



**The concerns about Bisphenol A (BPA) and recommendations for action.**

**A CHEM Trust Position Paper - Dec 2010**



**CHEM Trust gratefully acknowledges the support of The Body Shop Foundation for funding the production of this Position Paper on BPA.**

## Section 1: Overview and Introduction

This briefing summarises the basis for the concern about bisphenol A, which throughout, is referred to by its common abbreviated name, BPA.<sup>a</sup> It also highlights the regulatory action that has already been taken in some countries and the ongoing activities by industry to find alternatives. The main purpose of this briefing is to set out the rationale behind CHEM Trust's position on BPA, namely that exposure reduction is long overdue and that regulations should be put in place to try to eliminate exposure to BPA, particularly for pregnant women and children.

Data show that nearly everyone is exposed to BPA, with exposure arising through the use of products made of polycarbonate plastic, the consumption of tinned food and canned drinks, and the handling of thermal paper (eg. lottery tickets). Exposure may also arise from other routes, such as dental procedures using BPA-based compounds. Exposure of babies and infants can occur from the use of tinned baby foods as well as from polycarbonate babies' feeding bottles and toddlers' sucking mugs.

BPA has endocrine disrupting properties, which means it is able to alter or de-rail the chemical messenger system of the body. The potential health effects to which BPA has been suggested to contribute include the following: breast cancer, prostate cancer, endometriosis, heart disease, obesity, diabetes, altered immune system and effects on brain development and behaviour (see reviews<sup>1,2,3,4</sup> and Section 3). A large number of animal studies, but not all, have reported effects at low doses of BPA, that lead to serum levels similar to those found in the general population. The possibility that BPA may damage human health can not be dismissed, although regulatory assessments have noted some limitations in the low dose studies.

Future development may be de-railed by early life exposures to BPA, particularly in the womb. The 'foetal basis of adult disease' is a growing area of research, and it is increasingly evident that stressors *in utero*, such as malnutrition or chemical exposures, may cause permanent changes in physiology and metabolism that influence the development of, or susceptibility to, disease in adulthood. The mechanisms by which developmental exposure to BPA and other chemicals can cause adult disease are being elucidated. Many diseases in later life may result from epigenetic changes in the foetus and newborn - which is where a chemical exposure alters the functioning of genes, turning them on or off, leading to diseases that may take decades to occur - rather than causing mutations, which are changes in the actual structure of the gene, that were the prior focus of chemical exposure research. There is particular concern about early life exposures to hormone disrupting chemicals.<sup>5</sup> Indeed, much of the concern about BPA is related its ability to disrupt certain hormones.

BPA was first found to be oestrogenic by Charles Dodd in the 1930s while searching for non-steroidal oestrogens. However, it was never developed as

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<sup>a</sup> Bisphenol A is also called 2,2-bis(4-hydroxyphenyl)propane, and has a CAS number of 80-05-7.

a pharmaceutical, and BPA's mass-market production did not commence until the 1960s, after its ability to polymerise and form polycarbonate plastic was discovered. In 2005/2006 annual production of BPA in Western Europe was estimated at over 1 million tonnes, with global production estimated at around 3 million tonnes per year.<sup>6</sup> It is therefore one of the chemicals produced in the largest quantities worldwide.<sup>7,8</sup> In the USA alone, the value of the BPA market has been estimated at \$2 billion (=£1.3 billion or €1.435 billion).<sup>9</sup> This vast commercial investment in BPA, the number of manufacturers and processors involved, and the variety of its uses, all mean that there will be significant economic implications if tougher regulation is imposed. This might be conjectured to weigh heavily in the decisions of those involved in any assessment. Representatives of regulatory agencies have noted the heavy lobbying by industry, and indeed there is some indication that past decisions may have been unduly influenced by economic considerations (see Section 4, Classification of BPA).

Some regulatory agencies around the world have concluded that more research is needed, rather than immediate action, and have judged that many of the low dose studies are insufficient for use in regulatory risk assessment.<sup>10,11</sup> However, with a growing number of research publications raising the alarm, a few countries have now decided it would be better to be safe than sorry and have taken precautionary action to reduce children's exposure.

Section 2 lists the uses of BPA and summarises the evidence for widespread human exposure and notes some possible exposure routes. Some scientists have suggested that the European Food Safety Authority (EFSA) has underestimated human exposure to the active form of BPA, and furthermore, other scientists have suggested that BPA exposure may occur via other routes apart from through the diet or oral route. These are issues which need to be resolved as a matter of urgency.

Section 3 highlights the numerous adverse effects that have been reported in laboratory studies, and also summarises the epidemiological data. Studies reporting effects relevant for human health and wildlife are discussed, as are areas of controversy.

Section 4 outlines the regulatory initiatives that have taken place in the European Union (EU), North America and Japan, and furthermore, highlights some of the intense industry lobbying that has been reported. Section 4 also notes some action that has been taken by some companies and the availability of alternative products which do not contain BPA. It also highlights some statements made by groups of concerned scientists.

Section 5 draws conclusions and makes recommendations, including some suggestions for individuals, particularly pregnant women, who might wish to reduce their exposure. CHEM Trust is particularly concerned that as of October 2010, official regulatory assessments in the EU seemed to underplay the uncertainty in the risk assessment of BPA and did not give sufficient weight to the growing number of studies with converging and supportive

indications of adverse effects due to low dose exposure. Given the potential damage which may be accruing for our children in later life, CHEM Trust considers that action to reduce exposures to BPA is long overdue, particularly for young women and infants. Regulatory action should be taken on the basis of the precautionary principle, as the costs of such uncertainty about the safety of a product should be born by industry and not by future generations.

## **Section 2: Uses and Exposure**

### **Uses**

BPA is polymerized to form polycarbonate, and this accounts for the bulk of the BPA that is produced, whilst much of the rest is used for the production of epoxy resins. BPA is therefore used in many applications including baby bottles, food containers, water bottles used in cooled water dispensers, plastic tableware, CDs, toys, laptops, mobile phones, lenses for glasses, electrical equipment, medical devices, in a variety of applications in the automotive industry, and in the construction industry for uses such as plastic sheeting for glazing. Epoxy-phenolic resins which can leach un-reacted BPA are used as an internal protective lining for food and drinks cans and as a coating on metal lids for glass jars and bottles. They are also used as a surface-coating on residential drinking water storage tanks and wine vats.<sup>12</sup> BPA-based materials may also be used for lining water and waste-water pipes.<sup>13</sup> In addition, BPA is used in the manufacture of the brominated flame retardant, TBBPA, and as a polymerization inhibitor in PVC, although both these uses appear to have ceased in the EU, with BPA use in the manufacture of PVC resin being phased out by a voluntary agreement.<sup>14</sup>

In the USA, large releases are reported from foundries, where BPA is used in castings.<sup>15</sup> In the EU in the past, investment casting waxes have contained BPA, but according to a leading supplier and a technical consultant, this use has been discontinued in Europe. However, phenolic resins are used to stabilise foundry moulding sands, and it may be that epoxy BPA-based resins are used in this application, but as it would be in the form of a polymer, this is not subject to registration in REACH<sup>16</sup> and so definitive data is hard to come by.

In addition, BPA is used in thermal paper production as an additive that acts as a developing agent when the paper is heated. Thermal paper is used for point-of-sale receipts (e.g. supermarket till receipts), and also for self-adhesive labels, lottery tickets and thermal fax paper.<sup>17</sup> Apart from its use as an additive in thermal paper, BPA is also used in printing inks and as an additive in brake fluids and in tyres.<sup>18</sup>

### **Human exposure routes**

BPA is permitted for use in food contact plastics in the EU, with a migration limit of 0.6 mg/kg food. Human exposure arises from the use of products made of polycarbonate plastic, the consumption of food and drinks from cans lined with epoxy resin coatings, from BPA-related materials used in dentistry as sealants and coatings,<sup>19</sup> and even perhaps from the handling of thermal

paper till receipts, or in the case of young children, from the mouthing of plastic products. Recycled paper products, such as kitchen roll, may also be contaminated with BPA.<sup>20</sup> BPA-based materials used in lining water pipes might also result in some human exposure.<sup>21</sup> Exposure to BPA may also arise to some extent from the intake of dust in homes and offices.<sup>22</sup>

A study in the USA has reported that women who worked as cashiers or those who frequently ate canned vegetables tended to be more exposed as they were found to have higher levels of BPA in their urine.<sup>23</sup>

