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The metabolism of novel flame retardants and the internal exposure and toxicity of their major metabolites in fauna - a review

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Abstract

The worldwide production and usage of novel flame retardants increase their exposure to non-human fauna. Animals can accumulate and metabolize these novel flame retardants including novel halogenated flame retardants (NHFRs) and organophosphate flame retardants (OPFRs), which is of considerable significance to their internal exposure and final toxicities. In this review, recent studies on the metabolic pathways and kinetics of the two classes of novel flame retardants and the internal exposure and toxicity of their major metabolites are summarized. The results showed that the metabolic pathways of OPFRs were similar among various animals, while the metabolism kinetics (or toxicokinetics) were variable among species. O-dealkylation, hydroxylation and phase II conjunction were the most likely pathways for OPFRs. NHFRs might be metabolized through the pathways of debromination, hydroxylation, dealkylation, and phase II conjunction. We also suggested that di-alkyl phosphates (DAPs) and hydroxylated OPFRs (OH-OPFRs) were the predominant metabolites in the animal body. DAPs,

2,3,4,5-tetrabromobenzoic acid (TBBA) and 2-ethylhexyl tetrabromophthalate (TBMEHP) have relatively higher internal exposure levels in fauna, which might attribute to their high conversion rate and stability in the body. The metabolism of OPFRs and NHFRs in non-human animals may eliminate their acute toxicity but not their chronic toxicities (especially for endocrine-disrupting effects), which suggests attention should also be paid to the major metabolites. Based on the issues mentioned above, we proposed that the metabolic processes in multitrophic organisms, the transfer of major metabolites across the food web, and the co-exposure of the novel flame retardants and their metabolites in fauna are worth studying in the future.

Keywords: Novel halogenated flame retardants (NHFRs), organophosphate flame retardants (OPFRs), metabolism, metabolites, internal exposure

INTRODUCTION

In recent years, the use of traditional brominated flame retardants such as polybrominated diphenyl ethers (PBDEs), tetrabromobisphenol A (TBBPA), and hexabromocyclododecanes (HBCDs) has been restricted or prohibited[1]. As a result, novel halogenated flame retardants (NHFRs) and organophosphate flame retardants (OPFRs) have been increasingly used as substitutes in plastics, lubricants, rubber products, electronic equipment, furniture, food packaging, and other products[2-4]. Scholars have recently defined newly produced or newly detected brominated flame retardants as NHFRs[2,5-7]. The most representative NHFRs are 2-ethylhexyl tetrabromobenzoic acid (TBB), decabromodiphenyl ethane (DBDPE), and 1,2-bis (2,4,6-tribromophenoxy) ethane (BTBPE). Organophosphate flame retardants (OPFRs) have also been widely used as another kind of substitute in recent years[4]. The annual global production and usage of these novel flame retardants have also been growing rapidly in recent decades[8,9]. According to a research report from Ceresana, the global demand for flame retardants in 2018 was approximately 2.26 million tons, with brominated flame retardants (BFRs) and OPFRs accounting for 29% and 18% of the flame retardants used in the Asia Pacific region, respectively[10].

Similar to PBDEs, NHFRs have a stable brominated benzene ring structure, low solubility in water, and durability to physical, chemical, or biological degradation[9,11]. OPFRs can be divided into chlorinated (Cl-OPFRs), alkyl substituted (alkyl-OPFRs), and aryl substituted (aryl-OPFRs), according to the different ester bonds of substituents. Among them, Cl-OPFRs are more resistant to photolysis, chemical decomposition, and microbial degradation[4,12]. As a series of non-reactive additives[8,9], NHFRs and OPFRs can easily escape from the products, and distribute in various environmental matrices, such as indoor dust[13,14], atmosphere[15,16], soil[17,18], surface water[19-23], groundwater[24], and sediments[7,25], and enter into wastewater treatment plants[26-30]. With the extensive usage of new flame retardants, an increasing number of studies have gradually focused on the bioaccumulation, toxicity mechanism, and ecological risks of these pollutants.

Due to their lipophilicity, NHFRs and OPFRs can accumulate in various aquatic organisms[31-38]. Relatively higher concentrations of NHFRs and OPFRs have been detected in marine invertebrates, fish, marine mammals, and other biological samples (up to mg/g level by lipid weight), which were close to or even higher than those for traditional flame retardants (such as PBDEs and HBCDs)[11,20,39,40]. In addition, these novel flame retardants can be effectively transferred across the food chain/web and have shown potential biomagnification effects, for example, the NHFRs in food webs from the Bohai Sea, South China Sea, and Taihu Lake[41-44] and the OPFRs in food webs from the Laizhou Bay, South China Sea, and Taihu Lake[39,45,46]. Ecotoxicological studies have verified acute and chronic toxicity[47,48], reproductive toxicity[49,50], developmental toxicity[51-53], neurotoxicity[54-56], and endocrine-disrupting effects for several OPFRs[52,57,58]. The toxicological profile of NHFRs has been characterized for animals and humans[59], e.g., direct neurotoxicity, endocrine-related effects including dioxin-like effects, agonistic activity, steroidogenesis,

estrogenic activity, disruption of the neuroendocrine system, reproductive developmental toxicity, hepatotoxicity, and cytogenotoxicity[9,59,60].

Toxicokinetics is of particular relevance for understanding pollutant accumulation and toxicity within an organism, which determines the relationship between external exposure and internal exposure[61]. The metabolism of pollutants in organisms leads to the formation of products with different toxicities to their parent, which results in variations in their biological toxicity. In addition, novel FRs and metabolites share similar structures and might exhibit combined toxicity to organisms[62]. Therefore, the metabolism of novel FRs and the body burden of their metabolites were both important to reflect their actual risks to fauna. Several recent reviews have summarized the production, physicochemical properties, usage, environmental occurrence, analytical methods, bioaccumulation, human exposure, and toxicities of novel FRs[2,3,6,8,9,13,18,59,63-67]. However, very few studies have reviewed the mechanisms and kinetics of the metabolism of novel FRs in various organisms. Our previous two reviews of novel FRs only partly focused on metabolic processes[11,68]. Smythe *et al.* reviewed the biotransformation processes of FRs, but only BFRs were considered[69]. Another transformation review only provided information specific to the plant accumulation and transformation of the novel FRs[70]. A review by Yang *et al.* only provided information specific to the human internal exposure and health risks of OPFRs and their metabolites[71]. Accordingly, this review aims to summarize all of the published studies on the animal-mediated metabolism of NBFR and OPFRs, to compare the compound-specific metabolism pathways of these novel FRs, and to systematically collect the internal exposure results of the major metabolites in fauna. In addition, this study proposed the current and key knowledge gaps and research needs for future research on novel FR biomonitoring.

METHODOLOGY

Systematic searches covering the period from 1966 to 2023 were conducted on Web of Science and Google Scholar using the keywords of BFRs, OPFRs, organophosphorus esters (OPEs), or dechlorane plus (DPs) and keywords of metabolism, biotransformation, metabolites, toxicity, or internal exposure. The retrieved literature was carefully checked, and peer-reviewed studies related to non-human animals were selected. A total of 69 publications were finally selected and included in the review [Table 1].

In this review, three kinds of typical OPFRs were included, such as Cl-OPFRs [tris(2-chloroethyl) phosphate (TCEP), tris(2-chloroiso-propyl) phosphate (TCPP), and tris(2-chlorol-chloromethy) phosphate (TDCPP)], four alkyl-OPFRs [tributyl phosphate (TNBP), tris(2-butoxyethyl) phosphate (TBOEP), tri(2-ethylhexyl) phosphate (TEHP), and tripropyl phosphate (TPRP)], and five aryl-OPFRs [tripheny phosphate (TPHP), tricresyl phosphate (or so-called tris(methylphenyl) phosphate) (TCP or so-called TMPP), cresyl diphenyl phosphate (CDP), 2-ethylhexyl diphenyl phosphate (EHDPHP), and bisphenol A bis (diphenylphosphate) (BPA-BDP)]. NHFRs in this review are divided into the monoaromatic NHFRs [TBB, tis(2-ethylhexyl)-2,3,4,5-tetrabromophtalate (TBPH), pentabromotoluene (PBT), pentabromophenol (PBP), hexabromobenzene (HBB), pentabromoethylbenzene (PBEB), 2,3,4,5-tetrabromo-6-chlorotoluene (TBCT), tribromophenol (TBP), 2,4,6-tribromophenyl allyl ether (ATE), and pentabromobenzyl acrylate (PBBA)], polyaromatic NHFRs [DBDPE, BTBPE, tetrabromobisphenol A-bis(2,3-dibromopropylether) (TBBPA-DBPE)], naphthenic NHFRs [tetrabromoethylcyclohexane (TBECH)], and DPs.

In addition, *in silico* analysis was used for preliminary bioaccumulation and toxicity assessments of the major metabolites of novel FRs. The Log K_{OW} and BAF values were predicted for all the major metabolites using USEPA EPI suit v4.1. The EPA T.E.S.T., distributed by the EPA, was applied to estimate acute and chronic toxicities. For acute toxicity data, fathead minnow (96 h), *Daphnia magna* (48 h), and *T. pyriformis* (48 h) were considered based on the LC50. Developmental toxicity and mutagenicity were selected as the

Table 1. Summary of studies on metabolism of novel FRs in non-human fauna

No.	Locations	Species studied	Compounds	Studied area	Reference
Field study					
1	Great Lakes, USA	Herring gull egg	TNBP, TBOEP, TPHP, TDCPP, and TCPP	*In vitro* transformation pathway, kinetics, and metabolites formation	[31]
2	Great Lakes, USA	Bald eagle eggs	TBBA and TBMEHP	Internal exposure	[96]
3	Lake Huron, Canada	Herring gull plasma	BCPP, BDCPP, BBOEP, DNBP, DEHP, and DPHP	Internal exposure	[124]
4	Taihu Lake, China	Freshwater fish liver microsome	TCEP, TCPP, TDCPP, TIBP, TPHP, TCP, and EHDPHP	*In vitro* transformation kinetics	[39]
5	Taihu Lake, China	Freshwater fish liver microsome	ATE, BTBPE, TBPH, PBBA, TBCT, DBDPE, and TBECH	*In vitro* transformation kinetics	[41]
6	Troutman Lake, Austria	Stickleback	BCEP, DNBP, and DPHP	Internal exposure	[143]
7	Rivers in Beijing, China	Topmouth gudgeon (*Pseudorasbora parva*), crucian carp (*Carassius auratus*), and loach (*Misgurnus anguillicaudatus*)	BBOEP, DNBP, DEHP, and DPHP	Internal exposure	[38]
8	E-waste dismantling site in Guangdong, China	Chinese water snake (Enhydris chinensis), snake egg, and commo carp	BCPP, DNBP, DPHP, BBOEP, BCIPHIPP, and EHPHP, BBOEHEP, OH-TBOEP, OH-TPHP, 5-OH-EHDPHP	Internal exposure	[42]
9	South China Sea	Marine fish liver microsome	TBECH, PBT, PBP, TBB, HBB, TBPH, DBDPE, and TBBPA-DBPE	*In vitro* transformation kinetics	[44]
10	Costal area of Korea	Marine fish liver microsome	BTBPE, HBB, PBEB, PBT, TBB, and TBCT	*In vitro* transformation kinetics	[111]
11	Arctic sea	Marine mammal liver microsomes	DBDPE	*In vitro* transformation kinetics, and metabolites formation	[101]
12	East Greenland	Liver microsomes of polar bears and ringed seals	TNBP, TBOEP, TPHP, TDCPP, and TEHP	*In vitro* transformation pathway, kinetics, and metabolites formation	[144]
13	Pearl river estuary, China	Marine food web	BBOEP, DNBP, DPHP, BBOEHEP, OH-TBOEP, and OH-TNBP	Internal exposure	[125]
14	Across the globe	Fishmeal	BCEP, BDCPP, DMP, DPHP, DNBP, and DEHP	Internal exposure	[127]
15	Tarragona, Spain	Seafood species	BCEP, DPHP, DNBP, BDCPP, BBOEP, and DEHP	Internal exposure	[145]
16	Australia	Egg	BCEP, BCPP, BDCPP, DNBP, DEHP, BBOEP, and DCP	Internal exposure	[129]
17	30 countries	Cow milk	BCPP, DPHP, BDCPP, BBOEP, DCP, DNBP, BBOEHEP, and OH-BBOEP	Internal exposure	[126]
18	Beijing, China	Cow milk	BCPP, BDCPP, BBOEP, DNBP, DPHP, and DCP	Internal exposure	[146]
19	China	Meat meal, feather meal, and blood meal	BCEP BCPP, BDCPP, BBOEP, DNBP, DCP, DEHP, and DPHP	Internal exposure	[131]
20	Chengdu, China	Chickens, ducks, pigs, cattle, sheep, fish, and shrimp	BCEP, BCPP, BDCPP, DPHP, BBOEP, DNBP, and DEHP	Internal exposure	[130]
21	Southeast Queensland, Australia	Meat, fish, seafood, and egg	BCEP, BCPP, BDCPP, DNBP, DEHP, BBOEP, and DCP	Internal exposure	[128]
Laboratory study					
1	-	Embryonated eggs and chicks of Japanese quail	TPHP	*In ovo* transformation kinetics and metabolites formation	[73]

