

Dissipation, Fate, and Toxicity of Crop Protection Chemical Safeners in Aquatic Environments



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Contents

1	Introduction	28
2	Methods	34
3	Leaching	35
4	Sorption	37
5	Volatilization	40
6	Photolysis	42
7	Chemical Reduction and Nucleophilic Substitution	44
8	Biological Degradation	45
9	Toxicity	46
10	Conclusion	48
11	Methods for Laboratory Studies	49
	References	49

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Abstract Safeners are a group of chemicals applied with herbicides to protect crop plants from potential adverse effects of agricultural products used to kill weeds in monocotyledonous crops. Various routes of dissipation of safeners from their point of applications were evaluated. Despite the large numbers of safeners (over 18) commercially available and the relatively large quantities ($\sim 2 \times 10^6$ kg/year) used, there is little information on their mobility and fate in the environment and occurrence in various environmental matrices. The only class of safeners for which a significant amount of information is available is dichloroacetamide safeners, which have been observed in some rivers in the USA at concentrations ranging from 42 to 190 ng/L. Given this gap in the literature, there is a clear need to determine the occurrence, fate, and bioavailability of other classes of safeners. Furthermore, since safeners are typically used in commercial formulations, it is useful to study them in relation to their corresponding herbicides. Common routes of dissipation for herbicides and applied safeners are surface run off (erosion), hydrolysis, photolysis, sorption, leaching, volatilization, and microbial degradation. Toxic potencies of safeners vary among organisms and safener compounds, ranging from as low as the LC_{50} for fish (*Oncorhynchus mykiss*) for isoxadifen-ethyl, which was 0.34 mg/L, to as high as the LC_{50} for *Daphnia magna* from dichlormid, which was 161 mg/L. Solubilities and octanol-water partition coefficients seem to be the principal driving force in understanding safener mobilities. This paper provides an up-to-date literature review regarding the occurrence, behaviour, and toxic potency of herbicide safeners and identifies important knowledge gaps in our understanding of these compounds and the potential risks posed to potentially impacted ecosystems.

Keywords Adsorption · Bioavailability · Dichloroacetamide safener · Dissipation · Herbicides · Safeners

1 Introduction

The increased use of reduced tillage systems to minimize erosion and alterations of soil structures, weed resistance, monocropping, and other factors have led to continued, large-scale use of herbicides in agriculture globally (Farenhorst et al. 2011). Knowledge of potential hazards, fate, and possible dissipation of this class of chemicals and their formulations (including safeners) to ground and surface waters is important. Rates of usages of herbicides to control weeds in crops continue to increase. Used along with herbicides is a group of chemicals called safeners, which are used either in pre- or post-application of herbicides, to protect monocotyledonous plants, which are plants that have seeds with one cotyledon, such as sugarcane, corn, and rice from toxic effects of herbicides used to control weeds in these crops.

Safeners act when applied onto crop seeds through either soil treatment, seed treatment, foliar spray or as a mixture with herbicide to prevent, reduce, or suppress the adverse effects (e.g. phyto-toxicity) of herbicides to crops, by physiological or

molecular mechanisms, without reducing efficiency of suppressing targeted weeds (Davies and Caseley 1999; Hatzios and Burgos 2004; Sivey et al. 2015; Bolyard et al. 2017; Acharya and Weidhaas 2018). Chemical safeners can thus improve tolerance of herbicides by crops (Behringer et al. 2011).

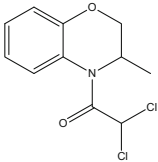
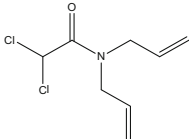
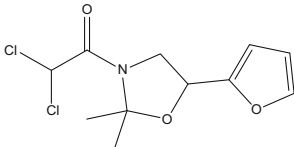
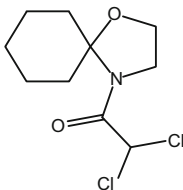
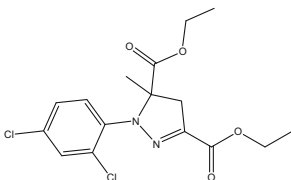
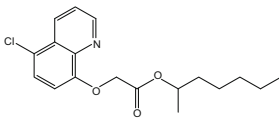
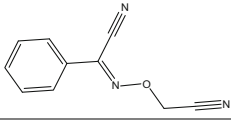
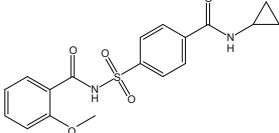
As a result of chemical safeners being classified as “inert” components of herbicide formulations, there is less information and research regarding their fates in the environment, effects on non-target species, and possible mechanisms of action (Sivey et al. 2015; Acharya and Weidhaas 2018). Safeners are designed to alter biochemistries in crop plants in order to impart protection from herbicide-induced damage, which suggests that they might have biological activity in non-target organisms at ecologically relevant concentrations (Sivey et al. 2015).

