Toxicity of Formaldehyde, Polybrominated Diphenyl Ethers (PBDEs) and Phthalates in Engineered Wood Products (EWPs) from the Perspective of the Green Approach to Materials: A Review

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Adhesives, flame-retardant chemicals, and paints are used in engineered wood products (EWPs) to increase some of the properties of wood. Most of the engineered wood composites, including plywood, particleboard, and fiberboard, used as furniture components contain formaldehyde resins as an adhesive. The International Agency for Research on Cancer (IARC) added formaldehyde to the list of human carcinogens (Group 1) in 2004. Flame-retardant chemicals are semi-volatile organic compounds that can migrate from the products to the air. There are developmental neurotoxic effects from flame-retardant additives, among which polybrominated diphenyl ethers (PBDEs) are commonly used in EWPs. The flexibility and durability of plastics are increased using phthalates, which are a class of synthetic chemicals, by adding them to the polyvinyl chloride (PVC) that is used in the wood-plastic composites (WPC). Formaldehyde, PBDEs, and phthalates are toxicants that are commonly present in value-added furniture products. This review summarized the toxic effects of these chemicals from the aspect of human health and from the perspective of green products.

Keywords: Format; Engineered wood products; Formaldehyde; PBDEs; Phthalates

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INTRODUCTION

Engineered wood products (EWPs) can be used for different purposes in various applications. Wood composite materials are produced as an alternative to solid wood materials and provide some advantages due to both their economy and their various technical advantages. They are mainly preferred in the manufacturing of furniture products used in kitchens, bathrooms, lockers, and other places in houses and offices. The EWP industry has been significantly growing to meet the high production capacity that is a result of new technology and rising living standards. Wood-based materials are economical and easy to process at their beginning. Consequently, wood-based panels are preferred by kitchen and design companies. In addition, they can be easily, quickly, and homogeneously produced in different sizes, and the surface of the products can be layered with different colors and patterns. This property provides diversity for the desired features and aesthetics. Medium-density fiberboard (MDF), hardwood plywood, and particleboard are three types of EWPs (Milner and Woodart 2016). Wood-plastic composites (WPCs), mixtures of wood fibers with plasticizers, are one of the developing areas in the wood industry. Flame-retardant chemicals, formaldehyde-based adhesives, and phthalates are used for enhancing overall product quality and durability. However, these chemicals are also emitted during the production process. Therefore, there is a great health concern associated with furniture manufactured from wood-based materials due to the different chemicals used in their production process.

There has been a decrease in indoor air quality (IAQ) due to the emissions in the indoor air from these compounds in furniture; the IAQ is important for human health. According to the World Health Organization (WHO), human beings spend more than 80% of their lifetime indoors, including living and working spaces (WHO 2000; Weschler 2009). The recent increase in illness frequency, such as allergies and asthma, is being attributed to indoor air pollution. Therefore, the IAQ of residential units and workplaces is a serious concern (Cincinelli and Martellini 2017). Formaldehyde, polybrominated diphenyl ethers (PBDEs), and phthalates are the widely present toxicants in EWPs and WPCs.

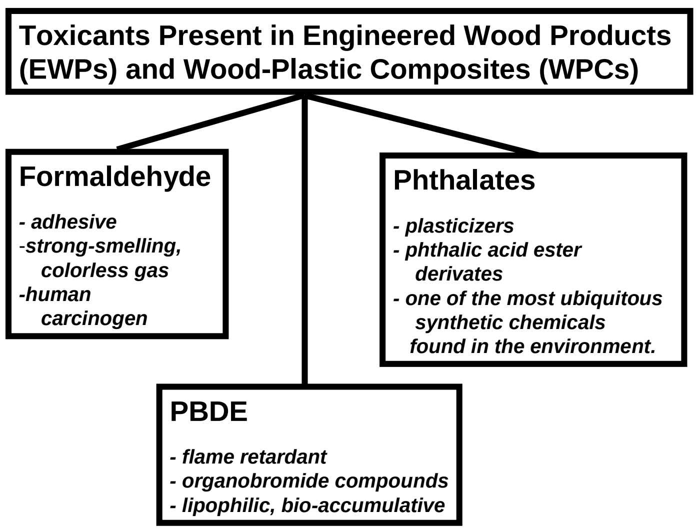

Fig. 1. The widely present toxicants in EWPs and WPCs

At room temperature, formaldehyde is a strong-smelling, colorless gas. Binders for wood composites composed of formaldehyde-based resins were first used between 1900 and 1930. The first particleboard was produced in Bremen, Germany during World War II. It has been used for furniture manufacturing since 1950 as a significant alternative to solid wood. Reports on the adverse health effects of formaldehyde started to be published in the mid-1960s (Salthammer *et al*. 2010). Formaldehyde was studied by the former International Agency of Research on Carcinogens (IARC) Working Groups in 1982, 1987, 1995, and 2004. Formaldehyde was classified as 'probably carcinogenic' to humans prior to 2004. In 2004, the IARC changed its decision on formaldehyde and classified it as a human carcinogen (IARC 2004).

The formaldehyde emission from EWPs and wood buildings is one of the main reasons for poor IAQ. To be able to carry out risk assessment, it is necessary to measure and control the emitted formaldehyde to the indoor air. Various standard test methods include the American ASTMD 5582 (the desiccator method), ASTMD 6007–2, and ASTM E1333 (the environmental chamber method); European EN120 (the perforator extraction method), EN 717–1 (the environmental chamber method), EN 717–2 (the gas analysis method), EN717–3 (the flask method), ENV 13419–2 (the field and laboratory emission cell method), and the Japanese JIS A1460 (the desiccator method) are proposed for measuring formaldehyde emission by the governments (Song *et al.* 2015).

