



Brominated flame retardants, a cornelian dilemma

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Introduction

Dying immediately in flames or from poisoning in the long run is the cornelian dilemma induced by the use of brominated flame-retardants. Indeed, these compounds have been intensively used to slow down fires in houses and buildings, thus increasing escape time from about 2 min to 20 min. They were initially thought to be safe, notably because their adhesive properties make them unlikely to reach human tissues. However, recent research has disclosed that brominated flame-retardants are developmental neurotoxicants that trigger neurodevelopmental deficits in young children (Gray and Billock 2017) (Fig. 1). Since infants and young children have been exposed to brominated flame-retardants since the early 1970s, we are now observing the long-term developmental impact of this 50-year-old ticking time bomb. Here we discuss the occurrence of brominated flame-retardants, exposure at home, neurodevelopmental diseases and alternative flame retardants.

Industrial products

Brominated flame-retardants are industrial chemicals used to reduce the risk of fatal fire injuries (Ryan and Rawn 2014). They are extensively incorporated into consumer products such as domestic insulation, carpets, electronic devices, clothes, toys, and plastic products. They inhibit fire ignition or slow down the speed of fire combustion, and, consequently, they reduce the risk of fire-injury and property damage. Brominated flame-retardants belong to a wide family of more than 175 different flame retardants (Birnbaum and Staskal 2004). They occur in building materials worldwide and are still incorporated in many new materials (Frederiksen et al. 2009; Malliari and Kalantzi 2017).

Brominated flame-retardants are particularly abundant indoors. For instance, electronics and furniture contain polybrominated diphenyl ethers, circuit boards contain tetrabromobisphenol A, and polystyrene building materials contain hexabromocyclododecane. These three compounds are predominant both in indoor dust and in human tissues (Frederiksen et al. 2009). Hexabromocyclododecane has not been imported in the USA since 2018 (USEPA 2020). In Europe, hexabromocyclododecane and polybrominated

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Fig. 1 Brominated flame-retardants are synthetic chemicals incorporated in a wide variety of products such as plastics, textile and electric equipment, to make them less flammable. Once thought to be safe, there is now growing concern on their toxic effects because they occur widely in natural media



diphenyl ethers are strictly controlled by legislation and import restriction, both in marketable goods and in waste (Sharkey et al. 2020a). Tetrabromobisphenol A is still used in manufactured products in Europe and only regulated at concentration above 0.1%. Implementating a new regulation in Europe could be an effective method to reduce the release of tetrabromobisphenol A in the environment (Lucattini et al. 2018; Malkoske et al. 2016).

Electronics and textile are major contributors of brominated flame-retardants in the environment. Here, the three largest producers of e-waste worldwide are the European Union with 10.07 million tons (Mt), China with 7.21 Mt and the USA with 6.3 Mt, which are also global leaders as manufacturers and exporters of textile (Sharkey et al. 2020b). In the Middle East, Australia, and Africa, levels of brominated flame-retardants are usually low in indoor spaces (Malliari and Kalantzi 2017).

Exposure at home

Indoor air quality is a major source of concern in health risk assessment (Azuma et al. 2020). Indeed, indoor air is much more polluted than the outdoor atmosphere. As a consequence, opening windows regularly is recommended to evacuate airborne contaminants. In sharp contrast, during the previous decades, many residences were almost sealed to save energy, e.g. to avoid heating loss. This has highly reduced air exchange with the exterior, thus increasing the concentration of pollutants. Breathing indoor gases and

airborne particulate matter are therefore a major source of inhaled or ingested exposure (Koivisto et al. 2019). Recently, pollutant exposure further escalated during the coronavirus disease 2019 (COVID-19) pandemic due to people lockdown and rising teleworking (Moretti et al. 2020). Today, we spend approximately 80–90% of our time indoors, thus getting exposed to both indoor contaminants, and outdoor contaminants that enter homes and buildings via ventilation (Hussein et al. 2013). Remarkably, this exposure to mixtures of several chemicals induces adverse health effects in an additive or even supra-additive way (Lucattini et al. 2018).