2	-	Embryonated eggs of Japanese quail	TDCPP and DPs	*In ovo* transformation kinetics and metabolites formation	[74]
3	-	American kestrel (*Falco sparverius*) egg	TBBPA-DBPE and BTPBE	*In ovo* transformation kinetics	[98]
4	-	Laying hens and egg	TCPP, TPHP, TNBP, TBOEP, and TEHP	*In vivo* transformation kinetics and metabolites formation	[76]
5	-	Chicken embryos	TCPP and TDCPP	*In vivo* transformation kinetics	[147]
6	-	Chicken embryos	DPs	*In vivo* transformation kinetics	[97]
7	-	Chicken embryo	TDCPP	*In vitro* transformation kinetics and metabolites formation	[75]
8	-	Bird and rat liver microsomes	BPA-BDP	*In vitro* transformation pathway, kinetics, and metabolites formation	[77]
9	-	Zebrafish	TPHP	*In vivo* transformation pathway, kinetics, and metabolites formation	[78]
10	-	Zebrafish	TPRP, TNBP, TBOEP, TCEP, TDCPP, and TCP	*In vivo* transformation pathway and metabolites formation	[148]
11	-	Zebrafish	EHDPHP	*In vivo* transformation pathway and metabolites formation	[84]
12	-	Zebrafish	TBECH and TBP	*In vivo* transformation pathway and kinetics	[113]
13	-	Zebrafish	PBT, HBB, BTBPE, and DBDPE	*In vivo* transformation kinetics	[105]
14	-	Zebrafish	DBDPE	*In vivo* transformation pathway and kinetics	[102]
15	-	Zebrafish	DBDPE	*In vivo* transformation pathway and kinetics	[103]
16	-	Chinese rare minnow	TNBP, TBOEP	*In vivo* transformation kinetics and metabolites formation	[82]
17	-	Chinese rare minnow	TEHP	*In vivo* transformation pathway, kinetics, and metabolites formation	[81]
18	-	Rainbow trout (*Oncorhynchus mykiss*)	BTBPE and TBPH	*In vivo* transformation kinetics	[149]
19	-	Rainbow trout (*Oncorhynchus mykiss*)	DPs	*In vivo* transformation kinetics	[109]
20	-	Rainbow trout (*Oncorhynchus mykiss*)	BTBPE	*In vivo* transformation kinetics	[112]
21	-	Rainbow trout (*Oncorhynchus mykiss*) liver microsome	TBBA	*In vitro* transformation pathway	[104]
22	-	Crucian carp	TNBP, TBOEP	*In vitro* transformation kinetics and metabolites formation	[80]
23	-	Crucian carp	CDP	*In vitro* transformation kinetics	[85]
24	-	Common carp	TCEP, TNBP, TBOEP, TCIPP, TDCPP, TPHP, and EHDPHP	*In vivo* transformation pathway, kinetics, and metabolites formation	[83]
25	-	Common carp	DPs	*In vivo* transformation kinetics	[108]

26	-	Fathead minnows (Pimephales promelas)	BTBPE, TBBPA-DBPE, TBPH, and TBB	*In vivo* transformation kinetics	[106]
27	-	Killifish (*Fundulus heteroclitus*)	TBPH	*In vivo* transformation kinetics	[114]
28	-	Redtail catfish and oscar fish	DPs	*In vivo* transformation kinetics	[110]
29	-	White rat	TEHP	*In vivo* transformation pathway and kinetics	[150]
30	-	Rat	TPHP	*In vivo* transformation pathway and metabolites formation	[134]
31	-	Rat	TCEP, TCPP, TDCPP, TCP, TPHP, and TNBP	*In vivo* transformation pathway and kinetics	[87]
36	-	Rat	BTBPE	*In vivo* transformation pathway and kinetics	[116]
37	-	Rat	DBDPE	*In vivo* transformation pathway and kinetics	[115]
38	-	Rat	TBB and TBPH	*In vivo* transformation pathway and kinetics	[120]
39	-	Rat	TBB and TBPH	*In vivo* transformation pathway, kinetics, and metabolites formation	[117]
40	-	Rat	TBPH	*In vivo* transformation kinetics and metabolites formation	[119]
41	-	Rat liver microsome	TPHP and TDCPP	*In vitro* transformation kinetics and enzyme mechanisms	[88]
42	-	Rat liver and intestinal subcellular fractions	TBB, TBPH	*In vitro* transformation pathway, kinetics, and metabolites formation	[118]
43	-	Earthworm (*Eisenia fetida*)	TNBP	*In vivo* transformation pathway and kinetics	[93]
44	-	Earthworm (*Eisenia fetida*)	TPHP	*In vivo* transformation pathway and kinetics	[94]
45	-	Earthworm (*Eisenia fetida*)	TBOEP	*In vivo* transformation pathway and kinetics	[95]
46	-	Earthworm (*Eisenia fetida*)	PBT, HBB, BTBPE, and DBDPE	*In vivo* transformation kinetics	[123]
47	-	Mudsnails (*Bellamya aeruginosa*)	PBT, HBB, and DBDPE	*In vivo* transformation pathway and kinetics	[121]
48	-	Marine mussel	TCP, TNBP, TBOEP, TPHP, TCPP, and EHDPHP	*In vivo* transformation kinetics	[92]
49	-	Clam (*Corbicula fluminea*)	PBT, HBB, BTBPE, and DBDPE	*In vivo* transformation kinetics	[122]
50	-	*Daphnia magna*	TPHP	*In vivo* transformation pathway and kinetics	[89]
51	-	*Daphnia magna*	TBOEP, TCEP, TDCPP, and TPHP	*In vivo* transformation kinetics	[91]
52	-	Invertebrates (*Daphnia magna*) and fish (*Oryzias latipes*)	TPHP	*In vivo* transformation pathway and kinetics	[90]

TNBP: tributyl phosphate; TBOEP: tris(2-butoxyethyl) phosphate; TPHP: tripheny phosphate; tripheny phosphate; TDCPP: tris(2-chlorol-chloromethy) phosphate; TCPP: tris(2-chloroiso-propyl) phosphate; TBBA: 2,3,4,5-tetrabromobenzoic acid; TBMEHP: 2-ethylhexyl tetrabromophthalate; BCPP: bis(1-chloro-2-propyl) phosphate; BDCPP: bis(1,3-dichloropropyl) phosphate; BBOEP: bis(2-butoxyethyl) phosphate; DNBP: di-n-butyl phosphate; DEHP: di(2-ethylhexyl) phosphate; DPHP: diphenyl phosphate; TCEP: tris(2-chloroethyl) phosphate; TCPPL: tris(2-chloroiso-propyl) phosphate; PBEB: pentabromoethylbenzene; TDCPP: tris(2-chlorol-chloromethy) phosphate; TPHP: tripheny phosphate; TCP: tris(2-chloroiso-propyl) phosphate; EHDPHP: 2-ethylhexyl diphenyl phosphate; ATE: 2,4,6-tribromophenyl allyl ether; BTBPE: 1,2-bis (2,4,6-tribromophenoxy) ethane; TBPH: tis(2-ethylhexyl)-2,3,4,5-tetrabromophtalate; TBB: 2-ethylhexyl tetrabromobenzoic acid; TEHP: tri(2-ethylhexyl) phosphate; PBBA: pentabromobenzyl acrylate; OH: hydroxylated; TBCT: 2,3,4,5 tetrabromo-6-chlorotoluene; DBDPE: decabromodiphenyl ethane; OH-EHDPHP: 2-ethyl-hydroxyhexyl diphenyl phosphate; TBECH: tetrabromoethylcyclohexane; BCEP: bis(2-chloroethyl) phosphate; DNBP: di-n-butyl phosphate; BCIPHIPP: 1-hydroxy-2-propyl bis(1-chloro-2-propyl) phosphate; EHPHP: 2-ethylhexyl phenyl phosphate; BBOEHEP: bis(2-butoxyethyl) hydroxyethyl phosphate; OH-TBOEP: bis(2-butoxyethyl) 3-hydroxyl-2-butoxyethyl phosphate; OH-TPHP: hydroxyphenyl diphenyl phosphate; TBBPA-DBPE: tetrabromobisphenol A-bis(2,3-dibromopropylether); DCP: dicresyl phosphate; DPs: dechlorane plus; BPA-BDP: bisphenol A bis (diphenylphosphate); TBP: tribromophenol; CDP: cresyl diphenyl phosphate; PBT: pentabromotoluene; HBB: hexabromobenzene.

endpoints for chronic toxicity.

METABOLIC TRANSFORMATION PROCESS OF NOVEL FLAME RETARDANTS

OPFRs

Birds

Studies on the metabolic transformation of OPFRs in avian species are mainly conducted by *in vitro* (i.e., liver microsome experiment) and *in ovo* methods (i.e., egg exposure experiment) [Table 2]. An *in vitro* study using liver microsomes of herring gulls from the Great Lakes found a general metabolic pathway for OPFRs in forming their respective di-alkyl phosphates (DAPs)[31]. The O-dealkylation pathway was confirmed for TPHP *in vitro* in chicken embryonic hepatocytes[72] and *in ovo* in embryonated eggs and chicks of Japanese quail[73], where this pathway was suggested to depend on cytochrome P450 (CYP) enzymes. Briels *et al.* also showed the formation of bis(1,3-dichloropropyl) phosphate (BDCPP) in the embryo of Japanese quail during *in ovo* exposure with TDCPP[74]. An efficient transformation from TDCPP to BDCPP was found in chicken embryonic hepatocytes with a molar conversion ratio of 1:1, indicating the significance of O-dealkylation in the metabolism of Cl-OPFRs[75]. BDCPP could not be metabolized further in chicken embryonic hepatocytes after 36 h of exposure[75].

