Ecotoxicology and Environmental Safety 182 (2019) 109402

Contents lists available at ScienceDirect

Ecotoxicology and Environmental Safety

journal homepage: www.elsevier.com/locate/ecoenv

Review

A review of sources, multimedia distribution and health risks of novel fluorinated alternatives

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ARTICLE INFO

Keywords:
PFAS alternatives
Contamination
Potential impact
Risk assessment
Toxicity
Sources

ABSTRACT

Per- and polyfluoroalkyl substances (PFASs) are a class of emerging persistent organic pollutants (POPs). They are widely used in industrial and consumer applications. Due to their persistence, bioaccumulation, long-distance migration and toxicity, it is important to find new compounds that can replace PFASs. The present review investigated the sources, fates and environmental effects of alternative PFAS compounds using surveys have been conducted over the past several years. Concentrations of PFAS alternatives in various environmental media, as well as human tissues, are summarized based on the available data. The results showed that hexafluoropropylene oxide dimer (HFPO-DA), hexafluoropropylene trimer acids (HFPO-TA), and 6:2 chlorinated polyfluorinated ether sulfonic acid (6:2 Cl-PFESA) have become the dominant global perfluorinated pollutants. Currently, there are a few toxicity assessments of these novel fluorinated alternatives, showing that they have systemic multiple organ toxicities. PFAS alternatives exhibited comparable or even more serious potential toxicity than legacy PFASs, indicating that these fluorinated alternatives are also harmful to the environment. Therefore, these alternatives require additional toxicological studies to confirm whether they can be used for a long time.

1. Introduction

Per- and polyfluoroalkyl substances (PFASs) are widely used in industrial and consumer applications because of their unique surface activity and stability properties. The widespread usage of PFASs enables them to access a variety of environmental media. Currently, toxicological studies indicate that PFASs are one kind of environmental pollutants with systemic toxicities to multiple organs. It has been found that PFASs, especially those with longer carbon chains (perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA)), have the characteristics of persistence, long-distance mobility, bioaccumulation potential, and toxic effects. The widespread and environmental hazards of pollution by PFASs have attracted attention, which has triggered the supervisal actions and voluntary phase-out project by the relevant chemical lines. Eight leading global companies reached an agreement to consume PFOA in 2006, while PFOS were added to the list of "persistent organic pollutants (POPs)" under the Annex B of the Stockholm Convention in 2009 (Wang et al., 2009). PFOA and its salts were also proposed for inclusion in the Stockholm Convention and are still being evaluated, and PFOS was limited on used mostly in the metal plating industries, semiconductor, and photolithography. This means that these PFASs can only be used for specific exemptions and acceptable purposes.

This restriction has led to the rapid increase research into PFAS alternatives to long-chain PFASs, especially the PFOS and PFOA alternatives. Following global actions to work out PFOS, considerable efforts have been made to develop safer alternatives. A large number of PFAS alternatives are being used in increasing quantities. Concentrations of PFOS in humans are decreasing (Calafat et al., 2007; Glynn et al., 2012), while numerous alternatives are being produced (Wang et al., 2014; Gomis et al., 2015). Research on environmental behaviors and related risks of PFAS alternatives has become a new hot topic.

Currently, research on PFAS alternatives has been initiated (Fig. 1). In the past five years, studies on PFAS alternatives have focused on the detection in different environmental media, the estimation of sources and emissions and the toxicology to organisms of these alternatives (Wang et al., 2013, 2016a; Heydebreck et al., 2015; Ruan et al., 2015; Gebbink et al., 2016; Pan et al., 2017; Lin et al., 2016; Shi et al., 2016; Chen et al., 2017; Liu et al., 2017; Cui et al., 2018). Previous studies have summarized and compared PFASs concentrations and their

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https://doi.org/10.1016/j.ecoenv.2019.109402
Received 7 May 2019; Received in revised form 27 June 2019; Accepted 29 June 2019
Available online 04 July 2019
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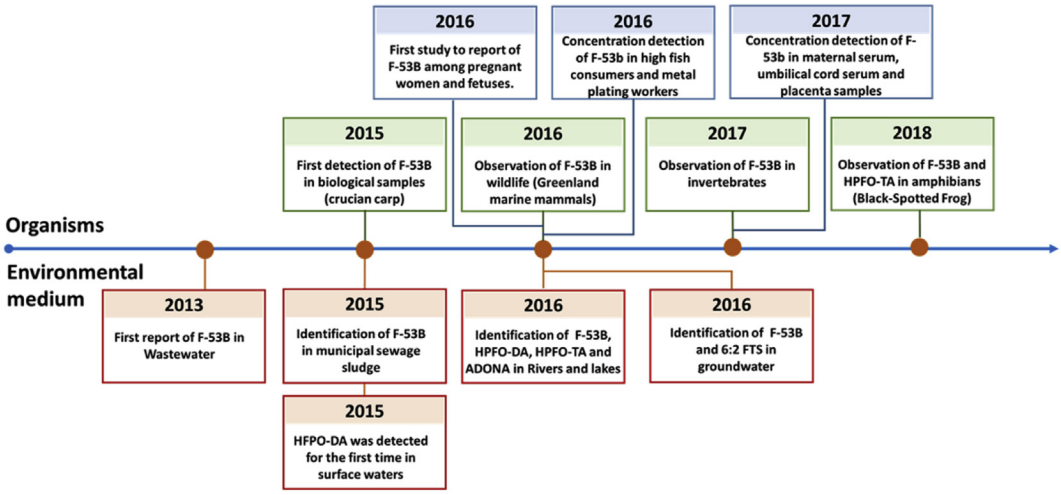


Fig. 1. Temporal trends of research progress on PFAAs alternatives (Reference: Wang et al., 2013; Heydebreck et al., 2015; Ruan et al., 2015; Gebbink et al., 2016; Pan et al., 2017; Lin et al., 2016; Wang et al., 2016a; Shi et al., 2016; Sun et al., 2016; Chen et al., 2017; Liu et al., 2017; Cui et al., 2018).

contamination profiles in the biota, human tissues and bioaccumulation processes (Cui et al., 2018; Shi et al., 2016, 2017a). However, limited information about the profile of these alternatives is available in the existing literature.