The concentration of brominated flame-retardants, to which we are exposed indoors from dust particles, exceeds in general that of outdoor air (Fromme et al. 2014; Harrad et al. 2010; McGrath et al. 2018; Ni and Zeng 2013). Exposure mainly occurs through ingestion of foodstuff and inhalation of dust and airborne particles, increasing the body's burden of internal brominated flame-retardants. Health concerns have arisen following the detection of some brominated flame-retardants released into the indoor environment and subsequently taken up into human tissues (Birnbaum and Staskal 2004; USEPA 2020). Due to their persistence in the environment and their lipophilic properties, polybrominated diphenyl ethers and hexabromocyclododecane accumulate in lipidic tissues (Rivière et al. 2019; Sharkey et al. 2020a). Children are particularly exposed to brominated flame-retardants because of their hand-to-mouth behaviour and their playing on dusty grounds (Landrigan et al. 2004). Indeed, dust ingestion is the main route of exposure in children followed by indoor air inhalation and dermal contact.

High risk for children's brains

There is growing evidence that human sensitivity to brominated flame-retardants changes at different life stages (Street et al. 2018). In particular, the toxicity of brominated flame-retardants may induce diseases a very long time after initial body contamination. In other words, an adult disease may result from foetal exposure (Grova et al. 2019). This phenomenon is rather similar to the poorly-explored phenomenon of 'pollutant resurrection' whereby some pollutants stay trapped as bound residues in complex media, e.g. soils, then are liberated years later to induce a second wave of toxicity (Charles et al. 2021). The early-life window of susceptibility of 1000 days between the child's conception and the age of two years old is crucial in the development of health and diseases because major changes occur during this time period in gene expression by epigenetic modifications as the infant develops (Barker and Osmond 1986). Therefore, pollutant exposure may modify epigenetic mechanisms and, in turn, implement changes that will cause adult diseases. When development is disrupted during organogenesis, there is no 'going back' and the damage becomes irreversible.

The brain is probably the most sensitive of all organs during development. For instance, exposure to polybrominated diphenyl ethers is estimated to be responsible for a cumulative loss of 162 million intelligent quotient points in American children from 2001 to 2016 (Gaylord et al. 2020). This loss is higher than that of well-known neurotoxins such as lead, mercury and pesticides. Brain development is a lifelong process starting with fertilization and continuing throughout life. In contrast to many other tissues, there are critical periods of brain sensitivity during pregnancy, the post-natal period and the first 3–6 years of life where synaptic plasticity, neurogenesis, neuronal differentiation, myelination, migration, synaptogenesis and apoptosis occur in a tightly-controlled schedule (Rice and Barone 2000). In particular, during neurogenesis, neuronal differentiation and synaptogenesis take place before birth, myelination and synaptic plasticity continue from childhood to adulthood (Lenroot and Giedd 2006). As a consequence, pregnant women, neonates, infants and young children are particularly sensitive to brominated flame-retardants, which may lead to neurodevelopmental disorders such as autism spectrum disorders and attention-deficit hyperactivity disorder (Grova et al. 2019). Pollutant-induced alteration of foetal germ cells in utero and gametes in later life may also induce transmission of the latent disease to the next generation. Thus, even though correlations between brain disorders and exposure to brominated flame-retardants are difficult to assess with absolute certainty, notably due to the presence of other

pollutants, research should decipher the mechanisms of neurodevelopmental disorders induced by brominated flame-retardants.

Autism spectrum disorders

Neurodevelopmental diseases such as the autism spectrum disorder have dramatically increased recently, of 38.3% from 1997 to 2017 (Zablotsky et al. 2019). This disorder induces a deficit in communication, struggles with social interactions, poor interests, and repetitive behaviours that appear early in life (Cattane et al. 2018; Roux and Bossu 2016). One per cent of individuals are affected by autism spectrum disorder in France (Ha et al. 2020). In the USA, the disorder for children rose from 1 out of 166 in 2004 to 1 out of 59 in 2018 (Baio et al. 2018). The disorder is probably due to a disruption in brain development, with a prevalence 3–4 times higher in boys than in girls. Research on hereditary and genetic components has disclosed more than 400 genes associated with autism spectrum disorders (Bourgeron 2015; Chaste and Leboyer 2012; Roux and Bossu 2016). Epigenomic analyses suggest that methylation-dependent transcriptional regulation is a driver in the aetiology of autism spectrum disorders (Tremblay and Jiang 2019). There is now a clear and pressing requirement to define the precise role of gene-environment interactions in autism spectrum disorders.