Polybrominated diphenyl ethers (PBDEs) are organobromide compounds. Since the 1970s, PBDEs have been added to EWPs as flame retardants (Vonderheide *et al.* 2008). Approximately 98% of the global market for one of PBDE congeners named penta-BDE was in North America in 1999. Additionally, penta-BDE was added in the US to furniture before 2006. Information on alternatives to penta-BDE was given in a regional survey in the US. Although alternatives are available and used to replace penta-BDE in many countries, their possible adverse effects on the environment and human health should be considered. PBDEs are persistent organic compounds; they are resistance to degradation and have lipophilic, bio accumulative properties. The studies observed the emission of PBDEs from materials that had been treated with PBDE congeners. PBDEs can bind to dust, so they are commonly found in indoor air and dust. Recently estimating PBDEs concentration in indoor dust takes much attention as a marker for making risk assessment. Chromatography-mass spectrometry (GC-MS) has been employed for detecting PBDE congeners and their concentration in dust by many researchers (Fromme *et al.* 2014; Bennett *et al.* 2015; Abafe and Martincigh 2015; Civan and Kara 2016).

Phthalates are a group of chemicals that are used for making plastics more flexible. They were developed in the 1920s, and in 1931 the phthalate industry started to expand with the development of di-2-ethylhexyl phthalate (DEHP). Studies about phthalates on health effects in the human population were first published in the 1970s. After phthalate exposure, the chemical is rapidly metabolized and excreted in urine. Scientists can estimate the quantity of phthalates that have entered bodies by detecting and measuring phthalate metabolites in urine samples. Exposure to phthalates is widespread in the US population according to the findings of the Centers for Disease Control and Prevention (CDC). Based on these findings, the US Consumer Product Safety Commission (US CPSC) proposed new phthalate requirements for children's products in 2008 (US CPSC 2008). Phthalate plasticizers are emitted from the product into the indoor air slowly based on their low volatility properties, because they are not chemically bound to the product materials (Koch *et al.* 2006). In addition, they can diffuse into water, soil, house dust, food, living organisms, and other media, especially in conditions involving heat. Phthalates are major indoor pollutants because they mainly bind to dust particles in the home. Various chamber systems such as the FLEC (Field and Laboratory Emission Cell) (Wolkoff 1996) and CLIMPAQ (Chamber for Laboratory Investigations of Materials, Pollution and Air Quality) (Gunnarsen *et al.* 1993) have been used for detecting the concentrations of phthalates congeners. It is possible to analyze different congeners in the dust by GC-MS (Clausen *et al.* 2002).

This review aims to summarize the chronic (systemic) toxic effects of these chemicals by ingestion or inhalation of the contaminated indoor air from the aspect of human health and the perspective of green products.

CURRENT STUDIES ON FORMALDEHYDE; PBDEs AND PHTHALATES

Chronic Toxic Effects of Formaldehyde Resins

Durable and water-resistant resins are used for gluing together many layers of wood and adhesives during the production of EWPs. Due to their low cost and high performance, urea formaldehyde, phenol formaldehyde, and melamine formaldehyde are used frequently in the wood industry. However, highly toxic formaldehyde is emitted into indoor environments during the production and post-production processes. Generally, the formaldehyde concentration in a normal home environment is 0.02 mg/m^3 to 0.06 mg/m^3 (IARC 2006). Temperature, humidity, ventilation rate, building age, use of the product, presence of flammable sources, and smoking habits affect the formaldehyde level in an indoor environment. The air formaldehyde concentration was found to be higher during the summer compared to winter due to the difference in ultraviolet (UV) light intensity and humidity. Minimal risk levels (MRLs) of inhalation exposure to formaldehyde are 0.05 ppm for acute exposure (14 days or less), 0.01 ppm for sub-chronic exposure (15 days to 364 days), and 0.003 ppm for chronic exposure (1 year or more) (ATSDR 1999). The WHO investigated the health effects of formaldehyde at different concentrations by bringing together all the research data available. Formaldehyde concentrations of 0.1 mg/m^3 and 0.38 mg/m^3 in indoor air are recommended for preventing sensory irritation and eye irritation, respectively, in the general population. The WHO reported that the highest acceptable concentration is 0.21 mg/m^3 to protect human health from long-term effects, including cancer (WHO 2010).

Toxicokinetic properties of formaldehyde

Formaldehyde is produced in all cells as a metabolic intermediate product and is formed during the normal metabolism of glycine, serine, methionine, and choline, as well as the N-, S-, and O-methyl compound demethylation process. The endogenous formaldehyde level is multidimensional (ATSDR 1999). Formaldehyde is easily absorbed orally and *via* inhalation, but the dermal absorption is poor. Endogenous and exogenous formaldehyde, metabolized by formaldehyde dehydrogenase (FDH), is initially converted into formate and CO_2, and then it is excreted in the form of metabolites (Casanova-Schmitz *et al.* 1984). Formaldehyde, which cannot be metabolized by FDH, may form cross-links between single strands of protein and DNA, or it may be incorporated into a single carbon-mediated metabolic pool through binding to tetrahydrofolate. Formaldehyde may react with proteins and nucleic acids in tissues and bind to a single strand chain to form DNA-adduct products (Bolt 1987).

The effect of formaldehyde on the respiratory system

Human exposure to formaldehyde is mainly by inhalation. Formaldehyde has been suggested to show irritant effects resulting from its cross-linking to the cell DNA and proteins and from the precipitation of proteins after exposure by inhalation (ATSDR 1999).

