Review

Species-specific dechlorane plus isomer fractionation during bioaccumulation: phenomenon and potential mechanisms

Ke-Lan Guan[1,2], Hong-Ying Liu[3], Xiao-Jun Luo[1]

[1]State Key Laboratory of Organic Geochemistry and Guangdong Key Laboratory of Environmental Resources Utilization and Protection, Guangzhou Institute of Geochemistry, Chinese Academy of Sciences, Guangzhou 510640, Guangdong, China.
[2]University of Chinese Academy of Sciences, Beijing 100049, China.
[3]College of Chemistry and Chemical Engineering, Hubei University, Wuhan 430062, Hubei, China.

Correspondence to: Dr. Xiao-Jun Luo, State Key Laboratory of Organic Geochemistry and Guangdong Key Laboratory of Environmental Resources Utilization and Protection, Guangzhou Institute of Geochemistry, Chinese Academy of Sciences, Guangzhou 510640, Guangdong, China. E-mail: luoxiaoj@gig.ac.cn

Abstract

The occurrence and behavior of dechlorane plus (DP), an additive chlorinated flame retardant, have been intensively studied since it was identified in 2006. The commercial products of DP are a mixture of two stereoisomers: *syn*-DP and *anti*-DP. Stereoselective bioaccumulation of DP isomers in biota was reported in field monitoring and laboratory experiments. This review summarizes stereoselective bioaccumulation of DP in biota samples and provides the potential mechanisms for this stereoselective bioaccumulation. Stereoselective enrichment of *syn*-DP was widely observed in fish, whereas selective enrichment of *anti*-DP was mainly found in some birds. This species-specific stereoselective enrichment of DP might reflect that two different types of DP isomer fractionation occurred in bioaccumulation between ectotherms and endotherms. Anti-DP is more readily metabolized through biotransformation in all animals. However, a preferential excretion of *anti*-DP in fish and *syn*-DP in birds was observed based on the available data. Both processes determine the DP isomer fractionation in bioaccumulation. A direct comparison in DP composition between biological samples and commercial products was conducted for most studies to determine the occurrence of stereoselective DP enrichment, which may lead to underestimating the potential stereoselective enrichment of DP in organisms. The factors which affected the DP isomer composition in organisms included the tissues or organs used, DP concentration, organisms' trophic levels occupied, and sex. Inconsistent results were obtained considering the effects of these influence factors. The

underlying cause of these inconsistent results is unclear based on present data. Further research on DP biotransformation and interactions between DP and biomacromolecule is needed.

Keywords: Dechlorane plus, bioaccumulation, stereoselective enrichment, species-specific

INTRODUCTION

Dechlorane plus (DP), also called bis(hexachlorocyclopentadiene)cyclooctane, is a type of chlorinated additive flame retardant, which has been widely used in textiles, paints, circuit boards, and especially in the plastic polymers of electrical appliances, such as carbons, wires, computer connectors, *etc.* DP makes up 10%-35% of the components in some commercial polymer products[1].

As an additive chlorinated flame retardant, DP is inevitably released into the environment through production, usage, and recycling[1]. DP was first identified in sediment and fish samples from the Great Lakes of North America in 2006[2]. Since then, DP has been widely reported in environmental and biological matrices worldwide, indicating that it is widespread in the environment[3,4]. According to toxicity research, oral exposure to DP can lead to hepatic oxidative damage, perturbations of metabolism, and signal transduction for male mice[5]. A high concentration and extended exposure to DP induced oxidative damage and neurotoxicity on earthworms (*Eisenia fetida*)[6]. DP has been identified as a Substance of Very High Concern by the European Chemicals Agency (ECHA) and is being reviewed for addition to the list of the Stockholm Convention on Persistent Organic Pollutants[7].

Intensive research has been conducted over the past decade on the occurrence and behavior of DP in environment, biota, and humans[3,4,8-12]. Species-specific stereoselective enrichment of DP isomers was observed in previous field monitoring and laboratory experiments. However, the stereoselective enrichment of DP in organisms and its potential mechanisms are rarely discussed comprehensively. This study aims to review the current knowledge about DP bioaccumulation; summarize research results, including species-specific stereoselective enrichment in different organisms and existing problems in the current studies; and guide future research. The keywords "dechlorane plus" and "organisms" were used to perform a literature search in the Web of Science. Literature reporting the change of DP isomer composition in the environmental matrix is also included, and 80 articles are covered in this review.

ISOMER COMPOSITION OF DP COMMERCIAL PRODUCTS AND ITS CHANGE IN ENVIRONMENT

DP was developed by Hooker Chemical (presently OxyChem) in the 1960s as a substitute for Mirex, and its annual production is estimated to be 450-4500 tons. In China, Jiangsu Anpon Electrochemical Co., Ltd has manufactured 300-1000 tons of DP annually since 2003[1]. DP commercial products contain two stereoisomers (*syn-* and *anti-*DP, Figure 1); the ratio of *syn-* and *anti-*DP is approximately 1:3; *i.e.*, the fraction of *anti-*DP [f_{anti} = *anti*-DP/(*anti*-DP + *syn*-DP)] is 0.75[2].

Most of the commercial product and analytical standard f_{anti} values measured by researchers ranged from 0.7 to 0.8 [Table 1], which are consistent with the theoretical ratio (0.75). A low ratio such as 0.65 for commercial products by OxyChem[14] and 0.60 for products from Anpon Electrochemical were also reported[15]. Differences in the f_{anti} values may be related to the composition of different production batches.