Both polycarbonate and epoxy resins can leach residual, un-reacted BPA into food or the environment. Epoxy resins are generally stable, but some BPA can also be released from polycarbonate particularly when it is exposed to high heat, UV light or strongly basic (alkaline) or acidic conditions.<sup>24,25,26</sup> It seems that the degree of leaching from polycarbonate depends more on the temperature of the contained liquid,<sup>27</sup> than the age of the container, although it seems migration may increase with repeated use due to cleaning treatments such as dishwashing, sterilization and brushing.<sup>28</sup>

Polycarbonate babies' bottles have come under scrutiny, and the levels of BPA found to be leaching have given rise to the realistic worst case exposure estimate of 50 microgram BPA per litre of milk (50µg/l).<sup>29</sup>

It has been reported that additional exposure to BPA might also originate from the baby milk powder or particularly baby formula liquid<sup>30</sup> stored in cans lined with BPA-based epoxy-phenolic resins.<sup>31</sup> However, the updated EU risk assessment considered that in the EU, infant formula is not packaged in food cans lined with a BPA based epoxy-resin.<sup>32</sup>

BPA has also been found in breast milk, although as shown in the table below, a breast fed infant is typically exposed far less than a bottle fed infant. Furthermore, as BPA is not a very persistent or highly bioaccumulative chemical it should be possible to reduce contamination levels if the mother seeks to avoid exposure (see Section 5, Recommendations). BPA levels in breast milk from Japan have been reported to range from 0.28-0.97µg unconjugated or 'active' BPA /l; while a US study reported a mean of 1.3µg unconjugated BPA /l for the 60% of samples with BPA (see<sup>33</sup>).

<b>Food/Beverages consumed</b>	<b>Dietary exposure to BPA in microgram (µg) /kg bw/day for a 3 month old milk fed baby, based on realistic 'worst case' migration values and assuming a 3 month old consumes 174ml of milk per kg bw/day<sup>34</sup></b>
Breast milk only	0.2
Infant formula fed with polycarbonate bottle	8.7

Food cans are frequently lined with an epoxy-resin which can leach BPA and the EU risk assessment is based on what is considered to be a realistic worst case assumption. For infants up to 12 months, a value of 100µg BPA per

kilogram (kg) of tinned food and beverages is used. For adults, with a more varied diet, it was considered that 50µg BPA/kg might arise from canned solid foods.<sup>35</sup>

There have been several surveys of the levels found in food from cans, and for example, a 2003 study for the UK Food Standards Agency (FSA) found the highest mean BPA level in a retail canned foodstuff was 96µg/kg (0.096 mg/kg), from the analysis of 5 cans of spaghetti bolognese.<sup>36</sup> For the baby food analysed in this study, the mean BPA level (of a total of 5 cans) found in one type of baby food was 38 µg/kg. Furthermore, it was noted that assuming a worst case scenario that three cans (384 g in total) were eaten by a 8.8 kg baby every day, this would give a daily intake 1.7 micrograms per kilogram of body weight per day (1.7µg/kg bw/day) which is below the current EU tolerable daily intake (TDI) of 50µg/kg bw.<sup>37</sup> An earlier UK study had found BPA at up to 70 µg/kg in 37 samples of canned food and at up to 420µg/kg in one food sampled,<sup>38</sup> which although relatively high, was still predicted to result in intakes being within the EU TDI. Similarly, a recent non-EU study of tinned food sold in New Zealand and Australia, reported that samples of tinned tuna and tinned banana custard baby food contained BPA at relatively high levels, that is between 300 and 420µg BPA/kg food.<sup>39</sup>

A recent Canadian study investigated the level of BPA in canned drinks and found levels of up to 4.5µg/l.<sup>40</sup> Low levels of BPA have typically been found in canned beer and another Canadian survey reported levels ranging from 0.081-0.54 µg/l, with only one bottled beer having BPA at a level of 0.054 µg/l, where it perhaps originated from the cap.<sup>41</sup> For beverages, the EU risk assessment worked on a worst-case figure of 10µg/l from canned drinks and wine, and assumed a worst-case two litre consumption.<sup>42</sup>

### **Measured exposure in humans and comparisons between species**

It is clear that there are differences between rodent and human metabolism of BPA, in that excretion in the rodent is mainly via the faeces whilst in humans it is via urine. The important issue is the amount of the active form of BPA that can reach the target tissues in humans, and in relation to this there are conflicting opinions.

Pharmacokinetic studies in humans have reported that BPA has a biological half-life of <6 hours,<sup>43</sup> but other recent data suggest that BPA may have a longer half-life, and that there may be oral and non-oral exposure sources, and furthermore, that it may deposit to some extent in fat tissue.<sup>44,45</sup> Given the octanol water co-efficient of BPA is between 2.2 - 3.82 it may be that it partitions to fatty tissue and remains in the body longer than the previous predictions of 6 hours,<sup>46</sup> a suggestion which is supported by calculations of Stalhut and co-workers.<sup>47</sup> Widespread exposure has been reported in many biomonitoring studies, which are studies measuring the actual levels found in human tissues. Studies have reported BPA in human urine, breast milk,<sup>48</sup> serum,<sup>49</sup> maternal<sup>50</sup> and foetal plasma, amniotic fluid and placental tissues.<sup>51</sup> A survey during 2003-2004, urine from people living in the USA was analysed and detectable levels of BPA were found in over 90% of the more than two thousand samples from people aged six and over, with the data showing

young people to be slightly more exposed.<sup>52</sup> The median levels of BPA in humans doubled (to 2.6 µg/l) and the 95<sup>th</sup> percentile values tripled to 15.9 µg/l between this study and an earlier smaller study from 1988-1994,<sup>53,54</sup> although the results of these 2 surveys are not totally comparable.<sup>55</sup> A more recent study of USA urine sampled in 2005-2006 suggested levels had subsequently decreased by around 30%.<sup>56</sup> A study of 715 adults living in Italy, reported a mean urinary BPA concentration of 3.59 µg/l (with wide variation around the mean) and a mean daily excretion rate of 5.63 µg BPA per day.<sup>57</sup> Urine samples of pregnant women in Norway had slightly higher mean BPA levels (4.5 µg/l) than those found in a study of pregnant women in the Netherlands.<sup>58</sup> Premature babies may be particularly exposed, and for example, a recent US study from 2 different intensive care facilities, found the mean concentration of total BPA in their urine was an order of magnitude higher (mean 30.3 µg/l) as compared to the general population.<sup>59</sup>

In 2010, Vandenberg and colleagues published a review of over 80 biomonitoring studies involving measurements in thousands of individuals from several different countries, and concluded that unconjugated, that is 'free' or active BPA is present in humans. Unconjugated BPA was routinely detected in blood in the micrograms per litre range (µg/l) and conjugated BPA was routinely detected in the vast majority of urine samples (also in the low µg/l range).<sup>60</sup> Enzymes that glucuronidate BPA conjugate or metabolise it to an inactive form, and it is the levels of the unconjugated or active form that are important with regard to potential health effects.

Vandenberg and colleagues went on to point out that in stark contrast to the levels noted in biomonitoring studies, some regulatory agencies, such as EFSA, had in their opinion erroneously relied only on toxicokinetic studies in their risk assessments.<sup>61</sup> Indeed, the EFSA 2008 opinion relied only on two toxicokinetic studies carried out in just 15 adults, which suggested minimal or no internal exposure to free BPA. These toxicokinetic studies measured the change in concentration of the glucuronidated metabolite over time in the urine of a few people dosed with BPA, with the second study also looking at an environmentally exposed population. Vandenberg et al heavily criticised these studies by Volkel and colleagues, on several grounds, including for example, that the method of analysis used had a relatively high limit of detection. In contrast to the toxicokinetic studies by Volkel et al, the review by Vandenberg of the biomonitoring studies indicated that humans are internally exposed to doses of unconjugated BPA, typically in the range of 0.5-3 µg/l.<sup>62</sup>

Several scientists have therefore expressed worries that regulatory agencies have grossly underestimated current human exposure levels because they have relied on the prediction that rapid first pass metabolism in the liver will mean that biologically active BPA will not be present in human blood, when in fact many human biomonitoring studies report this to be false. When a team of researchers compared measured internal levels in monkeys and mice with the known dose levels in these species, and compared them with measured levels in humans, they suggested that current human oral doses would have to be in the hundreds of micrograms per kilogram range to reach such internal

levels, and therefore that it is likely the higher than predicted serum levels of unconjugated BPA in adults might also reflect significant *non-oral* BPA exposure.<sup>63</sup>