In a 14 d exposure and 28 d depuration experiment of laying hens, the half-lives ($t_{1/2}$) of five OPFRs were in the range of 11.3-106 d in the egg, with DAPs detected as main metabolites[76]. Other kinetic results showed that the non-halogenated OPFRs (i.e., TNBP, TBOEP, and TPHP) were more quickly metabolized by the liver microsomes, whereas the halogenated OPFRs were transformed to their metabolites (DAPs) more efficiently to non-halogenated OPFRs[31]. In another study, no significant metabolism of BPA-BDP was found in the herring gull liver microsomes[77].

Fish and marine mammals

The metabolism of OPFRs in fish was found to be more complex than that in birds. Wang *et al.* first elucidated the metabolic pathways of TPHP, TPRP, TNBP, TBOEP, TCEP, TDCPP, and TCP in zebrafish[78,79], including O-dealkylation, hydroxylation, di-hydroxylation, dichlorination (for Cl-OPFRs) and glucuronic acid (GLU) conjugation after hydroxylation. DAPs were detected as the major metabolite of OPFRs, which were mainly distributed in the fish liver

Table 2. Available information on metabolism pathways and toxicokinetics of OPFRs in non-human fauna

Compounds	Species/assays	Methods	Metabolism pathway	Major metabolites	Available toxicokinetic constants	References
TCEP	Laying hens	*In vivo*	O-dealkylation	BCEP	22.6 d ($t_{1/2}$)	[76]
	Zebrafish	*In vivo*	O-dealkylation and hydroxylation	BCEP and OH-BCEP	-	[79]
	Common fish	*In vivo*	-	-	9.2-18.3 h ($t_{1/2}$)	[83]
	Liver microsomes of yellow catfish, catfish and crucian carp	*in vitro*	-	-	0.50-1.10 mL/min/mg protein	[39]
	Daphnia magna	*In vivo*	-	-	4.13-6.03 h ($t_{1/2}$ for waterborne exposure)	[91]
TCPP	Laying hens	*In vivo*	O-dealkylation		30.1 d ($t_{1/2}$)	[76]
	Herring gull liver microsome	*In vitro*	O-dealkylation	BCPP	27 ± 1	[31]
	Catfish liver microsome	*In vitro*	-	-	1.33 mL/min/mg protein	[39]
	Common fish	*In vivo*	O-dealkylation and hydroxylation	BCIPP and BCIPHIPP	10.5-14.5 h ($t_{1/2}$)	[83]
TDCPP	Herring gull liver microsome	*In vitro*	O-dealkylation	BDCPP	8 ± 1 mL/min/mg protein	[31]
	Embryonated eggs of Japanese Quail	*In vitro*	O-dealkylation	BDCPP	-	[74]
	Chicken embryo	*In vitro*	O-dealkylation	BDCPP	-	[75]
	Zebrafish	*In vivo*	O-dealkylation	BDCPP	-	[79]
	Common fish	*In vivo*	Hydroxylation	BDCPP and OH-BDCPP	9.4-19.8 h ($t_{1/2}$)	[83]
	Liver microsomes of yellow catfish, catfish and crucian carp	*In vitro*	-	-	0.944-0.778 mL/min/mg protein	[39]
	Rat	*In vivo*	Glutathione conjugation	GSH-TDCPP	-	[151]
	Rat	*In vivo*	O-dealkylation	BDCPP	-	[152]
	Rat liver microsome	*In vitro*	O-dealkylation	1,3-dichloro-2-propanol, 3-chloro-1,2-propanediol, and BDCPP	-	[151]
	Rat liver microsome	*In vitro*	-	-	1.8083 h ($t_{1/2}$)	[88]
	Daphnia magna	*In vivo*	-	-	4.36-6.60 h ($t_{1/2}$ for waterborne exposure)	[91]
TNBP	Laying hens	*In vivo*	O-dealkylation		82.5 d ($t_{1/2}$)	[76]
	Herring gull liver microsome	*In vitro*	O-dealkylation	DNBP	73 ± 4 mL/min/mg protein	[31]
	Marine mammal liver microsome	*In vitro*	O-dealkylation	DNBP	-	[73]
	Zebrafish	*In vivo*	O-dealkylation, hydroxylation, and GLU conjugation	DNBP, OH-TNBP, and GLU-TNBP	-	[79]
	Rare minnow	*In vivo*	O-dealkylation and hydroxylation	DNBP and OH-TNBP	0.6-2.0 d ($t_{1/2}$)	[82]

	Crucian carp liver microsomes	*In vitro*	O-dealkylation and hydroxylation	DNBP and OH-TNBP	3.1 mL/min/mg protein	[80]
	Common fish	*In vivo*	O-dealkylation and hydroxylation	DNBP	8.8-15.9 h ($t_{1/2}$)	[83]
	Liver microsomes of yellow catfish, catfish and crucian carp	*In vitro*	-	-	0.74-1.17 mL/min/mg protein	[39]
	Mice	*In vivo*	O-dealkylation	DNBP	-	[87]
	Marine mussel	*In vivo*	-	-	1.93 d ($t_{1/2}$)	[92]
	Earthworm	*In vivo*	O-dealkylation, hydroxylation, ethylene glycol conjugation, sulfation, and phosphate conjugation	DNBP, OH-TNBP, PA-TNBP, DNBHEP, SUL-TPHP, and GLU-TPHP	-	[93]
TBOEP	Laying hens	*In vivo*	O-dealkylation	BBOEP	11.3 d ($t_{1/2}$)	[76]
	Herring gull liver microsome	*In vitro*	O-dealkylation	BBOEP	53 ± 8 mL/min/mg protein	[31]
	Marine mammal liver microsome	*In vitro*	O-dealkylation	BBOEP	-	[73]
	Zebrafish	*In vivo*	O-dealkylation, hydroxylation, and GLU conjugation	BBOEP, BOEHEP, BBOEHEP, GLU-TBOEP, and GLU-BBOEHEP	-	[79]
	Rare minnow	*In vivo*	O-dealkylation and hydroxylation	BBOEHEP, BBOEP, and OH-TBOEP	0.7-2.3 d ($t_{1/2}$)	[82]
	Crucian carp liver microsomes	*In vitro*	O-dealkylation and hydroxylation	BBOEHEP, BBOEP, and OH-TBOEP	3.9 mL/min/mg protein	[80]
	Common fish	*In vivo*	O-dealkylation and hydroxylation	BBOEHEP, BBOEP, and OH-TBOEP	10.5-17 h ($t_{1/2}$)	[83]
	Daphnia magna	*In vivo*	-	-	4.28-5.33 h ($t_{1/2}$ for waterborne exposure)	[91]
	Earthworm	*In vivo*	O-dealkylation and hydroxylation	BBOEP, BOEHEP, BBOEHEP, OH-TBOEP, *etc.*	-	[95]
TEHP	Laying hens	*In vivo*	O-dealkylation	DEHP	43.3 d ($t_{1/2}$)	[76]
	Marine mammal liver microsome	*In vitro*	O-dealkylation	DEHP	-	[144]
	Rare minnow	*In vivo*	O-dealkylation, hydroxylation, and GLU conjugation	DEHP, OH-TEHP, and GLU-TEHP	1-2.57 d ($t_{1/2}$)	[81]
TPRP	Zebrafish	*In vivo*	O-dealkylation, hydroxylation, and GLU conjugation	DPRP, OH-DPRP, and GLU-TPRP	-	[79]
TPHP	Laying hens	*In vivo*	O-dealkylation	DPHP	-	[76]
	Herring gull liver microsome	*In vitro*	O-dealkylation	DPHP	22 ± 2 mL/min/mg protein	[31]
	Marine mammal liver microsome	*In vitro*	O-dealkylation	DPHP	-	[73]
	Embryonated eggs and chicks of Japanese Quail	*In vivo*	O-dealkylation	DPHP, OH-TPHP, 2OH-TPHP, and OH-DPHP,	1.1-1.8 d ($t_{1/2}$)	[74]
	Zebrafish	*In vivo*	O-dealkylation, hydroxylation, di-hydroxylation, and GLU conjugation	MPHP and GLU-TPHP	20.5 h ($t_{1/2}$)	[78]
	Common fish	*In vivo*	O-dealkylation and hydroxylation	DPHP and OH-TPHP	9.7-18.6 h ($t_{1/2}$)	[83]
	Black carp (*O. latipes*)	*In vivo*	O-dealkylation, hydroxylation, methylation, GLU conjugation, CYS conjugation, and sulfation	DPHP, OH-TPHP, SH-TPHP, SUL-TPHP, GLU-TPHP, and MET-TPHP	-	[90]
	Liver microsomes of yellow	*In vitro*	-	-	1.33-1.50 mL/min/mg protein	[39]

	catfish, catfish and crucian carp					
	Rat liver microsome	*In vitro*	-	-	0.1531 h ($t_{1/2}$)	[88]
	Mice	*In vivo*	O-dealkylation	DPHP	-	[87]
	Marine mussel	*In vivo*	-	-	1.47 d ($t_{1/2}$)	[92]
	Daphnia magna	*In vivo*	O-dealkylation, hydroxylation, GSH conjugation, CYS conjugation, and sulfation	DPHP, OH-TPHP, GSH-TPHP, CYS-TPHP, and SUL-TPHP	-	[89]
	Daphnia magna	*In vivo*	-	-	6.66-7.88 h ($t_{1/2}$ for waterborne exposure)	[91]
	Earthworm	*In vivo*	O-dealkylation, hydroxylation, CYS conjugation, mercaptolactic acid conjugation, mercaptoethanol conjugation, and GLU conjugation	DPHP, OH-TPHP, CYS-TPHP, MCL-TPHP, MCH-TPHP, and GLU-TPHP	-	[94]
TCP	Zebrafish	*In vivo*	O-dealkylation, hydroxylation, and GLU conjugation	DCP, OH-DCP, and GLU-TCP	-	[79]
	Mice	*In vivo*	O-dealkylation	DCP	-	[87]
	Marine mussel	*In vivo*	-	-	3.15 d ($t_{1/2}$)	[92]
	Liver microsomes of yellow catfish, catfish and crucian carp	*In vitro*	-	-	2.11-2.71 mL/min/mg protein	[39]
CDP	Crucian carp liver microsomes	*In vitro*	-	-	1,2700 ± 2,120 mL/min/mg protein	[85]
EHDPHP	Common fish	*In vivo*	O-dealkylation and hydroxylation	EHPHP and OH-EHDPHP	8.8-17.6 h ($t_{1/2}$)	[83]
	Zebrafish	*In vivo*	O-dealkylation, hydroxylation, GLU conjugation, and sulfation	EHPHP, OH-EHDPHP, DPHP, OH-DPHP, GLU-DPHP, MPHP, and SUL-EHDPHP	-	[84]
	Liver microsomes of yellow catfish, catfish and crucian carp	*In vitro*	-	-	2.44-3.86 mL/min/mg protein	[39]
	Marine mussel	*In vivo*	-	-	5.78 d ($t_{1/2}$)	[92]
BPA-BDP	Rat liver microsomes	*In vitro*	O-dealkylation and hydroxylation	DPHP, BPA, phenol, BPA-(diphenyl phosphate), BPA-(diphenyl phosphate)-(monophenyl phosphate), BPA-BDP + O metabolite, *etc.*	-	[77]
	Bird liver microsomes	*In vitro*	Too slow	-	-	[77]