Table 1. f_{anti} **values of technical DP mixtures**

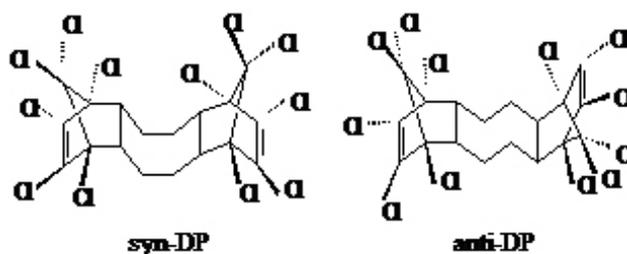| Products	f_{anti}	References
OxyChem	0.75-0.80	Hoh *et al.*, 2006[2]
	0.75	Qiu *et al.*, 2007[13]
	0.65	Tomy *et al.*, 2007[14]
Anpon Electrochemical	0.60	Wang *et al.*, 2010[15]
	0.75, 0.78	Luo *et al.*, 2013[10]
	0.70	Wu *et al.*, 2010[16]
Cambridge Isotope Laboratories	0.74-0.76	Zhu *et al.*, 2007[17]
	0.75-0.77	Gauthier and Letcher, 2009[18]
	0.75	Kang *et al.*, 2010[19]

DP: Dechlorane plus.

Figure 1. Chemical structure of DP isomers. DP: Dechlorane plus.

Information on DP environment behavior remains scarce. A significant change in f_{anti} was observed after long-distance transport. Möller *et al.* observed that f_{anti} decreased from 0.63 to 0.37 with increasing transport distance during transport from Europe to the Arctic and Antarctica through sea and air[20]. Stereoselective photodegradation of *anti*-DP through UV light during long-range transport was proposed as the main cause for this alternation. Zheng *et al.* compared the DP composition in indoor dust collected from an e-waste site and two control areas (rural and urban) and found that the indoor dust in the e-waste recycling workshops had an average f_{anti} value of 0.54, which was significantly lower than indoor dust from the residences in the rural (0.76) and urban control areas (0.70)[21]. The f_{anti} value of indoor dust from residences living in the e-waste site (0.66) was between that of the e-waste recycling workshops and control area. The ratios of dechlorination product of anti-DP (anti-Cl_{11}-DP) to anti-DP were also provided in this study. The average ratio in the indoor dust from the e-waste workshops (0.014) was one order of magnitude higher than that (0.0012) in the indoor dust from the residences, indicating a stereoselective degradation of anti-DP in e-waste recycling process.

The above results indicate that the composition of DP can be influenced by environmental processes. Thus, a direct comparison in DP composition between organisms and industrial products is unreasonable for determining the occurrence of stereoselective accumulation. The result is reliable when the f_{anti} values of the environmental matrix and food fed to organisms are simultaneously provided.

ISOMER COMPOSITION OF DP IN BIOTA SAMPLES

Regarding the DP stereoselective bioaccumulation in organisms, three categories are reported in the literature: *syn*-DP enrichment, *anti*-DP enrichment, and no clear stereoselective enrichment. The literature is summarized as follows according to the standard of whether a conclusion was given by the authors of the study.

Syn-DP enrichment in organisms

Hoh *et al*. first reported the occurrence and composition of DP in sediments and fish of the Great Lakes of North America in 2006[2]. The average f_{anti} of fish was found to be 0.60, which was significantly lower than that of sediments ($P < 0.001$), indicating a selective enrichment of *syn*-DP in fish. Subsequently, numerous studies have reported that, compared to *anti*-DP, *syn*-DP is preferentially accumulated in fish worldwide [Table 2], although a few studies reported inconsistent results. For example, the *anti*-isomer was reported to be dominant in walleye and goldeye in Lake Winnipeg; the f_{anti} in Lake Michigan fish (0.82 ± 0.15) reported by Guo *et al*. was higher than that of the technical DP mixture. Sühring *et al*. reported an evident enrichment of *syn*-DP in eels (f_{anti} = 0.0.4-0.48) in German rivers, which was consistent with that of Hoh *et al*.[2,14,23,26]. However, another study on the bioaccumulation and maternal transfer of DP in the European eels from Ems and Schlei Rivers reported an *anti*-DP enrichment in eels[39]. The former study predominantly analyzed yellow eels (no mature), while the latter used mature silver eels. The difference in the observed f_{anti} patterns can be attributed to the difference in maturation. The selective maternal transfer of syn-DP to egg and gonad tissues was observed in silver eels, and hence the proportion of anti-DP in the mother's body increased.

The f_{anti} values used for comparison with those of fish included both f_{anti} values in sediments where fish were collected and in technical DP mixtures. The f_{anti} values in sediments reported in the literature are consistent with those reported in the technical DP mixtures, which indicate no obvious stereoselective degradation of DP in the sediments. Thus, a direct comparison between fish, which are bottom-dwelling, sedentary, and feed on benthic organisms, and technical DP mixtures can provide a reliable result on the stereoselective accumulation of *syn*-DP in fish.

In addition to fish, some aquatic organisms at high trophic levels, such as seals, water snakes, dolphins, whales, and water birds, were also reported to show selective enrichment of *syn*-DP [Table 2]. However, the f_{anti} values used for comparison were those of sediment or industrial products, but not their prey. Generally, fish are the main prey of these high trophic level organisms, and it is not credible to draw a *syn*-DP enrichment conclusion from these organisms because of the low f_{anti} that they may acquire from their prey.

