Title

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

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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 are 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.

Chapter 1. Introduction

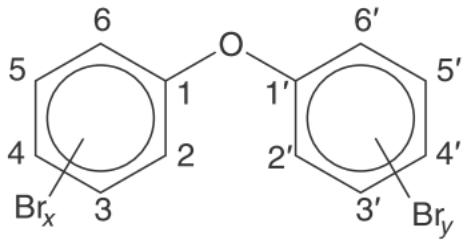
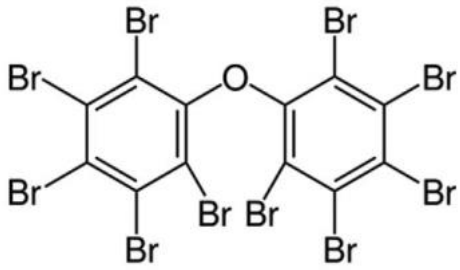
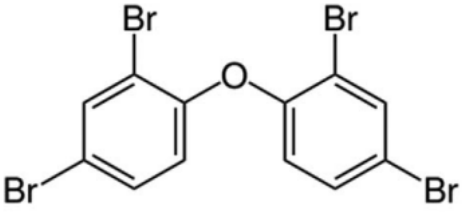
Nowadays, environmental pollution caused by persistent organic pollutants (POPs) has increased the challenge for scientific communities. POPs are defined as highly toxic chemical compounds, persistent in the environment, capable of bioaccumulating and biomagnifying. They are used in various applications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

Brominated flame-retardants (BFRs) and its sub-group polybrominated diphenyl ethers (PBDEs) as an organobromine compounds are considered a wide group of "additive" materials to prevent the increment of fire in industrial, chemical and domestic products including building materials, polyurethane foams, textiles, electronic devices, plastics, among others, for several past decades (Li, Liu et al. 2012, Liu, Zhao et al. 2017, Wu, Liu et al. 2021). The PBDEs compounds are additive materials, therefore, they are not link to their polymers by chemical reactions, thus easily leach to various environmental media, and recently, these compounds have become important and widespread environmental pollutants (Costa and Giordano 2014, Huang, Sjodin et al. 2020). It is estimated that about 600,000 metric tons of flame retardants produce in the globe annually. From this amount, 150,000 tons and 60,000 tons are brominated and chlorinated compounds, respectively (Darnerud, Eriksen et al. 2001).

The general characteristics of PBDEs or their congeners were depicted in Table 1 (Darnerud, Eriksen et al. 2001, Siddiqi, Laessig et al. 2003, Costa and Giordano 2014, Huang, Sjodin et al. 2020, Wu, Liu 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, Convention 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, ter Schure et al. 2004, Zhao, Wang et al. 2009, Wang, Chen 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 (Siddiqi, Laessig et al. 2003, Agrell, ter Schure et al. 2004, Kim, Ikonomou et al. 2005, Wang, Chen et al. 2010, Ni, Lu et al. 2013, Park, Park et al. 2020, Wu, Liu et al. 2021).

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 (℃)	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).

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 reported that the EDCs potential of PBDEs may react as agonists or antagonists at estrogen, androgen, and progesterone receptors and change the reproductive function of rats (Meerts, Letcher et al. 2001, Legler and Brouwer 2003, Li, Liu et al. 2012, Tian, Wang et al. 2016, Liu, Zhao et al. 2017, Cao, Zheng et al. 2018, Wei, Xiang et al. 2018). Some of these compounds are responsible for DNA damage *via* reactive oxygen species (ROS) generation pathway (Pellacani, Buschini et al. 2012, Montalbano, Albano 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, Butt 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 occurrence but also its severity (Hoffman, Lorenzo 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, Caglieri 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.

