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Identification of health risks from harmful chemical agents – review concerning bisphenol A in workplace

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Abstract
Bisphenol A (BPA) is an industrial chemical used as an additive in conventional point-of-sale thermal paper receipts, in the production of many polycarbonate plastics, and epoxy resins lignin for food. BPA is xenoestrogen, a foreign compound that is not naturally produced in living organisms, but which acts similarly to natural 17-ß estradiol (natural estrogen). Due to its weak estrogenic activities, BPA exposure may influence multiple endocrine-related pathway, and is associated with prostate and breast cancer, neurobehavioral deficits, heart disease, and obesity. Furthermore, BPA may act as a DNA methylation agent and cause altered gene expression in the brain. Human exposure to bisphenol A is a matter of controversy. This review shows a potential risks in workplace resulting from contact with bisphenol A. The work presents the contribution of BPA exposure levels via dermal contact and the relationship between BPA exposure level and oxidative DNA damage.

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1. Introduction

Bisphenols are a group of synthetic chemicals containing two phenolic hydroxyl groups and include some analogues such as bisphenol A (BPA), bisphenol S (BPS), bisphenol F (BPF), bisphenol AF (BPAF), etc.. Bisphenols have been used in the manufacture of polycarbonate plastics and epoxy resins, as well as in daily products including food containers, baby bottles, dental sealants, and paper products (Andra et al., 2015a; Chen et al., 2016). The European Union plays an important role in the improvement of public health, prevention and treatment of diseases, reduction in the number of sources of hazards to human health (Bsoul-Kopowska 2019). According to the recent advancement in toxicology, the European Food Safety Authority reduced the safe level of BPA from 50 µg/kg bw/day to 4 µg/kg bw/day in 2015 (EFSA, 2015). Expanded restrictions on the presence of bisphenol A (BPA) and awareness of the risk of its presence in consumer products causes a constantly increasing demand for products labeled as "without BPA" (Rochester and Bolden, 2015).

Diglycidyl ether of bisphenol A (DGEBA) is one of conventional epoxy resins and has been founded in over 90% of thermosetting epoxy resins worldwide, in a market with a global production currently exceeding 2 million tons per year (Auvergne et. al., 2013). Epoxy resin, as one of the most important thermosetting materials, has been widely used in aerospace, electronics, coating, adhesives and electronic industry due to its lower density, outstanding adhesion and high strength, good durability, excellent chemical resistance (Guzel et al., 2016, Wang et.al., 2010, Tang et al., 2016). The one problem is bisphenol A (BPA) as the precursor of DGEBA possesses the similar structure to estrogens, which has been recognized as an endocrine disruptor. The estrogenic activity of BPA could increase the risk of reproductive disorder and cancer (Ben-Jonathan et al., 2019, Bilancio et. al., 2017, Lim et al., 2018).

It has been estimated the exposure to BPA of the general pollution based on the dermal absorption rate of 27%, reported Biedermann et al., 2010. Compared to the exposure through food intake, this signifies an additional exposure source for the general population and especially cashiers, which warrants further inclusion in the overall risk assessment of BPA.

The aim of the paper is to present the dangers arising from permanent exposure to bisphenols - BPA, BPS, BPF, BPAF and TBBPA exposure and influence for health. In order to

identify the potential risks from BPA and its influence on health, some solutions which reduce the exposure to BPA from thermal paper receipts have been shown. This includes investigating and assessing alternative substance, as well as alternative technologies.

2. BPA and human health

2.1. Endocrine disruption (BPA: an endocrine disruptor, Estrogen receptor pathway)

Changes in endogenous sex hormone concentrations such as estrogens, androgens and gonadotropins in relation to BPA exposure in adults is well documented (Rochester, 2013). BPA has been in commercial use since the 1930s, being used as a synthetic estradiol for women (Jalal et al., 2017). BPA is chemical similar to beta-estradiol (E2). It has the ability to bind with ER receptors alpha and beta (estradiol receptors). However, affinity of BPA to ER receptors is much less that for estrogen. BPA has agonist interaction with ER receptors, but in vitro it has antagonist activities on ER alpha receptor.