Some other studies also reported a *syn*-DP enrichment in organisms. However, after carefully checking the data, these statements were found to be incorrect. For example, the f_{anti} value of oysters collected in the coastal area of Dalian, China, was 0.55, which is lower than that of industrial products; this was considered a selective enrichment of syn-DP[40]. However, the value of the surrounding sediment was 0.56, which was similar to that in the oysters. Thus, no stereoselective accumulation occurred in this species. Na *et al*. collected alga, limpet, starfish, gammarid, krill, cod, penguin, seal, and skua samples in Fildes Peninsula in Antarctica and found that the f_{anti} value of DP ranged from 0.23 to 0.53[41]. They believed that these lower f_{anti} values than those of industrial products implied a selective removal of *anti*-DP or selective enrichment of *syn*-DP during long-distance migration. However, compared with the previously reported f_{anti} value (0.35) of the surrounding seawater, there was no obvious tendency of *syn*-DP selective enrichment in organisms.

Amphibians and terrestrial organisms were also reported to enrich *syn*-DP selectively. Wu *et al*. collected frogs in an e-waste recycling area in Qingyuan, Guangdong Province[42]. The f_{anti} values in muscle (0.65), liver (0.58), and egg (0.53) were significantly lower than the average f_{anti} value of its prey item (insects: 0.73), indicating a selective enrichment of *syn*-DP in frogs. Venier *et al*. collected serum samples from four American pet dogs and found that their f_{anti} value was 0.61 ± 0.08, which was lower than that in the dog food (0.76 ± 0.02), implying a slight *syn*-DP enrichment[43]. Given the limited number of samples, the authors warned that the conclusion could not be over interpreted. Chen *et al*. collected biological samples (plants,

Table 2. Enrichment of *syn*-DP in organisms reported in the literature

Regions	Organisms f_{anti}	Reference f_{anti}	Reference
Lake Ontario	Trout: 0.44-0.58 (1979-2004)	Sediment: 0.76-0.86 (1980-2004)	Shen *et al.*, 2011[22]
Lake Ontario Superior Erie Lake Michigan	Fish: 0.65±0.06 Fish: 0.63±0.07 Fish: 0.60±0.07 Fish: 0.82±0.15	Technical DP mixture: 0.75	Guo *et al.*, 2017[23]
Iberian river basins in Spain	Fish: 0.48 ± 0.16	Sediment: 0.64-0.80	Santín *et al.*, 2013[24]
France	catfish: 0.60 ± 0.12	Industrial products: 0.75	Malak *et al.*, 2018[25]
River Rhine	Eels: 0.04-0.48	Industrial products: 0.75	Sühring *et al.* 2013[26]
E-waste site in Qingyuan, South China	Fish: 0.14-0.68	Sediment: 0.72	Wu *et al.*, 2010[16]
The Pearl Rivers, China	Mud carp: 0.60 Nile tilapia: 0.59 Plecostomus: 0.70	Sediment: 0.77	He *et al.* 2014[27]
The Pearl Rivers, China	Mud carp: 0.52 Nile tilapia: 0.57 Plecostomus: 0.65	Technical products: 0.65-0.80	Sun *et al.*, 2016[28]
The Yellow River Delta, China	Fish and shellfish: 0.56-0.60	Technical products: 0.65-0.80	Zhang *et al.* 2020[29]
Daling river in northeastern China	Fish: 0.53	Water: 0.72 Sediment: 0.75 Reed: 0.73	Wang *et al.*, 2012[30]
E-waste site in Guiyu, South China	Fish: 0.56-0.68, average of 0.65	Surrounding soil: 0.67-0.83, average of 0.76.	Tao *et al.* 2015[31]
Urban river in South Korea	Fish: 0.67 ± 0.060,	Technical products: 0.75	Kang *et al.* 2010[19]
Japanese market	Fish: 0.62 ± 0.05	Technical products: 0.75	Kakimoto *et al.* 2012[32]
The coast of Concepcion, Chile	Fish: 0.47-0.61	Technical products: 0.75	Barón *et al.*, 2013[33]
San Francisco Bay, USA	Seals: 0.43-0.49	Sediment: 0.65	Klosterhaus *et al.* 2012[34]
E-waste site in Qingyuan, South China	Water snake: 0.41	Sediment: 0.72	Wu *et al.* 2010[16]
Southern European waters	Short-beaked common dolphin: 0.37 Bottlenose dolphin: 0.49 Long-finned pilot whale: 0.49	Technical products: 0.75	Barón *et al.*, 2015.[35]
E-waste Site in Qingyuan, South China	Five water birds: 0.34-0.61	Technical products: 0.75	Zhang *et al.*, 2011[36]
DP production plant, China	Human serum and hair: 0.51-0.61	Technical products: 0.68	Zhang *et al.* 2013[37]
Minzu University of China	Human hair: 0.727	Dust in house: 0.78-0.79	Chen *et al.* 2019[38]

DP: Dechlorane plus.

insects, birds, reptiles, and mammals) and abiotic samples (air, water, and soil) at two sites in Xilingol, Inner Mongolia[44]. They found that the f_{anti} of plant samples (0.68) were lower than those in water (0.72), soil (0.73), and air (0.71), showing *syn*-DP enrichment. The f_{anti} in ectotherms, including lizards, toads, and snakes (0.44-0.61), was significantly lower than that of the surrounding environmental matrix, indicating a selective enrichment of *syn*-DP.