There are conclusions about the impacts of chronic formaldehyde exposure on pulmonary parameters. In two different studies involving 0.34 ppm to 0.40 ppm and 0.1 ppm to 1 ppm formaldehyde exposure in furniture and wood enterprises, respectively, formaldehyde changed some parameters related to respiration in workers (Alexandersson and Hedenstierna 1989; Khamgaonkar and Fulare 1991). These studies showed the reduction in lung functions, such as forced expiratory volume, forced vital capacity, and flow rate. The workers inhaled 0.3 ppm (0.36 mg/m^3) of formaldehyde based on these two studies. Studies on chronic exposure to formaldehyde vapor in workplaces reported similar symptoms as coughing, shortness of breath, and chest tightness (Khamgaonkar and Fulare 1991). It was reported by the Agency for Toxic Substances and Disease Registry (ATSDR) that formaldehyde concentrations below 3 ppm do not greatly affect pulmonary function parameters and do not increase pulmonary hyperreactivity in animals or humans (ATSDR 1999). Researchers explained that because formaldehyde is mainly metabolized in the upper respiratory tract, such as the nasal mucosa, the normal level of formaldehyde exposure in the lower airways is not usually detected. It is reported that formaldehyde, which cannot be metabolized in small amounts, progresses to the trachea, bronchus, and lungs, but its effect is weak (ATSDR 1999). According to animal studies, the lesions in the respiratory system are suggested to be dose-dependent, and formaldehyde toxicity may change with the nasal defense mechanism (Wilmer *et al*. 1987, 1989).

The effect of formaldehyde on the skeletal muscle system

There are studies suggesting that chronic inhalation of formaldehyde in humans may cause mild side effects such as muscle and joint stiffness in the musculoskeletal system (Holness and Nethercott 1989). However, the occurrence of these complaints has not been associated with formaldehyde, and other unknown factors may contribute (Morgan *et al.* 1986).

The effect of formaldehyde on the endocrine system

There is little evidence that exposure to formaldehyde orally, dermally, or *via* inhalation affects the human endocrine system. It was reported in some animal studies that formaldehyde did not have any adverse effects on the endocrine system (Rusch *et al.* 1983; Vargová *et al.* 1993). However, it was found in one study that thyroid tissue weight decreased, triiodothyronine (T3) and thyroxine (T4) levels were reduced, and thyroid stimulating hormone (TSH) levels increased in rats treated with 10 mg/kg and 15 mg/kg of formaldehyde for 30 days. Additionally, it has been reported that thyroid follicle activity increased and T4 synthesis capacity is impaired and may cause atrophy with repeated exposure (Patel *et al.* 2003).

The effect of formaldehyde on the eyes

There are reports of frequent occurrence of eye irritation resulting from the chronic exposure of 0.1 ppm formaldehyde contained in indoor air (Holness and Nethercott 1987; Ritchie and Lehnen 1987).

The effect of formaldehyde on the nervous system

Men exposed to formaldehyde vapor at concentrations of 1 ppm and higher for 5.5 h may display symptoms such as headache and fatigue (Bach *et al.* 1990). Neuropsychological improvement may decrease in those showing deliberate symptoms, such as sleep, seizures, unconsciousness, and coma, following oral exposure to formaldehyde in humans (Eells *et al.* 1981; Burkhart *et al.* 1990; Köppel *et al.* 1990; Marceaux *et al.* 2008). In addition, formaldehyde at non-toxic concentrations has reduced the expression of tyrosine hydroxylase, which limits dopamine synthesis and therefore increases dopamine-like effects (Lee *et al.* 2008). There are considerable toxic effects on the nervous system from exposure to high doses of formaldehyde; however, there may be moderate effects at low doses in long-term exposure. Formaldehyde is predicted to be a possible neurotoxic agent for chronic exposure (Pitten *et al.* 2000).

The effect of formaldehyde on the reproductive system

Low birth weight infants and spontaneous abortions are seen in pregnant women who are exposed to formaldehyde *via* their occupation (IARC *et al.* 2006). Birth defects have been reported in babies of two mothers who were exposed to formaldehyde from household goods (Thrasher and Kilburn 2001). Most of the current epidemiological studies report that formaldehyde in women woodworkers, laboratory staff, and beauticians has delayed conception and increased the risk of spontaneous abortion.

The effect of formaldehyde on the immune system

There is conflicting data on the effects of formaldehyde exposure on the immune system in both humans and animals. Formaldehyde is suggested to cause immune system activation, and Immunoglobulin E (IgE) antibodies specific for formaldehyde were detected after inhalation in a few studies (Dykewicz *et al.* 1991; Wantke *et al.* 2000). In a school's interior air with a formaldehyde level that does not exceed 0.08 ppm, 38% of the children in the 8 years of age group had higher IgE levels (Wantke *et al.* 2000). The number of T and B lymphocytes significantly decreased in those living in furnished houses with formaldehyde release (Thrasher *et al.* 1987).

The effect of formaldehyde on cancer formation

Exposure to formaldehyde increases the risk of cancer in the respiratory tract, colon, skin, bone, prostate, bile duct, liver, kidney, bladder, and lymphatic system (*e.g.*, leukemia and Hodgkin's lymphoma) (Hansen and Olsen 1995; ATSDR 1999; Luce *et al.* 2002; Collins 2004; Collins and Lineker 2004; IARC 2006; Hauptmann *et al.* 2009). Exposure to formaldehyde orally, dermally, or *via* inhalation causes carcinogenic effects in experimental animals (Dalbey 1982; Kerns *et al.* 1983; Rusch *et al.* 1983; Takahashi *et al.* 1986; Iversen 1988; Wilmer *et al.* 1989; Soffritti *et al.* 2002). The IARC classified formaldehyde as a Group 1 carcinogen (human carcinogen) because of the conclusions of the studies (IARC 2004; Cogliano *et al.* 2005). Most importantly, there is enough evidence from animal studies and strong mechanistic evidence from humans exposed to formaldehyde to classify it as a carcinogen (IARC 2004).