To date, several PFAS alternatives have been detected in multiple samples (Heydebreck et al., 2015; Ruan et al., 2015; Wang et al. 2016a, 2016b). At present, there are a few toxicity assessments of these novel fluorinated alternatives. In the present review, we aim to summarize and update the status and trends in concentrations of PFAS alternatives, especially PFOS and PFOA alternatives, in various media, and provide information to assess the risks of humans and wildlife.

2. Classification of PFASs alternatives

Currently, there are mainly two kinds of current fluorinated alternatives to replace PFOS and PFOA, the two dominant PFASs in the environment. One kind of alternative to PFOS and PFOA includes perfluoroalkyl ether sulfonic and carboxylic acids (PFESAs and PFECAs). PFESAs has been accepted for use in the electroplating industry instead of PFOS (Wang et al., 2014; Sheng et al., 2018), while PFECAs have been produced to replace PFOA for high performance materials as processing aids. (Pan et al., 2018). The chemical structures of PFESAs and PFECAs are shown in Table 1. They were supposed to be easy breakdown into short perfluorinated chains than PFOS and PFOA because of insertion of oxygen atoms between perfluorinated chains and fluorine atoms replaced by chlorine and hydrogen (Buck et al., 2011). Chlorinated PFESA (Cl-PFESAs), with a commercial name of F-53B, has been widely applied as a mist suppressant in China for over 30 years (Wang et al., 2013). The predominant form of Cl-PFESAs is 6:2 Cl-PFESA in commercial products, while 8:2 Cl-PFESA is produced as an impurity (Li et al., 2018). With the implementation of the global ban on PFOS, F-53B is expected to gain more market share (K. Zhang et al., 2016). PFECAs have been recently produced to replace PFOA as emulsifiers in polymerization processes, mainly includes the following four kinds: hexafluoropropylene oxide dimer acid (HFPO-DA), HFPO trimer acid (HFPO-TA), HFPO tetramer acid (HFPO-TeA) (Millauer et al., 1985), and ammonium 4,8-dioxa-3H-perfluorononanoate (ADONA). Among them, the ammonium salt of HFPO-DA, whose business name is GenX, is widely used (Sun et al., 2016). ADONA was firstly developed to replace ammonium perfluorooctanoate (APFO) as an emulsifier in the manufacture of fluoropolymers (Gordon, 2011; Fromme et al., 2017).

Another kind of novel fluorinated alternative to PFOS and PFOA is fluorotelomer sulfonic and carboxylic acids (FTSA and FTCA). The 6:2 FTSA compound is usually applied as PFOS alternative in Europe (UNEP, 2012; Wei et al., 2018), while 6:2 fluorotelomer carboxylic acid (6:2 FTCA) has been used as PFOA alternative in China (Xu et al., 2011; Shi et al., 2017b). The 6:2 FTSA is applied as PFOS alternative in the surface treatment of metal and plastic components in the emulsion polymerization of fluoropolymers (Poulsen et al., 2011; Urtiaga et al., 2018). PFCAS is formed by fluorinated precursors, fluorotelomer alcohols (FTOHs) through a series of biodegradation processes. (Dinglasan et al., 2004). The main names and chemical structure of these substances are shown in Table 1.

3. Potential sources of PFASs alternatives

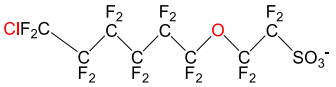
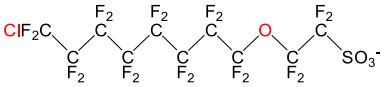
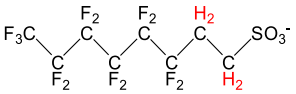
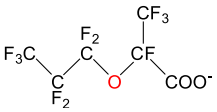
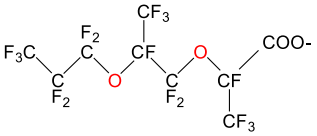
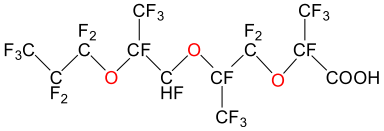
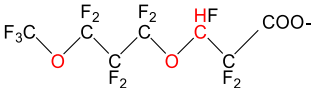
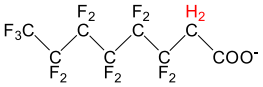
Industrial processes are the main sources of PFAS alternatives releasing into the environment. Nevertheless, studies on PFAS alternatives emissions are still in an initial research stage. Sources of the PFAS alternatives emitted to the environment are illustrated in Table S1.

Most of the PFAS alternatives have been manufactured and used globally for a period. China is the only country with a documented usage of PFESAs (Ruan et al., 2015), and it has been using F-53B for more than 30 years. Commercial products containing 6:2 Cl-PFESA and 8:2 Cl-PFESA are applied as mist suppressants to protect workers from exposure to airborne chromium (VI) in the electrolytic process (Ruan et al., 2015). In 2009, F-53B production was estimated to be 20–30 tons in the Chinese decorative and hard metal plating industry (Huang et al., 2010a, 2010b), and annual F-53B consumption is estimated to be 10–14 tons in 2006–2015 (Shi et al., 2018; Ti et al., 2018). However, annual F-53B production since 2015 is lacking.

GenX, from DuPont, has been used as replacements for PFOA as a processing aid in fluoropolymer resin manufacturing since 2010 (Dupont, 2010; Sun et al., 2016; Heydebreck et al., 2015), with an annual production volume of 10–100 tons in Europe (Dupont, 2010; Pan et al., 2017). HFPO-TA is used as a processing aid in the manufacture of fluorinated polymers (Pan et al., 2017), but its annual production information is scarce, as well as its environmental occurrence. No data are available regarding the annual production or distribution in environmental matrices of HFPO-TeA, ADONA, 6:2 FTSA and 6:2 FTCA (Wang et al., 2016b; Gordon, 2011).

As mentioned above, little information is available on the sources of PFAS alternatives. It is necessary to assess the sources and regional emissions of PFAS alternatives systematically.

Table 1
List of the 7 fluorinated alternatives chosen in this study, together with their abbreviation, Chemical Formula, CAS number, structure, and Emission sources.

