Endocrine Disrupting Chemicals and Bioaccumulative Substances – The Next Wave of Regulated Substances in Electronics

Bruce Calder
Claigan Environmental Inc.
Ottawa, Ontario

Abstract
Until recently, virtually all restricted materials in electronics were classified as eithercarcinogens (e.g. Pb) or reproductive toxins (e.g. phthalates). Two new categories of restricted materials have emerged - endocrine disrupting chemicals (EDCs) and persistent organic pollutants (POP). These two new categories of restricted materials will bring into regulation chemicals that have not historically been restricted. This significant increase in material at risk of substance regulation is expected to change the design and procurement landscape in a way not seen in the electronics industry since the original EU RoHS Directive.

Endocrine Disruptors
Endocrine disruptors are chemicals that can interfere with endocrine (or hormone) systems. Endocrine disruptors are a distinct hazard classification from reproductive toxicity, even though many endocrine disruptors are also reproductive toxins.

Regulatory Driving Forces
The main driving force behind the regulation of endocrine disrupting chemicals is the EU REACH (Regulation (EC) No 1907/2006) authorisation process. The EU REACH Regulation has a regularized process [i]of identifying and classifying endocrine disrupting chemicals. This process is fed by a regularized assessment of all potentially harmful substances by the European Chemical Agency (ECHA) under the Community Rolling Action Plan (CoRAP)[ii]. Under CoRAP, the ECHA is expected to complete at least the initial evaluation of all potential EDCs by the end of 2021. California Proposition 65 is also a contributing factor to the regulation of endocrine disruptors due to the classification of changes in morphology to sperm and ovaries as reproductive toxicity.

Estrogenic Endocrine Disruptors
Estrogenic endocrine disrupting chemicals are chemicals that interfere or mimic the effect of estrogen hormones. The most common estrogenic EDCs are xenoestrogens, which artificially cause the body to undergo a female response by mimicking female hormones such as estradiol. The principal form of mimicry is hypothesized to be related to the similarity between the phenol groups of these chemicals (or their metabolites) and the phenol group of common female hormones such as estradiol (Refer to Figures 1-6).

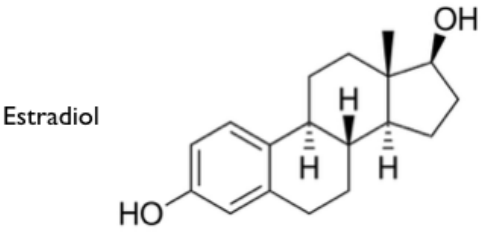

Figure 1 Estradiol

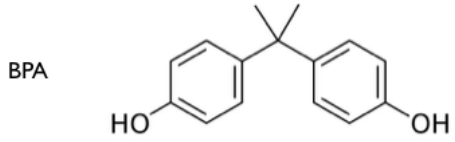

Figure 2 BPA

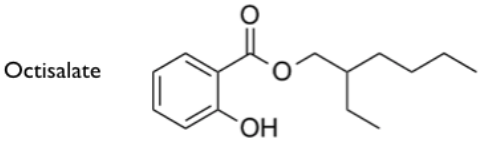

Figure 3 Octisalate

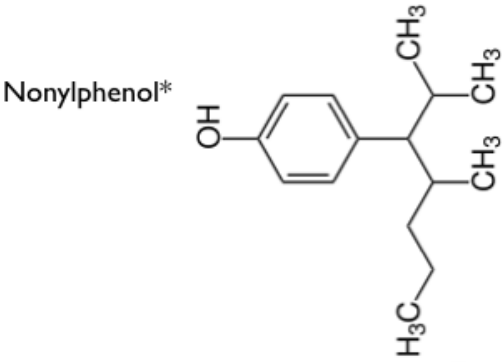

Figure 4 Nonylphenol

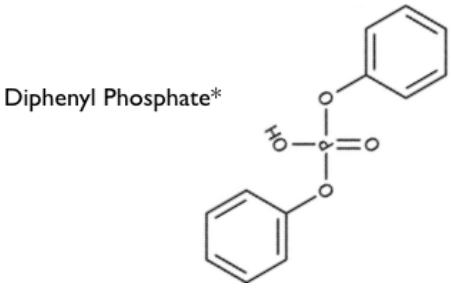

Figure 5 Diphenyl Phosphate

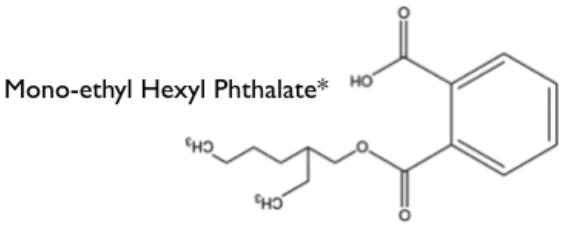

Figure 6 Mono-ethyl Hexyl Phosphate

* metabolites of nonylphenol ethoxylate, triphenyl phosphate, and DEHP respectively.