Chapter 2. Methods

2.1 Strategy of search and extraction of main data

This research does not required 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, Altman et al. 2009, Moher, Shamseer et al. 2015, Mirzaee, Noorimotlagh et al. 2021, Noorimotlagh, Azizi 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 systematically search was performed from May 1, 1980 to June 1, 2022 in four international literature data bank including Web of Science, Scopus, PubMed, and Google scholar engines by Medical subject Heading (MeSH) terms. The search terms with medical subject heading were used in all possible combinations (Supplementary section). After finishing the article search, two independent reviewers (SAM, SM) imported all articles to Endnote and Mendeley software for removing duplicate articles. Finally, a data list was applied to extract the relevant findings from full texts of all the remaining studies. This form contains information such as Study ID, country, type of study, pollutant(s), and type of cancer, study model, number of cases, main finding, mechanism (mode of action) and biological end-point. Fig. 1 depicted a Summary of PRISMA protocol in terms of records selection method.

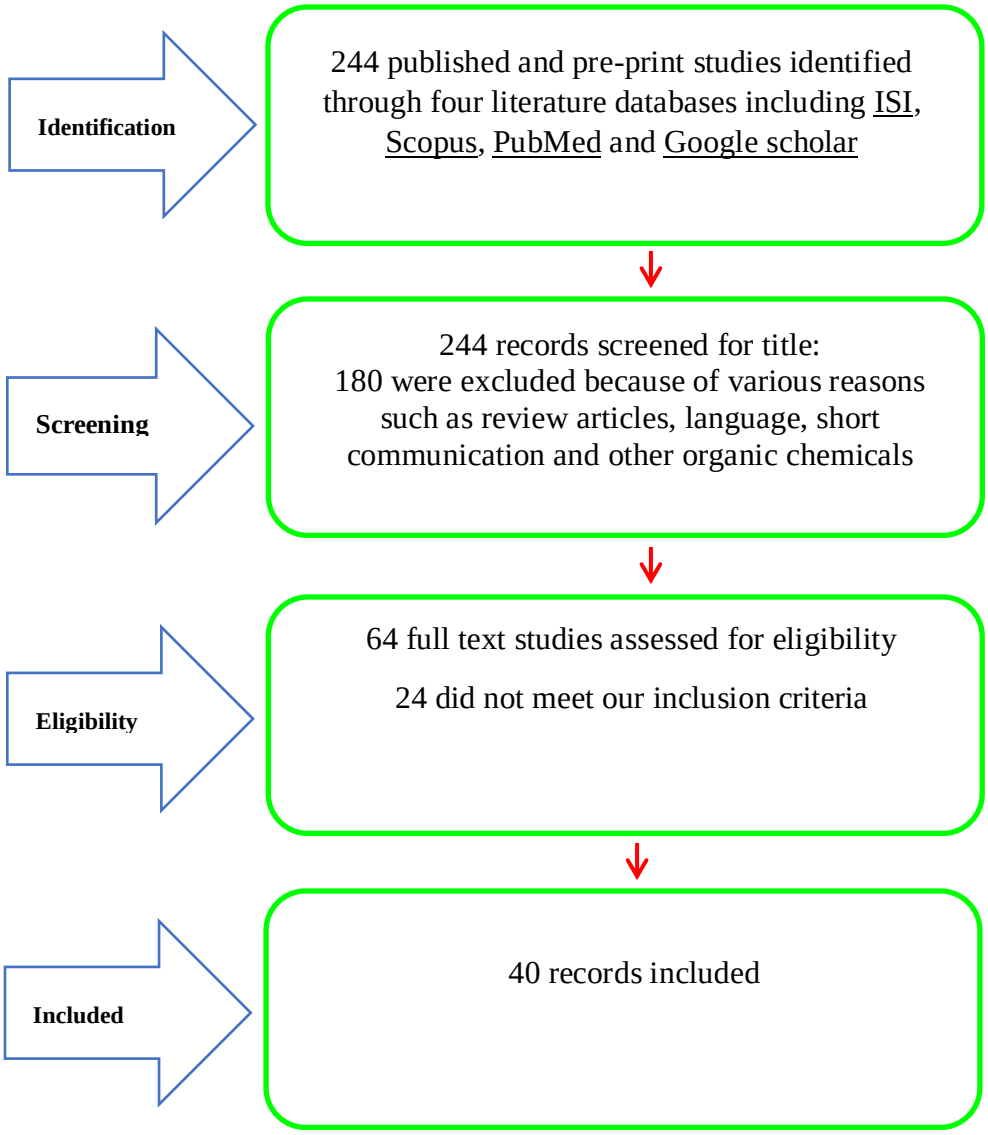


Fig. 1 Summary of PRISMA protocol in terms of records selection method.

