chemicals from fracking could affect Wildlife and People in the UK and EU, briefing by CHEM Trust, with accompanying report “Chemical Pollution from Fracking” by Philip Lightowlers (2015)


vi. Frogs at risk and possible implications for humans? Why EU chemicals legislation needs updating to address chemicals that damage the immune system, report by Professor Susan Jobling, Dr Alice Baynes and Dr Trenton W.J Garner (2013)

vii. A review of the science linking chemical exposures to obesity and diabetes, (available in French, Spanish and German), report and briefing, by Professor Miquel Porta and Professor Duk-Hee Lee (2012)


ix. A review of the role pesticides play in some cancers: Children, farmers and pesticide users at risk? By Gwynne Lyons of CHEM Trust and Professor Andrew Watterson (2010)


xi. Male Reproductive Health Disorders and the Potential Role of Exposure to Environmental Chemicals, report by Professor Richard Sharpe of the Medical Research Council (2009)


xiii. Breast Cancer and exposure to hormonally active chemicals: An appraisal of the scientific evidence, including briefings in French, Spanish, German and Italian, by Professor Andreas Kortenkamp of the London School of Pharmacy (2008)