There are also worries that levels of the active form of BPA may be higher in the foetus, and although an EFSA panel in 2008 stated that the neonate has sufficient capacity to metabolise BPA to the inactive form, other scientists considered that there were no studies to support such an assertion.<sup>64</sup> The US National Toxicology Program (NTP) has noted that the specific enzymes that glucuronidate BPA have not been identified in people, but there is evidence of postnatal maturation for a number of glucuronidation enzymes in humans. Therefore, a reduced ability or efficiency to glucuronidate is predicted for human foetuses and infants.<sup>65</sup> A study in rodents adds to the concern as it has shown that the conjugated form can cross the placenta and be de-conjugated to the active form in the foetus.<sup>66</sup> Moreover, the unconjugated active form of BPA is able to cross the human placenta.<sup>67</sup>

In contrast to the studies which have raised these concerns, in 2010 EFSA noted that new findings in adult and new born monkeys strengthen their view that BPA is eliminated faster in humans than rodents, and that this results in lower internal levels of free BPA in humans as compared to rodents.<sup>68,69</sup> Furthermore, based on the study of newborn human babies by Calafat and co-workers,<sup>70</sup> EFSA concluded that even human premature babies can metabolise and excrete BPA efficiently.<sup>71</sup>

EFSA's 2010 opinion therefore dismissed the concerns and concluded that the reported presence of free BPA in human tissues at higher levels than expected only raised questions about the validity of such results. EFSA concluded that many of the biomonitoring studies have reported erroneous data, and suggested that the unconjugated BPA arose from hydrolysis of the conjugated form after collection of the tissue samples or due to leakage of BPA from the plastic sampling containers.

CHEM Trust considers that in view of the many scientists now reporting data which raise concerns about the amount of active BPA actually present in the human body, getting a definitive answer as to whether there is indeed internal exposure of people to significant levels of the free, active form of BPA, is crucial. This is an issue which needs to be resolved as a matter of urgency.

### **Section 3: Effects on humans and wildlife**

There is widespread agreement that BPA can cause harm at high dose levels. The NOAEL (No Observed Adverse Effect Level) used by EFSA to derive the current TDI of 0.05mg/kg bw/day (= 50µg/kg bw/day) is 5mg/kg bw/day from a multi-generation reproductive toxicity study in rats, and the application of an uncertainty factor of 100.<sup>72</sup>

In the EU, BPA has been classified as a reproductive toxicant category 3, although some Member States wanted a tougher category 2 classification (see Section 4, under Classification of BPA). A category 3 reproductive

toxicant, by definition, means that based on animal studies BPA causes concern for human fertility and/or for developmental toxic effects in humans.

However, despite the vast number of publications on the effects of BPA in animals, there are deeply conflicting opinions as to whether or not *low doses* of BPA are harmful. This is partly because of conflicting opinions about the relevance of some of the animal studies for human health, and partly because of some conflicting results.

In many of the studies, animal strains, doses, routes of exposure (oral, subcutaneous etc) and the end-points being measured have varied, making it sometimes difficult to compare results and reconcile the findings. But most controversial is that some of the low dose effects found by academic researchers have not been found in large experiments funded by industry, where effects were only reported at much higher dose levels. Some researchers have published detailed and well laid out arguments as to why these large industry studies, done under what is called 'good laboratory practice' (GLP) conditions, should not be used to dismiss other smaller studies.<sup>73</sup> However, it is not possible within the scope of this briefing to discuss such arguments in detail. Nevertheless, it is certainly interesting to note that a review reported that as of December 2004, there were 115 published animal studies concerning low dose effects of BPA, and 94 of these reported significant effects. Moreover, in 31 publications addressing effects in vertebrate and invertebrate animals, significant effects occurred below the predicted "safe" or reference dose/TDI of 0.05 mg/kg bw/day (=50µg/kg bw), but no industry-funded studies had reported significant effects of low doses of BPA.<sup>74</sup> It remains to be seen whether or not these industry studies were right to indicate that low doses of BPA are safe, but it might be prudent to remember that this is not the first time that those with a vested interest in a product have not found harmful effects. For example, some time ago it was noted that review articles written by authors with affiliations to the tobacco industry were 88 times more likely to conclude that passive smoking was not harmful than if the article was written by authors with no connection to the tobacco industry.<sup>75</sup>

A 2007 review of BPA studies by a group of independent scientists has concluded "We are confident that adult exposure to BPA affects the male reproductive tract, and that long lasting, organizational effects in response to developmental exposure to BPA occur in the brain, the male reproductive system, and metabolic processes. We consider it likely, but requiring further confirmation, that adult exposure to BPA affects the brain, the female reproductive system, and the immune system, and that developmental effects occur in the female reproductive system."<sup>76</sup>

However, although high dose effects are not disputed, it is not just industry studies which have reported not finding any low dose effects. Scientists working for the US EPA have undertaken a study in rats exposed in-utero and during lactation which also did not report any low dose effects in either the male<sup>77</sup> or female pups.<sup>78</sup> This study was heavily criticised by many

independent researchers,<sup>79</sup> but a rebuttal of these criticisms was forthcoming from the original workers.<sup>80</sup>

Unfortunately, the full implications of long-term, low dose exposures to BPA, and other endocrine disrupting chemicals, will take many more years of research to fully clarify. However, a growing number of studies, including both studies in animals and epidemiological studies, already suggest that low level in-utero and early life exposure to BPA may be harmful to humans.

**Summarised below are some of the low dose effects of BPA reported in mammalian animals.** (see <sup>81,82</sup>):

- A variety of effects related to neural and behaviour alterations (including altered gender-specific behaviour). (see under the heading 'Altered brain development', below).
- Reduced immunity<sup>83,84</sup> and altered immune system function.<sup>85</sup>
- Potentially precancerous lesions in the prostate, and effects on the prostate gland<sup>86,87</sup> (see under heading, 'Effects on the prostate', below)
- Other effects on male development, including effects on urinary tract development,<sup>88</sup> on sperm production,<sup>89</sup> and reduced postnatal testosterone production.<sup>90</sup>
- Potentially precancerous lesions in the mammary gland and an increased risk of mammary cancer following subsequent exposure to a carcinogen (see under the heading 'Breast cancer', below).
- Other effects on the female offspring including deleterious effects on the vagina,<sup>91</sup> damage to the female reproductive tract and ovary,<sup>92,93</sup> and early onset of puberty.<sup>94</sup>
- Effects suggesting BPA may be a risk factor for diabetes. The reported effects in mice included aggravation of the insulin resistance produced during pregnancy and decreased glucose tolerance and increased plasma insulin concentrations.<sup>95</sup>
- Effects suggesting BPA may play a part in obesity.<sup>96</sup> (see under heading 'Obesity', below)
- Endometriosis-like structures in female mice offspring (see under the heading 'Endometriosis', below).
- Altered chromosome numbers in the egg, due to effects on meiosis. Female mice exposed in the womb to BPA were reported to develop abnormal eggs which the researchers speculated might, in humans, increase the risk of spontaneous abortion and genetic disorders such as Down's syndrome,<sup>97</sup> although a study by other researchers has disputed these findings.<sup>98</sup>

In addition to the possibility that in-utero exposure to low doses of BPA may be causing harm, cell based studies have raised the suggestion that BPA exposure in adult men may adversely affect the treatment of prostate cancer.<sup>99,100</sup>

### **BPA's hormone disrupting properties**

BPA has endocrine disrupting properties, with some effects suggested to be mediated through oestrogen activity. BPA can bind to the nuclear oestrogen

receptor (ER) alpha and ER beta, but test tube studies show it also has other activity. For example, it interacts with a variety of other cellular targets and binds to several other receptors,<sup>101</sup> including,

- a non-classical membrane-bound form of the ER (ncmER),<sup>102</sup>
- a recently identified orphan nuclear receptor, termed oestrogen-related receptor gamma (ERR gamma),
- a seven-trans-membrane oestrogen receptor called GPR30,
- the aryl hydrocarbon receptor (AhR),
- thyroid hormone receptors,<sup>103</sup>
- acting as an androgen receptor antagonist,<sup>104,105</sup>
- inhibiting aromatase activity, the enzyme which converts testosterone to oestradiol.<sup>106</sup>

It is not appropriate, therefore, to consider the biological effects of BPA exclusively within the context of oestrogen receptor (alpha or beta) binding or even its action as a selective oestrogen receptor moderator (SERM), a term applied to a compound that binds nuclear oestrogen receptors and acts as an oestrogen agonist (mimic) in some tissues and as an oestrogen antagonist (or block) in others.