Two studies reported possible *syn*-DP enrichment in human samples. Zhang *et al.* collected human serum and hair samples from a DP production plant and its surrounding areas in China[37]. The f_{anti} value of serum and hair of workers was between 0.54 and 0.61, lower than the f_{anti} value of factory products (0.68). Chen *et al.* analyzed the composition of DP in hair, dormitory dust, and classroom dust of students of Minzu University of China and found that the f_{anti} value in hair (0.727) was significantly lower than that in dormitory dust (0.791) and classroom dust (0.783), indicating a *syn*-DP enrichment in hair[38].

Anti-DP enrichment in organisms

Organisms reported to enrich *anti*-DP were mainly birds. Zheng *et al.* analyzed absorption and tissue distribution of DP in chickens raised in an e-waste recycling site[45]. Soil in the yard was found to be the main source of DP in the chickens. The elevated f_{anti} in chickens (muscle, liver, brain, and fat: 0.64-0.65)

compared with the soil (0.52) implied a stereoselective enrichment of *anti*-DP in chickens. No significant difference in f_{anti} values was observed in chyme, intestinal contents, and feces ($P > 0.05$), indicating no stereoselective absorption of DP isomers during gastrointestinal absorption. Sun *et al*. found that the f_{anti} value in muscle and liver for three bird species (light-vented bulbul, 0.80 ± 0.017; long-tailed shrike, 0.78 ± 0.01; and oriental magpie-robin, 0.75 ± 0.01) was higher than in dust samples (0.70) in the Pearl River Delta[46]. In the Pearl River Delta, the eggs of three terrestrial birds (light-vented bulbuls, 0.80-0.91; yellow-bellied prinias, 0.77-0.94; and dark green white-eyes, 0.79-0.83) showed higher f_{anti} than that of commercial mixtures and dust[47].

In the southwestern Mediterranean, the f_{anti} value for yellow-legged gulls ranged from 0.73 to 0.85, with an average of 0.81, whereas the f_{anti} value for Audouin's gulls ranged from 0.70 to 1.00, with an average of 0.82[48]. A slight enrichment of *anti*-DP was anticipated in both species. The f_{anti} values ranged 0.71-0.78 in penguin samples and 0.69-0.89 in skua samples from King George Island in Antarctica, which were slightly higher than those of commercial mixtures[49]. In addition, Kim *et al*. reported the f_{anti} of DP in organisms of King George Island in Antarctica[50]. The f_{anti} values of limpets and Antarctic cod were 0.68 ± 0.24 and 0.57 ± 0.11, respectively. Gentoo and Chinstrap penguin samples had f_{anti} values of 0.74 ± 0.20 and 0.65, respectively, while the Antarctic icefish and the south polar skua had f_{anti} values of 0.71 and 0.79, respectively. The f_{anti} values could have decreased because of diastereomerization during long-range transportation; however, because of bioaccumulation, the f_{anti} values in biota samples, even in remote regions, were observed to be similar to or higher than those in commercial mixtures, indicating enrichment of *anti*-DP[11].

An enrichment of *anti*-DP was also reported in human samples. Chen *et al*. collected the serum and hair of workers in e-waste recycling workshops and observed that the average f_{anti} value in the serum (0.65) was higher than that in the hair (0.47) of the workers and the dust (0.54) in the workshops, indicating a selective enrichment of *anti*-DP in the human body[51]. Yan *et al*. also reported a similar result. The f_{anti} values in the serum were 0.67 ± 0.07 for female samples and 0.63 ± 0.06 for male samples[52]. These values were higher than those found in human hair (0.55 ± 0.11) and dust samples (0.54) in the workshops[21].

Chen *et al*. found that ectotherms, including lizards, toads, and snakes, stereoselectively enriched syn-DP when compared to the surrounding environmental matrix (Section 2.1)[44]. However, endotherms such as birds [Cuckoo (0.70) and swallow (0.72)] and weasels (0.66) exhibited elevated f_{anti} values when compared with their prey [insect (0.66) and mouse (0.58)], indicating an *anti*-DP enrichment. This is an intriguing study, which provided some insight into the stereoselective bioaccumulation of DP.

Unclear DP stereoselective enrichment in organisms
In addition to the selective enrichment of *syn/anti*-DP, some studies also reported no obvious selective enrichment of DP in organisms [Table 3]. Rjabova *et al*. reported that *anti*-DP has a significantly higher detection frequency than does *syn*-DP in salmon collected in the Baltic Sea, while samples containing both isomers showed f_{anti} values ranging from 0.56 to 0.94, with an average value of 0.71, which was close to the f_{anti} value of technical DP mixtures[53].