The phenol group (a benzene ring with an -OH alcohol) or the phenol-similar groups (such as exhibited by the DEHP metabolite MEHP) can trick the estrogen receptor into believing they are engaged with an estrogen hormone and produce a female response. Common effects by estrogenic EDCs are listed in Table 1.

Table 1. Effects of Estrogenic EDCs

Substances	Effects
Estrogenic EDCs	Attention deficit[iii]
	Low sperm count[iv]
	Ovarian cysts[v]

There are many families of estrogenic EDCs. Table 2 contains the most common families of classified or suspected estrogenic endocrine disruptors, examples of chemicals from each family, and 'high risk' materials known to use these estrogenic EDCs above 0.1% w/w. These high-risk materials include quite a few materials commonly used in electrical and electronic products.

Table 2 – Estrogenic EDCs and Risk Materials

Substance Group	**Example**	**High Risk Materials**
Low molecular weight orthophthalates	DEHP	PVC Polychloroprene (neoprene) Nitrile rubber Styrene butadiene rubber
Phenol ethoxylates	Octylphenol ethoxylate	Surfactant
Bisphenols	Bisphenol-A	PVC
Salicylates	Octisalate	Sunscreen
Phosphated phenols	Triphenyl phosphate	Flame retarded plastics
Benzidiols	Resorcinol	Ointments

Thyroid Disruptors

Thyroid disruptors are synthetic chemicals that disrupt the proper function of the thyroid – primarily through the disruption of the synthesis of T3 and T4 hormones.[vi] Common effects of thyroid disruptors are listed in table 3.

Table 3 – Effects of Thyroid-Disrupting EDCs

Substances	**Effects**
Thyroid disruptor	Hypothyroid[vii]
	Thyroid enzyme inhibition[viii]
	Fetal resorption[ix]

Estrogenic EDCs are also often thyroid disruptors, but there are a large range of non-estrogenic substances that also exhibit thyroid disruption. Table 4 contains most common families of classified or suspected non-estrogenic thyroid disruptors, examples of chemicals in each family, and common materials known to use these thyroid-disrupting EDCs above 0.1% w/w. Similar to materials with a high risk of containing estrogenic materials, the 'high risk' materials in Table 4 contain many common materials used in electronics.

Table 4 – Thyroid Disrupting EDCs and Risk Materials

Substance Group	Example	High Risk Materials
Thiazole	2-MBT	Vulcanized rubber
Thioureas	ETU (Ethylene Thiourea)	Vulcanized neoprene
Triazoles	Benzotriazole	Corrosion inhibitors Dishwasher tabs

Bioaccumulative Substances

Bioaccumulative substances are chemicals that are persistent, bioaccumulative, and toxic (PBT) or are very persistent / very bioaccumulative (vPvB). A chemical persistence is based on its biodegradation (or lack thereof) in water or soil. The key parameter for classification in the above categories is the bioaccumulative property of the substance. Bioaccumulation is a combination of bioconcentration (the concentration of the chemical in fish cells versus the concentration in the water) and biomagnification (the increasing concentration of the substance in tissue at successively higher levels in the food chain). There are multiple criteria / thresholds to be met, but generally the most important is whether a PBT substance has a bioconcentration factor (bcf) above 2,000 (the concentration that accumulation in fish cells is more than 2,000 times the concentration in the water) or over 5,000 (in the case of vPvB substances)[x].

Regulatory Driving Forces

The UN Stockholm Convention on Persistent Organic Pollutants[xi] and the related national implementations (such as the EU Regulation on Persistent Organic Pollutants (EU POP) and the Canadian Prohibition of Certain Toxic Substances) have been the driving forces behind regulation of bioaccumulative substances. Initially, the Stockholm Convention was the principle source of classification of bioaccumulative substances. More recently, the EU REACH classification process by the ECHA has been the major source of newly classified bioaccumulative substances.

Suspected and Classified Bioaccumulative Substances

Classification of bioaccumulative substances is an active and ongoing process. In general, most classified or suspected bioaccumulative substances fall into a relatively consistent family of substances. The substance groups (simplified), example chemicals in each substance group, and material with high risk of containing these substances above 0.1% w/w are listed in Table 5. This table includes many relatively 'biologically inert' materials. These materials have historically been seen as safe due to their lack of processability by or interaction with biosystems. However, it is often that the lack of bio-processability that is likely the cause of their bioaccumulation.