Alternatives to Formaldehyde-based Adhesives

Recently limitations have been introduced due to the toxic effects of formaldehyde that have been mentioned above. In many countries, wood composite industries try to reduce and control formaldehyde emissions from the EWPs. All green furniture products, including salvaged, refurbished, or remanufactured furniture products, must not contain formaldehyde in concentrations greater than 50 ppb (RPN 2013).

The aim of these studies was to increase the utilization of environmentally friendly raw materials in the wood-based composite industry to eliminate or reduce the use of urea formaldehyde resin (Sulaiman *et al.* 2013). Kannerth *et al.* (2009) investigated possibly producing particleboard by using animal protein glue. Several researchers have thought to use proteins as binders for hot-pressed boards (Pizzi 2006; Müller *et al.* 2007; Migneault *et al.* 2011; Nikvash *et al.* 2012; Nasir *et al.* 2013; Pizzi 2014; Zhang *et al.* 2015).

Low-emitting resins are not formaldehyde-free, but they can be regarded as a safer alternative. Phenol-formaldehyde is the most common, low-emitting resin that is used frequently for exterior panels and other non-decorative applications. The red-black color of this resin is a disadvantage when visibly used. Additionally, formaldehyde is still emitted in low concentrations and needs proper ventilation to maintain the near-undetectable formaldehyde concentration levels (Emery 1986).

Polymer methylene diphenyl diisocyanate (pMDI) resins are a popular alternative to formaldehyde. These resins contain polyurethanes. The Leadership in Energy and Environmental Design (LEED) recognizes MDI-based materials as "low-emitting;" however pMDI itself has resulted in clear indications of nasal toxicity (US EPA 1998). The EWPs made with MDI cannot be considered natural. Another problem with MDI resins is their considerably high prices.

Soybeans and various types of starches included among the green and environmentally friendly materials could potentially be used to produce composite panels. Several studies examined the use of starch as a binder for hot-pressed boards (Müller *et al.* 2007; Lamaming *et al.* 2013). Corn, potato, rice, wheat, and sago plants can provide starch. The chemical structure of starch, a carbohydrate, can be differentiated by the amylase and amylopectin it contains. Amylase is the linear α-(1→4) linked glucan, and amylopectin is an α-(1→4) linked glucan with 4.2% to 5.9% α-(1→6) branch linkages. The various modifications, such as esterification, etherification, oxidation, and crosslinking of starch, have been evaluated and well-documented (El Mansouri *et al.* 2007). These modifications yield different types of starch, *e.g.*, starch xanthate, dialdehyde starch, carboxymethyl starch, and hydroyethyl starch.

Additionally, researchers have studied the utilization of starch in the biodegradable thermoplastic field in addition to its food industry application. A main concern when using starch in panels is the dimensional stability of the test particleboard samples. Starch is a hygroscopic material even when modified by using glutaraldehyde. The water absorption and thickness swelling of the panels in the study by Amini *et al.* (2013) were unsatisfactory and did not meet the minimum requirements. A main concern when using starch in panels is that the dimensional stability of the sample were unsatisfactory and did not meet the minimum requirements of the JIS A 5908 (2003) standard (Amini *et al.* 2013). Water-repellent materials should be added to improve the dimensional stability of the panels for moisture, or the particleboards produced should be for dry condition usage only. Water absorption and thickness swelling of the samples can be enhanced through heat and chemical treatments. Better dimensional properties of the products can be obtained by using approximately 1% wax by commercial panel manufacturers (Amini *et al.* 2013). The physical and mechanical properties of formaldehyde-free plywood prepared from corn starch-tannin adhesives with phenol-formaldehyde plywood, which has already been commercialized, were compared in a study by Moubarik *et al.* (2010). They used hexamine, a non-toxic aldehyde hardener, for hardening the tannin. This yielded good and comparable mechanical properties for passing the international standards. A combination of lignin and tannin additives has additionally been suggested and has shown promise as wood panel adhesives (Pizzi 1983; Navarrete *et al.* 2010).

One of the newer natural adhesives, oil palm starch (OPS), can potentially be used in the particleboard industry. The use of OPS modified with epichlorohydrin for particleboard production was studied by Sulaiman *et al.* (2013). It can possibly be produced as a green adhesive due to the high starch content in the oil palm trunk (Noor *et al.* 2000). Epichlorohydrin is a colorless liquid that can react with many types of compounds due to the one epoxide ring and one chlorine atom in its molecular structure. A highly resistant starch is formed *via* the modification of starch with epichlorohydrin that could be used as a component for water-resistant adhesives in the paper industry or the food industry (National Toxicology Program 2011). Through the reaction of starch with epichlorohydrin, glycerol is formed by ether linkages between the hydroxyl groups and the cross-links in the starch (Jyothi *et al.* 2007). Particleboards made with OPS with epichlorohydrin met the JIS for mechanical strength (internal bond, modulus of rupture, and modulus of elasticity) compared to those manufactured with native oil palm starch. However, the minimum requirements of the JIS were not met for the water absorption and thickness swelling. Applying wax on the surface of panels can possibly solve this problem. Abuarra *et al.* (2014) suggest that for dry applications, such as indoor furniture, gum arabic could be used as a particleboard binder. Another particleboard adhesive from oil palm trunks could be the bacterially produced natural polyesters, such as polyhydroxyalkanoates (Baskaran *et al.* 2012).

In some recent studies, the utilization of bamboo green was suggested for developing new wood composite panels. Song and coworkers investigated the effect of different bamboo green/wood fiber mixture ratio, different hot-pressing temperature, and hot pressing duration time on the physical and mechanical properties of the composite panels. The optimum ranges were found for these variables as 35% to 49%, 173 °C to 198 °C, and 111 s to 134 s, respectively. It was suggested that over the optimum ranges, raising these values negatively impacted the physical and mechanical properties of the panels (Song *et al.* 2018a,b). Hubbe *et al.* (2018) published a recent review about reconstituted lignocellulose-based materials without the addition of formaldehyde. The hypothesis was that the development of strength is based on links in the chain (molecular contact, mechanical contact, chemical bonding, and structural integrity).