### **Altered brain development**

Some studies have suggested that doses in the micrograms per kilogram ( $\mu\text{g}/\text{kg}$ ) range affect the development of the central nervous system (CNS) in rodents. A useful table of animal studies published up to 2007, is provided in the EU risk assessment report.<sup>107</sup> For example, it has been reported that BPA at doses below or slightly above EFSA's TDI for humans of  $50\mu\text{g}/\text{kg}$  bw can interfere with behaviour, including play and maze learning in male and female rodents.<sup>108,109,110,111,112</sup> Reported behavioural changes in rodents after BPA exposure relate to play, maternal behaviour, aggression, cognitive function,<sup>113</sup> motor activity, exploration, novelty-seeking, impulsivity, reward response, pain response, anxiety and fear, and social interactions. In some experiments, BPA appears to reduce the differences in male and female behaviours, and also to affect the dopaminergic system in rodents.<sup>114</sup> (and see review<sup>115</sup>). Furthermore, a group of workers from the USA and Canada have looked at effects of BPA on the brain of the non-human primate, the African green monkey. They found that continuous BPA administration, at a daily dose of  $50\mu\text{g}/\text{kg}/\text{day}$  (which is the US human reference dose and the EU TDI), completely abolished the synaptogenic response to oestradiol, and they noted that this has profound implications because re-modelling of spine synapses may play a critical role in cognition and mood.<sup>116</sup> Leranthe considered that their experiments showed that in both rats and non human primates, BPA negated the 70-100 % increase in the number of hippocampal and prefrontal spine synapses induced by both oestrogens and androgens. Moreover they went on to conclude that such synaptic loss may have significant consequences, potentially causing cognitive decline, depression and schizophrenia.<sup>117</sup>

However, many governments have struggled with how to deal with the reported effects on brain function. For example, with regard to the rodent data available at the time, the updated EU risk assessment report of 2008 concluded the data on developmental neurotoxicity was not reliable because of limitations in the design and reporting of the studies. Three countries,

Denmark, Sweden and Norway, did not agree with this conclusion and expressed a minority opinion stating that the studies by Negishi et al 2004,<sup>118</sup> Carr et al 2003,<sup>119</sup> Ryan and Vandenberg 2006,<sup>120</sup> and Adriani et al 2003,<sup>121</sup> should be considered sufficiently reliable for regulatory use.<sup>122</sup> However, similar to the conclusion in the EU risk assessment report, Health Canada, has said that limitations in the studies make it difficult to determine the significance of the findings for human health risk assessment, and the US NTP has concluded that the current literature cannot be fully interpreted for relevance for human health.<sup>123</sup>

In 2010, a group of industry scientists (Stump and colleagues) published a study which concluded that there was no evidence that BPA is a developmental neurotoxicant in rats. These workers used the study procedure laid down in Organisation for Economic Co-operation and Development (OECD) and US Environmental Protection Agency (EPA) guidelines.<sup>124</sup> The study covered motor activity, learning and memory (spatial behaviour), auditory startle response, brain histopathology and morphology, but it did not cover some specific aspects of learning and memory (i.e. avoidance learning, schedule-controlled behaviour, and impulsiveness), anxiety-related behaviour or sexual dimorphic behaviour. Moreover, experts reviewing this publication for EFSA noted that due to major design faults in this industry study by Stump et al, no conclusion could in fact be drawn about the effect of BPA on learning and memory behaviour.<sup>125</sup>

Given that numerous studies have indeed found effects, CHEM Trust considers that it is not possible to be confident about the safety of BPA with regard to its effects on the brain.

### **Effects on the prostate**

Professor vom Saal is one of the foremost researchers who published studies showing that BPA exposure in utero affected the prostate gland.<sup>126</sup> Since this time, other teams of researchers have published studies which raise similar concerns about the effects of low levels of BPA on the prostate, such that in 2008 the US NTP had *some concern* for effects on the prostate. However, regulatory agencies around the world did not act on the basis of the low dose studies raising concerns about effects on the prostate, perhaps mainly because two large industry-sponsored studies in rodents,<sup>127,128</sup> did not find such low dose effects. Subsequent to the NTP's deliberations and EFSA's 2010 opinion, a further study directed by Professor Prins of Chicago has reported that when newborn rats were exposed to a low dose of BPA, it resulted in levels similar to that which has been reported in humans. Furthermore, this dose significantly increased the rats' susceptibility to lesions in the prostate and prostate inflammation, and in humans, these are the conditions which can precede prostate cancer. The research found the effect was the same whether the chemical was delivered to the rats by injection or

given orally at the same dose, which is important because many of the low dose studies in which BPA was injected were dismissed on the grounds that the route of exposure was not relevant.<sup>129</sup>

## **Breast cancer**

Studies with rodents suggest that BPA exposure may play a role in increasing the risk of breast cancer in later life. Soto and colleagues have shown that BPA exposure in utero can cause molecular changes in rodent mammary tissue, altering oestrogen sensitivity and predisposing to mammary ductal hyperplasia and an increase in carcinoma in situ of the breast.<sup>130,131,132</sup> They found that prenatal sub-cutaneous exposure to low doses of BPA perturbs the cellular structure of the mammary gland in animals and increases the carcinogenic susceptibility to a chemical challenge given after the BPA exposure.<sup>133</sup> Other research teams have also found similar effects after oral exposure of the animals. For example, Jenkins et al reported that BPA caused enhanced sensitivity of the mammary gland to carcinogen induced breast tumours in rat offspring following lactational BPA exposure of the pups.<sup>134</sup> Furthermore, Betancourt et al reported enhanced susceptibility for mammary gland carcinogenesis after in-utero exposure.<sup>135</sup> Betancourt and co-workers have also reported that in rat mammary tissue, key proteins involved in signalling pathways such as cellular proliferation are regulated at the protein level by BPA.<sup>136</sup> Furthermore, other workers from California have done test tube experiments and found that BPA has the ability to alter the activity of genes in normal breast cells in ways that resemble what is found in extremely dangerous breast cancers.<sup>137</sup> Work at Yale university has further explored mechanisms of action and suggested that altered developmental programming of EZH2 (Enhancer of Zeste Homolog 2) may be the process by which in utero exposure to endocrine disruptors like BPA can lead to epigenetic regulation of the mammary gland. EZH2 is a histone methyltransferase that has been linked to breast cancer risk and epigenetic regulation of tumorigenesis.<sup>138</sup> However, despite the increasing number of studies raising concerns about the potential role of BPA in breast cancer, regulatory risk assessors have not used the studies by Ana Soto's team to quantitatively compare possible effects due to exposure in humans because they considered the subcutaneous route of exposure used to dose the animals was not relevant to the oral exposure in humans.<sup>139</sup> Moreover, in its 2010 opinion, the EFSA panel suggested that both the oral studies of Jenkins and Betancourt had short-comings, particularly regarding the lactational and in-utero exposure and in the reporting of the studies, such that they too could not be used to derive a TDI. Nevertheless, the EFSA Panel did suggest these studies deserve further consideration.

## **Obesity**

Several studies suggest BPA may contribute to obesity:

- Mice and rats exposed to low doses of BPA during prenatal and neonatal periods have shown increased body weight. (see <sup>140</sup>)
- In mice, BPA exposure was reported to disrupt pancreatic beta-cell function and blood glucose homeostasis,<sup>141</sup> and cause insulin resistance.<sup>142</sup>
- In vitro studies with BPA provide further evidence and suggest specific targets;
  - BPA causes 3T3-L1 cells (mouse fibroblast cells) to increase their rate of differentiation into adipocytes, which are cells that make up adipose or fat tissue.<sup>143</sup>

- BPA in combination with insulin accelerates adipocyte formation.<sup>144,145</sup>
- Low doses of BPA impair calcium signalling in pancreatic alpha cells.<sup>146</sup>
- In human cells, BPA at environmentally relevant doses has also been reported to inhibit the release of a key adipokine that protects humans from metabolic syndrome. Adiponectin is an adipocyte-specific hormone that increases insulin sensitivity and reduces tissue inflammation. Any factor that suppresses adiponectin release could therefore lead to insulin resistance and increased susceptibility to obesity-associated diseases.<sup>147,148</sup>

### **Endometriosis**

Endometriosis is a chronic gynaecological disease which has a high incidence and can cause infertility. It occurs when endometrial tissue grows in the wrong place, that is, outside of the uterus. When mice were treated with BPA during pregnancy and during lactation for 7 days after birth (subcutaneously at doses of 100 or 1000µg/kg/day) and their pups were examined at maturity (age 3 months), endometriosis-like structures were seen in the tissue surrounding the genital tract, and these structures expressed the oestrogen receptor. Furthermore, cystic ovaries and some anomalies in tissues were significantly more frequent in treated animals.<sup>149</sup>

### **Altered epigenetic programming**

Many of the effects reported in animals include lasting changes in gene expression. BPA alters 'epigenetic programming' of genes in experimental animals and results in persistent effects that are expressed later in life. For example, BPA has been implicated in DNA hypomethylation resulting in aberrant expression of key growth regulatory genes in rodent prostate.<sup>150,151</sup> With regard to women's health, perhaps some of the most worrying research comes from the school of medicine at Yale University.<sup>152</sup> Research by Professor Taylor and colleagues has looked at the gene called Hoxa10, which controls uterine organogenesis, and how its expression is affected by in-utero BPA exposure. In mice exposed via their mothers to BPA on days 9-16 of pregnancy (5 mg/kg IP), expression of Hoxa 10 messenger RNA and protein in their reproductive tract was increased by 25%. These researchers found that altered methylation was the mechanism for the altered developmental programming, and suggested that permanent epigenetic alteration of sensitivity to oestrogen may be a general mechanism through which endocrine disruptors exert their action. As noted above, under 'Breast cancer', these Yale workers suggested that exposure to BPA can lead to altered epigenetic regulation of the mammary gland and that such epigenetic changes may predispose to breast cancer.

