Environmental Science and Pollution Research (2023) 30:9271–9289
https://doi.org/10.1007/s11356-022-24538-9

REVIEW ARTICLE

The role of polybrominated diphenyl ethers in the induction of cancer: a systematic review of insight into their mechanisms

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Received: 4 September 2022 / Accepted: 25 November 2022 / Published online: 5 December 2022

Abstract

Environmental pollution caused by persistent organic pollutants (POPs) has increased the challenge for the scientific communities. Polybrominated diphenyl ethers (PBDEs), classified as POPs, are widely applied in various materials as brominated flame retardants (BFRs). Because of the nature of these chemical compounds including toxicity, stability, and capability to bioaccumulate and biomagnify, PBDEs have posed a great challenge and risk to human health and wildlife. Therefore, the side effects of exposure to PBDEs as ubiquitous pollutants in the environment on cancer progression were investigated using a systematic review (SR) survey. To achieve this goal, forty studies were considered after defining the search terms and inclusion criteria, and/or exclusion criteria; the eligible records were collected from the international bibliographic databases. Based on the findings of the reviewed records, environmental exposure to the BFRs including PBDEs has a positive association with different mechanisms that induce cancer progression. However, the findings of the reviewed studies were not totally consistent with the mode of action and side effects are yet to be fully elucidated. Several articles have reported that BFRs can be carcinogenic and induce epithelial to mesenchymal transition via different mechanisms. The main mode of action involved in the environmental exposure to BFRs and the risk of cancer progression is endoplasmic reticulum and oxidative stress (OS). Generally, the imbalance of antioxidant mechanisms, reactive nitrogen species (RNSs) and reactive oxygen species (ROSs), during damage in cells, and stress caused OS, which increases tumorigenesis via multiple mechanisms, such as DNA damage, inflammation, and angiogenesis.

Keywords Polybrominated diphenyl ethers · Persistent organic pollutants · Oxidative stress · Brominated flame retardants · Cancer progression · Environmental exposure

Responsible Editor: Ludek Blaha

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Introduction

Nowadays, environmental pollution caused by persistent organic pollutants (POPs) has increased the challenge for scientific communities. POPs are defined as highly toxic chemical compounds, persistent in the environment, capable of bioaccumulating and biomagnifying. They are used in various applications such as manufacturing processes, agriculture, and industry. POPs are considered the endocrine disrupting compounds (EDCs) and, therefore, deteriorating the functional organs of the human body and wildlife (Zhao et al. 2009; Liu et al. 2017; Jaafarzadeh et al. 2019; Park et al. 2020; Mirzaee et al. 2021a, b).

Brominated flame retardants (BFRs) and their subgroup polybrominated diphenyl ethers (PBDEs) as organobrominated compounds are considered a broad group of "additive" materials to prevent the growth of fire in industrial, chemical, and household products, including construction materials, polyurethane foams, textiles, electronic devices, plastics, among others, during the last decades (Li et al. 2012; Liu et al. 2017; Wu et al. 2021). The PBDE compounds are additive materials; therefore, they are not link to their polymers by chemical reactions. Thus, they easily leach to various environmental media, and recently, these compounds have become important and widespread environmental pollutants (Costa and Giordano 2014; Huang et al. 2020). It is estimated that about 600,000 metric tons of flame retardants are produced in the globe annually. From this amount, 150,000 tons and 60,000 tons are brominated and chlorinated compounds, respectively (Darnerud et al. 2001).

The general characteristics of PBDEs or their congeners were depicted in Table 1 (Darnerud et al. 2001; Siddiqi et al. 2003; Costa and Giordano 2014; Huang et al. 2020; Wu et al. 2021). Due to their nature and physicochemical characteristics including their toxicity, capability of bioaccumulating and biomagnifying, and persistence in the environment, some of them such as hepta-, deca-, hexa-, tetra-, as well as penta-BDEs were categorized as POPs at the Stockholm Convention in 2009 and 2017 (Convention 2009, 2017). Despite the production and use of POPs, including PBDEs, were banned in the 1970s, environmental exposure to low concentrations of these chemical compounds continues. One of the most important environmental exposure to these type of compounds is the e-waste disassembly sites in the solid waste management section especially via solid waste incinerators (Agrell et al. 2004; Zhao et al. 2009; Wang et al. 2010). Regarding the characteristics of PBDEs, their use and their congeners were restricted; the evidence confirmed that due to the presence in different environmental media and products, the side effects of PBDEs or their congeners can be seen on the environment, human body, and wildlife (Table 2) (Siddiqi et al. 2003; Agrell et al. 2004; Kim et al. 2005; Wang et al. 2010; Ni et al. 2013; Park et al. 2020; Wu et al. 2021).

The mechanisms and mode of actions involved in the detrimental impacts of PBDEs are not completely known. Several pieces of evidence reveal that PBDEs or their congeners can disrupt endocrine system and induce toxic side effects, including neurotoxicity, estrogenicity, reproductive disorders, carcinogenicity, and teratogenicity. It is reported that the EDC potential of PBDEs may react as agonists or antagonists at estrogen, androgen, and progesterone receptors and change the reproductive function of rats (Meerts et al. 2001; Legler and Brouwer 2003; Li et al. 2012; Tian et al. 2016; Liu et al. 2017; Cao et al. 2018; Wei et al. 2018). Some of these compounds are responsible for DNA damage via reactive oxygen species (ROS) generation pathway (Pellacani et al. 2012; Montalbano et al. 2020). Recently, Leonetti et al. revealed that the sensitivity of total thyroid hormone sulfotransferases activity in placental cells exposed to brominated flame retardants occurs through unknown mechanisms (Leonetti et al. 2018). Hoffman et al. concluded that more studies are needed on exposure to some congeners of flame-retardant compounds, such as deca-BDE-209 could be related to progress of papillary thyroid cancer, not only its occurrence but also its severity (Hoffman et al. 2017). In another research, it was demonstrated that simultaneous exposure to some of the PBDEs (BDE-99 and BDE-47) can trigger synergistic OS-mediated neurotoxic effects in neuroblastoma cells in human body. It is worth noting that, in general in the environmental media, wildlife and even humans are exposed to mixtures of PBDEs (Tagliaferri et al. 2010).

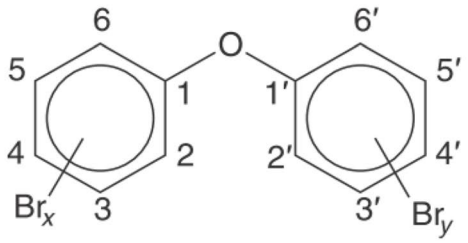
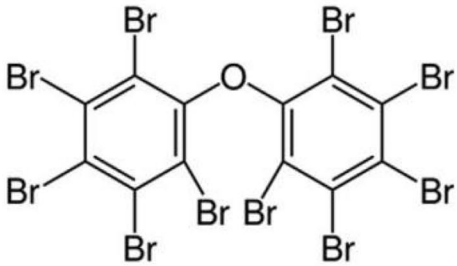
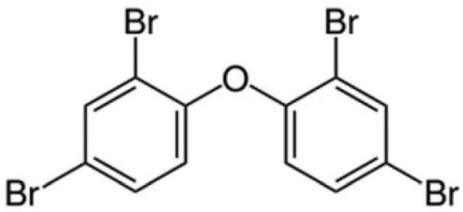
To our knowledge, there is no evidence related to the assessment of side effects of environmental exposure to PBDEs, especially on cancer progression. Therefore, in the present work, a systematic literature search was performed to collect and evaluate all the evidence on the impacts of environmental contact to PBDEs in the risk of cancer progression.