Figure 1 shows the metabolism of bisphenol A in the liver and extraction of metabolite.

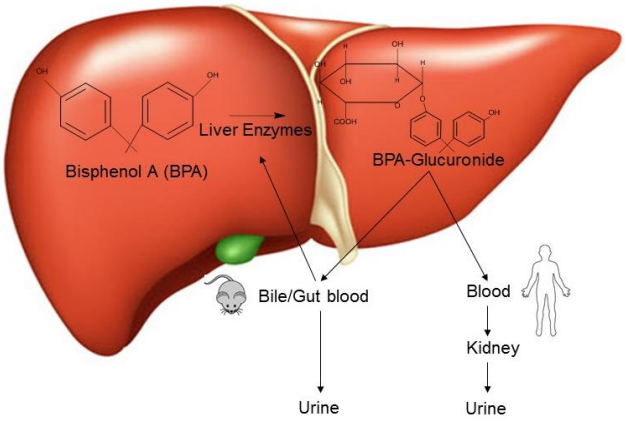

Fig. 1. Outlines the metabolism of unconjugated bisphenol A (BPA) in the liver and excretion of metabolite trough the urine in humans and in rodents

Very low doses of BPA can induce effects close to estrogen, besides disrupting the beta cell function in-vivo. It also promotes activity of estrogen response element in BG-1 ovarian carcinoma cell (type of cancer cell that is highly sensitive to estrogens) (Baldwin et. al., 1998). High dose expedites cell proliferation through ER receptors (Jalal et al., 2017). BPA can be an androgen receptor antagonist, since BPA dose-dependently suppresses transcription activity induced by DHT (dihidrotestosterone is a high androgen derivative of testosterone) (Jalal et al., 2017).

Bisphenol A may cause testosterone reduction. BPA decreased expression of estrogen receptor alpha-mRNA, which might be related to the decreased numbers of Leydig cells (this type of cell is product testosterone and sperm in human male). Thus, BPA directly affects not only the Leydig cells but also the pituitary gland (Nakamura et. al., 2010).

2.2. Metabolic disease - Type-2 diabetes and obesity

Based on the literature (Lee et al., 2018) of the subject it can be observed that there is a correlation between urinary BPA concentrations and biomarkers such as fasting insulin, insulin resistance, and total cholesterol. It shows that BPA might lead to adverse health outcomes, e.g., bad tolerance of glucose. Mechanism of BPA and insulin resistance is not clear. Nevertheless, the role of high estrogen levels in insulin resistance is well known. Therefore, binding BPA to estrogenic receptors could be a one of the pathways (Pjanic, 2017).

Bisphenol A is also positively correlated with insulin resistance in women with polycystic ovary syndrome (PCOS). Another observation of women in reproductive age in Korea shows that higher urinary BPA levels is associated with obesity and insulin resistance (Lee et al., 2018). Also the epidemiological studies have reported relationships between bisphenol A (BPA) and type 2 diabetes (Duan et al., 2018).

Do Minh et al. (2017) and Hu et al. (2017) indicate that BPA level is associated with obesity (Hu et al., 2017). Canadian researcher in 2017 documented that Urinary BPA is positively associated with BMI-defined obesity (Do Minh et al., 2017).

2.3. Cancer

At present, at least three types of hormone-associated cancers can be distinguished: breast, ovary, and prostate. Every type of this cancer is related to estrogens or androgens levels. BPA can increase both types of hormones (Gao et al., 2015). BPA is a synthetic estrogen, thus it can interact with estrogen receptors α and β (Jalal et al., 2017). This reaction leads to changes in cell proliferation, apoptosis, or migration and contributes to cancer development and progression (Ferris et al., 2016; Lama et al., 2019; Nomiri et al., 2019; Shafei et al., 2018).