2.2 Inclusion and exclusion criteria

Then reviewers screened all articles through title and abstract based on 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 about other chemicals.

2.3 Evaluation of the quality of reviewed records

In order to assess of the quality of reviewed records, the ARRIVE checklist were applied (Moher, Schulz et al. 2001, Kilkenny, Browne et al. 2010). This guideline has been fulfillment 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 evaluate the results of the studies and finally, represent 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).

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/Generalisability,translation)	7.29	19.11	73.6
20 (Discussion/Funding)	29.13	2.43	68.44

Chapter 3. 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, Sleight et al. 1982, Gupta, McConnell et al. 1983, Jensen, Sleight et al. 1983, Jensen, Sleight et al. 1984, Williams, Tong et al. 1984, Kavanagh, Rubinstein et al. 1985, Rezabek, Sleight et al. 1989, Rangga-Tabbu and Sleight 1992, Chhabra, Bucher et al. 1993, Meerts, Letcher et al. 2001, Madia, Giordano et al. 2004, Hu, Xu et al. 2007, He, He et al. 2008, Song, Duarte et al. 2009, Zhao, Wang et al. 2009, Tagliaferri, Caglieri et al. 2010, Man, Lopez et al. 2011, Li, Liu et al. 2012, Pellacani, Buschini et al. 2012, Sakamoto, Inoue et al. 2013, Zhang, Kuang et al. 2013, Harvey, Osborne et al. 2015, Qu, Yu et al. 2015, Wang, Ruan et al. 2015, Terrell, Rosenblatt et al. 2016, Tian, Wang et al. 2016, Hoffman, Lorenzo et al. 2017, Liu, Zhao et al. 2017, Zhang, Li et al. 2017, He, Peng et al. 2018, Leonetti, Butt et al. 2018, Wei, Xiang et al. 2018, Han, Wang et al. 2019, Hurley, Goldberg et al. 2019, Kanaya, Bernal et al. 2019, Li, Feldman et al. 2019, Tang, Li et al. 2019, Zhang, Peng et al. 2019, Huang, Sjodin et al. 2020, Zhao, Tang et al. 2022). The main information, mechanism and biological end-points of forty reviewed and included studies is provided in Table 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 to 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 BFRs-induced human neoplasia (Zhao, Wang et al. 2009, Terrell, Rosenblatt et al. 2016, Hoffman, Lorenzo et al. 2017, Liu, Zhao et al. 2017, He, Peng et al. 2018, Li, Feldman et al. 2019, Huang, Sjodin et al. 2020), ten studies are associated to animal-related neoplasia (Jensen, Sleight et al. 1982, Gupta, McConnell et al. 1983, Jensen, Sleight et al. 1983, Jensen, Sleight et al. 1984, Williams, Tong et al. 1984, Rezabek, Sleight et al. 1989, Rangga-Tabbu and Sleight 1992, Chhabra, Bucher et al. 1993, Sakamoto, Inoue et al. 2013, Harvey, Osborne 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).

