24 April 2017

Comments on Annex XV SVHC report: identification of Bisphenol A as SVHC due to endocrine disrupting properties (Article 57(f) - human health)

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ClientEarth

The Annex XV report proposing the identification of Bisphenol A (BPA) as a substance of very high concern (SVHC) for its endocrine properties prepared by ANSES is well evidenced, logical and sufficiently robust from a scientific point of view. In accordance with Article 57(f) of Regulation (EC) 1907/2006 (REACH), the report gathers scientific evidence of probable serious effects to human health which gives rise to an equivalent level of concern (ELoC) to those of CMR PBT or vPvB, i.e. "*so serious and [that] cannot normally be reversed so that such effects have to be prevented rather than remedied*".[1]

In support of the identification of BPA as SVHC for its endocrine disrupting properties, we provide:

- Additional evidence showing probable serious effects of BPA which give rise to ELoC;
- Comment on plausible link between the mode of action and the serious effect;
- Comment on the notion of "secondary toxicity".

1) Additional evidence of probable serious effects giving rise to ELoC

The scientific evidence provided below reveals additional probable serious effects of BPA on human health within the meaning of Article 57(f) of REACH, which reinforce the evidence gathered in the report.

It also shows that these effects give rise to an ELoC to those of CMR, PBT or vPvB, in particular because of their irreversibility, the consequences of those effects for society and impact of those effects on the lives of persons affected. It confirms, in addition, the difficulty of adequately assessing the risk due for example to the delayed effects of BPA.

Crosstalk between sex steroid hormones and thyroid hormones

The report itself clarifies[2] that its focus on the estrogenicity of BPA as an endocrine mode of action should not preclude the consideration of other (endocrine) mechanisms. There is also no reason to limit the assessment to the binding affinity of BPA to estrogen receptors (ERs). We therefore provide additional evidence of an endocrine mode of action beyond the estrogenicity.

An important mode of action that has not been considered in this report is the disruption of the Hypothalamus-Pituitary-Thyroid (HPT) axis. Thyroid hormones (THs) are involved in at least three of the adverse effects considered, namely reproductive function, neurodevelopment and metabolism. Indeed, THs are known to regulate sex steroid synthesis and action in both the brain and gonads. The crosstalk between these two endocrine axes was recently reviewed by Duarte-Guterman et al (2014).

[1] Judgement of the Court of Justice in Case C-323/15P, EU:C:2017:207, para. 37.
[2] Report, p. 160

BPA is known to be able to disrupt several important processes along the HPT axis (Wu et al 2016; Zoeller et al 2005). Additionally, some cross-sectional studies in humans have detected associations between exposure to BPA and THs (e.g. Sriphrapradang et al 2013; Wang et al 2013) in adults. More recently, two case-control studies have found associations between BPA exposure and incidence of thyroid nodular disease in adult women (Andrianou et al. 2016), or thyroid volume and structure in school children (Wang et al. 2015). Notwithstanding the limitations of such study designs, there is more crucially evidence of an effect of BPA exposure on maternal hypothyroidism in both humans (Chevrier et al 2013) and pregnant ewes, an animal model very relevant to humans due to its long pregnancy (Viguié et al 2013). The relationship between maternal hypothyroidism during pregnancy and subsequent suppressed psychomotor development and lower IQs in their children is established.

Therefore, disruption of TH action by BPA can contribute to adverse effects on neurobehaviour (e.g. Somogyi et al. 2016) and fat metabolism (Ahmed 2016).

Neurobehaviour

Several epidemiological studies investigating the association between prenatal BPA exposure and neurobehavioural effects in children were not considered in this report (Braun et al 2009; Braun et al 2011; Evans et al 2014; Harley et al 2013; Miodovnik et al 2011; Roen et al 2015). All but one of these studies, that measured urinary BPA metabolites during the third trimester of pregnancy, detect positive associations between prenatal BPA exposure and behavioural effects in children. Moreover, an experimental study in mice found that effects could be observed in the third, and therefore never exposed, generation (Wolstenholme et al 2013). The transgenerational nature of BPA action on behaviour further emphasizes the irreversibility of such effects.

Autism Spectrum Disorders

Autism is a spectrum of disorders that comprise a group of lifelong conditions characterised by impaired social interaction and communication, with stereotyped and repetitive behaviours, and some level of intellectual impairment in around 75% of cases. It is of great societal concern due to a recent dramatic increase in diagnoses considered by some as an epidemic. Recent epidemiological studies suggest an association between autism spectrum disorder and BPA exposure (Arbuckle et al 2016; Kardas et al 2016; Kondolot et al 2016; Stein et al 2015), and as such this endpoint should also be considered.

Neurodegenerative diseases

Another area of emerging concern that ought to be mentioned are the potential effects of BPA exposure in neurodegenerative diseases such as Parkinson’s disease, Alzheimer’s disease or dementia. This is crucially socially relevant in the ageing European population. Although this is currently understudied, there are indications that BPA exposure has an effect on neurodegenerative processes both through an estrogenic pathways or disruption of TH action (Preciados et al 2016; Jiang et al 2016; Boxian et al 2014).