Abbreviation	Chemical Names	Chemical Formula	CAS No.	Chemistry Structural Formula	Emission sources/ Industrial application
PFOS alternatives					
6:2 Cl-PFESA/ F-53B	6:2 chlorinated polyfluorinatedether sulfonate	$Cl\text{-}C_6F_{12}OCF_2CF_2SO_3^-$	73606-19-6		Metal plating
8:2 Cl-PFESA	8:2 chlorinated polyfluorinatedether sulfonate	$Cl\text{-}C_8F_{16}OCF_2CF_2SO_3^-$	83329-89-9		Metal plating
6:2 FTSA	6:2 fluorotelomer sulfonic acid	$C_8F_{13}H_4SO_3^-$	59587-39-2		Metal plating
PFOA alternatives					
HFPO-DA/ GenX	ammonium salt of hexafluoropropylene oxidedimer acid	$C_3F_7OC_2F_4COO\text{-}$	62037-80-3		Fluoropolymer processing aids
HFPO-TA	ammonium salt of hexafluoropropylene oxidetrimer acid	$C_3F_7OC_2F_5OC_2F_4COO^-$	13252-14-7		Fluoropolymer processing aids
HFPO- TeA	propanoic acid,2,3,3,3-tetrafluoro-2-[1,1,2,3,3,3-hexafluoro-2-[1,1,2,3,3,3-hexafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)propoxy]propoxy	$C_3F_7O(C_3F_6O)_2C_3F_4HO_2$	65294-16-8		Fluoropolymer processing aids
ADONA	ammonium 4,8-dioxa-3H-perfluorononanoate	$CF_3OC_3F_6OCHFCF_2COO^-$	958445-44-8		Fluoropolymer processing aids
6:2 FTCA	6:2 fluorotelomer carboxylic acid	$C_6F_{13}CH_2COOH$	53826-12-3		Fluoropolymer processing aids

4. Concentrations of PFASs alternatives in environmental medias

4.1. PFASs alternatives in surface water

Although novel PFAS alternatives have been used for several decades, scientific studies on their concentrations in surface water are still very limited. These emerging substances, including HFPO-DA, HFPO-TA, ADONA, 6:2 Cl-PFESA, 8:2 Cl-PFESA, 6:2 H-PFESA and 6:2 FTSA, were ubiquitously detected in worldwide surface waters (Table S1, Fig. 2) (Heydebreck et al., 2015; Wang et al., 2016a; Pan et al., 2018; Lin et al., 2016). HFPO-DA, HFPO-TA, and 6:2 Cl-PFESA were ubiquitously detected in 19 rivers from China, the United States, Germany, the United Kingdom, the Netherlands, Sweden and Korea, indicating ubiquitous distribution and dispersal in global surface waters of these alternatives.

FECAs have been reported firstly in surface waters at the worldwide scale was by Pan et al. (2018). Although 6:2 Cl-PFESA are only used in China (Wang et al., 2013), it was detected in 89% of samples from other countries. Most of the studies in lakes and rivers in China showed the concentration of 6:2 Cl-PFESA (1.1–7.8 ng/L) about the same as PFOS (1.8–11 ng/L) (Wang et al., 2016a; Pan et al., 2018) (Table S1, Fig. 2). HFPO-DA were detected at two sampling sites in the Rhine River, with concentrations of 86.1 ng/L and 73.1 ng/L, and were much higher than PFOS (1.84 and 1.71 ng/L) and PFOA (6.56 and 7.50 ng/L). The concentration range of HFPO-DA was n.d.-3060 ng/L in the Xiaoqing River waters of China and accompanied by the detection of high concentrations of PFOA (30.46–578970 ng/L) (Heydebreck et al., 2015). A current industrial discharge source of PFOA was not observed in Germany and the Netherlands because the industries seemed to respond to concerns by using replacement substances such as HFPO-DA.

The detection rates of 8:2 Cl-PFESA and 6:2 H-PFESA in China were 51% and 95%, respectively. No other countries detected them. FTSA was detected in most samples (0.05–6.75 ng/L), indicating that FTSA is an important fluoride alternatives used in these areas. HFPO-DA and HFPO-TA were also detected in 100% of the samples, while ADONA was only detected in the Rhine River (0.09 ng/L). The results show that these substitutes inevitably enter the environment because of their extensive use in the industrial production process. The different industrial production structures in different regions will lead to an increase in the environmental concentrations of fluorinated alternatives and may even exceed concentrations of PFOA and PFOS. One reason for the distribution of PFAS alternatives is that different countries use different types of alternatives. Such as F-53B, which is widely used in China, but not in other countries. On the other hand, Difference in areal distribution was attributed to the different physicochemical properties and hydrographic conditions of the river (Zhang et al., 2019; Yi et al., 2019). It was worth noticed that PFOS and PFOA still have high detection concentrations (578970 ng/L and 35.7 ng/L). However, increasing public awareness and stricter regulations of long-chain PFASs have transferred its affection to the production and usage of PFASs alternatives. Among these alternatives, 6:2 Cl-PFESA and HFPO-DA have become the dominant perfluorinated pollutants in the worldwide.