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, Sleight 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 & Nasal tumor
(Jensen, Sleight et al. 1983), USA	Case-control study	345-HBB	Rat	42	Hepatic tumor
(Gupta, McConnell et al. 1983), USA	Case-control study	PBBs	Fischer Rat and B6C3F Mice	344	Hepatocellular carcinoma
(Jensen, Sleight et al. 1984), USA	Case-control study	Firemaster BP-6	Female Sprague-Dawley Rats	36	-
(Williams, Tong et al. 1984), USA	Case-control study	PBBs	Adult male Fischer F-344 rats, Adult male CD-l mice, Adult male Syrian hamsters	-	Liver cancer
(Kavanagh, Rubinstein et al. 1985), USA	Case-control study	Firemaster BP-6, (2,4,5-HBB), (3,4,5-HBB), (3,4-TBB)	Cell line Rat & Hamster	-	-
(Rezabek, Sleight et al. 1989), USA	Experimental study	Firemaster BP-6 , 345-HBB	Rat	23	Hepatic tumor
(Chhabra, Bucher et al. 1993), North Carolina, USA	Case-control study	PBBs	F344/N Rats B6C3F1 Mice	480	-
(Meerts, Letcher 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, Giordano et al. 2004), USA	Case-control study	PBDE-99	Human 132-1N1 astrocytoma cells	-	-
(Hu, Xu et al. 2007), China	Case-Control Study	PBDE-209, PCBs	Human hepatoma Hep G2 line	-	Liver cancer
(He, He et al. 2008), China	Case-control study	BDE-47	Human neuroblastoma cells (SH-SY5Y)	-	Neuroblastoma
(Song, Duarte et al. 2009), USA	Case-control study	2-OH-BDE47 and 2-OH-BDE85	H295R adrenocortical carcinoma cells	-	Adrenocortical carcinoma cells

(Zhao, Wang et al. 2009), China	Case-control study	PBBs, PBDEs, PCBs	Tissue (liver, lung, kidney)	81	Kidney, liver, and lung cancer
(Tagliaferri, Caglieri et al. 2010), USA	Experimental study	BDE-47 and BDE-99	Human neuroblastoma cells (SK-N-MC)	-	Neuroblastoma
(Man, Lopez 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, Tang et al. 2012), China	Case-control study	BDE-47	Mouse Leydig tumor cells (mLTCs)	-	-
(Li, Liu 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
(Pellacani, Buschini et al. 2012), Italy	Case-control study	BDE-47, BDE-209	Human neuroblastoma cells (SK-N-MC)	-	-
(Sakamoto, Inoue et al. 2013), Japan	Case-control study	PBO, DBDE	C3H/HeNCrl Mice CAR knockout and wild type Mice	39	Liver cancer
(Harvey, Osborne et al. 2015), USA	Case-control study	TBBPA	Tissue from Wistar Han Rats	41	Endometrial Carcinomas
(Qu, Yu et al. 2015), China	Case-control study	6-OH-BDE-47	Human lung cancer cell line A549 and H358	-	Human lung cancer cells
(Wang, Ruan et al. 2015), China	Case-control study	BDE-99	CRC cell line (HCT-116)	-	Colorectal cancer
(Tian, Wang et al. 2016), China	Case-control study	BDE-47	Human neuroblastoma cell (SH-SY5Y)	-	Neuroblastoma
(Terrell, Rosenblatt et al. 2016), USA	Nested case–control study	PBBs	Human (women)	253	Breast cancer
(Hoffman, Lorenzo et al. 2017), China	Case-control study	BDE-209 and TCEP	Human (women and men)	140	Papillary thyroid cancer
(Liu, Zhao et al. 2017), China	Case-control study	PBDEs and OH-PBDEs	Human (male and female)	33	Thyroid cancer
(He, Peng et al. 2018), China	Case–control study	BDE-47, 71, 99, 100, 183 and 209	Human (women)	374	Breast cancer