Several fish-feeding bird samples exhibited similar DP composition as DP commercial products, and it was considered that there was no selective enrichment of stereoisomers of DP. Since the preferential enrichment of *syn*-DP was found in fish, the selective enrichment of *anti*-DP appeared to be the reason for the f_{anti} ratio of fish-eating birds being close to or higher than that of industrial products. For example, Mo *et al*. found that the f_{anti} values of kingfishers in an e-waste recycling region were similar to those of technical DP

Table 3. No clear DP stereoselective enrichment in organisms reported in the literature

Areas	Organisms f_{anti}	Reference f_{anti}	Reference
Daugava and Venta rivers	Baltic wild salmon: 0.71 (0.56-0.94)	Technical DP mixture	Rjabova *et al.*, 2016[53]
Great Lakes of North America	Eggs of herring gulls: 0.69 ± 0.08	Technical DP mixture	Gauthier and Letcher *et al.*, 2009[18]
Madrid in Spain Doñana National Park	White stork eggs: 0.64 White stork eggs: 0.66	Technical DP mixture	Muñoz-Arnanz *et al.*, 2011[54]
St. Lawrence River, Canada	Ring-billed gull liver: 0.72	Technical DP mixture	Gentes *et al.*, 2012[55]
An e-waste site in Qingyuan, South China	Home-produced eggs: 0.63-0.74	Technical DP mixture	Zheng *et al.*, 2012[56]
An e-waste site in Qingyuan, South China	Kingfishers: 0.65 (0.56-0.72) Reference site: 0.76 (0.66-0.91)	Fish: 0.18-0.47 Reference site 0.43-0.73	Mo *et al.*, 2013[57]
A nature reserve in South China	Terrestrial passerines: 0.34-0.97	/	Peng *et al.*, 2015[58]
Beijing, China	Scops owl: only *anti*-DP detected or 0.60-0.80	/	Chen *et al.*, 2013[59]
Beijing, China	Common kestrel: 0.79 Owl: 0.79	Sparrow: 0.75 Brown rat: 0.77	Yu *et al.* 2013[60]
E-waste site in Guiyu, South China	Chicken egg: 0.74-0.76 Goose egg: 0.64	Technical DP mixture	Zeng *et al.*, 2016[61]
Southeastern and Southern Coast of Brazil	Franciscana Dolphin: 0.71 ± 0.16	Technical DP mixture	de la Torre *et al.*, 2012[62]
E-waste site in Guiyu, South China	Human serum: 0.58 ± 0.11 Reference site: 0.64 ± 0.05	/	Ren *et al.*, 2009[63]
Kingston and Sherbrooke, Canada	Human milk: 0.67	Technical DP mixture	Siddique *et al.*, 2012[64]
France	Human serum: 0.75 (0.65-0.86)	Technical DP mixture	Brasseur *et al.*, 2014[65]

DP: Dechlorane plus.

mixtures (0.60-0.80) [57]. However, the fish had f_{anti} values ranging from 0.18 to 0.47 in this region. An enrichment of *anti*-DP was expected in kingfishers when compared with fish. This was also expected in other fish-feeding birds considering the stereoselective enrichment of *syn*-DP in fish.

Chicken eggs (f_{anti}: 0.63-0.74) collected from an e-waste recycling site in Qingyuan were also expected to exhibit unclear DP stereoselective enrichment[56]. However, the average f_{anti} values in the surrounding soil and dust samples were 0.52 and 0.54, respectively[21,45]. Compared with these samples, an enrichment of *anti*-DP in chicken eggs was evident. Raptors collected in Beijing, China, were found to have similar f_{anti} values (average: 0.79) compared with those of their prey (0.75-0.77)[59]. Terrestrial passerines collected from a nature reserve in South China exhibited a wide range (0.34-0.97) of f_{anti} values[58]. It was difficult to determine the stereoselective enrichment occurrence for these terrestrial birds.

Considering human samples, determining selective enrichment was impossible because no information on the isomer composition of DP in the exposure source is available. Overall, the credibility of the conclusion based on a direct comparison between organisms and technical DP mixture is questionable. The potential stereoselective enrichment of DP in organisms may be underestimated if organisms stereoselectively enrich one DP isomer but their prey enriches the other one.

FACTORS INFLUENCING THE DP FRACTIONATION DURING BIOACCUMULATION

The following factors can affect DP composition measured in the organisms discussed above.

(1) Tissue or organ: Values of f_{anti} were found to be tissue- or organ-specific in a given species. Zhang *et al.* reported that *anti*-DP was preferentially accumulated in the brain compared to the liver and muscle for mud carp and snakehead, suggesting that the *anti*-isomer can cross the blood-brain barrier of fish and has

high affinity to the brain[66]. Peng *et al.* found that the f_{anti} values in the heart and eggs of Chinese sturgeon (0.58 and 0.65, respectively) were significantly lower than those in the liver (0.72) and muscle tissue (0.72)[67]. Zheng *et al.* investigated the tissue distribution of DP in chickens in an e-waste area and found elevated f_{anti} values in the fat, brain, and liver (0.65, 0.64, and 0.64, respectively) compared with other tissues (0.54-0.59)[45]. Wu *et al.* found that frog eggs exhibited remarkably lower f_{anti} (0.53) than frog muscle (0.58) and liver (0.65), indicating preferential transfer of *syn*-DP during maternal transmission[42]. This was consistent with the lower f_{anti} value in Chinese sturgeon eggs than in other tissues.