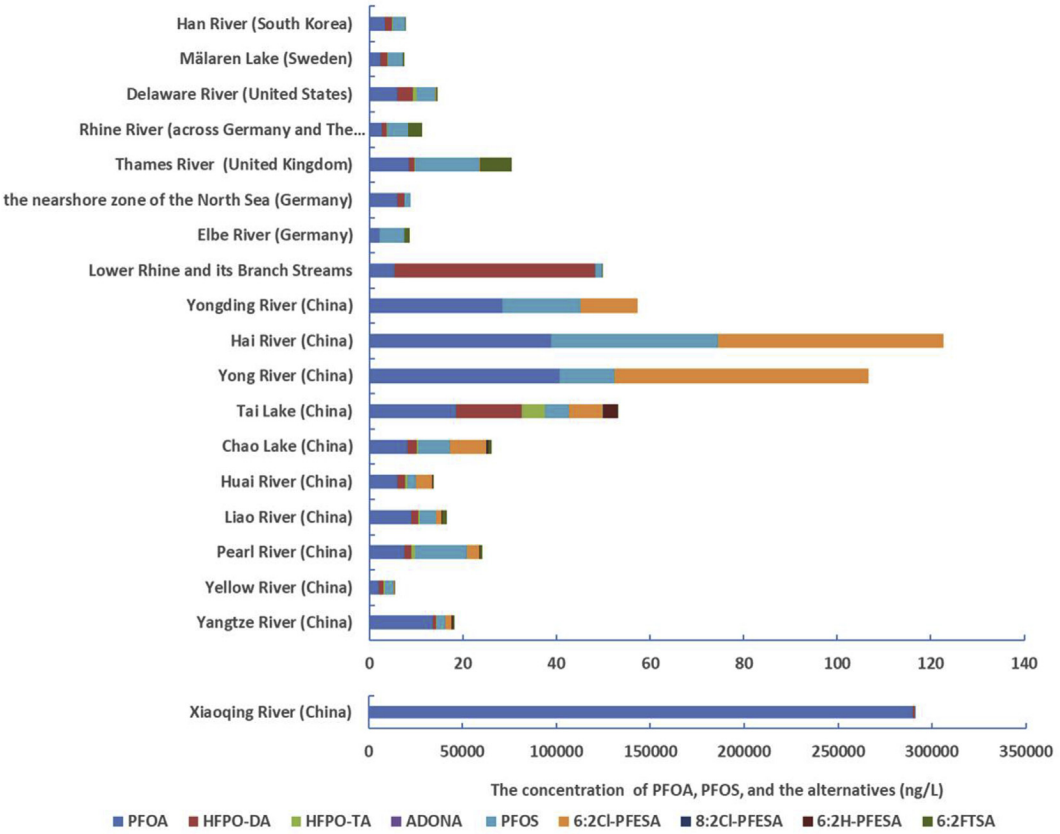


Fig. 2. Worldwide distribution of PFOA, PFOS, and the alternatives in surface water. (Reference: Heydebreck et al., 2015; Wang et al., 2016a; Pan et al., 2018).

4.2. Wastewater and municipal sewage sludge

Wastewater treatment plants (WWTPs) is one of the major point sources of water environmental pollution. 6:2 Cl-PFESA was detected in wastewater from the chromium plating industry in the city of Wenzhou, China (Wang et al., 2013). The influent concentration was high (65–112 μg/L) and the effluent concentration was 43–78 μg/L. Removal efficiency (28%) was similar to that of PFOS, indicating that residues may be released into the environment. 6:2 Cl-PFESA has not been effectively biodegraded in sewage treatment plants.

Discharges of 6:2 Cl-PFESA and FTSA from sludge in WWTPs were estimated by Ruan et al. (2015) in 20 provinces and municipalities in China. The occurrence and distribution of FTSA and Cl-PFESAs were investigated in 56 samples. The 6:2 Cl-PFESA (2.15 ng/g dry weight) and 8:2 Cl-PFESA (0.50 ng/g dry weight) compounds were found in almost all of the sampling locations, as well as the 6:2 FTSA (0.13 ng/g dry weight) and 8:2 FTSA (0.23 ng/g dry weight), which could suggest common usages and/or sources. The concentrations of these compounds are lower than the average proportion of PFOS (3.19 ng/g dry weight), which might imply more application purposes and/or consumer usage amounts of PFOS than those alternatives in China. Moreover, the detection rates of PFOS and 6:2 Cl-PFESA were high (98% and 100% respectively) and the maximum concentrations were similar (218 and 209 ng/g, respectively), which indicated that the two chemicals were widely used.

4.3. Ground water

To identify the possible sources of PFAS alternatives in groundwater, 6:2 Cl-PFESA and 6:2 FTSA were first analyzed in the Jiangsu province, located in a nonindustrial area in eastern China (Wei et al., 2018). Both 6:2 Cl-PFESA and 6:2 FTSA were detected in all water samples. The 6:2 Cl-PFESA concentrations (0.17–1.83 ng/L) in the groundwater were lower than those in the surface water from the studies above. However, 6:2 FTSA showed comparable or even higher concentrations (0.32–8.54 ng/L) in the groundwater than in the surface water. The results showed that domestic sewage and atmospheric sedimentation have important effects on the generation of PFAS alternatives in groundwater in non-industrial areas.

4.4. Drinking water

The first study on the concentration of HFPO-DA in drinking water estimated its fate in water treatment processes (Sun et al., 2016). The average concentration of HFPO-DA in raw water of drinking water treatment plant downstream from PFAS manufacturer is 631 ng/L. Traditional and advanced treatment processes (such as coagulation and ozonation of sedimentary water) have not removed HFPO-DA from drinking water. Moreover, HFPO-DA is less absorbable by powdered activated carbon (PAC) than PFOA. Thus, HFPO-DA has greater drinking water treatment challenges than PFOA.

5. Biological exposure levels

At present, studies on the biological and human exposure levels of these fluorinated alternatives include 6:2 Cl-PFESA, 8:2 Cl-PFESA and HFPO-TA (Table S2, Fig. 3).

The concentrations of 6:2 Cl-PFESA and PFOS in Crucian carp (*Carassius carassius*) in the Tangxun Lake and Xiaoqing River were quite different. In the Xiaoqing River, the concentration of 6:2 Cl-PFESA in blood of Crucian carp was 43.03 ng/g, which was approximately the same as PFOS (41.94 ng/g). In the Tangxun Lake, the concentration of 6:2 Cl-PFESA was 20.28 ng/g, which was much lower than that of PFOS (2256.8 ng/g) (Shi et al., 2015). This is related to the different pollution characteristics between the Tangxun Lake and the Xiaoqing River. PFOS has a highly elevated level in the Tangxun Lake, indicating that PFOS is