### **Epidemiological studies in people**

Epidemiological studies look for associations between BPA exposure (by measuring levels in the urine or blood) and health effects in the exposed populations. Such studies fall short of establishing that the exposure caused the health effect, as such associations may be due to chance or confounding

factors. Nevertheless, such studies have linked BPA exposure with the following:

- Altered levels of certain hormones that help regulate reproduction, including follicle stimulating hormone in occupationally<sup>153</sup> and non-occupationally exposed men,<sup>154</sup> and altered levels of testosterone in men<sup>155,156</sup> and women.<sup>157,158</sup>
- A decrease in the number of oocytes retrieved and peak oestradiol levels in women undergoing in-vitro fertilisation.<sup>159</sup>
- Miscarriage.<sup>160</sup>
- Chromosomal defects in foetuses (associated with higher BPA levels in maternal serum).<sup>161</sup>
- Obesity in women.<sup>162</sup>
- Effects on the endometrium (the tissue that lines the uterus).<sup>163</sup>
- Polycystic ovary syndrome.<sup>164,165</sup>
- Damage to sperm, which was reported in a study of 190 men which measured urinary BPA concentrations, semen quality and sperm DNA damage. BPA exposure was associated with a slightly elevated, but not statistically significant, decline in sperm concentration and increase in sperm damage.<sup>166</sup> In another study of Chinese men increasing levels of BPA in urine was associated with decreasing sperm concentration, fewer sperm overall, fewer live sperm and decreased sperm motility.<sup>167</sup>
- Decline in male sexual function.<sup>168,169</sup>
- Higher risk of diabetes, heart disease and increased liver enzyme activity. This was reported in a study by a team at Exeter University Medical School, which used exposure data collected by the US Centers for Disease Control.<sup>170</sup> (For an evaluation of this study see Section 4, under the heading 'The European Food Safety Authority (EFSA)'. The study has also since been repeated in a new population sample by the Exeter group using more recent data, and again they found an association with heart disease and diabetes, although the latter was only significant for pooled estimates.<sup>171</sup>
- Hyperactivity and aggression in two-year old female children.<sup>172</sup> The study suggested that prenatal BPA exposure may be associated with these 'externalizing' behaviours.

### **Effects on wildlife**

Studies show that BPA can affect growth, reproduction and development in aquatic organisms. Endocrine-related effects in fish, amphibians, reptiles and aquatic invertebrates (particularly snails) have been reported in laboratory experiments using environmentally relevant exposure levels; lower than those which cause acute toxicity. Many of these endocrine related effects fall within the range of 1µg/l to 1mg/l.<sup>173,174,175</sup>

Regulatory risk assessments typically derive a concentration which is termed the predicted no effect concentration (PNEC), based on a margin of safety from the lowest level of the substance found to cause effects. This PNEC is then compared with the known or predicted environmental concentration or PEC and if the PEC is lower then it is presumed that there is no risk for the environment.

Wild marine snails (*Nucella lapillus*) exposed in the laboratory to BPA at levels of 1-25µg/l exhibited reduced prostate and penis length.<sup>176</sup> Other studies in freshwater snails have reported that very low doses of BPA cause super-feminisation and particularly cause the female snail, *Marisa cornuarietis*, to lay so many eggs that the female ruptures. However, these studies were not considered to be reliable and acceptable for use by themselves in the EU risk assessment, despite there being more than one such study by the team finding low dose effects, and their reporting of effects in more than one species of snail.<sup>177</sup> It should be noted that if the snail lowest EC<sub>10</sub><sup>b</sup> value of 0.0148µg/l from Oehlmann et al. (2006)<sup>178</sup> were used with an assessment factor of 10, the PNEC<sub>water</sub> would be 1.48 ng/l,<sup>179</sup> which is an extremely low level. Instead, the EU set a PNEC of 1.5µg/l, based on an amalgamation of data. In Japan, a similar PNEC of 1.6 µg/l has been set,<sup>180</sup> but this was based on a 16 µg/l no effect concentration for egg hatchability in fathead minnows reported in an experiment conducted by Sumpter and colleagues.<sup>181</sup> Canada has set a lower PNEC of 0.175µg/l,<sup>182</sup> based on a study by Lahnsteiner, and using a lowest observed effect concentration of 1.75 µg/l for reduced semen quality and delayed ovulation in brown trout.<sup>183</sup>

Nevertheless, it seems that many regulatory agencies still have reservations about the potential effects on wildlife and have therefore stressed the need for more data. The US EPA has noted that towards the end of 2010, it intends to consider initiating rulemaking to develop environmental effects data relevant to a further determination of whether BPA does or does not present an unreasonable risk to the environment.<sup>184</sup> In the EU, the UK rapporteur commissioned another study to expose the snail *Planorbis Corneus* to BPA for 6 month period, and suggested that if an effect was indeed found, then they would have to consider the need for a full life-cycle test.<sup>185</sup> However, practical difficulties meant that the results of this study were considered inconclusive, and not usable for risk assessment.<sup>186</sup> The UK rapporteur therefore finally considered that no further work should be performed until a more closely controlled and statistically robust partial life cycle snail reproduction test method was available. As of 2010, work to this end is very slowly progressing within the OECD.<sup>187</sup>

## **Section 4: Regulatory Initiatives**

### **Regulatory Initiatives in the EU**

#### **EU-wide ban on polycarbonate babies' feeding bottles**

On 25<sup>th</sup> November, Member States' representatives on the EU Standing Committee on Food Chain and Animal Health (SCoFAH) reached qualified majority agreement to ban polycarbonate babies' feeding bottles. The ban was announced in a Commission press release of 26<sup>th</sup> November and means that the manufacture of polycarbonate infant feeding bottles with BPA will be banned from 1<sup>st</sup> March, and all such products, including imports will be banned from the EU marketplace, from 1<sup>st</sup> June 2011. The European

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<sup>b</sup> The concentration causing an effect in 10% of the test organisms

Commissioner for Health and Consumer Affairs, Mr Dalli, stressed that new studies had highlighted areas of uncertainty and showed that BPA might have an effect on the development, immune response or tumour promotion. This EU-wide action was no doubt triggered to a large extent by earlier similar action by some individual Member States.

### **Classification of BPA**

In 2001, the UK rapporteur on BPA for the EU proposed that BPA should be given a category 2 classification for reproductive toxicity, despite coming in for some strong lobbying from industry, who were keen for a weaker classification.<sup>188</sup> Eventually, BPA was indeed classified only as a category 3 reproductive toxicant, as only Norway, Sweden, Denmark and France supported the UK and were in favour of a category 2 classification.<sup>189</sup> A category 2 classification would have meant that based on clear evidence in animals, there was a strong presumption that human exposure may result in impaired fertility and/or developmental toxicity. A category 3 classification is weaker and means that based on animal studies, BPA causes concern for human fertility and/or for developmental toxic effects in humans.