Dichloroacetamide safeners have the propensity to be transformed by reduction to herbicide-like products (Sivey and Roberts 2012). Dichlormid has been reported to degrade through dechlorination, dealkylation, oxidation, and hydrolysis (Abu-Qare 1912). Efforts have been made to understand modes and mechanisms of action of safeners on target plants (Sivey et al. 2015; Behringer et al. 2011; Abu-Qare and Duncan 2002); however, many of these mechanisms remain unclear. Same efforts have not been directed towards their fate, mobility, and effects on organisms in various environments, including the aquatic environment.

Safeners are part of the ingredients in formulations of commercial, weed control products (Acharya and Weidhaas 2018). For example, dichloroacetamide safeners contribute up to ~5% by weight of the herbicide formulation (Xu et al. 2020, and the references therein). This class of chemical are in continual usage. For example, the application of dichloroacetamide safeners in 2017 in the USA was estimated to be more than two million kg/year, which exceeded the application of the active ingredients of many common herbicides (Bolyard et al. 2017; Woodward et al. 2018; Xu et al. 2020). Safeners are applied in the same manner as herbicides, either sprayed as a mixture with active ingredient herbicides or as separate seed treatments (Davies and Caseley 1999). Their wide usage and mode of applications suggest that these chemicals will enter the environment like those of active herbicide ingredients and in proportions at which they were applied in the field. In 2004, Syngenta Crop Protection Canada submitted a field data report on application of cloquintocet-mexyl safener for protection of wheat (USEPA 2005) in Alberta, Manitoba, and Saskatchewan, further suggesting the potential for presence of safeners in aquatic environments outside the USA.

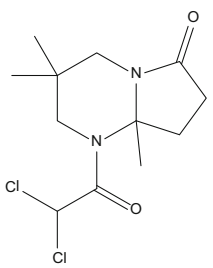
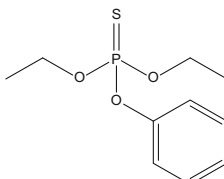
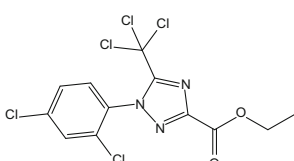
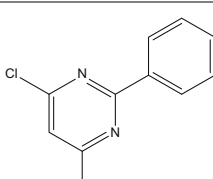
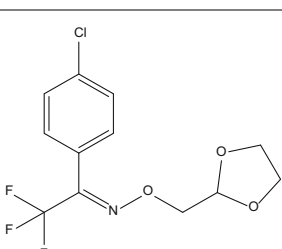
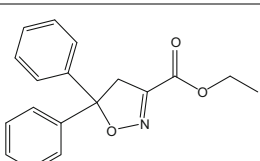
Herbicide safeners have diverse applications when it comes to protection of agriculturally important crops (see Table 1). Winter wheat and barley were protected from adverse effect of the herbicide pinoxaden (Axial) by converting its active ingredient into inactive metabolites by the safener cloquintocet-mexyl. However, this safener was ineffective for protecting wild oats or perennial ryegrass from adverse effects of pinoxaden herbicide (Brosnan et al. 2016). Effects of the herbicide carfentrazone-ethyl on spring wheat could be suppressed by simultaneous exposure to sulfonyleurea or flucarbazone-sodium (Howatt 2006). In this case, these two herbicides were used as safeners, not herbicides, because they were not effective against weeds, but were used to protect against effects of another herbicide. To

Table 1 Name and structure of herbicide safeners

Safeners	Structure	Common Herbicide	Crops
Benoxacor		Metolachlor	Corn, Soyabeans and Sorghum
Dichlormid		Chloroacetanilide, Thiocarbamate	Corn
Furilazole		Isoxaflutole	Corn, Rice
AD-67		Acetochlor, Butachlor, EPTC	Corn
Mefenpyr-diethyl		Fenoxaprop-P-ethyl, Iodosulfuron, ACCase inhibitors Sulfonylureas	Corn, Wheat, Rye, Barley, Triticale
Cloquintocet-mexyl		Clodinafop-propargyl, Pinoxaden	Winter wheat, Barley wild oats perennial ryegrass
Cyometrinil		Metolachlor	Sorghum
Cyrosulfamide		Thiencarbazone-methyl, Isoxaflutole, Tembotrione, Iodo sulfran, Nicosulfuron	Corn