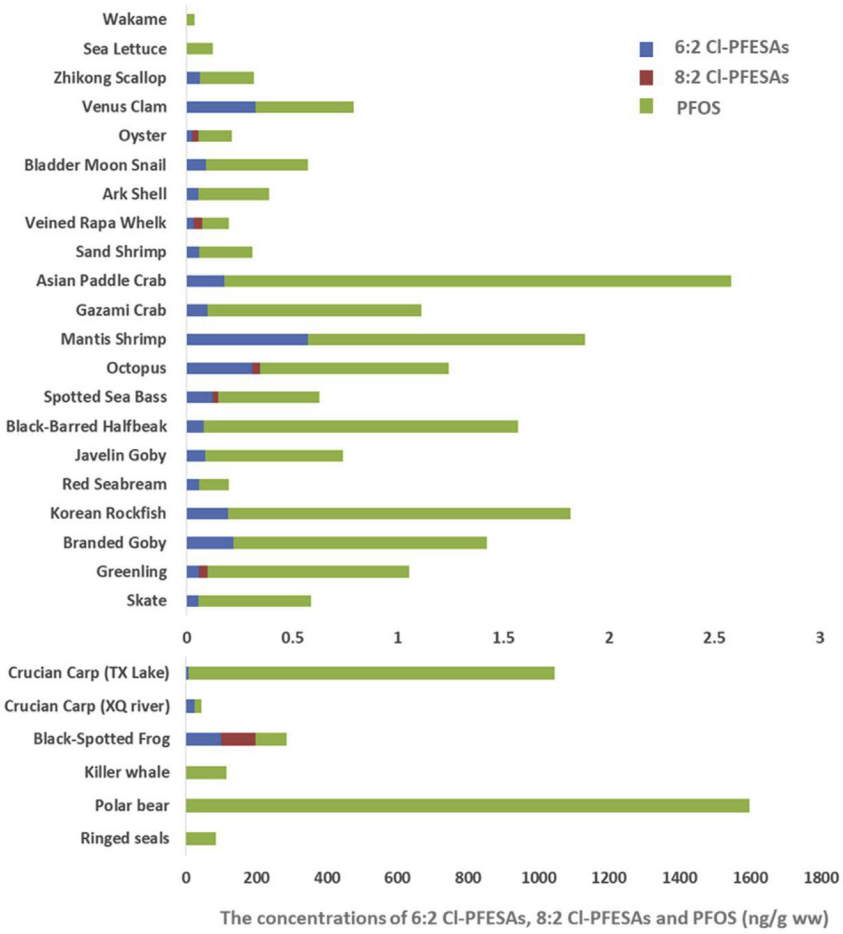


Fig. 3. The concentrations of 6:2 Cl-PFESAs, 8:2 Cl-PFESAs and PFOS in marine Organisms from Bohai Sea (8 fishes, 11 invertebrates, and 2 algae species), freshwater fish (Crucian Carp from Tangxun Lake and Xiaoqing River, China), amphibians (black-spotted frog) and Greenland marine mammals (ringed seals, polar bears, and killer whales). The whole bodies of algae, soft tissue of invertebrates, flesh of fishes from Bohai Sea and livers of crucian carp, black-spotted frog and marine mammals were submitted to chemical analysis. (Reference: Shi et al., 2015, 2016; Liu et al., 2017; Cui et al., 2018).

still the main pollutant around the Tangxun Lake. Due to the presence of 6:2 Cl-PFESA factories, the pollution around the Xiaoqing River has changed forms from traditional PFOS to PFOS alternatives. The concentration of 6:2 Cl-PFESAs in different tissues varied greatly, with the greatest concentrations in the kidney, liver, heart and gonad, indicating that these organs may be the target organs of 6:2 Cl-PFESA.

The PFOS alternatives in amphibians also showed different distribution characteristics (Cui et al., 2018). The tissue distribution of 6:2 Cl-PFESA, 8:2 Cl-PFESA and HFPO-TA in the black-spotted frog (*Pelophylax nigromaculatus*) was first detected in east China. The concentrations of 6:2 Cl-PFESA and 8:2 Cl-PFESA were both high, and there was no significant difference between their concentrations. The concentrations in the black-spotted frog were 100–1000 times higher than those in the Crucian carp in the Tangxun Lake and Xiaoqing River (Shi et al., 2015). The highest concentrations of 6:2 Cl-PFESA in the black-spotted frog were in the heart, at approximately 105.3 ng/g, and the liver, at approximately 100.2 ng/g. There were no significant differences in the accumulation levels in the organs. The concentrations of Cl-PFESAs were comparable with PFOS. The concentrations of HFPO-TA and PFOA were also measured. The above data indicated that the heart and liver are the main accumulation organs. It is worth noting that the levels of these fluorinated alternatives are also very high in gonads. The concentration of HFPO-TA in the ovaries is 93.2 ± 2.8 ng/g, which is higher than in the liver and heart (Cui et al., 2018). The concentration of F-53B in the gonads of Crucian carp is next to the kidney and liver, suggesting that the gonads may be one of the important target organs for these alternatives.

According to the results of a two-year study on the Tangxun Lake (Shi et al., 2015, 2016), the accumulation of 6:2 Cl-PFESA in the muscles of organisms (mainly fish) showed an upward trend. In 2015, the concentration of Cl-PFESAs in Crucian carp muscle was 0.84 ng/g. In 2016, the concentration of Cl-PFESAs in the muscles of six species of fish was higher than 0.84 ng/g, except for in the yellow catfish (0.718 ng/g). The highest concentration was 2.76 ng/g, indicating the accumulation of Cl-PFESAs.

A study including 8 fish, 11 invertebrates and 2 algae species in the Bohai Bay showed that PFASs and their alternatives accumulated differently in marine organisms from those in rivers and lakes (Liu et al., 2017). Compared with other PFASs, the level of Cl-PFESAs in marine organisms is relatively low. The content of 6:2 Cl-PFESA in fish muscle in Bohai Bay was approximately one-tenth of that in fish muscle in Tangxun Lake. In Bohai Bay, 8:2 Cl-PFESA was not detected in most of the organisms. From 2010 to 2014, detection frequencies and concentrations of Cl-PFESAs in the Bohai Bay are on the rise. Similar to PFOS and PFCAs, 6:2 Cl-PFESA could be amplified along the food chain and accumulated more easily in marine organisms at relatively high nutrient levels.