-: Not available. BCEP: bis(2-chloroethyl) phosphate; BCPP: bis(1-chloro-2-propyl) phosphate; BDCPP: bis(1,3-dichloropropyl) phosphate; BCIPHIPP: 1-hydroxy-2-propyl bis(1-chloro-2-propyl) phosphate; GSH: glutathione; PBEB: pentabromoethylbenzene; TDCPP: tris(2-chlorol-chloromethy) phosphate; DNBP: di-n-butyl phosphate; TNBP: tributyl phosphate; OH: hydroxylated; GLU: glucuronic acid; DNBP: di-n-butyl phosphate; SUL: sulfation; TPHP: tripheny phosphate; tripheny phosphate; BBOEP: bis(2-butoxyethyl) phosphate; TBB: 2-ethylhexyl tetrabromobenzoic acid; DNBP: di-n-butyl phosphate; BBOEHEP: bis(2-butoxyethyl) hydroxyethyl phosphate; OH-TBOEP: bis(2-butoxyethyl) 3-hydroxyl-2-butoxyethyl phosphate; DEHP: di(2-ethylhexyl) phosphate; TEHP: tri(2-ethylhexyl) phosphate; OH-DPRP: hydroxylated DPRP; MET: methylation; CYS: cysteine; DCP: dicresyl phosphate; TCP: tricresyl phosphate; EHPHP: 2-ethylhexyl phenyl phosphate; OH-EHDPHP: 2-ethyl-hydroxyhexyl diphenyl phosphate; EHDPHP: 2-ethylhexyl diphenyl phosphate; BPA: bisphenol A; BDP: bis diphenylphosphate.

and intestine[78,79]. Our previous *in vivo* and *in vitro* studies have also identified that the hydroxylation, other oxidation pathways, and GLU conjugation, as well as the O-dealkylation process from TBOEP, TNBP, and TEHP to their respective DAPs, are significant for the metabolism of OPFRs in fish (Chinese rare minnow)[80-82]. In addition, Tang *et al.* quantified the formation of DAPs and hydroxylated OPFRs (OH-OPFRs) metabolites in common fish exposure experiments of TCPP and EHDPHP[83]. The *in vitro* biotransformation pathways [including O-dealkylation, hydroxylation, sulfation (SUL), and GLU conjugation] of EHDPHP were also identified in the liver and intestine homogenates of zebrafish[84]. Furthermore, the gut microbiota of zebrafish was analyzed to possess CYP450 catalysis-related enzymes, which might also be involved in the EHDPHP transformation[84].

Considering the liver to be the most important tissue for the metabolism of flame retardants in fish, liver microsomes isolated from various fish species have been used as a promising approach to evaluate the metabolism kinetics of OPFRs. According to two previous *in vitro* studies, the hepatic metabolism rates of OPFRs in fish were structure dependent, where aryl-OPFRs or OPFRs with larger Log K_{OW} have faster metabolism rates than others under the same conditions[39,85]. In a study of hepatic *in vitro* metabolism of OPFRs in East Greenland polar bears and ringed seals, the mass balance results indicated a very efficient conversion from TDCPP and TPHP to their respective DAPs[77], which was similar to the findings in fish[78,80,86]. Both NADPH-dependent enzymes (e.g., CYP450 enzymes) and NADPH-independent enzymes are involved in the transformation of OPFRs into DAPs in the marine mammal liver[77].

Rodents

Our previous review provided a basic discussion on the metabolic processes of OPFRs in rodents (including rats and mice), where dealkylation, hydroxylation, glutathione (GSH) conjugation, and GLU conjunction were proposed as the main metabolic pathways[68].

The latest studies can provide novel insights into the metabolism of OPFRs in rodents. A study of BPA-BDP metabolism in rat liver microsomes suggested that the metabolism rate of BPA-BDP was much slower than TPHP and O-dealkylation and oxidation were the main biotransformation pathways for BPA-BDP[77]. In PM2.5-bound OPFR exposure at environmentally realistic concentrations, chlorinated OPFRs (TDCPP, TCEP, and TCPP) accumulated more in mice than other OPFRs (TCP, TPHP, and TNBP)[87]. The DAPs [dicresyl phosphate (DCP), diphenyl phosphate (DPHP), and di-n-butyl phosphate (DNBP)] were detected as urinary metabolites for their corresponding parents in the mice[87]. TPHP was found to be more easily metabolized than TDCPP by rat liver microsomes, which can explain the accumulation potential for chlorinated OPFRs in rodents[88]. NADPH-independent enzymes play an important role in the metabolism of OPFRs in rodents. CYP2E1, CYP2D6, CYP1A2, and CYP2C19 were identified as the specific enzymes for the metabolism of TDCPP, whereas CYP2E1 was the primary CYP450 isoform for the *in vitro* metabolism of TPHP[88].

Invertebrates

Although many studies are available concerning the metabolism of OPFRs in vertebrates, studies in invertebrates are insufficient. *Daphnia magna* is a primary consumer in aquatic ecosystems and prey for higher-level consumers, which was used to identify the biotransformation mechanism of TPHP in aquatic invertebrates[89,90]. Both phase I reactions (hydrolysis, hydroxylation, reduction, and (de)hydration) and phase II reactions [GSH conjugation, cysteine (CYS) formation, and sulfate conjugation] were identified for the metabolism of TPHP in *D. magna*[89]. More than 70% of the TPHP in water was accumulated by the *D. magna* during 24 h of exposure, and the major biotransformation pathway was estimated to be CYS conjugation and sulfation based on the depuration ratio[89]. In an exposure study of TPHP using an aquatic

food chain (*R. subcapitata*, *D. magna*, and *O. latipes*), elevated bioconcentration factor (BCF) of TPHP was found along with trophic level[90]. Liu *et al.* investigated the bioaccumulation characteristics and relative importance of different exposure routes in OPFR exposure (TBOEP, TCEP, TDCPP, and TPHP) to *D. magna*, where dietary exposure showed a generally lower uptake rate than waterborne exposure[91]. TPHP has a higher uptake rate and lower depuration rate in *D. magna* than those of other OPFRs[91]. The structure-relative bioaccumulation and depuration of OPFRs have also been reported in a recent laboratory study of marine mussels (*Mytilus galloprovincialis*), where a relatively higher uptake rate was found for the aryl-OPFRs (TPHP, TCP, and EHDPHP)[92].

As a hotspot terrestrial specie, earthworms have recently been used to assess OPFR metabolism. The metabolism of TPHP and TNBP has previously been studied *in vivo* in earthworms (*E. fetida*)[93,94]. Major phase I metabolites for TPHP are DPHP, para- and meta-hydroxyphenyl diphenyl phosphate (OH-TPHP), and $(OH)_2$-TPHP[94], while DNBP and dibutyl hydroxybutyl phosphate (OH-TNBP) were the major phase I metabolites for TNBP[93]. Reported phase II metabolites included the thiol conjugates and glucoside conjugates of TPHP and TNBP[93,94]. TBOEP can accumulate in *E. fetida* and activate the CYP and glutathione pathways to promote the metabolism of TBOEP[95]. Bis(2-butoxyethyl) phosphate (BBOEP), 2-butoxyethyl hydroxyethyl phosphate (BOEHEP), bis(2-butoxyethyl) hydroxyethyl phosphate (BBOEHEP), and bis(2-butoxyethyl) 3-hydroxyl-2-butoxyethyl phosphate (3-OH-TBOEP) were identified as the main metabolites of TBOEP in earthworms[95].

NHFRs

Birds

To the best of our knowledge, very few studies on the metabolism and biotransformation of NBFRs in birds have been reported [Table 3]. 2,3,4,5-Tetrabromobenzoic acid (TBBA) and 2-ethylhexyl tetrabromophthalate (TBMEHP) were respectively detected as the metabolites of TBB and TBPH in eagle eggs from the Great Lakes Region, indicating that O-dealkylation occurred for the metabolism processes of the two NHFRs[96]. In an exposure experiment with Japanese quail eggs, neither single- nor mixture-exposed DPs showed metabolism during incubation[74]. However, relatively rapid depurations for DP isomers ($t_{1/2}$ of 2.46-5.59 d for *anti*-DP and 2.76-5.87 d for *syn*-DP) were found in chicken embryos, indicating the species-specific metabolism of DPs[97]. Although several other studies have been conducted *in ovo* exposure to NHFRs (including BTBPE and TBBPA-DBPE)[98-100], no evidence for their metabolic pathways was reported.

Fish and marine mammals

DBDPE could be rapidly metabolized (39.6-66.6 pmol in 90 min) to phenolic metabolites by marine mammal liver microsomes from arctic areas (polar bear, beluga whale, and ringed seal)[101]. DBDPE debromination (7 unknown compounds) was also confirmed in zebrafish after water-borne exposure[102]. They tentatively assigned them to nona-BDPE, nona-brominated products, octa-BDPE, hepta-BDPE, and other-brominated products[103]. BTBPE can be transformed into TBP and tribromophenoxyethanol (TBPE) during *in vitro* incubation using rainbow trout liver microsomes[104]. The formation of TBP was also confirmed in metabolism of BTBPE in zebrafish[105], whereas dibromophenol (DBP) was identified as a metabolite of BTBPE in fathead minnow[106]. HBB went through multiple debromination to metabolites of penta-bromobenzene (PBB), 1,2,4,5-tetra bromobenzene (Tetra-BB), 1,2,4-tribromobenzene (Tri-BB), and dibromobenzene (Di-BB) in zebrafish, and PBT could be gradually transformed to tetrabromotoluene (Tetra-BT), tribromotoluene (Tri-BT), and dibromotoluene (Di-BT)[105]. Ganci *et al.* identified TBBA as the major metabolite of TBB by trout liver microsomes[104]. Except for TBBA, Di-BB, and 2,3,4,5-tetrabromomethylbenzoate (TBMB), formed via dealkylation and methylation, were detected as metabolites for the mixture of TBB and TBPH in fathead minnow and common carp liver S9 fraction[107]. Fathead minnow (*P. promelas*) exposed to TBBPA-DBPE was found to produce TBBPA via hydrolysis (O-

Table 3. Available information on metabolism pathways and toxicokinetics of NHFRs in non-human fauna