(2) Trophic level: Wu *et al.* first reported that f_{anti} values decreased up the trophic ladder in the aquatic food chain[16]. Subsequently, a significantly negative correlation between f_{anti} values and the trophic level of organisms in aquatic and terrestrial food chains in the same region was also reported[36,68]. A significantly negative linear relationship between *anti*-DP fraction and stable nitrogen isotope ratio ($\delta^{15}N$) of biological individuals was also observed in three terrestrial birds collected in different regions of the Pearl River Delta[46]. In a food chain composed of seven species of aquatic organisms collected from Huai'an in Jiangsu province of China, Wang *et al.* found that shrimp occupied the lowest trophic level with the highest f_{anti} value of 0.81, while snakes occupied the highest trophic level with the lowest f_{anti} value of 0.51[69]. There was a significantly negative linear correlation between f_{anti} values and the trophic level of organisms. However, an inconsistent result was observed in the food chain of Fildes Peninsula by Na *et al.*: the f_{anti} first increased and then decreased with increasing trophic levels. The f_{anti} value decreased through the food chains composed of ectotherms, while the value initially decreased before increasing in the food chains composed of endotherms[41,44].

(3) DP concentration: Mo *et al.* found that there was a significant negative relationship between DP composition and its concentration in kingfishers and fish and proposed that DP concentration could be an important factor influencing isomeric fraction[57]. A similar phenomenon was also found in terrestrial bird eggs and muscles in the Pearl River Delta. However, f_{anti} values increased with increasing DP burdens in muscle and liver in Eurasian sparrowhawk, which is in contrast with the above results[46,58,59].

(4) Gender: Yan *et al.* collected serum samples from 33 male and 37 female workers in e-waste recycling plants[52]. Samples from female workers exhibited significantly higher DP concentrations (mean: 265 ng/g lw) and f_{anti} values (median: 0.70) than those from the males (121 ng/g lw, and 0.64, respectively). Additionally, the ratios of *anti*-Cl_{11}-DP to *anti*-DP were remarkably higher in males (mean: 0.017) than in females (mean: 0.010). Lower DP loading and lower f_{anti} values in males can be ascribed to males having stronger metabolic ability for DPs than females and *anti*-DP having a higher metabolism capacity in organisms. Studies on maternal transfer of DP in Chinese sturgeons[67], eels[39], and frogs[42] revealed that *syn*-DP more readily transferred to eggs than does *anti*-DP. This may cause higher f_{anti} values in females than in males. Wu *et al.* verified this hypothesis in their work, wherein the observed concentration of DP in female frogs was significantly lower than that in male frogs, while the f_{anti} value was higher than that in male frogs[42].

POTENTIAL MECHANISMS REVEALED BY LABORATORY EXPOSURE EXPERIMENT

A series of laboratory experiments have been conducted to explore the mechanism of DP fractionation during bioaccumulation.

Exposure experiments in fish

Tomy *et al.* first exposed juvenile rainbow trout to DP isomers through their diet for 49 days (uptake phase) before feeding them with untreated food for 112 days (depuration phase), were conducted by L[70]. *Syn*- and

anti-isomer loads increased during the entire uptake phase and did not reach plateau during the uptake phase. The uptake rates for *syn*-DP and *anti*-DP were 0.045 ± 0.005 and 0.018 ± 0.002 nmol/day, respectively, while the measured half-lives were 53.3 ± 13.1 days for *syn*-isomer and 30.4 ± 5.7 days for *anti*-isomer. These results verify *syn*-DP selective accumulation in the fish species. No suspected degradation products, including dechlorinated, hydroxylated, methoxylated, and methyl sulfone metabolites, were detected in the liver samples, indicating that *in vivo* biotransformation of DP could hardly produce these metabolites.

Common carp was exposed to DP industrial products and DP isomers successively in two studies[71,72]. Despite differences in exposure and depuration times, sampling intervals, and sample collection, both studies found higher absorption efficiency of *anti*-DP in the gastrointestinal tract but significantly lower assimilation efficiency of *anti*-DP, indicating the stereoselective metabolism of *anti*-DP in fish. DP tissue distribution was a dynamic process. During the uptake phase, the DP concentration in liver was remarkably higher than those in other tissues, indicating a selective accumulation of DP in the liver. However, in the depuration period, the highest elimination rate of DP was found in the liver, which subsequently reduced the concentration gap between liver and other tissues. The liver showed preferential enrichment of *anti*-isomer, intestine and muscle preferred *syn*-DP, and the whole fish exhibited selective accumulation of *syn*-DP. Tang *et al.* observed an increasing f_{anti} value trend in the feces of common carp along with a decreasing trend of f_{anti} value in the whole fish during the depuration phase, indicating that selective excretion of *anti*-DP was likely the primary reason for the low f_{anti} values[72].

These three DP exposure experiments confirmed the selective enrichment of *syn*-DP in fish. Despite no direct evidence of selective degradation of *anti*-DP, there was clear evidence of selective excretion of *anti*-DP. Therefore, the selective excretion of *anti*-DP should be an important factor for enriching *syn*-isomer in fish, but selective degradation of *anti*-DP also cannot be ruled out.

Exposure experiment in bird and mammal

Sprague-Dawley rats[73] and male common quails[74] were consecutively exposed to commercial DP for 90 days at 0, 1, 10, and 100 mg/kg/day doses and endured 45 days of depuration to investigate the DP composition in the liver, muscle, and serum. The studies found that the liver had the highest DP concentration among all tissues, implying that DP preferred to accumulate in the liver. DP composition was found to be dose dependent. The f_{anti} values (0.7) in the low-exposure group (1 mg/kg/day) were close to those in DP industrial products, while the f_{anti} values (0.16-0.34) in the high-exposure groups (10 and 100 mg/kg/day), were significantly lower than DP industrial products. The activity of erythromycin N-demethylase (ERND) and the antioxidant enzyme catalase significantly increased in high-exposure groups[74]. The activity of ERND is mainly CYP3A-dependent, and forms of CYP3A are among the most abundant and important xenobiotic-metabolizing CYP enzymes, mediating the metabolism of numerous xenobiotics[74]. Therefore, high-dose DP exposure might induce a high metabolism rate of DP, while *anti*-DP is more prone to metabolizing[2], which might be the reason for these dose-dependent results. During the depuration phase for Sprague-Dawley rats, the f_{anti} values in the liver and muscle increased compared to the end of the uptake phase, implying a selective elimination of *syn*-DP during the depuration period.