However, BPA is not only a hormonal problem. It affects a human body on a genetic level in multiple oncogenic signalling pathways (Gao et al., 2015). Serum BPA levels are associated with an increase in mammographic breast density after adjustment for age, body mass index, and other potentially confounding factors in the study of humans. BPA also induced a profile of tumour aggressiveness in high-risk cells from breast cancer patients characterized by a high histologic grade and a large tumour size, resulting in decreased recurrence-free patient survival (Gao et al., 2015; Hafezi and Abdel-Rahman, 2019).

The data show that early life BPA exposure induces/increases prostate lesions in rodent prostate cancer models. Moreover, elevated urinary BPA levels are associated with prostate cancer in humans (Tarapore et al., 2014). Moreover, BPA may also interact with other steroid receptors (such as androgen receptor) and plays a role in prostate cancer development. This type of cancer is highly correlated with high level of DHT (Schatten and Ripple, 2018; Tse et al., 2018; Zhu et al., 2018).

3. Alternative to bisphenol A

Potential alternatives to BPA for use in thermal paper, household application and manufacture were initially identified through literature and internet searches, and focused on chemicals of similar structure and physical/chemical properties. In 2014 the French Parliament published the French Government report on Bisphenol A substitution. This report describes some alternatives to BPA for several practical industries used. Report based on a series of interviews with French industrial players, gathers possible alternatives to BPA. More than twenty bisphenols, among which bisphenols A, S and F seem to be the most widely used.

In Table 1, information on various families of molecules that are the alternatives to bisphenol (isosorbides, polyesters, etc.), or alternatives to materials that require bisphenols, by illustrating them with accurate examples substitution and from concrete practices or experiences in supply chains have been presented (Targaryen, 2010).

Table 1. Application of BPA and alternative materials

Substance	Activity sector	Alternative material	Trade name of the alternative	Developers/Producers
Bisphenol A	Thermal paper	Polymer containing hollow particles	ROPAQUE NT-2900 BLUE 4EST	DOW/KOEHLER
		PHBB ($C_{14}H_{12}O_3$) (Benzyl 4-hydroxybenzoate) (n°CAS : 94-18-8)		
		BPS-MPE ($C_{19}H_{16}O_4S$) (4-Hydroxy-4'-benzyloxydiphenylsulfone) (n°CAS : 63134-33-8)		
		UU ($C_{42}H_{36}N_2O_6S_2$) (Urea Urethane Compound) 321860-75-7		
	Sport and leisure	MABS ((Methyl methacrylate/Acrylonitrile/Butadiene/Styrene)	TERLUX POLYLAC MABS LG MABS	INEOS CHIMEI LG CHEM
	Medical equipment	SBS (Styrene-Butadiene Copolymer)	TERLUX POLYLAC MABS LG MABS	
	Automotive industry	Bio-based polycarbonate made with limonene and CO_2	PLimC	University of Bayreuth ICREA ICREA (Catalan Institute of Research and Advanced Studies) / ICIQ (Institute of Chemical Research of Catalonia)
	Food containers			
	Baby equipment	Copolymer based on styrene and butadiene monomer	TSC-M copolymer	CVI MODERN TECHNOLOGY DEVELOPMENT LTD
	Household appliances	SAN (Styrene/AcryloNitrile [10-28%])	ABSOLAN et LURAN KIBISAN SAN LG SAN TYRIL	INEOS CHIMEI LG CHEM TRINSEO

Bisphenols are named with the common name of the "bisphenols" family to which is added one or more letters symbolizing the reagent or reagents used to achieve the synthesis of the substance under consideration: bisphenol A is, thus, a bisphenol synthesized by reaction of Acetone (A) with phenol. Due to the reprotoxic character ant their potential application (in particular for the manufacture and for the majority of thermal papers), the use of some of bisphenols is regulated in the EU.