Compounds	Species/assays	Methods	Metabolism pathway	Major metabolites	Available toxicokinetic constants	References
DBDPE	Zebrafish larvae	*In vivo*	Debromination	Dibrominated metabolites without confirmed structures	-	[102]
	Zebrafish larvae	*In vivo*	Debromination	nona-BDPE, octa-BDPE, hepta-BDPE, hexa-BDPE, and penta-BDPE	-	[103]
	Zebrafish	*In vivo*	Debromination	nona-BDPE, octa-BDPE, hepta-BDPE, hexa-BDPE, and penta-BDPE	1.50-8.33 d ($t_{1/2}$)	[105]
	Marine mammal liver microsome	*In vitro*	-	No metabolites detected	-	[101]
	Marine fish liver microsome	*In vitro*	-	-	0.044-0.050 mL/h/mg protein	[44]
	Freshwater fish liver microsome	*In vitro*	-	-	0.073-0.162 mL/h/mg protein	[41]
	Marine mammal liver microsomes	*In vitro*	Debromination	Phenolic metabolites	≈ 0.185 mL/h/mg protein	[101]
	Rat	*In vivo*	Debromination	$MeSO_2$-nona-BDPE and $EtSO_2$-nona-BDPE	-	[115]
	Clam	*In vivo*	Debromination	nona-BDPE, hexa-BDPE, and penta-BDPE	0.9-11.6 d ($t_{1/2}$)	[122]
	Mudsnails	*In vivo*	Debromination	nona-BDPE, octa-BDPE, hepta-BDPE, hexa-BDPE, and penta-BDPE	3.0-3.8 d ($t_{1/2}$)	[121]
BTBPE	Rainbow trout juvenile	*In vivo*	-	No metabolites detected	54.1 ± 8.5 d ($t_{1/2}$)	[112]
	Zebrafish	*In vivo*	Debromination and O-dealkylation	TBP and vinyl tribromobenzene ether	1.00-7.25 d ($t_{1/2}$)	[105]
	Fathead minnow	*In vivo*	O-dealkylation and hydroxylation	DBP	-	[106]
	Rainbow trout Liver microsome	*In vitro*	O-dealkylation and hydroxylation	TBP and TBPE	-	[104]
	Marine fish S9 fraction	*In vitro*	-	-	0.13-0.20 mL/h/mg protein	[111]
	Rat	*In vivo*	Hydroxylation, debromination, and O-dealkylation	OH-BTBPE, $(OH)_2$-BTBPE, TBP, and TBPE	-	[116]
	Clam	*In vivo*	O-dealkylation, hydroxylation, and methylation	OH-BTBPE, MeOH(OH)-BTBPE, TBP, and TBPE	2.07-5.87 d ($t_{1/2}$)	[122]
TBB	Bald eagle eggs	*In ovo*	O-dealkylation	TBBA	-	[96]
	Fathead minnow liver S9 fraction	*In vitro*	O-dealkylation and methylation	TBBA, Di-BB, and TBMB	2.40 ± 0.15 pmol/h/mg protein	[107]
	Common carp liver S9 fraction	*In vitro*	O-dealkylation and methylation	TBBA, Di-BB, and TBMB	2.34 ± 0.12 pmol/h/mg protein	[107]
	Rainbow trout liver microsome	*In vitro*	O-dealkylation	TBBA	-	[104]
	Marine fish liver microsome	*In vitro*	-	-	0.053-0.065 mL/h/mg protein	[44]
	Marine fish S9 fraction	*In vitro*	-	-	0.18-0.50 mL/h/mg protein	[111]
	Rat	*In vivo*	O-dealkylation	TBBA	-	[120]
	Rat	*In vivo*	O-dealkylation	TBBA and TBPA	-	[117]
	Rat liver microsome	*In vitro*	O-dealkylation	TBBA	6.25 ± 0.58 nmol/min/mg protein	[118]

	Rat liver cytosol	*In vitro*	O-dealkylation	TBBA	0.203 ± 0.004 nmol/min/mg protein	[118]
	Rat intestinal microsome	*In vitro*	O-dealkylation	TBBA	0.422 ± 0.093 nmol/min/mg protein	[118]
TBPH	Bald eagle eggs	*In ovo*	O-dealkylation	TBMEHP	-	[96]
	Killifish (*Fundulus heteroclitus*)	*In vivo*			22 d ($t_{1/2}$)	[114]
	Fathead minnow liver S9 fraction	*In vitro*	O-dealkylation and methylation	TBBA, Di-BB, and TBMB	0.629 ± 0.066 pmol/h/mg protein	[107]
	Common carp liver S9 fraction	*In vitro*	O-dealkylation and methylation	TBBA, Di-BB, and TBMB	0.620 ± 0.103 pmol/h/mg protein	[107]
	Rat	*In vivo*	O-dealkylation	TBBA	-	[120]
	Rat	*In vivo*	O-dealkylation	TBBA and TBPA	-	[117]
	Rat liver microsome	*In vitro*	-	No metabolites found	-	[118]
	Marine fish liver microsome	*In vitro*	-	-	0.016-0.017 mL/h/mg protein	[44]
TBBPA-DBPE	Fathead minnow	*In vivo*	O-dealkylation	TBBPA	-	[106]
	Marine fish liver microsome	*In vitro*	-	-	0.047-0.048 mL/h/mg protein	[44]
PBT	Zebrafish	*In vivo*	Debromination	Tetra-BT, Tri-BT, and Di-BT	1.14-10.37 d ($t_{1/2}$)	[105]
	Marine fish liver microsome	*In vitro*	-	-	0.043-0.049 mL/h/mg protein	[44]
	Marine fish S9 fraction	*In vitro*	-	-	0.05-0.28 mL/h/mg protein	[111]
	Clam	*In vivo*	Debromination	Tetra-BT	3.22-6.48 d ($t_{1/2}$)	[122]
	Mudsnails	*In vivo*		Tetra-BT, Tri-BT, and Di-BT	4.7-5.9 d ($t_{1/2}$)	[121]
PBP	Marine fish liver microsome	*In vitro*	-	-	0.053-0.055 mL/h/mg protein	[44]
HBB	Zebrafish	*In vivo*	Debromination	PBB, Tetra-BB, Tri-BB, and Di-BB	0.85-10.34 d ($t_{1/2}$)	[105]
	Marine fish liver microsome	*In vitro*	-	-	0.017-0.025 mL/h/mg protein	[44]
	Marine fish S9 fraction	*In vitro*	-	-	0.048-0.13 mL/h/mg protein	[111]
	Clam	*In vivo*	Debromination	PBB, Tetra-BB, Tri-BB, and Di-BB	1.82-.6.54 d ($t_{1/2}$)	[122]
	Mudsnails	*In vivo*	Debromination	PBB, Tetra-BB, Tri-BB, and Di-BB	2.5-3.5 d ($t_{1/2}$)	[121]
PBEB	Marine fish S9 fraction	*In vitro*	-	-	0.052-0.40 mL/h/mg protein	[111]
TBECH	Zebrafish	*In vivo*	-	-	1.3 d ($t_{1/2}$)	[113]
	Marine fish liver microsome	*In vitro*	-	-	0.061-0.067 mL/h/mg protein	[44]
	Freshwater fish liver microsome	*In vitro*	-	-	0.006-0.027 mL/h/mg protein	[41]
TBP	Zebrafish	*In vivo*	-	-	0.9-1.3 d ($t_{1/2}$)	[113]
	Rat	*In vivo*	Glucuronic acid conjugation, sulfation	GLU-TBP and SUL-TBP	2-5 h ($t_{1/2}$)	[119]
TBCT	Marine fish S9 fraction	*In vitro*	-	-	0.052-0.40 mL/h/mg protein	[111]
	Freshwater fish liver microsome	*In vitro*	-	-	0.015-0.114 mL/h/mg protein)	[41]

PBBA	Freshwater fish liver microsome	*In vitro*	-	-	0.122 mL/h/mg protein	[41]
DPs	Embryonated eggs of Japanese Quail	*In vivo*	Too slow	-	-	[74]
	Chicken embryos	*In vivo*	-	-	2.46-5.59 d ($t_{1/2}$ for *anti*-DP) 2.76-5.87 d ($t_{1/2}$ for *syn*-DP)	[97]
	Common carp	*In vivo*	-	-	16.3-50.2 d ($t_{1/2}$ for *anti*-DP) 17.8-45.6 d ($t_{1/2}$ for *syn*-DP)	[108]
	Rainbow trout (*Oncorhynchus mykiss*)	*In vivo*	-	-	53.3 ± 13.1 d ($t_{1/2}$ for *anti*-DP) 30.4 ± 5.7 d ($t_{1/2}$ for *syn*-DP)	[109]
	Redtail catfish	*In vivo*	-	No metabolites found	19.1-39.7 d ($t_{1/2}$ for *anti*-DP)	[110]
	Oscar fish	*In vivo*	-	No metabolites found	22.3-34.5 d ($t_{1/2}$ for *syn*-DP)	[110]

-: Not available. DBDPE: decabromodiphenyl ethane; BTBPE: 1,2-bis (2,4,6-tribromophenoxy) ethane; DBP: dibromophenol; TBP: tribromophenol; TBPE: tribromophenoxyethanol; BTBPE: 1,2-bis (2,4,6-tribromophenoxy) ethane; TBB: 2-ethylhexyl tetrabromobenzoic acid; TBBA: 2,3,4,5-tetrabromobenzoic acid; TBMB: 2,3,4,5-tetrabromomethylbenzoate; Di-BB: dibromobenzene; TBMEHP: 2-ethylhexyl tetrabromophthalate; TBPH: tis(2-ethylhexyl)-2,3,4,5-tetrabromophtalate; TBMEHP: 2-ethylhexyl tetrabromophthalate; TBBPA: tetrabromobisphenol A; Tetra-BT: tetrabromotoluene; Tri-BT: tribromotoluene; Di-BT: dibromotoluene; HBB: hexabromobenzene; PBB: penta-bromobenzene; PBEB: pentabromoethylbenzene; TBECH: tetrabromoethylcyclohexane; TBCT: 2,3,4,5 tetrabromo-6-chlorotoluene; PBBA: pentabromobenzyl acrylate; OH: hydroxylated; DPs: dechlorane plus.

dealkylation)[106]. DPs have been inferred to be metabolized in the liver of freshwater fish[108-110], but no metabolite could be detected in the fish body.

In vitro incubation using liver microsomes was conducted in several studies to assess the biotransformation clearance rates of NHFRs in fish. Lee *et al.* first found chemical-to-chemical variations in the metabolism rate of 6 NHFRs (BTBPE, HBB, PBEB, PBT, TBB, and TBCT) in marine fish (*Epinephelus septemfasciatus*, *Konosirus punctatus*, *Lateolabrax japonicus*, *Mugil cephalus*, and *Sebastes schlegelii*) from Koera[111]. Generally, the fully brominated NHFRs were metabolized slower than the less brominated NHFRs in fish. TBB exhibited the fastest metabolism rate in fish liver S9 fractions, whereas HBB and TBCT were the two slowest depleted NHFRs[111]. Our previous study using marine fish from the South China Sea liver microsome also reported the lowest *in vitro* clearance rate constants for HBB compared with TBB and PBT[44]. The clearance rates of NHFRs in marine fish from our study were 1.16 (TBB) - 7.68 (PBT) times lower than the values obtained in the marine fish from Korea, which might be attributed to the difference in enzyme activities between liver S9 and microsomes. In a study using freshwater fish liver microsomes (crucian carp, catfish, and yellow-head catfish), ATE, BTBPE, and TBPH showed no significant metabolism, and the clearance rate of DBDPE was much higher than that in marine fish from our previous study[41]. These results imply the occurrence of species-specific metabolism of NHFRs in aquatic animals.

The $t_{1/2}$ of BTBPE was estimated to be approximately 54.1 ± 8.5 d in juvenile rainbow trout (Oncorhynchus mykiss)[112], and the estimated $t_{1/2}$ for TBECH and TBP were < 2 d in zebrafish[113]. Qiao *et al.* also found that the liver, intestine, and gill were the top three tissues for the accumulation of PBT, HBB, BTBPE, and DBDPE in zebrafish with $t_{1/2}$ lower than 7 d[105]. In a dietary exposure of TBPH to Atlantic killifish (*Fundulus heteroclitus*), only a very small proportion of the TBPH in diet (< 0.5%) was bioaccumulated in fish by 28 d and the depuration $t_{1/2}$ was estimated to be 22 d[114]. DP isomers showed consistent uptake kinetics

but selective depuration kinetics in various fish species, where a rapid metabolism of *syn*-DP than *anti*-DP occurred in these species[108-110].

Rodents

Recent *in vitro* and *in vivo* studies in humans and rodents have confirmed the basic metabolic pathways of typical NHFRs. DBDPE is slowly metabolized in rats to $MeSO_2$-nona-BDPE and $EtSO_2$-nona-BDPE[115]. A study based on *in vivo* exposure of rats found that BTBPE could be metabolized into monohydroxylated and polyhydroxylated BTBPE and the debromination products (i.e., TBP and TBPE)[116]. In addition, 2,3,4,5-tetrabromo phthalic acid (TBPA) is another urine metabolite in rats that results from the metabolism of the TBB and TBPH mixture[117]. In previous studies using rat liver microsomes, TBBA was identified as an *in vitro* metabolite for TBB, whereas no metabolites were found for TBPH[118]. TBP can be phase II metabolized to GLU-TBP and SUL-TBP by both pregnant and nursing rats[119].