In ovo exposure and *in vivo* exposure to DP of chicken eggs and hens, respectively, were conducted by Li *et al.*[75]. The results of *in ovo* exposure experiment indicate that approximately 12% and 28% of the absorbed *syn*- and *anti*-isomers, respectively, were eliminated during egg hatching, resulting in a relative enrichment of *syn*-DP in chick tissues. Because there was no excretion pathway during hatching, the loss can only be attributed to biotransformation. This result provides solid evidence that *anti*-DP is preferably metabolized in the organisms. The *in vivo* exposure experiment provided a completely reversed result. In

the uptake period, the f_{anti} value in eggs laid by the hens was just slightly higher than that in the food. However, the eggs laid during the depuration phase showed a sharp increase in f_{anti}, and the f_{anti} in the tissue of hens was higher than the original f_{anti} in the food [Figure 2]. The increase of f_{anti} in the depuration period agreed with the results in Sprague-Dawley rats[73]. Selective accumulation of *anti*-DP was observed in adult chickens, but the isomer preferentially metabolized in developing chicken embryos, indicating that selective excretion for *syn*-DP played a more important role compared to selective metabolism for *anti*-DP.

These exposure experimental results verify the earlier hypothesis that *anti*-DP may be more reactive than *syn*-DP in biotransformation[2]. However, selective biotransformation for *anti*-DP and selective excretion for *syn*-DP coexisted in the organisms. Only at high concentration levels, where the selective biotransformation surpasses the selective excretion, can organisms show a relative enrichment of *syn*-DP. In the case of low exposure concentration, selective excretion plays a leading role in the accumulation of DP. If the intensity of the two processes is equal, no obvious selective enrichment of DP stereoisomers will be observed.

If this assumption is correct, there will be a selective excretion of *anti*-DP for fish but *syn*-DP for birds. The underlying cause of this species difference in excretion of DP isomer is unclear based on the present data, which could be explained by the difference in the interaction between DP and macromolecules in organisms.

In vitro studies using liver microsomal
In addition to *in vivo* exposure experiments, some *in vitro* studies using liver microsomes were conducted to investigate the potential DP biotransformation. Peng *et al.* conducted *in vitro* experiments using microsomal fraction of the liver in Chinese sturgeon but failed to detect any dechlorinated metabolites[67]. Chabot-Giguère *et al.* conducted an *in vitro* assay of DP using liver microsomes in ring-billed seagulls collected from a polluted hotspot area of the St. Laurence River in Canada[76]. The results show no obvious degradation products of dechlorination and hydroxylation. During field monitoring, dechlorination products of DP, anti-Cl_{11}-DP, and ayn-Cl_{11}-DP were detected in birds[46] and human hair samples[21]. However, these dechlorination products were also found in the environmental matrix. The dechlorination products may be directly derived from the environment rather than biological metabolism.

Plant absorption of DP
Zhao *et al.* studied *Ulva pertusa* exposed to DP solution for 21 days before transferring them to seawater without DP for 14 days[77]. It was observed that syn-DP was rapidly accumulated in *Ulva pertusa* during the uptake phase, and the uptake rate of *syn*-isomer (0.164 ± 0.056 day^{-1}) was higher than that of the *anti*-isomer (0.083 ± 0.071 day^{-1}). However, the elimination rate of *syn*-DP (0.337 ± 0.057 day^{-1}) was higher than that of *anti*-DP (0.236 ± 0.095 day^{-1}), which resulted in lower syn-DP in the depuration phase. Zhang *et al.* investigated absorption and translocation of DP for rice planted in an e-waste contaminated site[78]. It was found that the f_{anti} values of the root, stem, and leaf in the rice were significantly lower than those of soil, indicating a selective enrichment of *syn*-DP from the soils to the root. Similarly, Cheng *et al.* found the f_{anti} values of root (0.54) and stem (0.65) were significantly lower than that of the corresponding soil (0.75) in the rhizobox[79]. Fan *et al.* studied DP isomer fractions in peanuts planted in the e-waste recycling area and observed that the f_{anti} value in different growth stage [seed (0.37-0.50) and growth (0.37-0.50) stages] was lower than that of the soil and air, which verified that the *syn*-DP was preferably accumulated in the plant[80].