Cardiovascular diseases

Cardiovascular disease is a major contributor to mortality and morbidity worldwide. The epidemiological, experimental and mechanistic evidence for effects of BPA exposure on cardiovascular were recently reviewed by Gao et al (2014) who suggested that the underlying molecular mechanisms may involve estrogen receptor rapid signalling.

Several epidemiological studies indicate that BPA exposure in adult populations is associated with increased risk for CV diseases, including coronary artery heart disease, angina, heart attack, hypertension, and peripheral artery disease (e.g. Bae et al 2015; Lang et al 2008; Melzer et al 2010; Melzer et al 2012a; Melzer et al 2012b; Shankar et al 2012; Romano et al 2015).
More recently, a study detected an association between prenatal BPA exposure and higher diastolic blood pressure in children (Bae et al 2017) suggesting that BPA may also have delayed developmental effects on cardiovascular health.

Experimental studies suggest BPA exposure could affect the physiological functioning of CV system (Gao et al 2014). Of note, maternal BPA exposure has been found to affect the fetal heart transcriptome in non-human primates (Chapalamadugu et al 2014). There is also evidence in the zebrafish, an animal model considered relevant to humans in the clinical setting, that effects on cardiovascular function may be transgenerational (Lombo et al 2015).

Metabolism/fetal exposure

Studies in the sheep (Corbel et al 2015) and non-human primates (VandeVoort et al 2016) indicate that rapid maternal metabolism of BPA does not alleviate exposure to the developing fetus. This evidence on potential fetal exposure increases further the level of concern.

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2) Comment on plausible link between the mode of action and the serious effect

The report includes sections dedicated to the evidence of a plausible link between an estrogenic mode of action and each adverse effect considered. These typically start with a statement on whether such link has been observed experimentally in the same study. Observing both mechanism and effect in the same study, however, should not be considered a requirement for identification as a SVHC for endocrine disrupting properties as it would be far too high a burden of proof. As mentioned in the report, a link may not be observed in one and the same study due to the latency between exposure and effect, or because of experimental practicalities. This does not call into question the plausibility of the link.

This notion of 'plausible link' should rather be defined following the approach of Bradford Hill (1965):

> *"It will be helpful if the causation we suspect is biologically plausible. But this is a feature I am convinced we cannot demand.* ***What is biologically plausible depends upon the biological knowledge of the day****. […] In short, the association we observe may be one new to science or medicine and we must not dismiss it too light-heartedly as just too odd. As Sherlock Holmes advised Dr. Watson, 'when you have eliminated the impossible, whatever remains, however improbable, must be the truth.'"* (emphasis added)

In light of this, assessing the plausible link should be done by considering the body of evidence within the context of the current state-of-knowledge, as opposed to looking at whether the body of evidence itself internally demonstrates a plausible link. In that regard, the report (background information and human relevance) contains sufficient information showing a plausible link between the endocrine mode of action and the serious adverse effects.

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3) Comment on the notion of "secondary toxicity"

In the context of endocrine disruption, the term 'secondary toxicity' was probably first used in the WHO/IPCS 2002 State-of-the Art report (IPCS, 2002) when describing criteria for attribution to an endocrine mode of action. It was introduced as follows:

> *"Dose–response observations that indicate the perturbance of the endocrine system is a critical response of the organism, and not the* ***secondary result of general systemic toxicity****"* (emphasis added)

Kortenkamp et al (2012) noted that the WHO/IPCS definition leaves the interpretation of which modes-of-action should be considered to "**alter the function of the endocrine system**" relatively open. The concept of endocrine disruption first developed when it was observed that some environmental chemicals were able to mimic the action of the sex hormones oestrogens and androgens. This notion has now evolved to encompass a range of mechanisms incorporating the many hormones secreted directly into the blood circulatory system by the glands of the endocrine system and their specific receptors, transport proteins and associated enzymes. The definition does not explicitly address the issue of indirect endocrine toxicity, or when an effect on endocrine function is observed secondarily to overt toxicity in other organs or systems. This is related to what is referred to as "**specificity"** or sometimes also "lead toxicity", to describe the requirement for endocrine disruption to occur at lower doses than other mechanisms of toxicity.

As such, 'secondary toxicity' refers to overt systemic toxicity resulting from toxic effects to other organs that are eventually reflected in changes in hormone levels. Subtle changes such as meiotic alterations and (epi)genetic changes that disrupt the programming and ultimately the functioning of the endocrine communication system should therefore not be described as 'secondary toxicity' but rather as a endocrine disrupting mechanism (as stated on page 43 of the report).

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24 April 2017

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ClientEarth is funded by the generous support of philanthropic foundations, institutional donors and engaged individuals.

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