Exposure to chemical pollutants contributes to the aetiology of autism spectrum disorders (Grova et al. 2019; Kalkbrenner et al. 2014). Brominated flame-retardants are suspected to disrupt the thyroid axis, the oxidative stress system, immune response, and neuroinflammation (Hertz-Picciotto et al. 2011; Messer 2010). Hexabromocyclododecane disrupts the thyroid system in humans and other animals, and is a substance of concern for foetuses, new-borns exposed by breastfeeding, and children exposed via food and dust ingestion (Chain et al. 2021; ECHA 2019; Kim and Oh 2014). Pre-clinical early-life models confirm the toxicity of hexabromocyclododecane for the developing brain (Fernandes et al. 2021; Maurice et al. 2015). Epidemiological data suggest that in utero exposure to hexabromocyclododecane induces modifications in motor skills, attention span and metabolism (Roze et al. 2009). Nonetheless, a recent study failed to validate this hypothesis for children aged 18 months, born in mothers with a median blood hexabromocyclododecane level of 0.82 ng/g of lipids (Goodman et al. 2020).

Perinatal exposure to hexabromocyclododecane at realistic doses induced behavioural deficiencies including anxiety, locomotion and sexual activity in rats, from the age of 4 weeks until adulthood (Maurice et al. 2015). Hexabromocyclododecane exposure may induce neurodevelopmental disorders through the regulation of DNA methylation. For

instance, 6-methyl adenine modifications have been linked to phenotypic diseases such as tumorigenesis (Xiao et al. 2018). This methylation increases with chronic stress in mice's prefrontal cortex (Yao et al. 2017). Another study suggests a potential overlap between genes that show dynamic changes in 6-methyladenine expression and genes that are involved in the onset of neuropsychiatric disorders (Armstrong et al. 2019).

Demonstrating the mechanisms underlying the developmental neurotoxicity induced by hexabromocyclododecane, especially the role of DNA methylation and other epigenetic processes, should help in understanding the pathophysiology of autism spectrum disorders and identify future therapeutic research lines. Further research is required to understand the mechanisms by which certain brominated flame-retardants could act as a factor of susceptibility in the aetiology of autism spectrum disorders. This will help in developing safer alternative products.

Alternative flame retardants

In 2017, 120,000 people died and 9 million were injured in heat-related incidents, with higher death tolls of children and the elderly (James et al. 2020). Moreover, the proportion of flammable materials in new products has increased and, in turn, has reduced the time available to escape a blaze to 3–6 min, and the time to flashover, i.e. the time when a fire is no longer controllable, to less than 20 min. Flame retardants therefore remain essential for building materials and furniture. Historically, organochlorines were used until evidence of their persistence, accumulation and toxicity. In the 1970s organochlorines were replaced by brominated compounds such as polybrominated diphenyl ethers, tetrabromobisphenol A and hexabromocyclododecane, which are still currently incorporated into furniture, textile, children's products, building materials and electronics. Nonetheless, from the early 2000s, the use of all organohalogenated flame retardants has declined due to mounting scientific evidence on their toxicity. Three polybrominated diphenyl ethers were banned in 2009 and 2017 by the Stockholm convention, and hexabromocyclododecane is currently under scrutiny.

Organophosphate flame retardants have started to replace polybrominated diphenyl ethers, but recent research has disclosed toxicity at exposure levels currently reported in biota and humans (Blum et al. 2019). The incorporation of a brominated styrene-butadiene copolymer into polystyrene has been developed as an alternative to hexabromocyclododecane. This copolymer is more stable, inert and shows little to no bioavailability in environmental matrices, yet the sole published toxicological data are that of the manufacturer and the US-EPA report, which indicates a lack of acute toxicity genotoxicity, sensitization and irritation, and ecotoxicology

after only 28 days of exposure (Beach et al. 2013). Hints of possible toxicity come from the fact that the brominated styrene-butadiene copolymer is synthesized from styrene and butadiene, which are known for their neurotoxic and developmental toxicity (Khalil et al. 2007).

Sustainable alternatives include glass or mineral fibres of very low organic content, which therefore do not release toxic fumes. Sandwiching a polystyrene or polyurethane layer with steel, aluminium, or mineral layers is an alternative to limit contamination and maintain insulation. The use of non-combustible interliners in aircraft seats is also very effective in reducing post-ignition fire spread and development in upholstered furniture. Last, intumescent coating systems are deposited on steel or timber surfaces to inhibit ignition and flame propagation. These coatings are made by incorporation of carbon, ammonium polyphosphate and melamine in a paint that forms a blown char when heated (Camino et al. 1989).

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Declarations

Conflict of interests All the authors declare that they have no known conflict of interest.

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