Unfortunately, it might be conjectured that the reason behind this weakened classification might have more to do with the strength of the industry lobby than with the strength of the science. On its website, the industry lobbying organisation, the Weinberg Group, has highlighted its success specifically related to the Classification and Labelling of BPA. Their work on this issue has included advocacy and contacts with authorities in EU Member States. Moreover, the Weinberg Group website noted that on behalf of the BPA industry it provided a socioeconomic evaluation of the contribution of the industry to the EU and to Member States in term of jobs and value added, and that briefing sheets were developed to support the advocacy effort. These briefings were “designed to target political hot buttons, such as the risk to high-tech jobs” and “went beyond the numbers to indicate specific industries, regions, and possible firms that might be vulnerable to an adverse classification for BPA.” The Weinberg Group further noted that its efforts proved very effective, as ultimately, in one of the few times in the history of the classification process, the EU ‘Classification & Labelling Working Group’ did not follow the recommendation of the rapporteur Member State to classify BPA as a Category 2 reproductive toxicant, agreeing instead on the more benign Category 3 classification. The industry lobby group pointed out that the classification of a chemical is critical. A category 2 classification can cause the product to face restrictions in market access, and product stigmatization.<sup>190</sup> The Weinberg Group has since removed this case-study on BPA, which was copyrighted in 2005, from its website.

It is a matter of some concern, however, if such intense lobbying did indeed influence the decision on classification, which is **not** supposed to be based on socio-economic considerations, but rather only an evaluation of the scientific data.<sup>191</sup> Socio-economic concerns could legally have influenced decisions as to the appropriate risk management options, but classification decisions should have only been based on an appraisal of the science with respect to BPA’s toxic properties. It can only be surmised as to how far reaching the

lobbying tentacles of industry may have been and whether or not they have influenced other decisions about the risks posed by BPA.

### **EU Existing Substances Regulation and REACH**

The EU risk assessment of BPA, under the Existing Substances Regulation, was ongoing for over a decade, with a final amalgamated Risk Assessment Report published in 2010.<sup>192</sup> The UK was the rapporteur Member State for this risk assessment which found that for consumers there was no need for risk reduction measures beyond those which were already being applied. Several of the reported studies indicating developmental neurotoxicity were dismissed as not being reliable enough for regulatory use, although Denmark, Sweden and Norway did not agree with this, and insisted in noting this in a footnote to the report.

The EU Existing Substances Regulation has now been superseded by REACH, and an Annex XV restrictions report on BPA (which is actually not a proposal for restrictions although it is in the same format) was submitted by the UK in November 2008 as part of the transitional measures for moving to the REACH regime. It similarly proposed no restrictions on the manufacture or use of BPA.<sup>193</sup>

Over two years ago, in May 2008, CHEM Trust wrote to the then UK Minister, Mr Phil Woolas MP, recommending that the UK Government should adopt a strong leadership position and draft a dossier to put BPA on the REACH candidate list for authorisation. Such a move would have stimulated the use of safer alternatives and could ultimately have led to BPA being more strictly regulated.

### **The European Food Safety Authority (EFSA)**

EFSA is responsible for food safety in the EU, and so over the last few years it has addressed many questions related to BPA. BPA was first evaluated in 1984 by the Scientific Committee on Food for use in plastic materials and articles intended to come into contact with food stuffs.<sup>194</sup> Since this time, EFSA has published several opinions, and for example in July 2008, EFSA addressed the potential difference between infants and adults in clearing BPA from the body, and confirmed its opinion that exposure to BPA was well below the Tolerable Daily Intake (TDI) of 0.05 mg/kg bw/day for both adults and newborns. The TDI is an estimate of the amount of a substance, expressed on a body weight basis that can be ingested daily over a lifetime without appreciable risk. However, the EFSA exposure assessment has been heavily criticised by Vandenberg et al.,<sup>195</sup> and moreover, several studies have raised concern as to whether the 0.05 mg/kg bw/day TDI is really protective.

In September 2008, the European Commission (EC) asked EFSA to assess the conclusions of the study by Lang et al. published in the Journal of the American Medical Association which suggested a link between increased levels of BPA in the urine and the occurrence of serious medical conditions, including heart disease and diabetes. In its response, EFSA noted that the study included no information on long term exposure to BPA, which would be important in order to establish a correlation between BPA and the

development of such chronic medical conditions. Furthermore, it noted that the study did not provide sufficient proof of a causal link between BPA and these health conditions, and therefore did not bring into question the established TDI.

In October 2009, the EC subsequently requested EFSA to assess the relevance of a new industry study by Stump et al addressing the possible neuro-developmental effects of BPA and, in the light of new information, if necessary, to update the existing TDI. The EFSA 2010 opinion therefore addressed four issues

- i) an evaluation of the study by Stump et al study relating to the neurodevelopmental effects of BPA in rats
- ii) a review of the scientific literature on BPA
- iii) a review of the scientific arguments supplied by Denmark in support of their Government's decision to ban the use of BPA in food contact materials for infants
- iv) overall conclusions.

In June 2010, CHEM Trust and an unprecedented number of 60 scientists and international environment, health and women's organisations from around the globe wrote a joint letter to EFSA stating that "It is ... our opinion that any objective and comprehensive review of the scientific literature will lead to the conclusion that action is necessary to reduce the levels of BPA exposure, particularly in groups at highest risk, namely young infants and pregnant mothers."

On 30 September 2010 EFSA published its updated opinion which included not reducing the TDI but keeping it at 0.05mg/kg bw. The EFSA Panel noted that some studies conducted on developing animals had suggested BPA-related effects, in particular including biochemical changes in the brain, immune-modulatory effects and enhanced susceptibility to breast tumours, but felt that these studies had several shortcomings. The EFSA panel furthermore noted that the relevance of the findings for human health could not be assessed.<sup>196</sup> However, one member of the panel expressed a minority opinion. This panel member felt that there were too many uncertainties, particularly with regard to the low dose effects, to establish the TDI with confidence, and therefore felt it should have been designated as a temporary TDI.

### **Summary of EFSA's deliberations on BPA**

- In 1986 EU Scientific Committee for Food (SCF) established a TDI of 0.05 mg/kg bw/day (=50µg/kg bw/day) (based on a 90 day rodent study and an uncertainty factor of 500).
- In 2002, EU SCF reviewed TDI and set a Temporary TDI of 0.01 mg/kg bw/day (based on a 90 day and a 3 generation study in the rat, and an uncertainty factor of 500).
- In November 2006, the European Food Safety Agency (EFSA) put the TDI back to 0.05mg/kg bw/day (as new data meant the extra uncertainty factor of 5 was no longer required).

- In July 2008, EFSA looked at data on age-dependent toxicokinetics and considered no implications for the TDI.
- In Oct 2008, EFSA reviewed study showing links with heart disease, diabetes and liver changes – and considered not sufficient proof of a causal link.
- In September 2010 – EFSA kept the TDI at 0.05 mg/kg bw/day (although the EFSA panel considered that no conclusions could be drawn from the industry study by Stump and colleagues as regards BPA's effects on learning and memory, they concluded that there was currently no convincing evidence of the neurobehavioural toxicity of BPA).

## **Action by Individual Member States**

### **Denmark**

In March 2009, the Danish government, together with the Danish People's Party, invoked the precautionary principle and introduced a temporary national ban on BPA in food contact materials for children aged 0 – 3 years. This would ban BPA in infant feeding bottles, feeding cups and packaging for baby food.<sup>197</sup> This is based on the risk assessment of the National Food Institute at the Technical University of Denmark (DTU Food), which expressed some concern about the possibility of low dose effects on learning ability. From 1 July 2010 BPA was therefore not allowed to be sold in Denmark in the products covered by the ban. This ban was invoked using the safeguard clause in Art 18 of the framework Regulation on food contact materials.<sup>198</sup>

### **France**

In June 2010, the French Government temporarily suspended the use of BPA in baby bottles, with a vote on whether to ban the chemical in additional products planned for 2011.<sup>199</sup> This temporary measure is subject to an upcoming opinion of the French Agency for the Safety of Food Products (AFSSAPS).<sup>200</sup>

### **Sweden**

In July 2010, the Swedish Government followed Denmark's lead and issued a press release stating that they were preparing a national ban on BPA in baby bottles. Lamenting that action in the EU was too slow, and noting that alternatives to BPA already existed, the Government instructed the Swedish Chemicals Agency and the National Food Administration to propose how a national ban on BPA in baby bottles and in certain plastic products could be designed.<sup>201</sup>

### **Austria**

On 24th September 2010, the Austrian Minister of Health announced the intention to ban BPA in children's products if the EU did not adopt measures to protect children.<sup>202</sup>

### **Germany**

Germany has not taken legislative action, but in June 2010 the Umweltbundesamt (UBA - the German Environment Agency) released a background paper entitled "*Bisphenol A – a chemical with adverse effects*

*produced in large quantities.*<sup>203</sup> In the UBA press release, which accompanied their report, the president of UBA recommended that based on current knowledge, both producers and users of BPA should take precautionary action to use alternative substances.