Methods

Strategy of search and extraction of main data

This research does not require patient consent or ethical approval because the present research was a study on previously published papers. This SR was done according to the PRISMA guideline (www.prisma-statement.org) (Liberati et al. 2009; Moher et al. 2015; Mirzaee et al. 2021a, b; Noorimotlagh et al. 2021). We identified articles that describe the relationship between the effects of the environmental contact to BFRs and the threat of cancer progress. A systematic search was performed from May 1, 1980 to June 1, 2022

Table 1 General characteristics of PBDEs or their congeners

Parameters	Value
material name	PBDEs
congeners of PBDEs	209 possible congeners of PBDEs
chemical formula	$C_{12}H_{(9-0)}Br_{(1-10)}O$, with the sum of H and Br atoms always equal to 10. TetraBDE($C_{12}H_6OBr_4$), PentaBDE ($C_{12}H_5OBr_5$), OctaBDE($C_{12}H_2OBr_8$) and DecaBDE ($C_{12}OBr_{10}$)
CAS number	CAS 40088-47-9 (tetra-BDE); CAS 32534 81-9 (penta-BDE); CAS 36483-60-0 (hexa-BDE); CAS 68928-80-3 (hepta-BDE); CAS 32536-52-0 (octBDE); CAS 63936-56-1 (nona-BDE); CAS 1163-19-5 (deca-BDE)
Open general chemical structure	
BDE-209 (2,2,3,3,4,4,5,5 - decabromodiphenyl ether)	
BDE-47 (2,4,4-tetrabromodiphenyl ether)	
Molecular mass	Tetra-BDE(458.8), Penta-BDE(564.8), Octa-BDE(801.5) and Deca-BDE(959.2)
boiling point (°C)	310 and 425
water solubility (µg/L)	less than 1
log octanol-water partition coefficient (Kow)	4.3 and 9.9
The half-life (days)	15(for deca-BDE), more than 90 (for lower brominated congeners)
PBDEs half-lives (in humans)	2 to 12 years

(Darnerud, Eriksen et al. 2001, Siddiqi, Laessig et al. 2003, Costa and Giordano 2014, Huang, Sjodin et al. 2020, Wu, Liu et al. 2021).

in four international bibliographic databases, including Web of Science, Scopus, PubMed, and Google scholar engines for Medical subject Heading (MeSH) terms. Search terms with a medical subject heading were used in all possible combinations (Supplementary section). After completing the article search, two independent reviewers (SAM, SM) imported all articles into Endnote and Mendeley software to remove duplicate articles. Finally, a data list was applied to

Table 2 Percentage of reviewed records ($n = 40$ hints) according to ARRIVE guidelines

Items	Score grading		
	0	1	2
1 (Title)	2.43	97.56	-
2 (Abstract)	0	2.43	97.56
3 (Introduction/Background)	0	0	100
4 (Introduction/Objectives)	24.14	75.86	-
5 (Methods/Ethical statement)	0	5.17	94.83
6 (Methods /Study design)	2.43	2.43	95.13
7 (Methods/Experimental procedures)	2.43	2.43	95.13
8 (Methods/Experimental animals)	0	4.86	95.13
9 (Methods/Housing and husbandry)	0	9.72	90.28
10 (Methods/Sample size)	2.43	2.43	95.13
11 (Methods/Allocating animals to experimental groups)	4.86	95.13	-
12 (Methods/Experimental outcomes)	2.43	2.43	95.13
13 (Methods/Statistical methods)	2.43	27.58	70.69
14 (Results/Baseline data)	2.43	97.56	-
15 (Results/Numbers analyzed)	0	4.86	95.13
16 (Results/Outcomes and estimation)	0	0	100
17 (Results/Adverse events)	0	2.43	97.56
18 (Discussion/Interpretation, scientific implications)	4.86	0	95.13
19 (Discussion/Generalizability,translation)	7.29	19.11	73.6
20 (Discussion/Funding)	29.13	2.43	68.44

extract relevant findings from full texts of all remaining studies. This form contains information such as study ID, country, study type, pollutant(s) and cancer type, study model, number of cases, main finding, mechanism (mode of action), and biological end-point. Figure 1 shows a summary of the PRISMA protocol in terms of the record selection method.

Inclusion and exclusion criteria

The reviewers then screened titles and abstracts of all articles for inclusion criteria, including article language based on English, original articles, and studies on the effect of BFRs and the risk of cancer progress. Articles were excluded if they were review articles, short communications, letter to the editor, book chapter, and articles on other chemicals.

Evaluation of the quality of reviewed records

In order to assess of the quality of reviewed records, the ARRIVE checklist was applied (Moher et al. 2001; Kilkenny et al. 2010). This guideline has been fulfilled and developed based on CONSORT statement. The ARRIVE checklist was applied to evaluate observational studies such as case control studies. It has 20 questions according to the study sections and evaluates the results of the studies and, finally, represents a quantitative scale to assessing the overall quality of the studies. Herein, the obtained results of the checklist for the quality of the studies are shown in the Supplementary section (Tables S1 and S2).

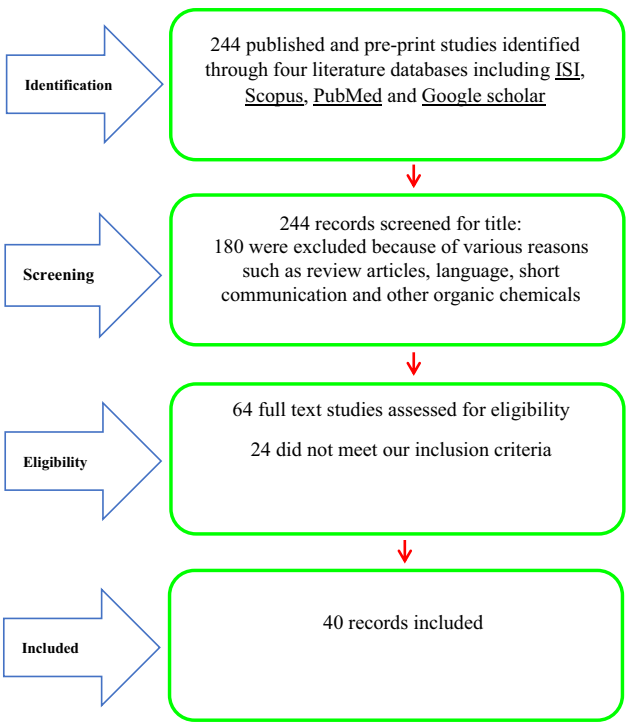


Fig. 1 Summary of PRISMA protocol in terms of records selection method

Results

Based on systematic searching of electronic databases, this is the first work on the impacts of the environmental contact to BFRs and the risk of cancer progression. Of 244 articles collected from the initial search on ISI, Scopus, PubMed, and Google scholar, 45, 31, 11, and 93 papers were removed because they were duplicates, review articles, short communication, and not related to the effect of BFRs and the risk of cancer progression, respectively. Then, in the next step, we studied the full text of all 64 articles and 24 studies were removed from this research because they did not meet our inclusion criteria. Finally, in this SR, forty studies were reviewed and included (Jensen et al. 1982, 1984; Gupta et al. 1983; Jensen et al. 1983; Williams et al. 1984; Kavanagh et al. 1985; Rezabek et al. 1989; Rangga-Tabbu and Sleight 1992; Chhabra et al. 1993; Meerts et al. 2001; Madia et al. 2004; Hu et al. 2007; He et al. 2008; Song et al. 2009; Zhao et al. 2009, 2022; Tagliaferri et al. 2010; Man et al. 2011; Li et al. 2012, 2019; Pellacani et al. 2012; Sakamoto et al. 2013; Zhang et al. 2013, 2017, 2019; Harvey et al. 2015; Qu et al. 2015; Wang et al. 2015; Terrell et al. 2016; Tian et al. 2016; Hoffman et al. 2017; Liu et al. 2017; He et al. 2018; Leonetti et al. 2018; Wei et al. 2018; Han et al. 2019; Hurley et al. 2019; Kanaya et al. 2019; Tang et al. 2019; Huang et al. 2020). The main information, mechanism, and biological end-points of forty reviewed and included studies are provided in Tables 3 and 4.