The metabolism of TBB was significantly slower in rat intestinal microsomes and liver cytosol than in rat liver microsomes[118]. In DBDPE-exposed rats, adipose tissue accumulated the majority of DBDPE rather than liver and kidney tissues at 90 d of exposure[115]. For BTBPE, a high proportion of 14C (> 94%) was excreted in the feces at 72 h rather than accumulated in rat tissue[116]. In addition, the lactational transfer of TBB and TBPH was found to be approximately 200- to 300-fold higher than that of placental transfer in dosed Wistar rats, and their common metabolite TBBA was detected in the urine of pups[120]. The TBP-administrated rat could rapidly accumulate in kidney and plasma at 30 min, and the exposed TBP pregnant and nursing rats resulted in the distribution of TBP and its metabolites in their offspring[119].

Invertebrates

In the sediment-water-mudsnail system, nona-BDPE, octa-BDPE, hepta-BDPE, hexa-BDPE, and penta-BDPE were found to be debromination metabolites of DBDPE by snails[121]. The debromination process for DBDPE also occurred in clams, where nona-BDPE and penta-BDPE were detected as major metabolites[122]. Debromination was also investigated as the main metabolic pathway for PBT and HBB in both snails and clams[121,122]. Tetra-BT, Tri-BT, and Di-BT were found to be the major metabolites of PBT, and PBB, Tetra-BB, Tri-BB, and Di-BB were the major metabolites of HBB in the two invertebrate species[121,122]. The hydrolysis and hydroxylation products of BTBPE also had been confirmed in clams[122].

The highest distribution of NHFRs in viscera was found for both snail and clam, and the $t_{1/2}$ values for PBT, HBB, and DBDPE for snail and clam were 2.5-5.9 d and 0.911-11.6 d, respectively[121,122]. In a study of NHFRs in oil-earthworm systems, HBB and PBT were mainly distributed in the intestine and epidermis (> 60% of the total load) during most of the exposure time, whereas the contents of BTBPE and DBDPE were both higher in the casts than in other tissues[123].

Summary of transformation processes of novel flame retardants

In general, based on the above literature, the metabolic pathways of NHFRs and OPFRs in the fauna can be clarified. The main metabolic pathways of OPFRs include dealkylation (ester hydrolysis) and hydroxylation, and phase II conjunction. DAPs and OH-OPFRs are the most important metabolites in the body. Debromination, hydroxylation, dealkylation, and phase II conjunction occupied the major metabolic pathways of NHFRs in fauna. The most important metabolic pathway for NHFRs with ether bonds is O-dealkylation (hydrolysis), such as BTBPE, TBB, TBPH, and TBPPA-DBPE. Other NHFRs share general metabolic pathways of mono- and multiple hydroxylation and debromination, and phase II metabolism can occur subsequently once hydroxyl is formed for the intermediates. Toxicokinetic results suggest that NHFRs are more resistant to metabolism than OPFRs, especially for DBDPE, DPs, and the monoaromatic

NHFRs. For OPFRs, the metabolism of non-chlorinated OPFRs is faster than Cl-OPFRs. Species-specific metabolism of novel flame retardants can be concluded according to the collected studies, where their metabolism rate in birds and rodents is generally faster than in fish and invertebrates.

INTERNAL EXPOSURE OF THE MAJOR NOVEL FR METABOLITES

Several studies are available concerning the internal exposure of novel FR metabolites in fauna. DAPs, formed from *in vivo* dealkylation, can act as biomarkers for assessing the internal exposure of OPFRs. The DAPs of bis(2-chloroethyl) phosphate (BCEP), bis(1-chloro-2-propyl) phosphate (BCPP), 1-hydroxy-2-propyl bis(1-chloro-2-propyl) phosphate (BCIPHIPP), BDCPP, BBOEP, DNBP, di(2-ethylhexyl) phosphate (DEHP), DPHP, DCP [or so-called bis(methylphenyl) phosphate (BMPP)], and 2-ethylhexyl phenyl phosphate (EHPHP) and OH-OPFRs of BBOEHEP, OH-TBOEP, OH-TNBP, OH-TPHP, and hydroxylated EHDPHP (OH-EHDPHP) were recently detected in fauna biomonitoring studies [Table 4]. The metabolite/parent ratio (MPR) was recently used in internal exposure studies to compare the relative persistence of OPFRs and metabolites [Figure 1], where an MPR ratio higher than one indicates that the metabolites, rather than the parent contaminants, should receive greater concern regarding their accumulation potentials.

In a recent report by Su *et al.*, BBOEP and BDCPP were detected at concentrations higher than 2 ng/g ww in herring gull plasma from the Great Lakes[124]. Our previous study investigated the accumulation of four DAPs (i.e., BBOEP, DNBP, DEHP, and DPHP) in wild freshwater fish from Beijing, China, and found that ΣDAPs concentrations were approximately 0.10-1.12 times (MPR) those of their parent compounds in fish[38]. The four DAPs in crucian carp and loach were mainly distributed in the fish liver (135 and 212 ng/g lw, respectively) than in other tissues[38]. Liu *et al.* investigated OPFR metabolites, including DAPs and OH-OPFRs, in ovoviviparous species (water snake and its egg) and freshwater fish[42]. The mean total concentrations of OPFRs metabolites were 1.3, 2.0, and 2.8 ng/g ww in water snake muscle, snake egg, and common carp, respectively, and higher MPRs were found in water snakes than in common carp[42]. In an estuarine food web of the Pearl River, China, the mean ΣmOPFRs among the marine species increased in the following order: fish (88.2 ± 78.7 ng/g lw) < shrimp (137 ± 90.0 ng/g lw) < snails (139 ± 132 ng/g lw) < crabs (336 ± 402 ng/g lw) and the DAPs of DNBP, BBOEP, and DPHP, rather than the OH-OPFRs, were the most abundant metabolites[125]. The MPRs of BBOEP/TBOEP and DNBP/TNBP in crabs were observed to be higher than those in several marine species[125].

In a global survey of OPFR metabolites in cow milk, samples from European countries presented higher OPFR metabolite concentrations in all countries (ΣmOPFRs = 0.135 ng/mL), while the metabolite levels in Asian countries were much lower (mean level < 0.021 ng/mL)[126]. TDCPP/BDCPP and TCPP/BCPP pairs presented significantly positive correlations, which indicated that they shared similar sources in milk[126]. BBOEP and BBOEHEP showed much higher concentrations than the hydroxyl metabolites (i.e., OH-TBOEP) in milk, which might be attributed to the high conversion rate from OPFRs to their corresponding DAPs[126]. However, the concentration of ΣmOPFRs in fishmeal showed a geographic order of China (56.7 ng/g dw) > South America (47.9 ng/g dw) > Southeast Asia (45.1 ng/g dw) > the United States (43.7 ng/g dw) > Europe (29.4 ng/g dw)[127]. High concentrations of OPFR metabolites were also detected in fish and seafood (1.8 ng/g ww), meat (1.0 ng/g ww), and eggs (1.0 ng/g ww) from Southeast Queensland, Australia, especially for DNBP and DPHP[128]. These DAPs accumulated more in yolk than in albumin[129]. The MPR for several pairs (i.e., DNBP/TNBP, DPHP/TPHP, BBOEP/TBOEP, and BCPHPP/TCPP) was lower in meat from animals (including chicken) than eggs, which could be explained by the fast excretion of these metabolites by the animals via urine[128]. Species-specific accumulation of BCEP was also found in fish and shrimp, which are highly edible portions of domestic birds and domestic mammals from Sichuan

Table 4. Internal concentration of NBFR metabolites in fauna (ng/mL or ng/g ww)

Sample types	Study area	BCEP	BCPP	BCIPHIPP	BDCPP	BBOEP	BBOEHEP	OH-TBOEP	DNBP	OH-TNBP	DEHP	DPHP	OH-TPHP	DCP	EHPHP	OH-EHDPHP	ΣmOPFRs	Reference
Cow milk	Asia	-	0.044 ± 0.079	-	0.037 ± 0.056	0.02 ± 0.027	0.017 ± 0.029	0.002 ± 0.003	0.024 ± 0.026	-	-	0.005 ± 0.016	-	0.156 ± 0.139	-	-	0.02 ± 0.025	[126]
	Europe	-	0.036 ± 0.046	-	0.078 ± 0.118	0.011 ± 0.014	0.023 ± 0.04	0.002 ± 0.006	0.044 ± 0.079	-	-	0.002 ± 0.004	-	0.821 ± 0.181	-	-	0.135 ± 0.716	[126]
	North America	-	0.039 ± 0.031	-	0.084 ± 0.109	0.005 ± 0.007	0.018 ± 0.01	0.002 ± 0.002	0.036 ± 0.043	-	-	0.001 ± 0.001	-	0.215 ± 0.128	-	-	0.043 ± 0.044	[126]
	South America	-	0.036 ± 0.019	-	0.081 ± 0.146	0.004 ± 0.004	0.032 ± 0.058	0.001 ± 0.001	0.048 ± 0.057	-	-	0.001 ± 0.002	-	0.261 ± 0.125	-	-	0.049 ± 0.058	[126]
	Oceania	-	0.024 ± 0.019	-	0.083 ± 0.071	0.021 ± 0.017	0.011 ± 0.013	0.002 ± 0.002	0.018 ± 0.018	-	-	0.002 ± 0.002	-	0.099 ± 0.165	-	-	0.017 ± 0.018	[126]
Cow milk	Beijing, China	-	0.998 ± 0.45	-	0.053 ± 0.12	0.274 ± 0.29	-	-	0.279 ± 0.15	-	-	0.917 ± 0.57	-	0.1 ± 0.03	-	-	2.62 ± 0.98	[146]
Fishmeal (in dry weight)	United States	5.36 ± 3.25	11.01 ± 3.67	-	1.5 ± 2.87	0.53 ± 0.63	-	-	0.32 ± 0.16	-	3.49 ± 5.87	3.6 ± 3.43	-	29.0 ± 9.1	-	-	41.9 ± 13.0	[127]
	China	4.08 ± 2.33	0.85 ± 0.75	-	2.21 ± 4.18	0.11 ± 0.43	-	-	0.65 ± 1.69	-	7.31 ± 6.8	2.05 ± 2.6	-	36.6 ± 19.6	-	-	52.8 ± 23.0	[127]
	Europe	ND	1.39 ± 0.62	-	1.99 ± 2.73	0.2 ± 0.38	-	-	0.08 ± 0.21	-	1.26 ± 1.68	1.86 ± 3.21	-	20.6 ± 6.57	-	-	28.9 ± 5.68	[127]
	South America	6.23 ± 3.45	1.18 ± 3.68	-	1.09 ± 2.37	0.09 ± 0.62	-	-	0.26 ± 0.68	-	2.69 ± 23.3	1.24 ± 2.18	-	31.8 ± 13.2	-	-	42.1 ± 33.9	[127]
	Southeast Asia	ND	1.7 ± 4.35	-	0.98 ± 0.4	0.09 ± 0.04	-	-	0.21 ± 0.41	-	3.46 ± 2.56	1.01 ± 1.17	-	35.7 ± 11.8	-	-	43.6 ± 10.4	[127]
Meat meal (in dry weight)	China	-	16.5	7.25	-	0.27	-	-	0.81	-	7.98	14.9	-	2.20	-	-	49.9	[131]
Feather meal (in dry weight)		-	12.5	1.83	-	0.04	-	-	0.21	-	2.24	4.15	-	2.36	-	-	23.3	[131]
Blood meal (in dry weight)		-	5.57	4.29	-	0.63	-	-	0.77	-	8.87	8.01	-	24.0	-	-	52.1	[131]
Beef	Southeast Queensland, Australia	ND	ND	ND	ND	ND	ND	ND	-	-	0.043 ± 0.026	0.098 ± 0.039	-	ND	-	-	0.152 ± 0.033	[128]