### **Action by the European Parliament**

Early in 2009, the European Parliament tried to take the initiative. A written declaration urging the banning of BPA in babies' bottles was tabled by MEPs Hanne Dahl, Christel Schaldemose, H  l  ne Goudin and Carl Schlyter. It was open for signature until 4 April, but got well below the 50 % of MEP signatories needed in order for it to be adopted.

## **Regulatory Initiatives in North America**

### **USA**

About half a dozen individual states in the USA have banned the sale of polycarbonate baby bottles, food containers and cups that contain BPA.<sup>204</sup> For example, it has been reported that Vermont, Connecticut, Wisconsin, Washington, Maryland, Minnesota, the city of Chicago and four counties in New York State - Albany, Schenectady, Suffolk and Rockland – all have BPA bans. The Washington ban takes effect from 1<sup>st</sup> July 2011, the Connecticut ban 1<sup>st</sup> Oct 2011, the Maryland ban 1<sup>st</sup> Jan 2012 and the Vermont ban 1<sup>st</sup> July 2012. The Chicago ban and the other state bans are already in effect. The Connecticut and Vermont bans are the most stringent. The Vermont ban will also apply to sports bottles and metal cans. The Connecticut ban also applies to all infant formula and baby food cans and containers, and all reusable food and beverage containers.<sup>205</sup>

With regard to assessing the need for national action in the USA, several government agencies have looked into the potential risks from BPA.

### **US NTP (National Toxicology Program)**

The US NTP is an interagency program with the mission to coordinate and conduct toxicological research across the U.S. government. Its investigation published in 2008, reached the following conclusions on the possible effects of BPA exposures on human development and reproduction.<sup>206</sup> It ranks its concern in 5 different levels, as negligible concern, minimal concern, some concern, concern, and serious concern.

The NTP (2008) has:

- *some* concern for effects on the brain, behaviour, and prostate gland in foetuses, infants, and children at current human exposures to BPA.
- *minimal* concern for effects on the mammary gland and an earlier age for puberty for females in foetuses, infants, and children at current human exposures to BPA.
- *negligible* concern that exposure of pregnant women to BPA will result in foetal or neonatal mortality, birth defects, or reduced birth weight and growth in their offspring.
- *negligible* concern that exposure to BPA will cause reproductive effects in non-occupationally exposed adults and *minimal concern* for workers exposed to higher levels in occupational settings.

### **US FDA (Food and Drug Administration)**

In a draft risk assessment in 2008, the US FDA noted that at the BPA levels found in products on the American market, it appeared to be safe. However, later in October 2008, a scientific panel of advisers to the FDA, condemned the earlier FDA conclusion, saying the agency had ignored crucial studies and used flawed research selection methods.<sup>207</sup> Indeed, on 3rd June 2009, the Milwaukee Journal Sentinel reported that a congressional committee was investigating whether the US FDA had given undue influence to chemical manufacturers after several reports in the Journal Sentinel revealed how government regulators relied heavily on industry lobbyists when considering the safety of BPA. Senators had written to FDA Commissioner Margaret Hamburg, asking the agency to examine its relationship with industry groups and to reconsider its assessment that the chemical is safe.<sup>208</sup>

In a statement of January 2010, the US FDA noted that it shared the perspective of the US NTP that recent studies provide reason for some concern about the potential effects of BPA on the brain, behaviour, and prostate gland of foetuses, infants and children. The FDA also recognized substantial uncertainties with respect to the overall interpretation of these studies and their potential implications for the human health effects from BPA exposure. These uncertainties relate to issues such as the routes of exposure employed, the lack of consistency among some of the measured endpoints or results between studies, the relevance of some animal models to human health, differences in the metabolism (and detoxification) of and responses to BPA, both at different ages and in different species, and limited or absent dose response information for some studies. The US FDA noted that infants are a potentially sensitive population for BPA because their brains and endocrine systems are still developing, and their livers are less efficient than adults' at detoxifying and eliminating foreign substances. The FDA therefore announced it was taking steps to reduce human exposure and supporting industry actions to get BPA out of baby bottles and feeding cups, and to find alternative liners for food and formula cans.<sup>209</sup>

### **US EPA (Environmental Protection Agency)**

The US EPA's action plan on the environmental impacts of BPA includes *consideration* of the following:

- Adding BPA to the Concern List because of potential environmental effects. The Concern List is designated under Section 5(b)4 of the Toxics Substances Control Act which authorises the compilation of a current list of chemicals for which the manufacture, processing, distribution in commerce, use, or disposal, or any combination of such activities, presents or may present an unreasonable risk of injury to health or the environment.
- Requiring information on concentrations of BPA in surface water, ground water, and drinking water to determine if BPA may be present at levels of potential concern.
- Requiring manufacturers to provide test data to assist the agency in evaluating its possible impacts.
- Using EPA's 'Design for the Environment' program to look for ways to reduce unnecessary exposures, including assessing substitutes, while additional studies continue.

- Continuing to evaluate the potential disproportionate impact on children and other sub-populations through exposure from non-food packaging uses.<sup>210</sup>

### **The US NIEHS (National Institute of Environmental Health Sciences)**

In order to try and resolve whether or not BPA does indeed cause low dose effects, in 2009, the US NIEHS announced a \$30 million dollar, 2 year research programme.<sup>211</sup>

Its aim is to fill the research gaps on BPA so that personal and public health decisions can be made. Some of the disease endpoints that researchers will be investigating include behaviour, obesity, diabetes, reproductive disorders, development of prostate, breast and uterine cancer, asthma, cardiovascular diseases and trans-generational or epigenetic effects.

### **Action in Canada**

In June 2009, Canada became the first country to take regulatory action against BPA and announced it proposed to prohibit the advertisement, sale and import of polycarbonate baby bottles that contained BPA. The Canadian Government concluded that “exposure levels for newborns and infants up to 18 months of age are below those that could cause health effects. However, due to uncertainty raised in some studies relating to the potential effects of low levels of BPA the Government wants to further limit exposure.”<sup>212</sup> The ban of polycarbonate baby bottles came into force on 11<sup>th</sup> March 2010.

Canada also proposed to develop stringent migration targets for BPA in infant formula cans, and to list BPA under schedule 1 of the Canadian Environmental Protection Act.<sup>213</sup> Indeed, on 13 October 2010 the Canadian Government formally added BPA to the Toxic Substances List, a move which had been delayed due to a formal industry objection to BPA's proposed addition to the list.<sup>214</sup>

### **Action in Japan**

In Japan, the Ministry of Health and Welfare (1998a), the Ministry of Health, Labour and Welfare (2001a), the Ministry of Economy, Trade and Industry (2002), the Ministry of the Environment (2004a) convened panels of experts on endocrine disruptors, and although they did not recommended prohibiting or restricting the use of BPA, a risk assessment was undertaken.<sup>215</sup> This assessment noted the conflicting observations in low dose developmental toxicity studies in rodents, and suggested that further research would be needed. However, because of concerns about children's intakes and the endocrine disrupting effects of BPA, in around 1998, many municipalities phased out the use of polycarbonate tableware used in schools. Also, companies were instructed to prevent the migration of BPA from drink cans. Two approaches were employed to reduce BPA exposure from such cans. These included either changing the inner surface inactivation of cans from the epoxy-resin coating to film lamination based on another substance or using epoxy-resin paint from which only a small amount of BPA migrates.

## **International collaboration**

Two United Nations bodies, the World Health Organisation (WHO) and the Food and Agriculture Organisation (FAO) have convened an international meeting in Canada in November 2010 on the safety of BPA in food packaging over growing anxiety about the chemical's possible threat to human health. The WHO press release from this meeting noted that, "A few recent experimental and epidemiological studies found associations between low BPA exposure levels and some adverse health outcomes. The meeting concluded that, at this stage, it is difficult to interpret the relevance of these studies in the light of current knowledge of this compound. Until these associations can be confirmed, initiation of public health measures would be premature."<sup>216</sup> It should come as no surprise that this meeting would not usurp the findings of other national and international assessments.