According to the results depicted in Table 3, of the 40 reviewed and included studies, nineteen studies, seventeen studies, one study, two studies, and one study were carried out at USA, China, Sweden, Italy, and Japan, respectively.

It is worth noting that most of the reviewed studies were case–control study. This systematic review based on the available articles provides different mechanisms to show the association of BFRs and the risk of cancer incidence. The findings of the included studies were not fully consistent. However, among 40 reviewed studies, seventeen studies examined BFR-induced human neoplasia (Zhao et al. 2009; Terrell et al. 2016; Hoffman et al. 2017; Liu et al. 2017; He et al. 2018; Li et al. 2019; Huang et al. 2020), ten studies are associated to animal-related neoplasia (Jensen et al. 1982, 1983, 1984; Gupta et al. 1983; Williams et al. 1984; Rezabek et al. 1989; Rangga-Tabbu and Sleight 1992; Chhabra et al. 1993; Sakamoto et al. 2013; Harvey et al. 2015), while twenty studies performed neoplasia by cell line (according to results depicted in Table 3), as well as some studies showed that BFRs induced the proliferation and growth of different tumor cells through a variety of mechanisms (according to results shown in Table 3). Eventually, some of the reviewed records reported that BFRs had no impacts to induce neoplasia (according to results shown in Table 3).

Quality assessment of the reviewed studies

ARRIVE guideline checklist with different items was used, and the percentage of the all included studies was classified in the Supplementary Section (Tables S1 and S2). Based on the finding depicted in Tables S1 and S2. According to the finding shown in Table S1 and S2, most of the reviewed studies obtained high rate; therefore, they were reviewed in the present study.

Discussion

Cancer mortality continues in the industrialized world despite the extensive research and quick progress shown in the last 10 years that appears to be due to changing patterns of cancer risk factors. Thus, a key way to identify cancer control opportunities is to learn about the causes and risk factors of common cancers that provide a foundation for understanding the potential to prevent and reduce cancer incidence (Anand et al. 2008). BFRs are commonly applied in various products, such as electronics, textiles and clothing, toys, automobiles, and plastics to alleviate flammability and have become ubiquitous and persistent environmental pollutants (Hoffman et al. 2017). Because laboratory and epidemiological studies have shown that BFR exposure can result in cancer, developmental and neurobehavioral disorders, reproductive and behavioral abnormalities, and immune system dysfunctions, there is increasing worry about BFR's global distribution and influence on life (He et al. 2010). Human exposure to BRFs occurs through the environment via water (Yang et al. 2015), air (Deng et al. 2007; Wu et al. 2021), dust inhalation as well as food ingestion (Ni et al. 2013), and especially E-waste (contain plastic waste) municipal solid waste incinerators (Kim et al. 2005; Zhao et al. 2009; Wang et al. 2010; Ni et al. 2013). Infants could also be exposed through ingestion of breast milk, and fetal exposure can occur through the placenta, leading to the highest body burden in infants and young children (Chen et al. 2014). Therefore, as the levels of BFRs in the environment and human body tissues are rising year after year, BRFs have posed a serious threat to both human health and safety due to their toxicity and widespread use in the environment (Chhabra et al. 1993; Zhao et al. 2009).

Multiple studies suggest exposure to various congener of BFRs (such as PBBs, PBDEs, and PCBs) can lead to tumors (Wu et al. 2020) and the greater tissue concentrations of FRs may contribute to the elevated cancer incidence in the disassembly locations (Zhao et al. 2009). Hoffman et al., in a case–control study, demonstrated that some FRs in the indoor environment of home such as TCEP and BDE-209 could be related with the severity and occurrence

Table 3 Chronological and general information on forty reviewed studies

Study ID	Study design	Pollutant(s)	Study model	No. of cases	Type of cancer
(Jensen et al. 1982), USA	Case–control study	Firemaster BP-6, HBB	Female Sprague–Dawley rats	51	-
(Rangga-Tabbu and Sleight 1992), USA	Case–control study	Firemaster BP-6	Rat	26	Liver and nasal tumor
(Jensen et al. 1983), USA	Case–control study	345-HBB	Rat	42	Hepatic tumor
(Gupta et al. 1983), USA	Case–control study	PBBs	Fischer rat and B6C3F mice	344	Hepatocellular carcinoma
(Jensen et al. 1984), USA	Case–control study	Firemaster BP-6	Female Sprague–Dawley rats	36	-
(Williams et al. 1984), USA	Case–control study	PBBs	Adult male Fischer F-344 rats, adult male CD-1 mice, adult male Syrian hamsters	-	Liver cancer
(Kavanagh et al. 1985), USA	Case–control study	Firemaster BP-6, (2,4,5-HBB), (3,4,5-HBB), (3,4-TBB)	Cell line rat and hamster	-	-
(Rezabek et al. 1989), USA	Experimental study	Firemaster BP-6, 345-HBB	Rat	23	Hepatic tumor
(Chhabra et al. 1993), NC, USA	Case–control study	PBBs	F344/N rats B6C3F1 mice	480	-
(Meerts et al. 2001), Sweden	Case–control study	HO-PBDEs (T2-like HO-BDE, T3-like HO-BDE, T4-like HO-BDE)	Human T47D breast cancer cell line	-	-
(Madia et al. 2004), USA	Case–control study	PBDE-99	Human 132-1N1 astrocytoma cells	-	-
(Hu et al. 2007), China	Case–control Study	PBDE-209, PCBs	Human hepatoma Hep G2 line	-	Liver cancer
(He et al. 2008), China	Case–control study	BDE-47	Human neuroblastoma cells (SH-SY5Y)	-	Neuroblastoma
(Song et al. 2009), USA	Case–control study	2-OH-BDE47 and 2-OH-BDE85	H295R adrenocortical carcinoma cells	-	Adrenocortical carcinoma cells
(Zhao et al. 2009), China	Case–control study	PBBs, PBDEs, PCBs	Tissue (liver, lung, kidney)	81	Kidney, liver, and lung cancer
(Tagliaferri et al. 2010), USA	Experimental study	BDE-47 and BDE-99	Human neuroblastoma cells (SK-N-MC)	-	Neuroblastoma
(Man et al. 2011), China	Ecological study	BDE-209	6 types of land, agricultural, organic farm, e-waste storage, e-waste dismantling workshop, e-waste open burning site, and open burning site	-	-
(Han et al. 2012), China	Case–control study	BDE-47	Mouse Leydig tumor cells (mLTCs)	-	-
(Li et al. 2012), China	Case–control study	PBDE-209	MCF-7 human breast cancer cell line, the multidrug-resistant MCF-7 cell line MCF-7/ADR, OVCAR-3 human ovarian cancer cell line, the HeLa human cervical cancer cell line, and CHO (Chinese hamster ovary) cell line	-	Breast, ovarian, and cervical cancer cells