In addition, 6:2 Cl-PFESA was detected in Arctic wildlife in East Greenland (Gebbink et al., 2016). The concentrations of 6:2 Cl-PFESA in the livers from ringed seals (n = 10), polar bears (n = 8) and killer whales (n = 6) were 3-4 orders of magnitude lower than those of PFOS. In this study, 6:2 Cl-PFESA was detected in the liver tissues of all ringed

seals and polar bears, as well as in five of six killer whales. The highest concentrations of 6:2 Cl-PFESA were detected in polar bears (0.27 ± 0.04 ng/g), followed by ringed seals (0.045 ± 0.004 ng/g) and killer whales (0.023 ± 0.009 ng/g). This study shows that 6:2 Cl-PFESA has spread to North America with the circulation of water, although it is only used in China. Maternal transfer was also estimated in killer whales. It is estimated that the transfer rate of 6:2 Cl-PFESA from mother to fetus was about 6.2%, which was higher than that of PFOS (4.7%). This indicated that the mother transfer is the exposure route of 6:2 Cl-PFESA to killer whale pups, leading to greater exposure of fetus to PFESAs (liver). Although China is the only known emission source, 6:2 Cl-PFESA has also been detected in Arctic wildlife (Gebbink et al., 2016), suggesting its long-distance transportation and global contamination.

Research on amphibian black-spotted frogs in polluted areas showed different patterns of these fluorinated alternatives compared to marine organisms and freshwater fish (Cui et al., 2018). The concentrations of 6:2 Cl-PFESA and 8:2 Cl-PFESA were comparable with PFOS, and both were significantly higher than those in fish. This is because these frogs were located in cities with large-scale fluorochemical industries. The skin, liver and muscle of frogs contributed nearly 80% to the total load of 6:2 Cl-PFESA in males, while only female ovaries accounted for 58.4% of the total load of 6:2 Cl-PFESA. Unlike fish and mammals, The relatively large proportion of Cl-PFESAs in the skin of black-spotted frogs might be a distinctive feature in amphibians, and there are significantly gender differences in its accumulation. It is interesting to note that both marine and amphibian outcomes are suggesting 6:2 Cl-PFESA can enter the fetus through the placental barrier. The developmental neurotoxicity of 6:2 Cl-PFESA should be strengthened.

Previous studies on PFAS alternatives *in vivo* are still very limited. The data of HFPO-TA and ADONA in organisms are still unknown, and the biomass accumulation characteristics and levels of PFAS substitutes are still unclear.

6. Human exposure levels

At present, there are a few studies on the exposure level of fluorinated alternatives in the human population (Table S3, Fig. 4), mainly containing ADONA and Cl-PFESA. The first measurements of ADONA in blood samples of the general population was obtained in South Germany (Fromme et al., 2017). This populations living close to a former PFOA production plant, in which ADONA has been used since 2008. ADONA was detected only in few samples of total 396 plasma samples in a low level (0.2 μg/L). About Cl-PFESAs, one study in occupationally exposed workers and high fish consumers has been reported (Shi et al., 2016). Two studies examined the placental transfer of Cl-PFESAs (Pan et al., 2017; Chen et al., 2017). Human exposure and elimination kinetics of Cl-PFESAs were detected by Shi et al. (2016). The median renal clearance rate of 6:2 Cl-PFESA (0.0016 mL/kg/day) was approximately five times lower than that of PFOS (0.0074 mL/kg/day), and a low detection frequency of 8:2 Cl-PFESA in urine samples indicated that 6:2 and 8:2 Cl-PFESAs had slower elimination kinetics than that of PFOS. The apparent trend of decreasing renal clearance rates in the order are: PFOS > 6:2 Cl-PFESA ≥ 8:2 Cl-PFESA. The median total elimination half-lives of 6:2 Cl-PFESA and PFOS were 15.3 and 6.7 years, respectively. To date, the most biopersistent PFAS reported in humans is 6:2 Cl-PFESA. In addition, 6:2 and 8:2 Cl-PFESAs were observed in high fish consumers (93.7 and 1.60 ng/mL, respectively) and metal plating workers (51.5 and 1.60 ng/mL, respectively) compared to the control group (4.78 and 0.08 ng/mL, respectively) in serum. The 20-fold higher median concentration of 6:2 Cl-PFESA in high fish consumers compared to controls demonstrates that fish may be a particularly important vector for human exposure. For metal plating workers, the elevated serum concentrations were probably due to inhalation of airborne Cl-PFESAs. The highest serum concentration of 6:2 Cl-PFESA in Chinese electroplating workers is 5.1 μg/ml (Table S3).

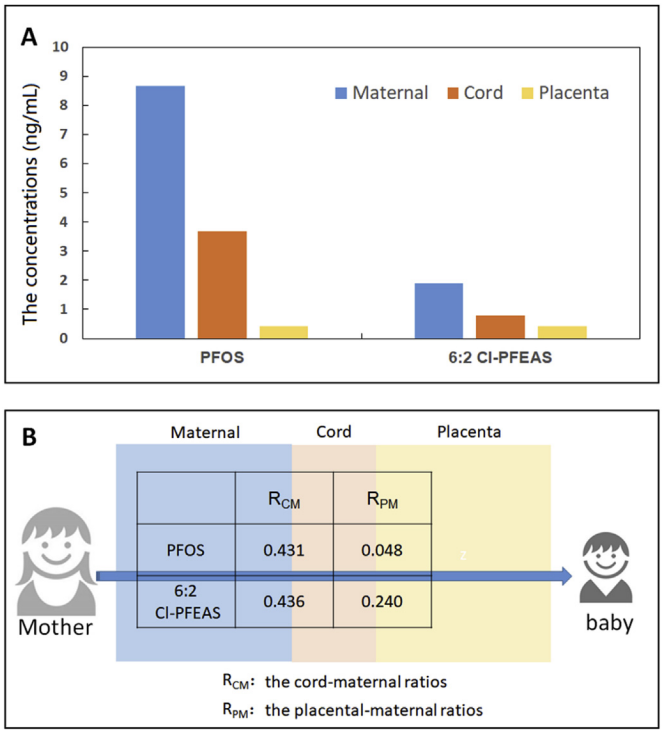


Fig. 4. The placental transfer efficiencies of 6:2 Cl-PFESA and PFOS. (A) The concentrations of 6:2 Cl-PFESA and PFOS in matched maternal serum, umbilical cord serum and placenta samples in Wuhan, China. (B) The cord-maternal and placental-maternal ratios for 6:2 Cl-PFESA and PFOS. R_{CM} and R_{PM} meant the cord-maternal ratios and the placental-maternal ratios, respectively. The R_{CM} of 6:2 Cl-PFESA was comparable to the R_{CM} of PFOS, while the R_{PM} of 6:2 Cl-PFESA was five times that of PFOS, indicating 6:2 Cl-PFESA is easier to transfer to fetus than PFOS.