These four uptake experiments showed selective enrichment of *syn*-DP in plants, but the mechanism remains unknown. It was speculated that the difference in solubility of the two isomers of DP might be the reason for the phenomenon. The solubility of the two isomers is 207 and 572 ng/L as reported by Oxychem, but no specific information is provided on the isomers' solubility[16]. *Syn*-DP could be prone to transfer from
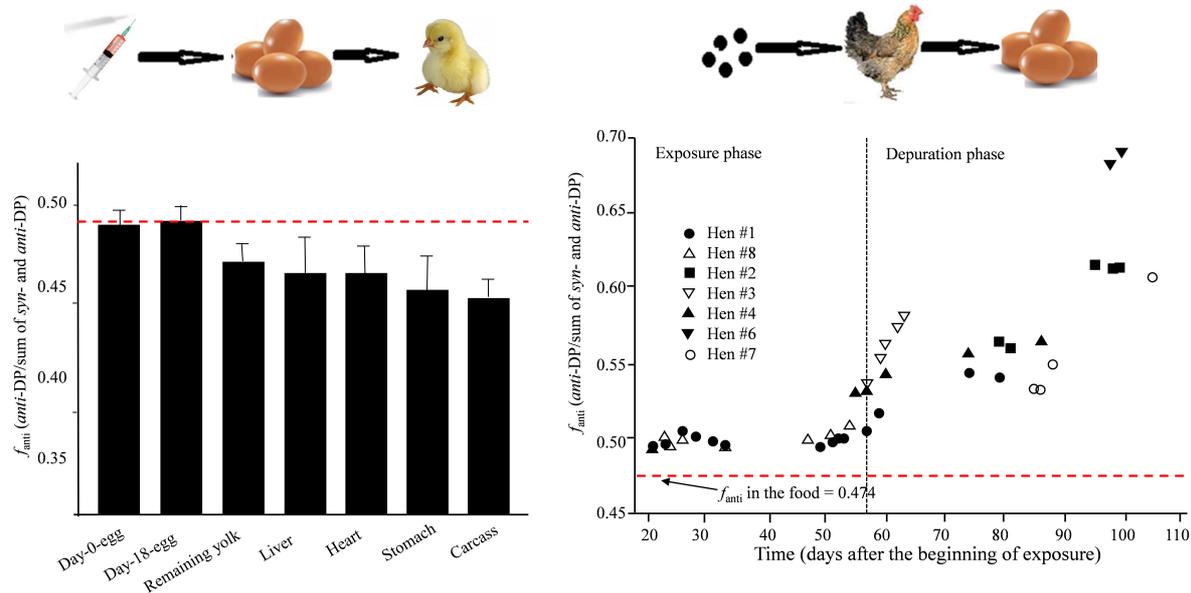
Figure 2. *In ovo* exposure and *in vivo* exposure to DP of chicken eggs and hens. DP: Dechlorane plus.

the soil into pore water and be absorbed by plant root systems because of its relatively high solubility. The relative content of *anti*-DP increasing during the depuration stage for *Ulva pertusa*[77] may be due to the high solubility of *syn*-DP, which leads to preferential distribution into the pure aqueous solution during the depuration phase. In addition to solubility, biotransformation of DP isomers in plants remains unclear, and further studies are needed.

CONCLUSION AND PROSPECTIVE

Stereoisomers of DP exhibited species-specific enrichment in organisms. Based on available data, selective enrichment of *syn*-DP was mainly observed in fish, while selective enrichment of *anti*-DP mainly appeared in birds. It is very likely that this different DP isomer fractionation during bioaccumulation exists between ectotherms and endotherms. Most studies reported that *syn*-DP enrichment was observed in ectotherms, while *anti*-DP enrichment was observed in endotherms. However, this hypothesis needs to be confirmed in future research.

A direct comparison of f_{anti} values between organisms and technical DP mixture was conducted to determine the occurrence of DP isomer fractionation. This will cause great uncertainty when considering the diversity of industrial DP products in f_{anti} and the alternation of DP composition after releasing into environment. A comparison of f_{anti} values between exposure source and organisms will provide more reliable results. For a given food chain/web, when the prey and predator selectively enrich different isomers, such as fish and fish-eating birds, the f_{anti} value in the predator will be close to that of the technical DP mixture. In that case, the predator was expected to have no clear stereoisomer selective enrichment. Thus, stereoselective enrichment of DP in organisms may be underestimated.

The hypothesis that *anti*-DP is more readily eliminated through biotransformation than *syn*-DP has been evidenced by some studies. Unfortunately, potential metabolites have not been identified yet. Screening the phase II type transformation, such as uridine diphosphoglucuronosyltransferase- or sulfotransferase-mediated conjugation, could be a possibility. Selective excretion of one DP isomer was found to be the main

reason for DP isomer fractionation in bioaccumulation. Both selective excretion of *anti*-DP and selective biotransformation of *anti*-DP facilitate *syn*-DP enrichment in fish. However, selective excretion of *syn*-DP and selective biotransformation of *anti*-DP seem to coincide in birds. This could be the reason for inconsistent results observed among different studies.

The influences of concentration and trophic levels on the DP composition were evident but did not provide consistent results in past studies and their mechanism remains unknown. Tissue- or organic-specific uptake and elimination of DP isomer were also observed. The preferential enrichment of DP in the liver was observed in both field and laboratory exposure experiments, and the f_{anti} was found to be tissue-specific. However, the key drivers of this process remain unknown. Future studies should address these knowledge gaps.

DECLARATIONS

Authors' contribution
Conceptualization, formal analysis, investigation, data curation, writing, original draft preparation, Writing, review and editing: Luo XJ
Investigation, writing and original draft preparation: Guan KL
Investigation, writing, review and editing: Liu HY
All authors have read and agreed to the published version of the manuscript.

Available data and materials
The data presented in this review are available from the corresponding author.

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All authors declared that there are no conflicts of interest.

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Consent for publication
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