(Wei, Xiang et al. 2018), China	Case-control study	BDE-47	Human breast cancer cells (MCF-7)	-	Breast carcinoma
(Leonetti, Butt 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, Feldman et al. 2019), USA	Case-control study	PCBs, OCPs, PBB-153, PBDEs, SMCs	Breast adipose tissue samples	50	Breast Cancer
(Han, Wang et al. 2019), China	Case-Control Study	BDE-209	MLTC-1 cells (mouse Leydig tumor cells)	-	-
(Tang, Li et al. 2019), China	Case-Control Study	BDE-47	Human neuroblastoma cells (SK-N-SH)	-	Neuroblastoma
(Hurley, Goldberg et al. 2019), USA	Case-control study	BDE-153, BDE-47, BDE-100	-	-	-
(Kanaya, Bernal 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, Sjodin et al. 2020), USA	Nested Case-Control Study (of cohort data)	BDE-28	Human	742	Papillary Thyroid Cancer
(Montalbano, Albano 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, Tang et al. 2022), China	Case-Control study	PBDE-99 (2,2′,4,4′,5-pentabromodiphenyl ether)	Pregnant ICR mice	32	-

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(Kavanagh, Rubinstein et al. 1985), USA	Case-control study	Firemaster BP-6, (2,4,5-HBB), (3,4,5-HBB), (3,4-TBB)	Cell line Rat & Hamster	-	-
(Rezabek, Sleight et al. 1989), USA	Experimental study	Firemaster BP-6 , 345-HBB	Rat	23	Hepatic tumor
(Chhabra, Bucher et al. 1993), North Carolina, USA	Case-control study	PBBs	F344/N Rats B6C3F1 Mice	480	-
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(Madia, Giordano et al. 2004), USA	Case-control study	PBDE-99	Human 132-1N1 astrocytoma cells	-	-
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(He, He et al. 2008), China	Case-control study	BDE-47	Human neuroblastoma cells (SH-SY5Y)	-	Neuroblastoma
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(Man, Lopez 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, Tang et al. 2012), China	Case-control study	BDE-47	Mouse Leydig tumor cells (mLTCs)	-	-
(Li, Liu et al. 2012), China	Case-control study	PBDE-209	MCF-7 human breast cancer cell line, the multidrug-resistant	-	Breast, Ovarian, and Cervical Cancer Cells

			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		
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(Wang, Ruan et al. 2015), China	Case-control study	BDE-99	CRC cell line (HCT-116)	-	Colorectal cancer
(Tian, Wang et al. 2016), China	Case-control study	BDE-47	Human neuroblastoma cell (SH-SY5Y)	-	Neuroblastoma
(Terrell, Rosenblatt et al. 2016), USA	Nested case–control study	PBBs	Human (women)	253	Breast cancer
(Hoffman, Lorenzo et al. 2017), China	Case-control study	BDE-209 and TCEP	Human (women and men)	140	Papillary thyroid cancer
(Liu, Zhao et al. 2017), China	Case-control study	PBDEs and OH-PBDEs	Human (male and female)	33	Thyroid cancer
(He, Peng et al. 2018), China	Case–control study	BDE-47, 71, 99, 100, 183 and 209	Human (women)	374	Breast cancer
(Wei, Xiang et al. 2018), China	Case-control study	BDE-47	Human breast cancer cells (MCF-7)	-	Breast carcinoma
(Leonetti, Butt 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, Feldman et al. 2019), USA	Case-control study	PCBs, OCPs, PBB-153, PBDEs, SMCs	Breast adipose tissue samples	50	Breast Cancer
(Han, Wang et al. 2019), China	Case-Control Study	BDE-209	MLTC-1 cells (mouse Leydig tumor cells)	-	-
(Tang, Li et al. 2019), China	Case-Control Study	BDE-47	Human neuroblastoma cells (SK-N-SH)	-	Neuroblastoma

(Hurley, Goldberg et al. 2019), USA	Case-control study	BDE-153, BDE-47, BDE-100	-	-	-
(Kanaya, Bernal 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, Sjodin et al. 2020), USA	Nested Case-Control Study (of cohort data)	BDE-28	Human	742	Papillary Thyroid Cancer
(Montalbano, Albano 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, Tang et al. 2022), China	Case-Control study	PBDE-99 (2,2′,4,4′,5-pentabromodiphenyl ether)	Pregnant ICR mice	32	-

3.1. Quality assessment of the reviewed studies

ARRIVE guideline checklist with different items were used and the percentage of the all included studies were classified in Supplementary section (Tables S1 and S2). Based on the finding depicted in Tables S1 and S2. According to the finding shown in Table 2, most of the reviewed studies were obtained high rate, therefore they were reviewed in the present study.