Lamb		ND	ND	ND	ND	ND	ND	0.11	-	-	ND	0.207 ± 0.112	-	ND	-	-	0.205 ± 0.205	[128]
Pork		ND	ND	ND	ND	ND	ND	ND	-	-	0.12	0.14	-	ND	-	-	0.114 ± 0.163	[128]
Chicken		ND	ND	ND	ND	ND	ND	ND	-	-	0.038	0.245 ± 0.078	-	ND	-	-	0.204 ± 0.182	[128]
Prawn		ND	ND	0.42	ND	0.23	ND	0.124 ± 0.034	-	-	0.297 ± 0.147	1.17 ± 1.42	-	5.00 ± 3.14	-	-	7.06 ± 4.79	[128]
Oyster		ND	ND	ND	ND	0.52 ± 0.156	ND	0.1	-	-	0.335 ± 0.149	4.53 ± 1.89	-	0.407 ± 0.161	-	-	6.45 ± 1.88	[128]
Salmon		ND	ND	ND	ND	ND	ND	0.083	-	-	ND	0.44	-	ND	-	-	0.202 ± 0.309	[128]
Egg		ND	ND	ND	ND	1.13 ± 0.603	ND	0.082	-	-	1.63 ± 1.53	3.86 ± 1.29	-	0.313 ± 0.118	-	-	8.28 ± 4.64	[128]
Egg albumin	Australia	ND	ND	0.33	ND	0.26	ND	ND	0.15	-	2.3	5.3	-	0.079	-	-	9.7	[129]
Egg yolk		ND	ND	ND	0.32	0.063	ND	ND	0.05	-	0.72	1.2	-	ND	-	-	3	[129]
Herring gull plasma (ng/g ww)	Lake Huron, Canada	-	ND	-	2.13 ± 1.13	5.32 ± 11.8	-	-	0.410	-	0.120 ± 0.079	ND	-	-	-	-	7.98 ± 11.4	[124]
Bald eagle eggs	Great Lakes, USA	5.4 ± 1.7	1.8 ± 0.25	-	2.5 ± 0.21	1.3 ± 0.3	-	-	2.4 ± 0.49	-	-	1 ± 0.23	-	-	-	-	27 ± 3	[96]
Water snake	E-waste dismantling site in Guangdong, China	-	0.17 ± 0.13	0.029 ± 0.013	-	0.076 ± 0.12	ND	ND	0.47 ± 0.30		-	0.39 ± 0.37	0.061 ± 0.057	-	0.11 ± 0.033	ND	1.3 ± 0.49	[42]
Snake egg		-	0.073 ± 0.13	0.037 ± 0.013	-	0.29 ± 0.37	0.022 ± 0.038	0.031 ± 0.033	0.39 ± 0.29		-	0.50 ± 0.15	0.28 ± 0.22	-	0.32 ± 0.10	0.046 ± 0.08	2.0 ± 0.41	[42]
Common carp		-	0.54 ± 0.11	0.19 ± 0.16	-	0.41 ± 0.24	0.019 ± 0.010	0.019 ± 0.0090	0.51 ± 0.32		-	0.61 ± 0.37	1.3 ± 1.9	-	0.24 ± 0.24	0.059 ± 0.045	2.8 ± 0.41	[42]
Topmouth gudgeon (in lipid weight)	Rivers in Beijing, China	-	-	-	-	33.4 ± 32.2	-	-	23.3 ± 15.3		26 ± 11.1	10.4 ± 6.3	-	-	-	-	93.1 ± 46.2	[38]
Crucian carp (in lipid weight)		-	-	-	-	25.1 ± 17.5	-	-	34 ± 18.7		30.9 ± 16.6	12.2 ± 9.1	-	-	-	-	102 ± 43.6	[38]
Loach (in lipid weight)		-	-	-	-	32.9 ± 28.7	-	-	113 ± 92.4		58.6 ± 52.3	16.3 ± 12.9	-	-	-	-	220 ± 150	[38]
Marine snail (in lipid weight)	Pearl river estuary, China	-	-	-	-	55.6 ± 97.6	0.49 ± 0.55	0.01 ± 0.01	68.9 ± 36.7	1.01 ± 0.93	-	11.5 ± 8.00	-	-	-	-	137 ± 134	[125]
Marine shrimp (in lipid weight)		-	-	-	-	18.2 ± 11.5	0.55 ± 0.31	0.29 ± 0.47	98.6 ± 63.7	1.55 ± 0.82	-	8.47 ± 7.64	-	-	-	-	140 ± 62.5	[125]
Marine crabs		-	-	-	-	23.9 ±	1.05 ± 0.43	0.19 ±	314 ±	1.70 ±	-	13.3 ±	-	-	-	-	384 ± 341	[125]

(in lipid weight)						13.4		0.08	360	1.61		9.21					
Marine fish (in lipid weight)		-	-	-	-	9.99 ± 10.0	0.40 ± 0.44	0.18 ± 0.31	66.9 ± 47.7	2.78 ± 3.27	-	11.4 ± 12.1	-	-	-	-	89.1 ± 59.4 [125]
8 marine fish species	Tarragona, Spain	ND	-	-	ND	ND	-	-	47.6 ± 18.2	-	ND	62.6 ± 18.4	-	-	-	-	110 ± 34.9 [145]
Stickleback	Troutman Lake, Alaska, USA	0.081 ± 0.009	ND	-	ND	-	-	-	0.436 ± 0.066	-	-	0.410 ± 0.143	-	-	-	-	0.927 ± 0.218 [143]

-: not available; ND: not detectable. BCEP: bis(2-chloroethyl) phosphate; BCPP: bis(1-chloro-2-propyl) phosphate; BCIPHIPP: 1-hydroxy-2-propyl bis(1-chloro-2-propyl) phosphate; BDCPP: bis(1,3-dichloropropyl) phosphate; BBOEP: bis(2-butoxyethyl) phosphate; BBOEHEP: bis(2-butoxyethyl) hydroxyethyl phosphate; OH-TBOEP: bis(2-butoxyethyl) 3-hydroxyl-2-butoxyethyl phosphate; DNBP: di-n-butyl phosphate; OH: hydroxylated; TNBP: tributyl phosphate; DEHP: di(2-ethylhexyl) phosphate; DPHP: diphenyl phosphate; TCEP: tris(2-chloroethyl) phosphate; OH-TPHP: hydroxyphenyl diphenyl phosphate; DCP: dicresyl phosphate; EHPHP: 2-ethylhexyl phenyl phosphate; OH-EHDPHP: 2-ethyl-hydroxyhexyl diphenyl phosphate.

Province, China[130]. In animal-derived protein supplement feeds from China, the average concentration of ΣDAPs in meat meal was highest (52.1 ng/g dw), followed by blood meal (49.9 ng/g) and feather meal (23.3 ng/g dw)[131]. DAPs from Cl-OPFRs were the major congeners in blood meal (47.7%) and feather meal (61.4%), while DAPs from alkyl-OPFRs (65.7%) contributed the most in meat meal[131].

Relatively little information exists regarding the internal exposure of NBFR metabolites in fauna. TBBA [from not detectable (ND) to 330 ng/g ww] and TBMEHP (ND-330 ng/g ww) were detected in the bald eagle (Haliaeetus leucocephalus) eggs from the Great Lakes region[96]. For the two metabolites, their corresponding parent compounds (i.e., TBB and TBPH) were not detected in the eggs, suggesting greater concern should be paid to the two metabolites rather than their parents[96].

In general, DAPs have relatively higher internal exposure concentrations in fauna than OH-OPFRs, which is related to their high conversion rate and stability in the body [Figure 1]. The higher MPRs than 1 were frequently reported for the DAP/alkyl-OPFR pairs, which may be related to the easy-to-metabolism characteristics of the alkyl-OPFRs [Figure 1]. However, the sources of novel FR metabolites in the body are complex. In addition to being formed from metabolic processes in the body, some can also be formed from biotic and abiotic degradation processes in the environment before accumulation by the fauna. Some of the metabolites can also be applied as industrial products. For example, DEHP, DPHP, DCP, DMPP, and DNBP can be used as FRs or plasticizers[65]. Thus, the internal exposure of metabolites in the body is not always relative to the external exposure to FRs.

TOXICITY OF THE MAJOR NOVEL FR METABOLITES

OPFR metabolites

The predicted Log K_{OW} values (using EPI suite v4.1) for the major OPFR metabolites were lower than those of their parent compounds [Table 5], which

Table 5. The estimated ecotoxicities and bioaccumulation values for the major novel FR metabolites

FRs	Metabolites	Fathead minnow LC50 (mg/L 96 h)[a]	*Daphnia magna* LC50 (mg/L 48 h)[a]	*T. pyriformis* IGC50 (mg/L 48 h)[a]	Developmental Toxicity[a]	Mutagenicitya[a]	Estimated Log K_{ow}[b]	Estimated BCF[b]
TCEP		14.53	0.040	228.51	-	+	1.63	3.465
	BCEP	17.91	0.095	NA	+	+	0.83	1.457
TCPP		5.80	0.018	150.20	+	+	2.89	36.66
	BCPP	12.77	0.180	NA	+	+	1.19	2.251
	BCIPHIPP	9.22	0.049	511.98	+	+	1.17	1.557
TDCPP		0.22	0.016	154.86	+	-	3.65	126.3
	BDCPP	2.09	NA	NA	+	NA	1.70	5.511
TBOEP		28.57	0.040	93.78	+	-	3.65	54.19
	BBOEP	14.88	0.27	NA	+	-	1.74	5.094
	BBOEHEP	61.71	0.061	310.34	+	-	0.82	1.079
	3-OH-TBOEP	36.66	0.15	465.24	+	-	1.53	1.737
TEHP		0.56	0.021	NA	-	-	9.49	1.4
	DEHP	0.42	NA	NA	-	NA	5.60	823.7
TNBP		18.60	0.030	124.47	-	-	3.82	69.65
	DNBP	5.20	0.66	NA	+	-	2.29	16.37
	3-OH-TNBP	11.15	0.20	383.34	+	-	2.28	7.905
TPHP		1.12	0.10	12.12	+	-	4.70	73.18
	OH-TPHP	0.12	0.16	19.69	-	-	4.22	46.75
	DPHP	6.95	NA	NA	+	-	2.88	40.14
EHDPHP		0.21	0.062	2.73	+	-	5.73	273.1
	EHPHP	1.08	NA	NA	+	-	4	195.5
	OH-EHDPHP	0.34	0.036	3.16	+	-	5.82	149
TCP		0.19	0.54	2.48	-	-	6.34	2.98×10^4
	DCP	4.90	NA	NA	+	NA	3.50	241.5
TBB		0.12	0.096	0.063	NA	+	8.75	2072
	TBBA	1.02	10.08	18.02	NA	-	5.09	835.2
TBPH		0.007	0.089	0.017	NA	-	11.95	2.401
	TBMEHP	0.032	1.16	0.54	NA	-	7.53	169.1
TBBPA-DBPE		0.004	0.003	3.83×10^4	NA	-	11.52	1.215×10^4
	TBBPA	0.069	0.033	0.11	NA	-	2.856	717.5