In 2017 the Dow and Koehler companies developed of ROPAQUE NT-2900 BLUE 4EST multilayer thermal paper to cover the same applications as conventional thermal paper (receipts, labels, etc.) without the use of chemical developers

such as BPA or BPS. Due to the health risks of BPA, alternative bisphenols, including bisphenol S (BPS), have been widely substituted as alternatives and BPS is now widely used as an alternative to BPA in paper products (Björnsdotter et al., 2017; Liu and Martin, 2019). Both the in vitro and human studies suggested lower percutaneous absorption of BPS compared with BPA, but a lower biotransformation efficiency of BPS should also be considered in its evaluation as a BPA substitute (Liu and Martin, 2019). Unlike common thermal papers, the appearance of the image is caused by a physical reaction rather than a chemical reaction. This thermal paper is composed of three layers: an opaque coating of polymer on the surface, over a coloured intercoat layer and a paper base layer. The polymer contains hollow particles that create pockets of air in the coating to hide the underlying colour layer. When heat is applied to the surface of the paper, it causes the hollow spheres to burst. The opaque coating then becomes transparent in these spots, and the underlying colour layer becomes visible.

The collaboration from the University of Beyreuth, as well from ICREA (the Catalan Institute of Research and Advanced Studies) with ICIQ (the Institute of Chemical Research of Catalonia) developed bio-based polycarbonates made with limonene and carbon dioxide (CO_2). These limonene polycarbonates is the substituted for bisphenol A as a monomer. Limonene can also be synthesized from orange or lemon peels, or from bio-waste generated by the production of orange juice. These bioplastics have better thermal properties than polycarbonates made with bisphenol A. For example, the glass transition temperature of the polycarbonate is higher than that of a conventional polycarbonate. This improved heat resistance allows us to visualize new applications for the material that we could not previously achieve with conventional polycarbonates. Thanks to its heat resistances and transparency, PLimC can be used in a variety of applications: interior coating for food storage containers, moulded parts for interior coatings for food storage containers, moulded part for interior and exterior trim pieces for cars, foams for thermal insulation, adhesives.

TSC-M copolymer is a substitute for polycarbonate in food contact applications. According to the manufacture, this product meets the requirements of the European Union for food contact applications. The TSC-M copolymer is currently used for the manufacture of food containers (milk bottles, sports water bottles, etc.), toys (caps for soap bubbles tubes, car hoods, etc.) and parts for refrigerators.

The alternative substances survey should summarize environmental and health hazard properties and address migration (both theoretically based on physical chemical properties and by analytical migration studies on a few alternative substances).

4. Summary

On the basis of the results from the study, it can be concluded that exposure for a long period of time to low concentration of BPA have influence of estrogen receptor pathway and through this increase the risk of cancer, especially this cancer is related with estrogens or androgens levels (breast, ovary, and prostate). The current literature date suggest that BPA exposure may have significant implications for human health and fertility, especially during development, and in sensitive populations.

BPA is still the most commonly used colour developer in Europe thermal paper receipts. The most frequently used alternative of BPA - ROPAQUE NT-2900 BLUE 4EST. The alternative technologies survey should address technical solutions that fulfil the same purpose as the thermal paper receipt, i.e. to provide documentation for proof of purchase. Identification of possible barriers for implementing new technology and possible mitigation of these should also be addressed.

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确定有害化学试剂对健康的危害-审查工作场所中的双酚

關鍵詞
双酚A
健康风险
有害化学试剂
人类暴露
DNA氧化损伤

摘要
双酚A（BPA）是一种工业化学品，在许多聚碳酸酯塑料和食品用环氧树脂木质素的生产中，用作常规销售热敏纸收据的添加剂。 BPA是异雌激素，这是一种在生物体内并非天然产生的外来化合物，但其作用类似于天然17-β雌二醇（天然雌激素）。由于其雌激素活性较弱，BPA暴露可能影响多种内分泌相关途径，并与前列腺癌和乳腺癌，神经行为缺陷，心脏病和肥胖症有关。此外，BPA可能充当DNA甲基化剂并导致大脑中基因表达的改变。人类对双酚A的暴露是一个有争议的问题。这项审查表明，与双酚A接触会在工作场所带来潜在的风险。这项工作提出了通过皮肤接触BPA暴露水平的贡献以及BPA暴露水平与氧化性DNA损伤之间的关系。