Table 5 – Bioaccumlative substances and Risk Materials

Substance Group	Example	High Risk Materials
PAHs	Benzopyrene	Black rubber
Flame retardants	Dechlorane plus	EPDM Nylon 6
Paraffins	SCCP	PVC Polychloroprene (neoprene) Nitrile rubber Styrene butadiene rubber
Perfluorinated acids	PFOA	PTFE FKM FEP PVDF
Siloxanes	Dodecamethylcyclo hexasiloxane (D6)	Silicone rubber Moisturizer

Materials at Risk of New EDCs and Bioaccumulative Substances

As interesting as the technical discussion above may be, the practical interest for most electronics designers and manufacturers is specifically which materials that they use that may require further control or replacement. The regulation of EDCs and bioaccumulative substances has greatly increased the range of materials that may need further control and replacement to meet regulatory requirements (see Table 6). This includes many substances that have never been a significant risk of containing regulated chemicals.

Table 6 – Electronics Materials with Increase Regulatory Risk

Risk Increase*	High Risk Materials
Increased risk (already high risk)	PVC Polychloroprene (Neoprene) Nitrile rubber Styrene butadiene rubber Flame retarded plastics
Now high risk (previously low risk)	Silicone rubber PTFE FKM FEP PVDF EPDM Nylon 6 Vulcanized rubber

* materials that were previously high risk of containing restricted materials and previously low risk materials that, with the addition of EDCs and bioaccumulative substances, are now high risk of containing restricted materials.

Conclusions

The re-classification and regulation of EDCs and bioaccumulative substances is expected to multiply the number of materials that will require control or replacement in electronic products. Many previous low risk substances (from a chemical regulation point of view) such as silicone rubber, PTFE, and EPDM will now require attention and controls that have not historically been in place in the supply chain. Furthermore, unlike 'classically' regulated substances such as Pb and Cd, these substances have not normally been declared on materials safety data sheets and are invisible in the supply chain. Future-proofing approaches such as 'full material declaration' have been found to have been unsuccessful in allowing detection of these substances from legacy information and screening test methods are still in development. Design of electronic products, and procurement of components and materials for electronics are expected to undergo a regulatory flux greater than what was experienced with the EU RoHS directive a decade ago.

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[i] "Guidance for the Identification of Endocrine Disruptors in the Context of Regulations (EU) No 528/2012 and (EC) No 1107/2009."*ECHA*, European Chemical Agency, https://echa.europa.eu/documents/10162/23036412/bpr_guidance_identif_ed_en.pdf/1a4d2811-3faa-fe61-1de2-3cbce8fd4d95.

[ii] "Community Rolling Action Plan." *ECHA*, European Chemical Agency, https://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan.

[iii] Rebuli, M.E. and H.B. Patisaul. "Assessment of Sex Specific Endocrine Disrupting Effects in the Prenatal and Pre-pubertal Rodent Brain." *The Journal of Steroid Biochemistry and Molecular Biology*, Volume 160, June 2016, pp. 148-159.

[iv] Welshons, W.V. "Large Effects from Small Exposures. I. Mechanisms for Endocrine-Disrupting Chemicals with Estrogenic Activity." *Environmental Health Perspectives*, Volume 111, Number 8, June 2003, pp. 994-1006.

[v] Hamdy, H. "Endocrine Disruption Induced by Bisphenol A in Young and Adult Female Sprague Dawley Rats."*Comparative Clinical Pathology*, Volume 27, Issue 4, July 2018, pp. 967-974.

[vi]Daniel R. Doerge, and Richard S. Takazawa, "Mechanism of thyroid peroxidase inhibition by ethylenethiourea.", Chemical Research Toxicology, Vol 3 (2), pp. 98-101.
[vii]Maranghi, F. "Reproductive Toxicity and Thyroid Effects in Sprague Dawley Rats Exposed to Low Doses of Ethylenethiourea." *Food and Chemical Toxicology*, Volume 59, September 2013, pp. 261-271.
[viii]Tietge, J.E. "Inhibition of the Thyroid Hormone Pathway in Xenopus Laevis by 2-mercaptobenzothiazole." *Aquatic Toxicology*, Volume 126, January 2015, pp. 128-136.
[ix] "Ethylenethiourea." *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Volume 79, 2001, pp. 659-701.
[x] "Guidance on Information Requirements and Chemical Safety Assessment - Chapter R.11: PBT/vPvB assessment", ECHA, European Chemical Agency, Version 3.0, June 2017, pg. 17.
[xi] "Overview - The Stockholm Convention on Persistent Organic Pollutants was adopted by the Conference of Plenipotentiaries on 22 May 2001 in Stockholm, Sweden", Secretariat of the Stockholm Convention, May 2001.http://chm.pops.int/TheConvention/Overview/tabid/3351/Default.aspx