Chapter 4. Discussion

Cancer mortality continues in the industrialized world despite the extensive research and quick progress shown in the last ten 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, Kunnumakara 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, Lorenzo 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, Wang et al. 2010). Human exposure to BRFs

occurs through the environment *via* water (Yang, Xie et al. 2015), air (Deng, Zheng et al. 2007, Wu, Liu et al. 2021), dust inhalation as well as food ingestion (Ni, Lu et al. 2013), and especially E-waste (contain plastic waste) municipal solid waste incinerators (Kim, Ikonomou et al. 2005, Zhao, Wang et al. 2009, Wang, Chen et al. 2010, Ni, Lu 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, Liu 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, Bucher et al. 1993, Zhao, Wang et al. 2009).

Multiple studies suggest exposure to various congener of BFRs (such as PBBs, PBDEs, and PCBs) can lead to tumors (Wu, He et al. 2020) and the greater tissue concentrations of FRs may contribute to the elevated cancer incidence in the disassembly locations (Zhao, Wang 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 of papillary thyroid cancer (PTC) (Hoffman, Lorenzo et al. 2017). Furthermore, in a cohort study with of 33 patients with of 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 are comparable to those in the general population in China (Liu, Zhao 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, Sjodin et al. 2020). The effect of BFRs also has been confirmed to induce gastrointestinal neoplasm (Gupta, McConnell 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, Sleight et al. 1982, Jensen, Sleight et al. 1983, Jensen, Sleight et al. 1984, Williams, Tong et al. 1984, Rezabek, Sleight et al. 1989, Smith, Francis et al. 1990, Chhabra, Bucher et al. 1993). For example, in a single oral dose study of FM (a commercial combination of PBBs), significantly enhanced the development of changed hepatocellular loci in rats challenged with N-Nitrosodimethylamine and N -nitrosopyrrolidine (NPYR) (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, Rubinstein et al. 1985). Other results also reported that exposure to PBDEs may influence the development and occurrence of breast cancer. In addition, Kwiecińska 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, Wróbel 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, Peng 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 be maintain homeostasis in cell (Lin, Jiang 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, Sarada et al. 2021). Meanwhile, mitochondrial function is disrupted by ERS and this caused that increased mitochondrial ROS production (Cao and Kaufman 2014, Arfin, Jha 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, Dinkova-Kostova 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 to DNA in neuroblastoma cells of human, which is mainly mediated by induction of OS (Pellacani, Buschini et al. 2012). It has also been shown that low concentrations of BFRs, can induce OS in neuroblastoma cells (Tagliaferri, Caglieri 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, He et al. 2008, Zhang, Li et al. 2017). Additionally, it was noted that PBDE-99, PBDE-47, and PBDE-209 may effects 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, Albano 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, Xiang 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. Fig. 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, has 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, Duarte 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 metabolism of pyrimidines and purines after OS, may have an adverse effect on human health (Wei, Xiang et al. 2018, Tang, Li 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, Liu 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 it acted like estrogen (Meerts, Letcher 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, Bernal 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 can increase the multiplicity of basophilic altered foci/adenomas in wild-type and CARKO mice (Sakamoto, Inoue 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 were 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, Osborne 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, Tang et al. 2012). In a related study, Han et al. demonstrated that deca-brominated 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, Wang 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, He 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 thyroid hormone function and neurobehavioral development (Man, Lopez et al. 2011, Leonetti, Butt 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, He et al. 2008).