Table 3 (continued)

Study ID	Study design	Pollutant(s)	Study model	No. of cases	Type of cancer
(Pellacani et al. 2012), Italy	Case–control study	BDE-47, BDE-209	Human neuroblastoma cells (SK-N-MC)	-	-
(Sakamoto et al. 2013), Japan	Case–control study	PBO, DBDE	C3H/HeNCrl Mice CAR knockout and wild type mice	39	Liver cancer
(Harvey et al. 2015), USA	Case–control study	TBBPA	Tissue from Wistar Han rats	41	Endometrial carcinomas
(Qu et al. 2015), China	Case–control study	6-OH-BDE-47	Human lung cancer cell line A549 and H358	-	Human lung cancer cells
(Wang et al. 2015), China	Case–control study	BDE-99	CRC cell line (HCT-116)	-	Colorectal cancer
(Tian et al. 2016), China	Case–control study	BDE-47	Human neuroblastoma cell (SH-SY5Y)	-	Neuroblastoma
(Terrell et al. 2016), USA	Nested case–control study	PBBs	Human (women)	253	Breast cancer
(Hoffman et al. 2017), China	Case–control study	BDE-209 and TCEP	Human (women and men)	140	Papillary thyroid cancer
(Liu et al. 2017), China	Case–control study	PBDEs and OH-PBDEs	Human (male and female)	33	Thyroid cancer
(He et al. 2018), China	Case–control study	BDE-47, 71, 99, 100, 183, and 209	Human (women)	374	Breast cancer
(Wei et al. 2018), China	Case–control study	BDE-47	Human breast cancer cells (MCF-7)	-	Breast carcinoma
(Leonetti et al. 2018), USA	Case–control study	BDE-99, 3-OH BDE-47, and 6-OH BDE-47	Horiocarcinoma placenta cell line (BeWo)	-	Choriocarcinoma placenta
(Zhang, Peng et al. 2019), China	Case–control study	BDE-47	Estrogen-dependent EC cells	-	Endometrial carcinoma
(Li et al. 2019), USA	Case–control study	PCBs, OCPs, PBB-153, PBDEs, SMCs	Breast adipose tissue samples	50	Breast cancer
(Han et al. 2019), China	Case–control study	BDE-209	MLTC-1 cells (mouse Leydig tumor cells)	-	-
(Tang et al. 2019), China	Case–control study	BDE-47	Human neuroblastoma cells (SK-N-SH)	-	Neuroblastoma
(Hurley et al. 2019), USA	Case–control study	BDE-153, BDE-47, BDE-100	-	-	-
(Kanaya et al. 2019), USA	Case–control study	BDE-47, BDE-100, and BDE-153	Breast cancer cell line (MCF-7aroERE and patient-derived xenograft (PDX) models of human breast cancer)	-	Breast cancer
(Huang et al. 2020), USA	Nested case–control study (of cohort data)	BDE-28	Human	742	Papillary thyroid cancer
(Montalbano et al. 2020), Italy	Experimental study	BDE-47, 99, 209	Normal human bronchial epithelial cell line (16HBE), primary normal human bronchial epithelial (NHBE) cells	-	-
(Zhao et al. 2022), China	Case–control study	PBDE-99 (2,2′,4,4′,5-pentabromodiphenyl ether)	Pregnant ICR mice	32	-

Table 4 The main findings, mechanism, and biological end-point on the forty-two reviewed studies

Study ID	Main finding	Mechanism	Biological end-point
(Jensen et al. 1982), USA	The ability to promote tumors was higher in the PBB mixture than in HBB	-	Induction of tumor by mixture of PBBs and HBB
(Jensen et al. 1983), USA	345-HBB as a strict 3-methylcholanthrene (MC) type of hepatic microsomal drug metabolizing enzyme inducer increase of cytochrome P450 and has tumor-promoting ability via dose-related	Increase of cytochrome P450	At dietary doses, 345-HBB accelerated the formation of enzyme-altered foci in the livers of rats initiated with DEN
(Gupta et al. 1983), USA	PBBs cause lesions such as cholangiocarcinomas, hepatocellular carcinomas, neoplastic nodules, and hepatocellular carcinomas in rats and mice. Male rats were more likely to develop gastric ulcers and hyperplastic gastropathy, particularly in the high dosage groups, in the glandular portion of the stomach	-	Induction of tumor by PBBs
(Jensen et al. 1984), USA	Short-term (acute) and long-term (chronic) exposure to PBBs is effective in increasing the development of enzyme-altered foci	-	The effects of firemaster BP-6 on enzyme-altered foci can promote tumors for a very long time after exposure to external sources has ended
(Williams et al. 1984), USA	In rat, mouse, or hamster hepatocytes in primary cultures, PBB did not induce DNA repair synthesis, so have an epigenetic membrane effect	-	PBB operates as tumor promoters in the development of rodent liver tumors
(Kavanagh et al. 1985), USA	No mutagenic effects were detected	-	These substances support liver tumors through a non-genotoxic route
(Rezabek et al. 1989), USA	The percentage of the liver volume occupied by foci was significantly greater in the low vitamin A with 345-HBB group than in the corresponding high-vitamin A group	-	High dietary vitamin A intake had some negative effects on 345-HBB's ability to promote hepatic-altered foci in rats
(Rangga-Tabbu and Sleight 1992), USA	In rats receiving NDMA or NPYR as a starting point, a single oral dose of PBB can considerably accelerate the development of AHF	-	Induction of tumor by PBBs
(Chhabra et al. 1993),North Carolina, USA	A combined study of the leukemia incidences in the adult-only, perinatal-only, and combined perinatal and adult exposure groups in male and female rats showed an apparent correlation between rising mononuclear cell leukemia incidences and exposure to PBB	-	Induction of tumor by PBBs
(Meerts et al. 2001), Sweden	Numerous pure PBDE congeners, particularly HOPBDEs and brominated bisphenol A-analogs, are ERα and ERβ receptor agonists, which promote ER-mediated luciferase activation	Agonists of both ERα and ERβ receptors	Brominated bisphenol A compounds, three hydroxylated PBDEs, and other PBDE congeners have estrogenic and anti-estrogenic activities

Table 4 (continued)