Chronic Toxic Effects of PBDEs

Additives to hinder fire and flames in EWPs, such as PBDEs, have been used. The National Health and Nutrition Examination Survey (NHANES) reported that 100% of the US population has at least one PBDE-type chemical in their blood at detectable levels (Sjödin *et al.* 2014). There are three types of commercial PBDE mixtures: deca-BDE, penta-BDE, and octa-BDE. However, the most commonly used is deca-BDE (Hites 2004; Vonderheide *et al.* 2008). Lower brominated compounds have more bioaccumulative properties than higher brominated compounds. Polybrominated diphenyl ethers release bromine radicals at high temperatures (Hooper and McDonald 2000). The ATSDR has established a minimal risk level (MRL) of 0.006 mg/m^3 deca-BDE for inhalation exposure at an intermediate duration. Problems in the nervous, reproductive, and endocrine systems are the main health problems following PBDE exposure. Due to the developmental toxic effects of PBDEs, children have the highest serum levels of PBDEs (Lunder *et al.* 2010). In addition, they are the most susceptible group because of frequent hand-to-mouth behavior, and they spend time on the floor (Jones-Otazo *et al*. 2005). In December 2009, the main US importer of deca-BDE guaranteed to end production, sale, and import by the end of 2013 (US EPA 2013, 2017). Octa-BDE and penta-BDE have been banned for over 15 years in the EU (EEC Directive 2003/11/EC 2003). On February 7, 2017, the EU Commission published a new regulation to add flame-retardant deca-BDE to the Registration, Evaluation, and Authorization of Chemicals (REACH) Annex XVII restricted substances' list (EU Commission Regulation 227/2012 2017). After March 2, 2019, the substances and mixtures are not allowed to be manufactured or sold in the EU market (EU Commission 2017).

Toxicokinetic properties of PBDEs

Inhalation or ingestion of PBDE-contaminated household dust in an indoor air environment is the main human exposure to PBDE. The PBDEs in humans and laboratory animals are metabolized *via* oxidative hydroxylation and converted to hydroxylated PBDEs. These metabolites are shown to be in human biological fluids and breast milk (Athanasiadou *et al.* 2008; Lacorte and Ikonomou 2009; Qiu *et al.* 2009; Rydén *et al.* 2012; Wang *et al.* 2012; Yu *et al.* 2012; Butryn *et al.* 2015; Caspersen *et al.* 2016; Parry *et al.* 2018). The uptake of PBDEs from breast milk is shown in animal and human studies. Additionally, it was confirmed that PBDEs are transferred across the placenta (Frederiksen *et al.* 2010). The half-lives of PBDEs in humans are much longer than in animals. These differences make it difficult to extrapolate data from animals to humans. However, human studies support a comprehensive understanding that higher-brominated PBDEs are more easily eliminated than the lower-brominated PBDE conjugates. The concentration in the body fluids and the breakthrough rates can vary for different congeners (ATSDR 2017).

The effect of PBDEs on the development of the nervous system

Fetuses and newborns are the most vulnerable to PBDE exposure. Brain development is one of the most sensitive endpoints for PBDE toxicity. Many epidemiological studies show the effect of PBDEs on the developing nervous system in infants (Chen *et al.* 2014; Herbstman and Mall 2014; Ding *et al.* 2015; Donauer *et al.* 2015; Chevrier *et al.* 2016; Martin *et al.* 2017; Vuong *et al.* 2017a,b,c; Gibson *et al.* 2018). A decreased IQ and increased occurrence of attention deficit hyperactivity disorder (ADHD) have been correlated with the PBDE concentrations in infant serum, maternal cord blood, and/or breast milk (ATSDR 2017). Additionally, animal studies and *in vitro* three-dimensional brain models report the development of neurotoxicity, including neurobehavioral changes and altered protein and gene expression levels (Hogberg *et al.* 2016; Dorman *et al.* 2018; Zhang *et al.* 2018). These animal and epidemiologic studies indicate that the development of the nervous system can be a target of concern, especially for lower-brominated PBDE exposure. Although the toxicity of PBDE exposure can potentially affect the development of the nervous system, evidence is too limited to determine the specific neurotoxic effects in adults by both human and animal studies (ATSDR 2017).

It is essential for proper neurodevelopment and healthy brain development in the fetus and early childhood to have thyroid hormones. Thyroid hormones regulate cell migration, differentiation, and proliferation during development; therefore, one of the mechanisms of the developmental neurotoxic effects of PBDEs in children may be related to developing the endocrine system (Jacobson *et al.* 2016; ATSDR 2017). Polybrominated diphenyl ethers have structural similarities to the two major thyroid hormones, thyroxine (T4), and triiodothyronine (T3) (Ibhazehiebo *et al.* 2011). When PBDEs enter organisms, they can replace the thyroid hormones, which can result in hypothyroidism. Severe hypothyroidism (*e.g.,* decreased T3 and/or T4 levels) in young children can lead to many neurological problems, such as poor auditory, fine motor, and executive processing skills, language and memory deficits, and intellectual disabilities (Porterfield and Hendrich 1993; Zoeller and Rovet 2004; Williams 2008). The potential for PBDEs and their metabolites to interfere with thyroid function has been the topic of extensive research in recent years. There are few epidemiological studies on children (Gascon *et al.* 2011; Xu *et al.* 2014). In a study that was conducted in the USA between 2011 and 2012 by Jacobson *et al.* (2016), thyroid hormones were evaluated in serum samples of 80 children (ages 1 to 5) from the southeastern United States. Serum levels of the seven PBDE congeners were also measured in this group. Their results suggest that exposure to PBDEs during childhood sub-clinically changes thyroid hormone function, and the disruption can cause hypothyroidism. There are many animal studies compatible with this study that show a decrease in serums T4 and/or T3 in puppies or other offspring following gestational or lactational exposure to PBDEs (Thuvander and Darnerud 1999; Hallgren and Darnerud 2002; Zhou *et al.* 2002; Stoker *et al.* 2004). According to this data, the developing thyroid can be a target of concern, especially for lower-brominated PBDE exposure.