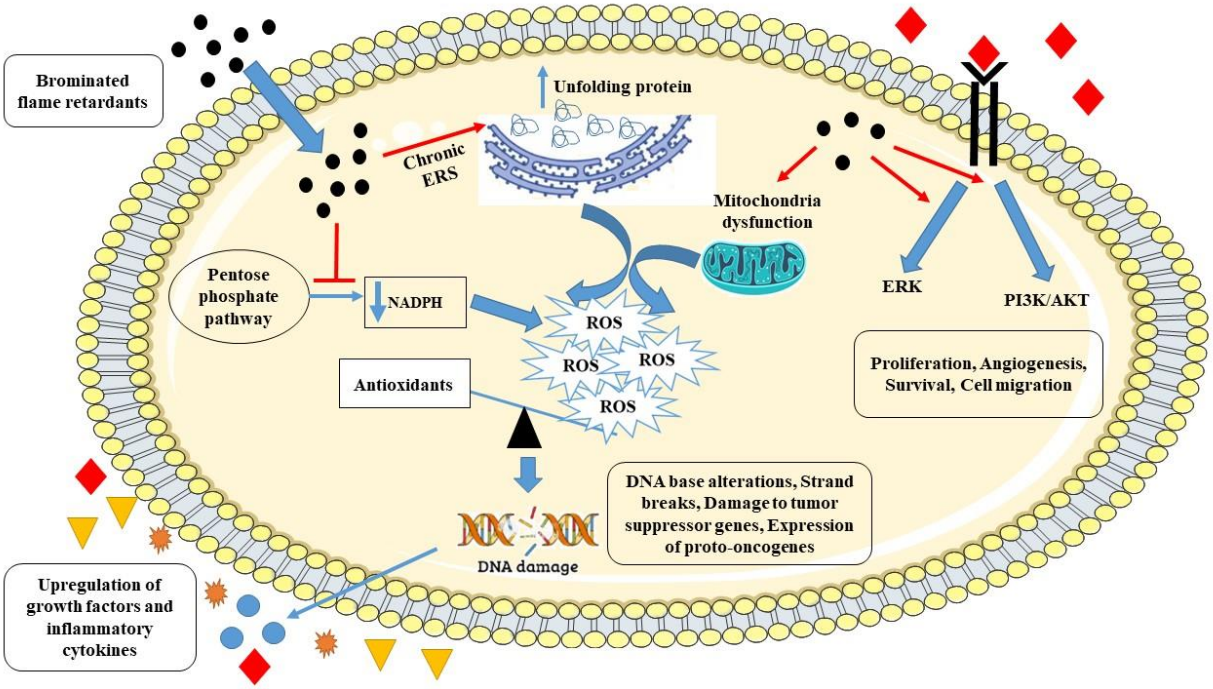

Fig. 2 Main processes that influence the risk of cancer progression and environmental exposure to BFRs. BFR accumulation impairs fundamental organelle function in cells and accelerates the aggregation of misfolded proteins in the ER lumen that cause ERS. Decreased protein synthesis, enhanced the protein 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.

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 up-regulated 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, Yu 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, Wang 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, Ruan 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, Feldman et al. 2019), and there was also no link between exposure to PBDEs and thyroid cancer (Aschebrook-Kilfoy, DellaValle et al. 2015). Similarly, in 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, Bernal 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, Rosenblatt 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, Xu et al. 2007, Kwiecińska, Wróbel 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, Kuang 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, Giordano et al. 2004). Overall, the conflicting findings suggested that more investigations are required to shows 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, Goldberg et al. 2019).

Chapter 5. 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 positive 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 shows 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, Arias 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.

The author’s declarations

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Consent to Participate

Not applicable

Consent to publish

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Declaration of competing interest

The authors have no relevant financial or non-financial interests to disclose.

*Ethics approval and consent to participate

Not applicable

*Availability of data and materials

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

*Authors' contributions

Mahdieh Azizi, Sanaz Mami and Nasrin Bazgir: Methodology, Validation, Writing - review & editing. Susana silva Martinez: Conceptualization, Validation, Writing - review & editing. Zahra Noorimotlagh: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Supervision. Seyyed Abbas Mirzaee: Conceptualization, Methodology, Validation, Resources, Writing - original draft, Writing - review & editing, Project administration.

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