Study ID	Main finding	Mechanism	Biological end-point
(Madia et al. 2004), USA	PBDE-99 caused apoptotic cell death in astrocytoma cells	Increasing in the expression of p53	Different cytotoxic effects of PBDE-99 are seen in human astroglial cells
(Hu et al. 2007), China	The inhibition of the cells viability was observed at time and concentration-dependent manner	OS	Anti-proliferation toxicity action and apoptosis induction were demonstrated in tumor cells
(He et al. 2008), China	PBDE-47 inhibited cell viability, increased LDH leakage, and induced cell apoptosis	OS	PBDE-47 is cytotoxic and genotoxic in SH-SY5Y cells
(Song et al. 2009), USA	2-OH-BDE85 and 2-OH-BDE47 at micromolar concentrations are cytotoxic in a dose-dependent manner	Endoplasmic reticulum stress	A micromolar concentration of OH-PBDEs causes the unfolded protein response and endoplasmic reticulum stress-related transcriptional alterations
(Zhao et al. 2009), China	In Zhejiang, China, e-waste disassembly sites, PBB and PBDE burdens were tested in tissues of cancer patients, and the results showed that PBB contents were significantly higher than those reported in the general US population. PBDE levels were comparable to those reported in the USA population, but significantly higher than those of the European population	-	Higher tissue concentrations of PBBs and PBDEs could explain the elevated cancer incidence in the disassembly locations
(Tagliaferri et al. 2010), USA	As people are exposed to mixtures of PBDEs, particularly tetra- and penta-BDE congeners, co-exposure to BDE-47 and BDE-99 could cause synergistic neurotoxic consequences	OS	The brominated flame retardants BDE-47 and BDE-99, when present in low concentrations, cause synergistic OS-mediated neurotoxicity in human neuroblastoma cells
(Man et al. 2011), China	The highest amounts of PCBs and PBDEs were found in the soils from e-waste dismantling workshop (EW (DW)) and e-waste open burning site (EW (OBS)), which led to relatively high cancer risks among the 6 types of land use. As a result, these soils were of the most concern in terms of endangering human health	-	BDE-209 created a very low cancer risk in all six different forms of land use
(Han et al. 2012), China	BDE-47's ability to reduce progesterone synthesis may be accompanied by decreased cAMP production and P450scc activity	Decrease of cAMP generation and reduction of P450scc activity	PBDEs are harmful to the reproductive system and damage the endocrine system
(Li et al. 2012), China	In a dose- and time-dependent way, PBDE-209 improved the viability and proliferation of the tumor cell lines and in CHO cells. It boosted ERK1/2 and PKC phosphorylation in the cell lines on a molecular level	PKCα and ERK1/2 phosphorylation	Induction of tumor by PBDE-209
(Pellacani et al. 2012), Italy	Human SK-N-MC cells are susceptible to DNA damage brought on by BDE-47 and BDE-209	OS	The primary mechanism by which PBDEs damage DNA is by the induction of OS

Table 4 (continued)

Study ID	Main finding	Mechanism	Biological end-point
(Sakamoto et al. 2013), Japan	PBO, DBDE, or PB (a positive control) therapy for 4 weeks caused hepatocellular hypertrophy in the wild-type mice as well as enhanced Cyp2b10 messenger RNA and Cyp2b protein expression. Only PBO displayed liver enlargement in CARKO mice when Cyp2b10 and Cyp3a11 were induced	Constitutive androstane receptor (CAR)-independent pathways	In both wild-type and CARKO mice, DBDE enhanced the quantity of basophilic altered foci/adenomas through CAR-independent mechanisms
(Wang et al. 2015), China	In HCT-116 cells, BDE-99 was found to promote motility and invasion as well as the epithelial to mesenchymal transition (EMT). BDE-99 treatment also increased the protein and mRNA levels of the transcription factor Snail, but not Slug, Twist, and ZEB1	PI3K/Akt/Snail signaling pathway	BDE-99 can cause EMT via the PI3K/AKT/Snail signaling pathway in colon cancer cells
(Qu et al. 2015), China	Through the activation of EMT, 6-OH-PBDE-47 encouraged the in vitro migration of both A549 and H358 cells. Treatment with 6-OH-PBDE-47 dramatically increased Snail expression but not that of other transcription factors. The 6-OH-PBDE-47 induced upregulation of Snail was mainly due to post-transcriptional through PI3K/AKT signals	Promoted the EMT of lung cancer cells via AKT/Snail signals	Through the AKT/Snail signal pathway, 6-OH-BDE-47 encourages the epithelial to mesenchymal transition in human lung cancer cells
(Harvey et al. 2015), USA	In comparison to spontaneous uterine carcinomas, TBBPA-induced uterine carcinomas in Wistar Han rats showed a substantial increase in tumor protein 53 mutation and overexpression of human epidermal growth factor receptor 2	Increased Tp53 mutations	Induction of tumor by TBBPA in rats
(Terrell et al. 2016), USA	The odd ratios of having breast cancer among women with high PBB concentrations compared to women with low PBB concentrations were 2.60, 95% CI 0.93 to 7.27 ($P=0.07$), when adjusted for age and family history of cancer in a first-degree female relative	-	The data indicate a link between increased PBB exposure and an increased risk of breast cancer; however, this link did not achieve statistical significance
(Tian et al. 2016), China	Treatment with BDE-47 significantly elevated matrix metalloproteinase-9 (MMP-9) expression while downregulating E-cadherin and zona occludin-1 expression	The GPER/PI3K/Akt signal pathway	BDE-47 activates the GPER/PI3K/Akt signal pathway to encourage the migration of human neuroblastoma SH-SY5Y cells
(Hoffman et al. 2017), China	Higher levels of some FRs, particularly BDE-209 and tris (2-chloroethyl) phosphate in dust, were associated with increased odds of papillary thyroid cancer	-	Induction of tumor by BDE-209. Also, BDE-209 was related with smaller, less aggressive tumors while TCEP was more strongly connected with larger, more aggressive tumors

Table 4 (continued)

Study ID	Main finding	Mechanism	Biological end-point
(Liu et al. 2017), China	PBDEs and OH-PBDEs are present extensively in the thyroid cancer population	-	By enhancing the clearance of serum FT4 with increased TSH levels, OH-PBDEs can change thyroid function
(Wei et al. 2018), China	BDE-47 could disrupt the metabolism of the entire cell and cause OS by blocking PPP	OS	BDE-47 effect of human health
(He et al. 2018), China	Breast cancer cases had higher levels of total PBDEs and the majority of individual PBDE congeners than controls	-	Induction of tumor by PBDEs
(Leonetti et al. 2018), USA	BFR substances can interfere with TH SULT activity in placental cells	-	BDE-99, 3-OH BDE-47, and 6-OH BDE-47 decreased 3,3-T2 SULT activity, but BDE-47 had no effect on SULT activity, and there was no observed effect of any BFR exposure on expression of SULT1A1, or thyroid nuclear receptors alpha or beta
(Zhang, Peng et al. 2019), China	Ishikawa-BDE-47 and HEC-1B-BDE-47 cells showed higher cell viability and improved metastatic capacity after being exposed to BDE-47	ERα/GPR30 and EGFR/ERK signaling pathways	Chronic BDE-47 exposure, at least in part, through ER/GPR30 and EGFR/ERK signaling pathways, enhances development and even chemoresistance in EC cells
(Li et al. 2019), USA	Organochlorine pesticides (OCPs) and synthetic musk compounds (SMCs) are ubiquitously found in breast adipose samples, with concentrations in the decreasing order: OCPs > PCBs > SMCs > PBDEs > PBB-153	-	There was no noticeable difference in PCB, PBDE, OCP, or SMC concentrations between cases of malignant and benign tumors
(Han et al. 2019),China	In the presence of human chorionic gonadotropin (hCG), cholera toxin (CT), and forskolin, BDE-209 did not alter the intracellular cAMP level, suggesting that the decrease in progesterone may not be connected to the hCG-cAMP signal pathway in MLTC-1 cells	Suppression of P450 side-chain cleavage enzyme (P450scc) and 3β-hydroxysteroid dehydrogenase (3β-HSD) mRNA expression	BDE-209 may reduce progesterone secretion primarily by downregulating P450scc and 3β-HSD expression
(Hurley et al. 2019), USA	With a CI that included one, the odd ratios for each of the three BDE congeners were very close to unity. Analyses stratified by menopausal status, tumor hormone responsiveness, BMI, and changes in body weight yielded similarly null results	-	The case–control study's findings show no proof that serum levels of BDE-47, BDE-100, or BDE-153 are linked to a higher risk of breast cancer in this group of middle-aged and older Californian women
(Tang et al. 2019), China	The exposure of BDE-47 triggered the molecular and metabolic mechanisms	OS	After treatment with BDE- 47 metabolic changes related to neurotransmitters, oxidative stress, and nucleotide-mediated signal transduction systems were the sensitive pathways mostly influenced