The effect of PBDEs on the reproductive system

In limited studies, reproductive effects have been reported in men associated with PBDE exposure. Akutsu *et al.* (2008) reported a significant correlation between increased serum HxBDE-153 one of the PPDE congeners concentration and reduced sperm concentration ($r = -0.841$, $p = 0.002$, Fig. 2) and reduced testis size ($r = -0.764$, $p = 0.01$). On the other hand, Albert and co-workers found no associations between human adult exposure to phthalates and sperm concentration (Albert *et al.* 2018). In a prospective cohort study in Michigan and Texas, the altered parameters of semen quality were found to be associated with BDEs (Robledo *et al.* 2015). Exposure to PBDEs during childhood may disrupt the reproductive system development, with the male reproductive system being a target of concern, especially for lower-brominated PBDE exposure in the light of the adequate animal data. However, there is not enough data available to determine whether PBDE exposure in children will cause reproductive function alterations. In contrast, the data for the female reproductive system in human and animal studies is inconsistent (ATSDR 2017).

The effect of PBDEs on cancer formation

The risk of cancer associated with PBDE exposure by inhalation or ingestion has been investigated in many human cohort and animal studies. These studies suggest that there is no evidence in humans and limited evidence in animals for the carcinogenicity of PBDEs (ATSDR 2017). There are limited case-control studies. Hoffman *et al.* (2017) suggested that exposure to flame retardants in the home, particularly BDE-209 and Tris(2-chloroethyl) phosphate) (TCEP), may be associated with the occurrence of papillary thyroid cancer. He *et al.* (2018) reported that exposure to PBDE may play a role in the occurrence and development of breast cancer. The animal studies indicate a significant increase in incidences of hepatocellular adenomas and carcinomas in mice and neoplastic liver nodules in rats ($P \leq 0.01$). (Dunnick *et al.* 2018).

Alternatives to PBDEs

Due to the health concerns of PBDEs and the limitations for manufacturers, there is a growing interest in new, flame-retardant chemicals with inherent flame resistance that do not contain halogen or any additives. Some furniture companies are requesting PBDE-free polyurethane foam from their manufacturers. The Environmental Protection Agency (EPA) published a final report in 2014 titled "An Alternatives Assessment for the Flame Retardant Decabromodiphenyl Ether (DecaBDE)." In this report, the EPA presents detailed hazard information for 29 alternative substances (US EPA 2014). Unfortunately, the long-term fate of these alternative chemicals in the environment is not yet known. It is suggested that halogenated polymer compounds can generate halogenated dioxin and furan during combustion.

Recently, interest in proposing environmentally friendly and safer flame retardants has increased. The development of flame retardants from renewable resources has become more important in the past five years (Sonnier *et al*. 2018).

The German government determined that ammonium polyphosphate, aluminum trihydroxide, and red phosphorus are less problematic in the environment. Inorganic flame-retardant compounds, such as phosphate compounds (*e.g.*, ammonium polyphosphate, di-ammonium phosphate, and melamine phosphate), boron compounds (*e.g.*, boric acid, borax, and boric oxide), nitrogen compounds, and hydroxide compounds, of aluminum or magnesium are thought to be environmentally friendly. During combustion, these inorganic flame retardants do not release dioxins or halogen acids as by-products. Therefore, these chemicals are becoming much more practical due to being safer alternatives in the case of a fire (Sharma *et al.* 2013; Özdemir *et al.* 2017).

The presence of N-P bonds in the phosphate compounds (*e.g.*, di-ammonium phosphate, ammonium polyphosphate, and melamine phosphate) makes them thermally stable. Volatile constituents are formed through the pyrolyzation of nitrogen compounds, and when they reach the gas phase, they act as free radical interceptors. A combination of phosphorus and nitrogen, compared to only phosphorus compounds or nitrogen compounds, can provide strong flame retardancy. During combustion, the nitrogen and phosphorus combination covers the outer layer of the substrate with a nonflammable char (Jin *et al.* 2017).

Boron salts are used as the major non-fixing flame retardant for wood products. They are water-soluble, and the water evaporates after treatment, leaving the salts inside of the wood material. Boric acid acts *via* both physical and chemical mechanisms to impart flame resistance. Physically, boric acid is formed by boron derivatives and first prevents oxygen diffusion, then it prevents the exothermic combustion reactions from propagation. Chemically, boric acid increases the amount of char formed on acid-catalyzed dehydration reactions during wood pyrolysis (Yu *et al.* 2017). Compounds containing boron act with an endothermic, stage-wise water release. When these compounds are heated, the mixture dissolves in its own water of hydration. Then, it swells to form a frothy substance before losing water and finally fusing into a clear melt. Adequate protection is given to cellulosic elements with this treatment system in protected non-ground contact situations. Flame retardants containing boron have been developed as alternatives to traditional flame retardants (*e.g.*, antimony oxide) because they are cheaper and less toxic. Another flame retardant used frequently is zinc borate. It produces non-volatile products in the presence of flame, promotes char formation, and releases water (Sharma *et al.* 2013; Jin *et al.* 2017; Terzi *et al.* 2018). The primary toxic health effect associated with inhalation exposure of humans to boron compounds is acute respiratory irritation in short exposure durations (up to 47 min) (ATSDR 2010). On the other hand, boron compounds were classified as toxic to reproduction (Cat 2) by the European Union, which means that they may impair fertility and may cause harm to the fetus. This classification based on the oral animal exposure studies (SCCS 2010).