[a]USEPA T.E.S.T; [b]USEPA EPI suit v4.1.; -: no significant toxicity; +: significant toxicity; NA: not available. TCEP: tris(2-chloroethyl) phosphate; TCPP: tris(2-chloroiso-propyl) phosphate; BCEP: bis(2-chloroethyl) phosphate; BCPP: bis(1-chloro-2-propyl) phosphate; BCIPHIPP: 1-hydroxy-2-propyl bis(1-chloro-2-propyl) phosphate; TDCPP: tris(2-chlorol-chloromethy) phosphate; BDCPP: bis(1,3-dichloropropyl) phosphate; BBOEP: bis(2-butoxyethyl) phosphate; TBOEP: tris(2-butoxyethyl) phosphate; BBOEP: bis(2-butoxyethyl) phosphate; BBOEHEP: bis(2-butoxyethyl) hydroxyethyl phosphate; TEHP: tri(2-ethylhexyl) phosphate; OH-TBOEP: bis(2-butoxyethyl) 3-hydroxyl-2-butoxyethyl phosphate; TEHP: tri(2-ethylhexyl) phosphate; DEHP: di(2-ethylhexyl) phosphate; TNBP: tributyl phosphate; DNBP: di-n-butyl phosphate; TPHP: tripheny phosphate; OH-TPHP: hydroxyphenyl diphenyl phosphate; DPHP: diphenyl phosphate; EHDPHP: 2-ethylhexyl diphenyl phosphate; EHPHP: 2-ethylhexyl phenyl phosphate; OH-EHDPHP: 2-ethyl-hydroxyhexyl diphenyl phosphate; TCP: tris(2-chloroiso-propyl) phosphate; DCP: dicresyl phosphate; TBB: 2-ethylhexyl tetrabromobenzoic acid; TBBA: 2,3,4,5-tetrabromobenzoic acid; TBPH: tis(2-ethylhexyl)-2,3,4,5-tetrabromophtalate; TBMEHP: 2-ethylhexyl tetrabromophthalate; TBBPA-DBPE: tetrabromobisphenol A-bis(2,3-dibromopropylether); TBBPA: tetrabromobisphenol A.

indicated their comparably limited potential for bioaccumulation. The estimated results from the EPA T.E.S.T. program indicate that DAPs and OH-OPFRs exhibit lower acute toxicities to aquatic animals. However, the estimated developmental toxicity for OPFRs is not eliminated after metabolism. BCEP, DNBP, OH-TNBP, and DCP show significantly positive developmental toxicity, while their parent compounds do not.

According to the literature, some transformation products might be more toxic than parent compounds, especially for endocrine-disrupting endpoints. TNBP shows both androgen receptor and glucocorticoid receptor antagonistic activity, whereas its metabolite DNBP cannot exhibit any nuclear receptor activity[132]. 5-OH-EHDPHP can elicit approximately 3.1 times the androgen receptor antagonistic activity of EHDPHP in Japanese medaka (*Oryzias latipes*)[133]. The metabolites BBOEHEP and 3-OH-TBOEP can act as pregnancy X receptor agonists at similar levels to their parent TBOEP[132]. DPHP can significantly dysregulate the avian genes associated with lipid/cholesterol metabolism, which is more than two times that of TPHP[72]. Low-dose chronic exposure to DPHP can interrupt the fatty acid metabolism in the rat liver and exert adverse consequences on overall physiology[134]. Similar adverse results were also observed in male zebrafish[135]. OH-TPHP elicited the upregulation of estrogenic genes and thyroid genes to induce growth inhibition in zebrafish embryos[136]. Both BCPP and BDCPP upregulated the genes encoding for estrogenic synthesis enzymes in H295R cells, which indicated that these metabolites may produce comparable or even higher endocrine-disrupting effects than OPFRs[137].

NBFR metabolites

All the estimated NBFR metabolites had lower Log K_{OW} values and aquatic toxicities (including LC50 to Fathead minnow and *Daphnia magna* and IGC50 to T. pyriformis) than those of their parent compounds using the *in silico* methods [Table 5]. However, certain metabolites of NHFRs also exhibit other adverse effects on organisms, according to previous studies. The metabolites TBBA and TBMEPH were shown to have comparable thyroid hormone, androgen, glucocorticoid, and pregnancy X receptor agonist activities[138,139] and induced stronger cytotoxicity than their parent compounds (TBB and TBHP)[140]. TBBA and TBMEHP exhibited binding potency to human PPARγ, but TBB and TBPH did not[141]. TBP, one of which was reported as a BTBPE metabolite, is an industrial additive with stronger neurotoxicity and can inhibit the expression of human steroidogenic enzymes, leading to a certain degree of endocrine-disrupting effect[60]. Bromophenol, another BTBPE metabolite, was found to have strong cytotoxic and genotoxic effects on aquatic organisms[142].

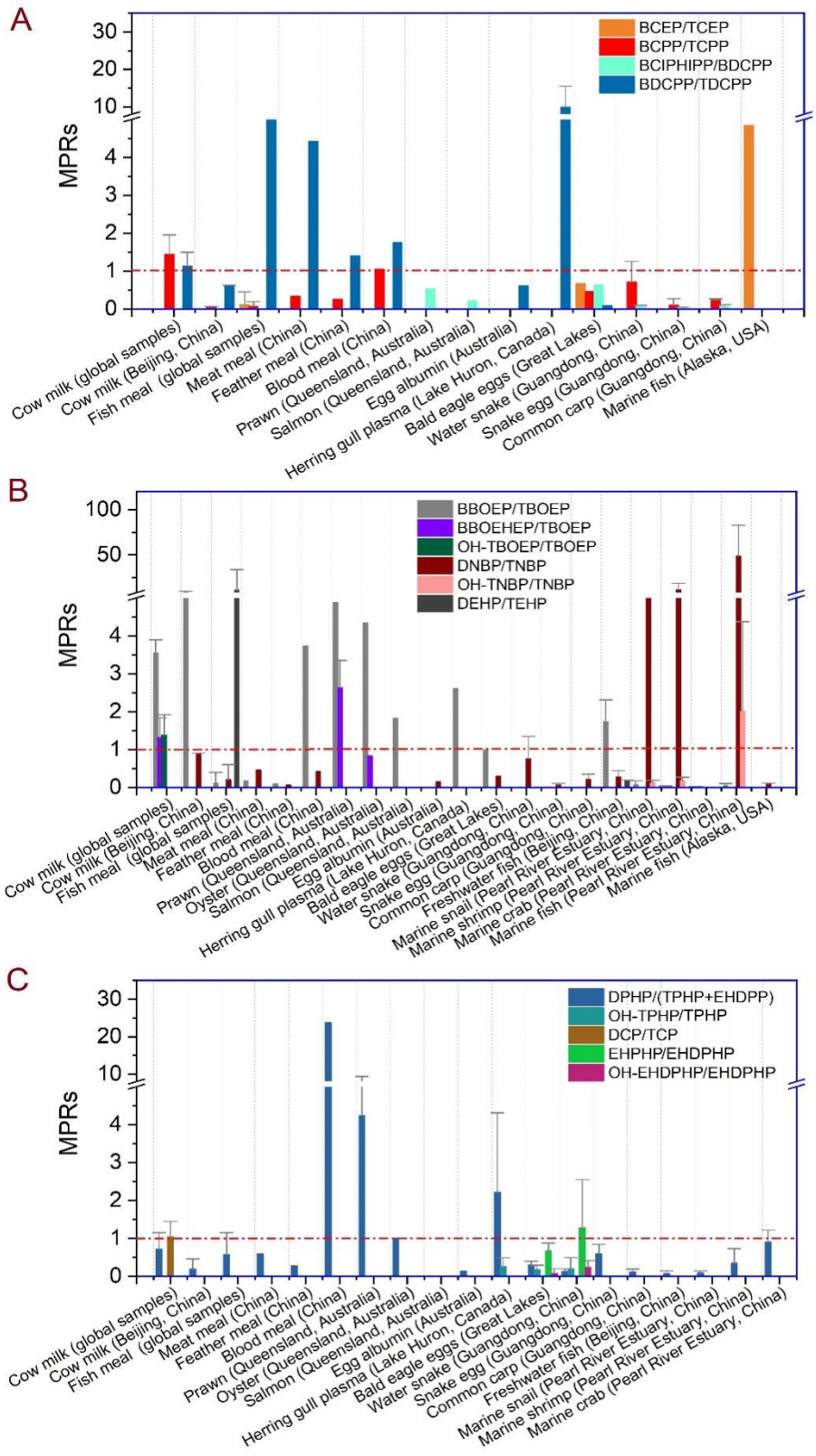

Figure 1. The metabolite/parent ratios (MPRs) of OPFRs in fauna across the internal exposure studies (A) Cl-OPFRs, (B) Alkyl-OPFRs, and (C) Aryl-OPFRs). Detailed data are compiled in Table 4.

CONCLUSION AND PERSPECTIVES

To date, great efforts have been made to study the metabolism of novel FRs in fauna, such as metabolic pathways and kinetics, metabolite formation, internal exposure of metabolites, and their toxicities. OPFRs share similar metabolic pathways in various animals, where O-dealkylation, hydroxylation, and phase II conjunction are the most likely pathways. DAPs and OH-OPFRs are the predominant metabolites in the body. O-dealkylation (hydrolysis) is the key pathway controlling the metabolism of NHFRs with ether bonds, while other NHFRs might metabolize through debromination, hydroxylation, dealkylation, and phase II conjunction. However, compared with OPFRs, there is still a lack of metabolism information on most of the NHFRs including their full metabolism pathways, the conversion efficiency of specific metabolites, and the stability of the intermediates in the body[6,11,69]. The metabolism kinetics (or toxicokinetics) of novel FRs are CYP enzyme-related and variable among species. Research has progressed to often evaluating the metabolism of novel FRs in a single species, but comparative studies of biotransformation between species remain insufficient. When invertebrates, which are at the lower levels of the food chain, are exposed to FRs, the parental compounds and their metabolites can affect the organisms at the upper levels[125]. Therefore, future research is necessary on the metabolic processes in multitrophic organisms and the transfer of major metabolites across the food web.

DAPs, as important OPFR metabolites, have been investigated as biomarkers for OPFR exposure in fauna. The occurring higher internal exposure of DAPs than the respective OPFRs also highlights their potential risk for animals and their importance in understanding the metabolism processes of OPFRs. Nevertheless, few studies have focused on the internal exposure of NBFR metabolites, and we recommended employing these biomarkers for biomonitoring fauna. A few studies have indicated that the residues of the major FR metabolites in the body may have adverse effects on fauna. These results underscore the importance of studying the occurrence and ecological risks of metabolites in organisms. In addition, internal exposure data of metabolites can provide valuable information for human exposure and risk assessments of novel FRs. Hence, more attention should concentrate on the co-exposure of FRs and their metabolites, especially for those FRs with easy-metabolic characteristics and stable metabolites in the body.

DECLARATIONS

Authors' contributions

Conceptualization and methodology, data analysis, writing-review & editing: Hou R
Reviewing and editing: Sun C, Zhang S, Huang Q, Liu S, Lin L, Li H
Project administration, resources and supervision: Hou R, Xu X

Availability of data and materials

All the data were included in this paper. No additional data are available.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for Publication

Not applicable.

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