Table 4 (continued)

Study ID	Main finding	Mechanism	Biological end-point
(Kanaya et al. 2019), USA	Studies conducted in vitro reveal that BDE-47 is a weak agonist of the estrogen receptor type α (ERα) and the estrogen-related receptor type α (ERRα); it has been shown to increase MCF-7aroERE proliferation and ER-regulated gene expression (including cell cycle genes). It was discovered that BDE-153 only slightly inhibited ERα. BDE- 100 could act as (1) an agonist of aryl hydrocarbon receptor (AhR), inducing expression of CYP1A1 and CYP1B1 and (2) as a very weak agonist/antagonist of ERα Results from in vivo: An ERβ PDX model was used to test a mixture of three congeners with ratios found in human serum. The mixture raised the expression of the proliferation marker Ki-67 and displayed estrogenic activity through apoptosis/cell cycle regulation	Modulation of ERα, ERRα, PR, and/or AhR pathways	Breast cancer is affected by BDE-47, BDE-100, and BDE-153 via altering the PR, AhR, ERa, ERRa, and/or ERRa pathways
(Huang et al. 2020), USA	BDE-28, was associated with significantly increased risk of classical papillary thyroid cancer	-	Induction of tumor by BDE-28
(Montalbano et al. 2020), Italy	In normal human bronchial epithelial cells, PBDEs (47, 99, and 209) trigger the process of DNA damage by inducing OS (in terms of NOX-4 expression as well as ROS and JC-1 production). Additionally, although they have no effect on cell viability, PBDEs cause bronchial epithelial cells to undergo cell apoptosis and have the ability to multiply into colonies (similar to the cancer phenotype). Finally, PBDE-47 had a greater effect than 99 and 209	OS, apoptosis dysregulation, DNA damage, and cell proliferation	In addition to having cytotoxic and genotoxic effects, PBDE-47, -99, and 209 congeners play a crucial role in the dysregulation of OS, breaking DNA and altering associated gene expression in bronchial epithelial cells

Table 4 (continued)

Study ID	Main finding	Mechanism	Biological end-point
(Zhao et al. 2022), China	Mice that were pregnant were exposed to PBDE-99 for the in vivo investigation. It was discovered that the testicular organ coefficient and anogenital index in male offspring were significantly lower, while the incidence of cryptorchidism was higher and the testicular histology was disturbed. Transcriptomic profiling showed that steroidogenesis disorders were significant in all PBDE-99 exposure groups. After PBDE-99 exposure, there was a significant reduction in the levels of testosterone, the expression of testosterone regulators, and the quantity of CYP11A1- and 11-HSD1-positive Leydig cells TM3 Leydig cells were exposed to PBDE-99 at gradient doses for the in vitro investigation. PBDE-99 elevated reactive oxygen species, activated the ERK1/2 pathway, blocked the ubiquitination degradation pathway, and ultimately triggered Leydig cell apoptosis. Overall, these results showed that prenatal exposure to environmentally relevant amounts of PBDE-99 cause testicular dysgenesis and abnormalities of steroidogenesis by causing Leydig cells to undergo apoptosis	Upregulated ROS, activated the ERK1/2 pathway,	Leydig cells undergo apoptosis as a result of prenatal exposure to environmentally relevant levels of PBDE-99, which results in testicular dysgenesis and abnormalities of steroidogenesis

of papillary thyroid cancer (PTC) (Hoffman et al. 2017). Furthermore, in a cohort study of 33 patients with thyroid cancer, body burdens of the serum thyroid status and 11-OH-PBDEs and 7-PBDEs demonstrated that OH-PBDEs and PBDEs were widely distributed in the population with thyroid cancer, and their concentration is comparable to those in the general population in China (Liu et al. 2017). According to a review study of cohort information from the US Department of Defense from 2000 to 2013, an increment in BDE-28 concentrations considerably raised the risk of papillary thyroid cancer (Huang et al. 2020). The effect of BFRs also has been confirmed to induce gastrointestinal neoplasm (Gupta et al. 1983). Several studies in different animal models such as rats, mice, or hamsters have shown that short and chronic (long-term) exposure to PBB and PCB have the potential to enhance the development of foci of enzymatic alteration, so these components act as promoters of experimental hepatocarcinogenesis (Jensen et al. 1982, 1983, 1984; Williams et al. 1984; Rezabek et al. 1989; Smith et al. 1990; Chhabra et al. 1993). For example, in a single oral dose study of FM (a commercial combination of PBBs), the development of changed hepatocellular loci in rats challenged with N-nitrosodimethylamine and N-nitrosopyrrolidine (NPYR) was significantly enhanced (Rangga-Tabbu and Sleight 1992). Furthermore, it has been reported that FM directly through inhibition of cell–cell communication may be involved in the promotion of hepatocellular neoplasms (Kavanagh et al. 1985). Other results also reported that exposure to PBDEs may influence the development and occurrence of breast cancer. In addition, Kwieciñska et al. demonstrated that in the presence of 17-estradiol, BDE-47 and BDE-209 can increase MCF-7 cell proliferation and decrease cell apoptosis in vitro (Kwiecińska et al. 2011). Additionally, researchers in China measured the concentrations of 14 distinct PBDEs in the adipose tissue of women without and with breast cancer. In comparison to controls, breast cancer cases had higher concentrations of the total PBDEs. Breast cancer risk factors have been proposed for some of the specific PBDE congeners (He et al. 2018). Although these studies have reported that exposure to these components could increase the incidence of cancer, the main mechanisms that could contribute to the tumorigenesis remain to be clarified.

In our study, several articles reported that BFRs may be carcinogenic through different mechanisms. Most studies have introduced endoplasmic reticulum stress (ERS) and OS as the main mechanism of these compounds in cancer induction. In general, the agglomeration of toxic compounds in the ER destroys the basic function of the organelles and increases the accumulation of misfolded proteins in the lumen of ER leading to ERS. Decreased protein synthesis, increased protein folding mechanism, and removal of terminal misfolded protein are multiple mechanisms that are induced by the unfolded protein response (UPR) after ERS to maintain homeostasis in cell (Lin et al. 2019). However, in a chronic ERS due to persistence of the risk factor, the UPR fails to restore ER homeostasis and UPR response promotes the production of ROS in the endoplasmic reticulum (Victor et al. 2021). Meanwhile, mitochondrial function is disrupted by ERS, and this caused increased mitochondrial ROS production (Cao and Kaufman 2014; Arfin et al. 2021). Thus, during cellular stress and injury, imbalance of antioxidant systems and ROS along with nitrogen reactive species (RNSs) led to OS which increases tumorigenesis via multiple mechanisms such as DNA damage, inflammation, angiogenesis, immune response evasion, and drug resistance (Hayes et al. 2020). In agreement with this issue, Pellacani et al., in their study, showed that two PBDEs flame retardants such as BDE-209 and BDE-47 could damage DNA in neuroblastoma cells of human, which is mainly mediated by induction of OS (Pellacani et al. 2012). It has also been shown that low concentrations of BFRs can induce OS in neuroblastoma cells (Tagliaferri et al. 2010). Furthermore, according to many research, PBDE-47 is cytotoxic and genotoxic and can cause LDH leakage, ROS production, cell death, and as well as DNA damage via ERS and OS (He et al. 2008; Zhang et al. 2017). Additionally, it was noted that PBDE-99, PBDE-47, and PBDE-209 may affect the function of the respiratory epithelium of human by causing OS and DNA damage in an in vitro and/ or ex vivo experimental model of bronchial epithelial cells, thereby encouraging inflammation, tissue damage, genetic anomalies, and oncogenesis (Montalbano et al. 2020). Wei et al. investigated the toxicity mechanism of BDE-47 in MCF-7 breast cancer cells in a study and found that exposure to BDE-47 hindered the production of NADPH in the PPP. Multiple ROS scavenging system pathways may be impacted by the absence of NADPH. Because antioxidases were unable to remove ROS in time without NADPH, OS was produced and eventually resulted in cell damage (Wei et al. 2018). Therefore, ROS produced after exposure to BFRs through oxidative stress, such as strand breaks, DNA base alterations, expression of proto-oncogene, and damage to tumor suppressor genes resulting in the alteration of normal cells in malignant (virulent) cells and the positive regulation of growth factors and cytokines, exerts its effect. Figure 2 shows a summary of the mechanisms mentioned above.