Chronic Toxic Effects of Phthalates

There is a mixture of wood, thermoplastics, and some additives in WPCs with a wood content between 50 wt% to 80 wt% (Clemons 2002). Recently, wood fiber reinforced polyvinyl chloride (PVC) has become more popular due to its acceptable mechanical properties, long lifetime, moisture and fungus resistance, recyclability, and wood-like surface performance (Clemons 2002). PVC is suggested as a thermoplastic resin to urea-formaldehyde due to the adhesive properties (Song *et al*. 2017). PVC is not a thermally stable polymer, but dimethyl phthalate can be used to add thermoplasticity to the wood. Phthalates are a class of synthetic chemicals commonly used in various consumer products to increase the flexibility and durability of plastics by adding it to PVC. In addition, they are popular due to their relatively low cost, low volatility, and ability to create elastic materials. There have been concerns about their effects on the environment and human health since the early 1980s. Currently, phthalates are one of the most ubiquitous synthetic chemicals found in the environment. Over 11 billion pounds of phthalates are annually produced worldwide. Phthalates are derived from phthalic acid esters. The seven phthalates extensively used in consumer products are benzyl butylphthalate (BBP or BzBP), dibutyl phthalate (DBP), di-(2-ethylhexyl) phthalate (DEHP), diisodecyl phthalate (DIDP), diisononyl phthalate (DINP), dinoctyl phthalate (DnOP), and di-n-butyl ppthalate (DnBP) (The Lowell Center for Sustainable Production 2011). Different phthalate esters have different uses due to their different chemical and physical properties. Most of the DEHP and BBzP produced are used in PVC products, *e.g.*, PVC flooring. The DnBP is widely used as a plasticizer in cellulose plastics, in latex adhesives, and as a solvent for certain dyes (Bornehag *et al.* 2005)

Exposure to phthalates has been associated with several adverse human health effects. They can impact the fetus developing *in utero* by crossing the placental barrier. Values can reach as high as 70 μg/kg per day for daily intake of phthalates (Net *et al.* 2015). Many phthalates are classified as reproductive and developmental toxicants, and they may also have effects as endocrine disrupters. The US EPA classifies BBP and DEHP as possible and probable human carcinogens, respectively. However, their toxicity varies depending on the structure of phthalate (US EPA 2012).

Toxicokinetic properties of phthalates

The inhalation of a contaminated indoor air environment and the ingestion of contaminated food during packaging are the main human exposures to phthalates. In addition, young children are exposed to phthalates through childcare products, teething toys, and other products containing phthalates. Studies suggest that there is 100% oral absorption because phthalates, such as DEHP and DINP, can dissolve in saliva and become absorbed during mouthing teething (Müller *et al.* 2003). The main metabolites of phthalates are DEHP, monobutyl phthalate (MBP), mono-benzylphthalate (MBzP), mono-(3-carboxypropyl) phthalate (MCPP), mono-ethylphthalate (MEP), mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono-(2-ethylhexyl) phthalate (MEHP), mono-(2-ethyl5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono-isobutyl phthalate (MiBP) (Frederiksen *et al.* 2007). Higher lipophilic compounds have long alkyl chains and can easily enter body systems (Koch *et al.* 2004, 2005, 2012, and 2013; Koch and Angerer 2007; Koch and Calafat 2009; Leng *et al.* 2014). Glucuronidation helps phthalate metabolites to be excreted *via* urine (Silva *et al.* 2003; Samandar *et al.* 2009).

The effect of phthalates on the liver system

According to a study by Ganning *et al.* (1984), phthalates change the function and structure of the liver. Phthalates can induce mitochondria, enzymes, and peroxisomes that participate in β-oxidation and fatty acid transport (Ganning *et al.* 1984). The prolonged administration of phthalate esters causes an accumulative effect on the liver (Ganning *et al.* 1987; Beliles *et al.* 1989).

The effect of phthalates on the reproductive system

Certain phthalates are reproductive toxins in the male groups of animal studies, but the human studies are more limited. In a human study, an inverse association between urine MBP levels and sperm motility and concentration was reported among 168 men (Duty *et al.* 2003). This result was confirmed in a follow-up study that included an additional 295 men (Hauser *et al.* 2006). In another study, workers were exposed to high concentrations of DEHP and DBP in a PVC flooring plant. The levels of these phthalate metabolites in urine samples were inversely associated with free testosterone levels, which means a high urine metabolite level results in decreasing free testosterone levels (Fong *et al.* 2015). In a case-control study, a female group that was diagnosed with endometriosis (n = 92) between 1996 and 2006 was compared with a population-based control group (n = 195) in the Pacific Northwest of the US. Endometriosis is a hormonally mediated disease among reproductive-aged females. In this study, urine phthalate metabolite concentrations measured in the cases and in population-based controls showed that exposure to phthalates might increase the risk of endometriosis (Upson *et al.* 2013).

The effect of phthalates on the endocrine system

It was demonstrated that phthalates can affect the thyroid signaling system in experimental animals, but the human studies with adults remain limited. In a human study conducted at the Massachusetts General Hospital between 2000 and mid-2004, the urine MEHP levels among 408 men were inversely associated with free T4 and total T3, but not TSH (Meeker *et al.* 2007). In girls and women, phthalate exposure is additionally associated with altered thyroid function (Meeker and Ferguson 2011).