Pan et al. (2017) and Chen et al. (2017) reported the concentrations of 6:2 Cl-PFESA and 8:2 Cl-PFESA in pregnant women and fetuses. The serum of pregnant women and the placenta and cord blood were collected from 2014 to 2016 in Wuhan, China. The concentration of 6:2 Cl-PFESA in maternal and cord serum was the third highest (after PFOS and PFOA), accounting for more than 10.0% of total PFASs. The concentrations of PFESAs in order are: maternal sera > cord sera ≥ placentas. The serum concentration of 6:2 Cl-PFESA was similar to that of PFOA, suggesting that exposure to 6:2 Cl-PFESA may be relatively high and widely distributed in pregnant women and fetuses in China. The serum concentration of 6:2 Cl-PFESA (1.88 ng/mL) in pregnant women was lower than that of PFOS (8.67 ng/mL), while the placenta concentration of 6:2 Cl-PFESA was the same as that of PFOS (0.42 ng/mL), indicating that Cl-PFESAs can be efficiently transported through the placenta. The placenta transplantation efficiency of 6:2 Cl-PFESA and 8:2 Cl-PFESA was higher than that of PFOS (40% and 100% respectively). The transport degree of 8:2 Cl-PFESA through placenta is greater than 6:2 Cl-PFESA, which may be due to the low binding affinity and high hydrophobicity of plasma protein. Both studies indicate that maternal and fetal albumin are important factors affecting these alternatives from placental serum to placental serum.

7. The potential impact of PFAS alternatives

7.1. Bio-accumulation

The whole body bioaccumulation factors ($BAF_{\text{whole body}}$) of 6:2 Cl-PFESA in crucian carp (*Carassius carassius*) was detected by Shi et al. (2015). It has obvious ubiquitousness and strong tendency of

bioaccumulation. Median Log BAF whole body values for F-53B (4.124 and 4.322 in Xiaoqing River and Tangxun Lake, respectively) exceeded the regulatory bioaccumulation criterion (3.7) and were significantly higher than those of PFOS (3.430 and 3.279 in Xiaoqing River and Tangxun Lake, respectively). Estimated half-lives of 6:2 Cl-PFESA's renal clearance (median 280 years) and total clearance (median 15.3 years) indicate that it is the most biologically persistent PFAS ever reported by humans (Shi et al., 2016). After exposure to 3 mg/L F–53B at 72 and 96 h post fertilization (hpf) in zebrafish, the uptake of F-53B rapidly reached 123.14 ± 9.1 ng/embryo, and decreased slightly to 112.30 ng/embryo at 120 hpf, indicating embryos were unable to significantly eliminate F-53B (Shi et al., 2017a).

The BAF of 6:2 Cl-PFESA and HFPO-TA was also detected in black-spotted frog (Cui et al., 2018). The results also suggest a stronger accumulative potential of 6:2 Cl-PFESA and HFPO-TA in the black-spotted frog than PFOS and PFOA.

These results suggested that 6:2 Cl-PFESA and HFPO-TA is easier to accumulate in aquatic organisms and amphibians than PFOS and PFOA, and it is estimated that their environmental fate and physicochemical properties are comparable to those of the chemicals they replace.

7.2. Toxicity

PFAS alternatives had comparable octanol-water partition coefficient (K_{ow}), bioconcentration factors (BCF), and BAF values as PFOS and PFOA (Gomis et al., 2015; Wang et al., 2013). At present, the improper use of these chemicals may lead to environmental hazards and health effects, and more detailed safety assessment is needed.

The slower elimination kinetics, higher placental transfer efficiencies, and higher trophic transfer behavior of alternatives (Shi et al., 2016; Chen et al., 2017; Liu et al., 2017) indicated that Cl-PFESAs might exhibit higher health risks than PFOS. Zebrafish embryos were exposed to 6:2 Cl-PFESA (1.5, 3, 6, and 12 mg/L) and 6:2 FTCA (0, 4, 8, and 12 mg/L) of 6–120 hpf, which resulted in delayed hatching, increased malformation and decreased survival rate of zebrafish embryos (Shi et al., 2017a, 2017b). These fluorinated alternatives also led to defects in cardiac function of zebrafish embryos. The exposure to 6:2 Cl-PFESA reduced the heart rate in zebrafish embryos, and the molecular mechanism involved in this may be associated with the Wnt/β-catenin pathway. The most common developmental malformation induced by 6:2 FTCA was pericardial edema, which occurred in the 8 and 12 mg/L 6:2 FTCA-exposed embryos from 60 hpf. Moreover, the median lethal concentration of 6:2 FTCA was 7.33 mg/L at 120 hpf, which was lower than that of PFOA. $LC_{50\text{-}96h}$ of 6:2 Cl-PFESA is 15.5 mg/L in zebrafish, which means that it should be classified as moderately toxic chemical (harmful to aquatic life) (Wang et al., 2013).

In addition to cardiac developmental toxicity and embryo toxicity, 6:2 Cl-PFESA also has neural development toxicity. The neurotoxicity of 6:2 Cl-PFESA on adult rats was studied by Q. Zhang et al., 2016. After acute intracerebroventricular (i.c.v.) injection of 100 μM 6:2 Cl-PFESA, the long-term potentiation (LTP) *in vivo* was inhibited, and 6:2 Cl-PFESA had similar potential to PFOS in interfering with LTP in the hippocampus CA1 region of adult rats. The baseline field excitatory postsynaptic potential (FEPSP) amplitude also decreased, but the input-output (I/O) curve and paired pulse stimulation (PPF) did not change significantly. The results complement the significant electrophysiological evidence that exposure to 6:2 Cl-PFESA can lead to damage of synaptic plasticity, and acute exposure to 6:2 Cl-PFESA mainly plays a role in the postsynaptic mechanism.