## **Action by industry and alternatives**

Wal-Mart, Whole Foods, Sears, CVS and other retailers have said they will stop selling baby bottles made with BPA, and some major formula manufacturers have also stopped using products linked with BPA exposure.<sup>217</sup> In the USA, six major baby bottle companies (Avent, Disney First Years, Gerber, Dr. Brown, Playtex and Evenflow) have agreed to voluntarily stop using BPA in their bottles.<sup>218</sup>

Nalgene, a maker of popular water bottles in the USA, stopped using BPA when customers began complaining about it. Sunoco, one of the companies that makes BPA, has said it would sell the chemical only to buyers who guaranteed that they would not use it in food or drink containers meant for children.<sup>219</sup>

Due to consumer concern and the impending regulation of polycarbonate baby bottles in some countries, plastic substitutes have appeared on the market. Such materials include, for example, polyether sulphone (PES), polypropylene (PP), pure silicone, polyamide and a new co-polyester polymer.<sup>220</sup>

The situation with respect to finding substitute materials for lining food cans is also now moving rapidly. In the USA, Eden uses BPA-free cans (which are steel cans coated with a baked on oleoresinous c-enamel) for its foods, such as organic beans. These cans are made by the Ball Corporation and cost 14% more than the industry standard cans.<sup>221</sup> In Japan, see above under 'Action in Japan' some companies have taken action to reduce the amount of BPA leaching from cans. Substitute can linings on the market today include polyester-based linings, such as thermoplastic polyester coatings and polyester coatings commonly used in Japan, or oleoresinous (plant oil based) linings such as those used by Eden Foods. Moreover, some companies, including Hain Celestial and Whole Foods, are reported to be exploring other packaging that is BPA-free, such as glass jars or cartons. There are also tests being done on additional substances that could prove useful substitutes in the future.<sup>222</sup>

In July 2010, Heinz announced that it was moving to BPA free baby food packaging as a priority.<sup>223</sup>

A 2010 report '*Seeking Safer Packaging*' by You Sow found that an increasing number of companies in the USA were proactively mitigating any BPA-related risks from food cans by testing and implementing substitute packaging.<sup>224</sup> Its survey ranked clear industry leaders, such as H.J.Heinz, ConAgra and Hain Celestial, (given A grades) as well as laggard companies (given F grades) who apparently had failed to keep pace with industry leaders in seeking substitutes and phasing out BPA. Companies given the lowest (F) grade included: Coca-Cola, Del Monte, Kraft, Unilever, Kroger, Safeway, Supervalu and Wal-Mart. Most of these companies were exploring substitutes for BPA to some degree, but did not commit to phasing out BPA, and were not reported to be funding the exploration of substitutes. Some other companies were also graded F (including Delhaize Group, Hershey, Hormel, and Sysco) for failing to respond to the survey in the allotted time and demonstrating a disconcerting lack of transparency on this issue.

The US EPA considers that there may be alternatives to BPA readily available for thermal and carbonless paper coatings (till receipts). The US EPA is also investigating alternatives for BPA used in foundry castings and for BPA-based materials lining water and waste pipes, since this application may have potential for human and environmental exposure.<sup>225</sup>

### **Statements made by concerned scientists**

- The Prague Declaration of 2005 has been signed by scores of international scientists. This Declaration on endocrine disrupting chemicals does not explicitly refer to human health concerns relating to BPA, but it does state that "In view of the magnitude of the potential risks associated with endocrine disrupters, we strongly believe that scientific uncertainty should not delay precautionary action on reducing the exposures to and the risks from endocrine disrupters."<sup>226</sup>
- The Chapel Hill Consensus Statement on BPA, published in 2007, was written by almost forty eminent scientists working in the field. They concluded that the "wide range of adverse effects of low doses of BPA in laboratory animals exposed both during development and in adulthood is a great cause for concern with regard to the potential for similar adverse effects in humans. Recent trends in human diseases relate to adverse effects observed in experimental animals exposed to low doses of BPA. Specific examples include: the increase in prostate and breast cancer, uro-genital abnormalities in male babies, a decline in semen quality in men, early onset of puberty in girls, metabolic disorders including insulin resistant (type 2) diabetes and obesity, and neurobehavioral problems such as attention deficit hyperactivity disorder (ADHD)."<sup>227</sup>

- The international Endocrine Society in 2009 noted that “the evidence for adverse reproductive outcomes (infertility, cancers, malformations) from exposure to endocrine disrupting chemicals is strong.”<sup>228</sup>
- The California Medical Association in 2010 adopted the following Resolution 116a-10, on BPA. “CMA recognize a public health concern for Bisphenol A (BPA), a known endocrine disruptor, and endorse efforts to reduce towards elimination of BPA in consumer products including food containers, baby products and thermal paper products.”

## **Section 5: Conclusions and Recommendations**

### **Conclusions**

- There is now overwhelming data showing that BPA disrupts mammalian hormone systems, and moreover, the effects reported in fish and invertebrates add weight to the concerns relating to BPA’s hormone disrupting properties. BPA can undoubtedly cause harmful effects in mammalian animals at high dose levels.
- The health effects to which BPA is suggested to contribute particularly include: breast cancer, prostate cancer, endometriosis, heart disease, obesity, diabetes, altered immune system, effects on the reproductive tract and effects on brain development and behaviour.
- The potential health effects of BPA are alarming, but data relating to the exposure levels encountered by people and the effects of such exposure are contradictory. However, the number of studies reporting low dose effects continues to grow. It is certainly worrying that scores of studies suggest effects at dose levels below the current tolerable daily intake (TDI) or ‘safe level’.
- Unfortunately, the full implications of long-term low dose exposure to BPA, and other endocrine disrupting chemicals, will take many more years of research to fully clarify. Nevertheless, a growing number of studies, including both studies in animals and epidemiological studies, already suggest that current BPA exposure levels may be harming human health.
- Experiments done by industry and research studies from the US EPA laboratory, which have failed to find low dose effects, should not serve to eliminate all the concern about BPA, because many of the endpoints where low dose studies have reported effects have not been covered in these ‘negative’ studies.
- Some novel experiments, including work done by scientists at Yale University, show that BPA can affect multiple genes.
- CHEM Trust considers that given the measured internal levels of active BPA reported in humans, it would be wise to put more weight on the findings in animal studies which have been reported after sub-cutaneous exposure, particularly as some researchers have suggested that BPA has a longer than expected half-life or substantial non food exposure, or both.

- Even if there is no one low dose study which, by itself, convinces the regulatory authorities to regulate BPA more strictly, CHEM Trust concludes that the wealth of low dose studies give rise to sufficient concern to merit urgent action to reduce exposures of children and pregnant women. This is particularly because many of the low dose studies reinforce each other by showing the same or similar outcomes, and moreover are complemented by studies highlighting possible mechanisms of action.

### **Recommendations**

- CHEM Trust considers that in view of the data which raise concerns about the amount of active BPA actually present in the human body, a definitive answer is needed as to the internal exposure to the active form of BPA in humans. This issue needs to be resolved as a matter of urgency, but should not delay measures to reduce exposures.
- All exposure routes and sources, including possible non-oral exposure routes, need to be identified.
- CHEM Trust's position is that exposure reduction is long overdue. In view of the widespread exposure and the potentially serious and irreversible effects, CHEM Trust recommends urgent action to reduce exposures on a precautionary basis.

### **Regulatory Action is Needed**

- Regulations should be put in place to greatly reduce or eliminate exposure to BPA, particularly to protect all pregnant women and children. Given that many chemicals with endocrine disrupting properties have been shown to act together, and given that offspring in the womb are particularly sensitive, exposures of pregnant women should be reduced on a precautionary basis. Exposures of children also need to be urgently reduced, because infants are also a potentially sensitive population, but this should not obscure the need for action to protect the unborn child.
- Action on BPA should be taken on several legislative fronts, including food contact materials legislation and REACH (the 2006 EU Regulation concerning the registration, evaluation authorisation and restriction of chemicals).
- The European Food Safety Authority (EFSA) and the Commission should take urgent action to reduce BPA exposure from food contact materials, particularly in groups at highest potential risk, namely infants and pregnant women.
- Under REACH, CHEM Trust recommends that a Member State or the European Chemicals Agency (ECHA) should draft a dossier to put BPA onto the Candidate List as a substance of very high concern, with the ultimate aim of subjecting it to tougher regulation.

### **Action by individuals may be warranted while regulation is lacking**

- Women intending to start a family, pregnant women and mothers should consider taking action to reduce BPA exposure for themselves and their children. This could include:

- Avoiding microwaving food in polycarbonate, which over time may leach BPA. Plastic containers are numbered for recycling, and those made using BPA carry a 7, although not everything with a 7 contains BPA.
- Using baby bottles that are BPA free, but if possible breast feeding because breast milk is considered best for baby.
- Trying to eliminate the use of polycarbonate plastic for food and drinks containers, but particularly replacing old or scratched polycarbonate food containers and not using them for warmed food.
- Eliminating consumption of canned food and drinks as much as possible, and trying to eat a variety of freshly produced organic food, including plenty of fruit and vegetables.
- Not putting till receipts or lottery tickets in the mouth, and washing hands after handling.
- Asking their dentists to avoid dental products made with BPA-related chemicals.



December 2010

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