The effect of phthalates on the development of the endocrine system

The relationship between the urine concentration of seven different phthalates and thyroid hormones was investigated in a cohort study on children. No association was found between the urinary phthalate metabolites and TT_4, FT_4, and TSH in boys. However, a significant negative association was found between T_3 and phthalate metabolites in girls ($P< 0.05$). In 845 children (both girls and boys), a significant inverse association was found between the urinary phthalate metabolites and TT_3 and FT_3 ($P<0.05$) (Boas *et al.* 2010). Additionally, DEHP is significantly related with insulin resistance in Mexican American adolescents ($P<0.02$) (Trasande *et al.* 2013). In a cohort study of participating mothers and children (n = 345) at the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS), the 10 urinary phthalate metabolite concentrations were measured twice in the mothers during pregnancy and in their children between 5 and 12 years of age as well. According to their results, exposure to certain phthalates *in utero* is associated with the risk for childhood obesity and increased BMI during childhood (Harley *et al.* 2017).

The effect of phthalates on the development of the nervous system

Higher levels of DEHP, DBP, and BBzP have been found in the urine samples of children. Children throughout the world are exposed to phthalates and therefore are at risk. For example, DBP is strongly associated with ADHD (Garner *et al.* 2013). Additionally, urine phthalate metabolites (*e.g.*, MMP, MEP, MBP, MBzP, MEHP, 5-oxo-MEHP, and 5-OH-MEHP) are related to a decrease in neurocognitive functions and intelligence through postnatal exposure (Sathyanarayana *et al.* 2008). One study suggests that DEHP metabolites can impact attention deficit disorder (ADD), and that girls are effected by both

ADD and learning defects more than boys (Diamond 2015). In addition, DEHP metabolites are shown to be related to autism (Testa *et al.* 2012).

Alternatives to Phthalates

Several compounds, including citrates and phosphates, have been identified as alternatives to phthalates. However, the potential effects of these alternative plasticizers on human health and the environment have not yet been studied thoroughly. These compounds are not chemically bound to polymers and can be emitted from the products into the air. Some of these plasticizers may cause eye, skin, and respiratory irritation. However, most of the data are from animal studies. The studies are new, and only a few epidemiologic studies have been conducted on these materials; thus, it is hard to predict their long-term health effects. The animal studies show that these materials can have toxic effects on the kidneys, liver, spleen, testes, and uterus, meaning that phthalate-free WCPs are not considered safe (Van Vliet *et al.* 2011).

Recently, the technology for using natural-based plasticizers has rapidly grown due to their low toxicity and low accumulation properties. This group of plasticizers contains epoxidized triglyceride vegetable oils from linseed oil, soybean oil, sunflower oil, castor oil, or fatty acid esters (Baltacioglu and Balkose 1999; Pedersen *et al.* 2008). Researchers and industries have increased their work to develop new, bio-based materials from renewable and biodegradable sources. This is related to the search for natural-based plasticizers to reduce the use of conventional plastic products (Vieira *et al.* 2011). Bioplastics are sourced from bioresources (*i.e.*, a renewable resource) and/or are biodegradable. Among the different bioplastics, polyhydroxyalkanoates (PHAs) have received considerable attention as new biopolymers due to their high functionality. In addition, they are truly biodegradable and are non-toxic to the environment (Vandi *et al.* 2018). They are microbiologically produced, and the choice of substrate, bacteria, and fermentation conditions determines their material properties, ranging from rigid thermoplastics to stretchy elastomers (Dietrich *et al.* 2017). For the manufacture of WPCs, PHA biopolymers are considered particularly suitable. Initial developments on wood-PHA composites indicate that properties like commercially available PVC-based WPCs are feasible (Chan *et al.* 2016, 2017, and 2018). The use of naturally based polymer films depends on several parameters, including mechanical properties such as resistance to water, barrier requisites (*e.g.*, water vapor), O_2 and CO_2 permeability, flexibility and strength, optical quality (*e.g.*, gloss and opacity), and other issues like cost, functional attributes, and availability.

CLOSING COMMENTS

The emission of formaldehyde, PBDEs, and phthalates from wood-based building products and EWPs is one of the main reasons of poor IAQ. There are various test methods and mathematical methods used for estimating the emission. These calculations are required for making risk assessment. If we can capture the relevant information about exposure assessment, then we may be able to utilize the knowledge to predict the possibility of toxicity.

The use of these chemicals, which are associated with health and environmental concerns, can be minimized by using green alternatives that require fewer or no chemicals using some surface modification techniques and by using natural-based adhesives or bio-plasticizers that have a lower toxicity. This approach recently has motivated research on the development of natural-based EWPs in various academic and industrial areas. The use of low-toxicity EWPs has become more attractive. However, both the mechanical and physical properties of natural-based EWPs still need to be improved.

As stated for flame-retardant compounds, alternatively produced chemicals may not always be safe, especially with long-term exposure. Regulations for these chemicals should be reevaluated by considering the toxic effects.

The production and consumption of MDF and particleboard that contains formaldehyde resin is quite common in both developing and undeveloped countries. This situation causes health concerns, especially in children and adults. The use of green alternatives in place of these preferred products will be an important step in the protection of public health.

Children are more susceptible to the toxic effects of chemicals that are used in EWPs. Long-term exposure to these chemicals during fetal and child development may cause permanent alterations in the nervous system, endocrine system, and reproductive system.

The amount of toxic chemicals in recycled products is increasing during the recycling processes for EWPs and WPCs produced by traditional methods. Green products are a good alternative to avoid this situation. One solution is using recycling processes in the furniture industry.

There are many parameters that are affected by the mechanical and physical properties of naturally based EWPs. These parameters are classified into four classes and called "links" by Hubbe *et al.* (2018). By changing these parameters, it is possible to manufacture natural-based EWPs that meet the requirements stated in international standards.

In the future due to environmental and toxicological concerns will become increasingly important, and the production and usage of green alternatives to these chemicals will rapidly increase.

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