6:2 Cl-PFESA also disrupted early mouse embryonic stem cell (mESC) neural differentiation (Yin et al., 2018). During mESC embryoid body global differentiation, the expression of the typical endoderm marker (Sox 17), the late nonneural ectoderm marker (Krt14), the neural ectoderm markers (Sox1 and Sox 3) and the neural progenitor cell (NPC) marker (Pax6) were downregulated by 0.1 μM F-53B treatment on Day 20. Conversely, the early and transient ectoderm marker (Fgf 5) was repressed by 0.1 μM F-53B treatment on Day 4. These results indicated that 6:2 Cl-PFESA can induce neuronal differentiation damage and exert developmental neurotoxicity. During monolayer neural differentiation, 6:2 Cl-PFESA decreased the expression of both neural ectoderm markers (sox1 and sox3) and NPC markers (Pax6). Moreover, F-53B treatments significantly inhibited the expression of Map 2 protein, indicating that 6:2 Cl-PFESA treatment affected the yield of mESC-derived neuron-like cells. It is worth mentioning that the 6:2 Cl-PFESA exhibited stronger effects than PFOS in the early development stage of neuroectodermal formation. The authors argue against the use of 6:2 Cl-PFESA to replace PFOS as a mist suppressant.

The *in vitro* T-screen assay showed that 6:2 Cl-PFESA is also proposed to cause thyroid dysfunction (Deng et al., 2018). *In vitro*, 6:2 Cl-PFESA enhances the proliferation of GH3 cells in a concentration-dependent manner, suggesting 6:2 Cl-PFESA may be considered a strong thyroid hormone agonist. In the *in vivo* assay, 6:2 Cl-PFESA binds to transthyretin by forming hydrogen bonds and T4 levels were significantly elevated, thereby interfering with thyroid hormone homeostasis.

Cl-PFESAs also have the ability to interfere with peroxisome proliferators-activated receptors (PPARs) signaling pathways (Li et al., 2018). 6:2 Cl-PFESA and 8:2 Cl-PFESA bound to all three PPAR ligand binding domains (LBDs) like PFOS, and exhibited stronger binding potency than PFOS. Molecular docking results showed that binding of the Cl-PFESAs activated the PPAR signaling pathways in the same manner as fatty acids. Because the environmental concentration of 8:2 Cl-PFESA is much lower than 6:2 Cl-PFESA, the environmental toxicity research of 8:2 Cl-PFESA was also much less than that of 6:2 Cl-PFESA.

HFPO-DA, HFPO-TeA, 6:2 FTSA and 6:2 FTCA exerted hepatotoxicity (Wang et al., 2016b; Sheng et al., 2017). After male mice (6–8 weeks of age) were given HFPO-DA or HFPO-TeA orally via gavage for 4 weeks in a dose of 1 mg/kg/day, the liver weight in the HFPO-DA and HFPO-TeA 4 treatment groups (1.91 g and 3.21 g, respectively) showed significant increases compared with that of the control (1.46 g). Moreover, mice exhibited hepatic histopathological lesions in the HFPO-DA treatment group, including lipid droplet accumulation and inflammatory cell infiltration. Furthermore, more focal hepatocyte necrosis were observed in the HFPO-TeA treatment group than in the HFPO-DA treatment group, probably because of the longer carbon chain of HFPO-TeA. Genes, involved in the PPAR pathway, were significantly increased in the HFPO-DA and HFPO-TeA groups, indicating that HFPO-DA and HFPO-TeA also have the ability to interfere with PPAR signaling pathways. Furthermore, 6:2 FTCA and 6:2 FTSA also showed hepatotoxicity. After 28 days of exposure to 6:2 FTCA or 6:2 FTSA for 5 mg/kg/day in adult male mice, 6:2 FTSA resulted in increased liver weight, inflammation and necrosis, while 6:2 FTCA did not cause significant liver injury. Further study on its toxicity mechanism showed that 6:2 FTSA induced the increase of PPARαa and related proteins, but did not induce the increase of lipid metabolism related genes such as PPARγ.

Chronic toxicity and carcinogenicity of HFPO-DA have also been reported (Caverly Rae et al., 2015). The no-observed-adverse-effect-level (NOAEL) in this study lies 1–50 mg/kg for males and 50–500 mg/kg for females. The toxicity ranking using modeled serum (HFPO-DA > PFOA) and liver (HFPO-DA > PFOA) concentrations indicated HFPO-DA have similar or higher toxic potency than their predecessors when correcting for differences in toxicokinetics (Gomis et al., 2018).

ADONA was evaluated in an acute toxicity study at doses of 298 mg/kg/day. All female Sprague-Dawley rats died between days 3 and 5. At the same dose, male mice suffer weight loss and liver tissue proliferation (Gordon, 2011). However, NOAELs in 28- and 90-day oral studies in rats were 10 mg/kg/day for males and 100 mg/kg/day for females, leading to the scarce safety assessment of ADONA. More experiments are needed to verify the toxicity of these alternatives.

8. Conclusions and perspectives

With poorly defined hazard properties, are these fluorinated alternatives truly safe? Are they truly safe for people and the environment? The fluorinated alternatives, especially the Cl-PFESAs, HFPO-DA, and 6:2 FTSA, exhibited comparable toxicity to PFOS. These studies confirm that the use of fluorinated alternatives does not truly solve the health risks caused by PFASs. The toxicological information on these compounds was incomplete and insufficient for assessment of their environmental impact.

The experiments are urgently needed to improve the hazard assessment of the aforementioned fluorinated alternatives and to determine if they are safe for humans and biota are as follows: 1) Information on PFAS alternatives such as characteristics, yield, dosage, emissions and toxicity needs to be made public; 2) Monitoring of these fluorinated alternatives and accelerating the study of degradation mechanisms in various environmental media; 3) Study the sources, distribution, migration and transformation of these fluorinated alternatives systematically; and 4) Further studies using environmentally relevant concentrations are needed, as well as exposure at multiple life stages. Low-dose, long-term, chronic toxicity and compound toxicity studies should be carried out. The results to these listed experiments will provide technical support for the development of new high-performance compounds without potential bioaccumulation and toxicity.

Acknowledgments

The study is financially supported by Hubei Key Laboratory of Environmental and Health Effects of Persistent Toxic Substances (Grant No: PTS2019-06) and the Shandong Medical and Health Technology Development Projects (2018WS376).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ecoenv.2019.109402.

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