The impacts of 11-OH-PBDE on the trigger of one of the UPR arms, namely the PERK pathway, have also been confirmed, and it appears that its bioaccumulation may disrupt adrenocortical secretory pathways via UPR pathways and ERS. The possible endocrine-disrupting effects of BFRs and their derivatives are mediated by ERS (Song et al. 2009). Other studies also reported that some of the BFRs resemble BDE-47 through disturbance in the metabolism of acidic amines, such as alanine, aspartate, and glutamate, and the

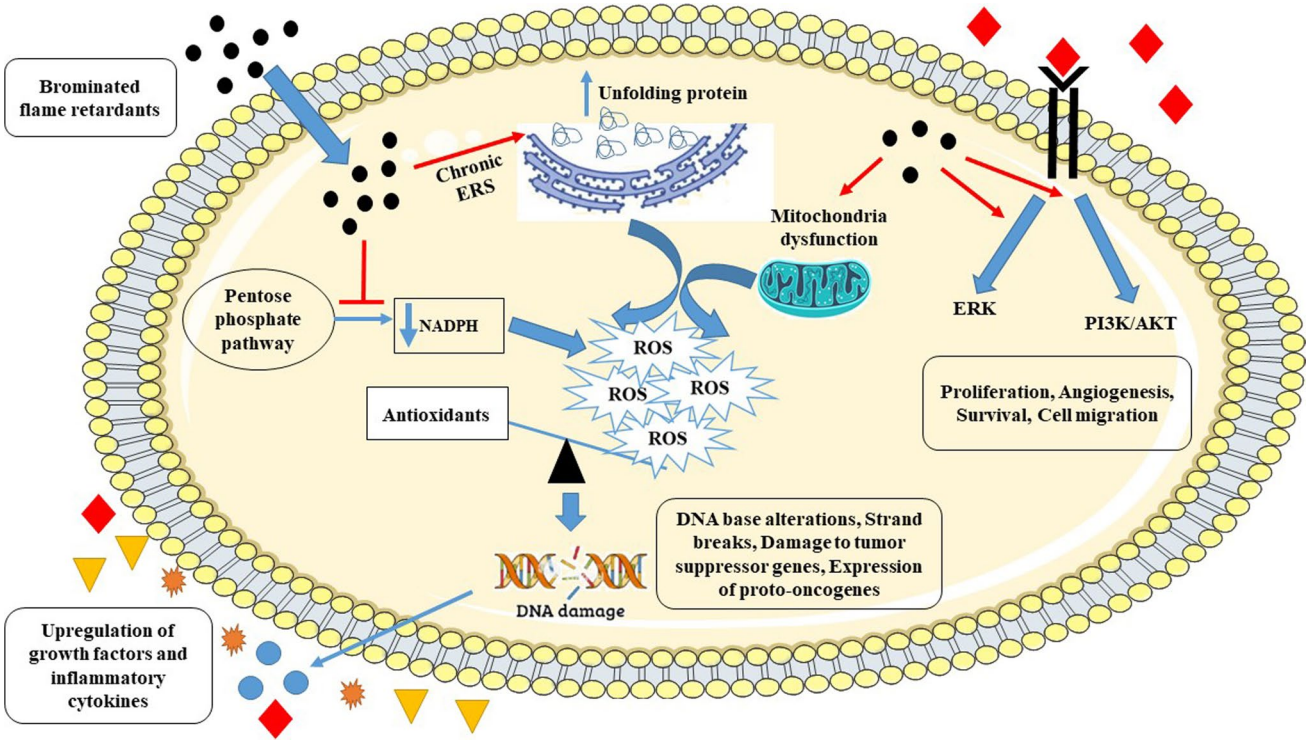


Fig. 2 Main processes that influence the risk of cancer progression and environmental exposure to BFRs. BFR accumulation impairs fundamental organelle function in cells and accelerates the aggregation of misfolded proteins in the ER lumen that cause ERS. Decreased protein synthesis, enhanced protein folding mechanism, and removal of terminal misfolded protein are multiple mechanisms induced by UPR response following ERS. In a chronic ERS due to persistence of the risk factor, the UPR fails to restore ER homeostasis and UPR response promotes the production of reactive oxygen species (ROS) in the endoplasmic reticulum. Meanwhile, mitochondrial function is disrupted by ERS, and this caused mitochondrial ROS production to increase. As a result, OS, which enhances carcinogenesis through a variety of mechanisms including DNA damage and inflammation, is induced by an imbalance between antioxidant systems and ROS during stress and injury in cells. Furthermore, BFRs induced the growth and proliferation of different tumor cells via the PI3K/Akt/Snail signaling pathway

metabolism of pyrimidines and purines after OS may have an adverse effect on human health (Wei et al. 2018; Tang et al. 2019).

Moreover, other mechanisms have been proposed to show that BFRs can exert their carcinogenic effects. Li et al. reported that PBDE-209 through activated protein kinase C (PKCα) and extracellular signal-regulated kinases (ERK1/2) phosphorylation has proliferative effects and antiapoptotic effects in the female reproductive system and normal ovarian CHO cells. They also treated breast cancer cells with PBDE-209 and showed that PBDE-209 neutralized the effects of the cancer drug tamoxifen (Li et al. 2012). Additionally, Zhang et al. observed that endometrial cancer (EC) has been linked to prolonged exposure to BDE-47, which can exacerbate malignant phenotypes and chemoresistance by triggering estrogen receptor (ER)/G protein-coupled receptor (GPR30) and epidermal growth factor receptor (EGFR)/ERK signaling pathways in EC cells both in vivo and in vitro (Zhang, Peng et al. 2019). Several pure PBDE congeners have been proved that activate the estrogen receptor signal transduction pathway in vitro because they are agonists of both the ERα and ERβ receptors and increased growth in breast cancer cells because they acted like estrogen (Meerts et al. 2001). An included study by Kanaya et al. also revealed that PBDEs such as BDE-47, -100, and -153 stimulated an estrogen-dependent proliferation in the cell line of breast cancer (MCF-7aroERE) by modulation of ERα, ERRα, progesterone receptor (PR)/AhR pathways, so they can exert their effect on human breast cancer cells (Kanaya et al. 2019). A study performed on wild-type and CARKO mice as well noted that DBDE (a brominated flame retardant) may act via constitutive androstane receptor (CAR)-independent pathways during hepatocarcinogenesis because it can increase the multiplicity of basophilic altered foci/adenomas in wild-type and CARKO mice (Sakamoto et al. 2013). The role of tetrabromobisphenol A (TBBPA), a widely used BFR, in the induction of uterine carcinomas was confirmed. Results have reported that TBBPA-induced uterine carcinomas in Wistar Han rats exhibited greater rates of proliferation, Tp53 mutation, a

tendency for reduced PR expression, and enhanced human epidermal growth factor receptor 2 expression compared to spontaneous uterine cancers (Harvey et al. 2015). In another study, BDE-47 was utilized to examine how steroidogenic activity was affected in mouse Leydig tumor cells (mLTC-1). Results demonstrated that BDE-47 lowered progesterone production via decreasing cAMP generation and cholesterol side-chain cleavage enzyme (P450scc) activity (Han et al. 2012). In a related study, Han et al. demonstrated that decabrominated diphenyl ether (BDE-209) can reduce progesterone secretion in mouse Leydig tumor cells, mostly by inhibiting the expression of the mRNA for P450scc and 3β hydroxysteroid dehydrogenase (3β-HSD) (Han et al. 2019). PBDEs as well may influence the production of thyroid hormone and estrogen in ways that raise the risk of breast and other cancers (Wu et al. 2020). In this regard, the two congeners of PBDE, such as BDE-99 and BDE-47 which are poisonous and persistent, attract the most public worry in this area because they may interfere with thyroid hormone function and neurobehavioral development (Man et al. 2011; Leonetti et al. 2018). It has also been suggested that by acting as epigenetic agents, PBDEs may have the same ability to promote cancer as PCBs (He et al. 2008).

The connection between PBDEs and the promotion of the epithelial to mesenchymal transition (EMT) has been validated by certain experimental studies of BFRs on various cancer cells. Qu et al. have discovered that the most prevalent OH-PBDE congener in human serum, 6-OH-BDE-47, increased the in vitro migration of lung cancer A549 and H358 cells through controlling the expression of epithelial markers E-cadherin (E-Cad), zona occludin-1 (ZO-1), mesenchymal markers vimentin (Vim), and N-cadherin (N-Cad). 6-OH- 6-OH-BDE-47 also upregulated the protein of expression Snail and increased the phosphorylation of AKT and ERK, so this component induced EMT via AKT/Snail signals and has effects of tumorigenesis and development of lung cancer (Qu et al. 2015). The role of BDE-47 in the induction of metastasis in another study, done in human neuroblastoma SH-SY5Y cells, has been reported. This study showed that BDE-47 can cause metastasis in human neuroblastoma by upregulating MMP-9 and downregulating the epithelial makers E-Cad and ZO-1 through the GPER/PI3K/Akt signal pathway in a dose- and time-dependent manner (Tian et al. 2016). It was also shown that BDE-99 boosted cell migration and invasion in colon cancer HCT-116 cells and caused the epithelial to mesenchymal transition through activating the PI3K/Akt/Snail signaling pathway (Wang et al. 2015).

Unlike the mentioned above, studies reported that PCBs and PBDE concentrations in the breast fat tissues of fifty patients of breast cancer and control cases were not substantially different (Li et al. 2019), and there was also no link between exposure to PBDEs and thyroid cancer (Aschebrook-Kilfoy et al. 2015). Similarly, the serum of Californian women showed no correlation between BDE-100, -47, or -153 levels and the risk of developing breast cancer, especially when they are present alone (Kanaya et al. 2019). Another study, with a smaller sample size, indicated an elevated risk of breast cancer with increased PBB exposure, but did not discover statistically significant connections between the incidence of breast cancer and higher serum PBB concentrations (Terrell et al. 2016). Furthermore, the above results are not in agreement with some of the studies that reported BFRs as an inducer of apoptosis. In this regard, it was shown that PBDE-209 has the harmful effect of inhibiting proliferation and inducing apoptosis in tumor cells in vitro at different doses. Kwieciska et al. have demonstrated that no PBDEs, including 47, 99, 100, and 209 congener, had an impact on cell proliferation (Hu et al. 2007; Kwiecińska et al. 2011). Another investigation found that exposure to PBDE-47 can cause apoptosis in SH-SY5Y cells by upregulating p53 and Bax, downregulating Bcl-2 and the Bcl-2/Bax ratio, enhancing Cyt c production, and activating caspase-3 (Zhang et al. 2013). The role of PBDE-99 in inducing cell cycle arrest and/or apoptotic cell death in human astroglial cells through increased p53 expression has also been reported (Madia et al. 2004). Overall, the conflicting findings suggested that more investigations are required to show the exact side effects of BFRs, and differences between previous studies may attribute dependence to the type of BFRs, concentration, route and time of exposure, cell type, sensitivity of several cell lines exposed to various PBDEs isomers, as well as to genetic polymorphisms and levels of endogenous estrogen in humans (Hurley et al. 2019).

Conclusion and suggestions

In this study, the role of environmental exposure to PBDEs as ubiquitous pollutants in the environment on cancer progression was analyzed. According to the findings of the reviewed investigations, environmental exposure to BFRs was positively associated with cancer progression. However, the findings of the reviewed studies were not entirely consistent. Several articles have reported that BFRs can be carcinogenic through different mechanism. The connection between PBDE and the induction of the epithelial to mesenchymal transition has been verified by some experimental studies of BFRs in various cancer cells. The main mechanisms involved in environmental exposure to BFRs and the risk of cancer progression are endoplasmic reticulum stress and OS. Overall, the accumulation of toxic substances in the ER destroys the basic function of the organelle and increases the accumulation of misfolded proteins in the lumen of ER leading to ERS. UPR response under chronic stress

promotes the generation of ROS in the endoplasmic reticulum. Mitochondrial function is disrupted by ERS, and this caused mitochondrial ROS production to increase. Thus, the imbalance of antioxidant mechanisms and ROS and nitrogen reactive species during stress and injury in cells caused OS which increases tumorigenesis via multiple mechanisms such as DNA damage, inflammation, angiogenesis, evading immune response, and drug resistance. Eventually, the conflicting finding of the reviewed studies suggested that more investigations are required to show the exact side effects of BFRs, and differences between reported studies may attribute dependence to type of BFRs, concentration, pathway and time of exposure, type of cell, sensitivity of different cell lines exposed to different PBDEs isomers, as well as to genetic polymorphisms and endogenous estrogen levels in humans.

The evidence reported that because of the voluntary and mandatory flammability standards for electronic devices, house furnishings, and construction made of plastic and other plastic-related materials, the use of the BFRs during the last decades increased, and, therefore, the exposure to these chemical contaminants may be increased (Alaee et al. 2003; van der Veen and de Boer 2012). Keep this in mind, it is suggested to increase monitoring of e-waste contaminated site including municipal solid waste for human and wildlife exposure, comprehensive study of join human exposure to the various types of BPRs (PBDEs), and upgrade the e-waste recycling system and strengthen incinerators for e-waste or plastic material in the integrated solid waste management system.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11356-022-24538-9.

Author contribution **MA, SM, and NB:** methodology, validation, writing—review and editing. **SSM:** conceptualization, validation, writing—review and editing. **ZN:** conceptualization, methodology, validation, formal analysis, investigation, supervision. **SAM:** conceptualization, methodology, validation, resources, writing—original draft, writing—review and editing, project administration.

Funding The authors would like to thank the Health and Environment Research Center, Ilam University of Medical Sciences, Ilam, Iran for its support (Grant No:401H003/22).

Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval The authors would like to thank the Health and Environment Research Center, Ilam University of Medical Sciences, Ilam.

Consent to participate Not applicable.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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