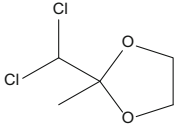
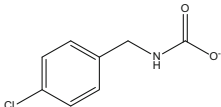
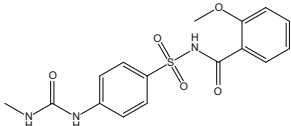
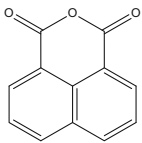
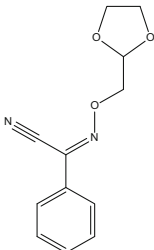
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Table 1 (continued)

Safeners	Structure	Common Herbicide	Crops
Dicyclonon		Metazachlor Metalochlor	Corn
Dietholate		Clomazone	Cotton
Fenchlorazole-ethyl		Fenoxaprop-ethyl, Fenoxaprop-P-ethyl	Wheat
Fenclorim		Pretilachlor	Rice
Fluxofenim		Metolachlor, S-metolachlor	Sorghum
Isoxadifen-ethyl		Foramsulfuron, Tembotrione, ACCase inhibitors Sulfonylureas	Corn, Rice

(continued)

Table 1 (continued)

Safeners	Structure	Common Herbicide	Crops
Jiecaowan			Corn
Mephenate			Corn
Metcamifen			Corn
Naphthalic anhydride		Thiocarbamates	Corn
Oxabetrinil		Chloroacetanilides	Sorghum

protect from effects of herbicides, flax seeds were coated with either BASF's Insure Pulse or Vitaflo (Staff 2019). Also, safeners have been used to protect hard, red spring wheat from injury from the herbicide, fenoxaprop (Staff 2019). Dichlormid was also an effective safener when added to S-Ethyl dipropylthiocarbamate (EPTC) and other thiocarbamates in preventing the onset of herbicide harm to maize plants (Abu-Qare 1912). Thus, safeners are used to protect different crops against injurious effects of herbicides.

While some safeners are believed to be crop-specific, there is evidence that mefenpyr-diethyl and cyprosulfamide can protect crops in addition to the target crop (Duhoux et al. 2018) and/or inhibit other herbicides through various modes of action (Ahrens et al. 2013). Cyprosulfamide has been reported to protect all varieties of corn from pre-emergent applications of isoxaflutole (Ahrens et al.

2013) and tembotrione herbicides. Corn and rice are the most common cereal crops protected with safeners against chloroacetanilide, sulfonyleurea, imidazolinone, cyclohexanedione, isoxazole, and triketone herbicides (Table 1) (Davies and Caseley 1999; Davies 2001; Guo et al. 2020). Winter cereal crops, such as wheat, also use safeners to protect against effects of post-emergence applications of aryloxyphenoxypropionate and sulfonyleurea herbicides on target plants (Hatzios and Burgos 2004). Examples of safeners that protect cereal crops from post-emergence applications of sulfonyleurea herbicides are isoxadifen-ethyl and mefenpyr-diethyl (Behringer et al. 2011), which can also work to protect *Arabidopsis thaliana* leaves (Behringer et al. 2011).

As with herbicides, safeners can dissipate in several ways, including leaching, adsorption, volatilization, biotic and abiotic degradation (Fig. 1) (Abu-Qare and Duncan 2002), hydrolysis and for some photolysis (Hertkorn et al. 2010). Dissipations of both herbicides and safeners are functions of their physico-chemical properties that govern behaviours in soil and water (Díez and Barrado 2010). Potential environmental mobilities of safeners are functions of their aqueous solubility and sorption to solid particles (Acharya and Weidhaas 2018). Environmental partitioning such as sorption and leaching from soils, uptake by plants, and accumulation in various environmental compartments can be estimated by use of fugacity based on the octanol-water partitioning coefficient ($\text{Log } K_{OW}$) (Acharya and Weidhaas 2018; Zhang et al. 2016). Therefore, determining $\text{Log } K_{OW}$ will give fundamental information on sorption in soil and the potential availability of safeners in the environment.

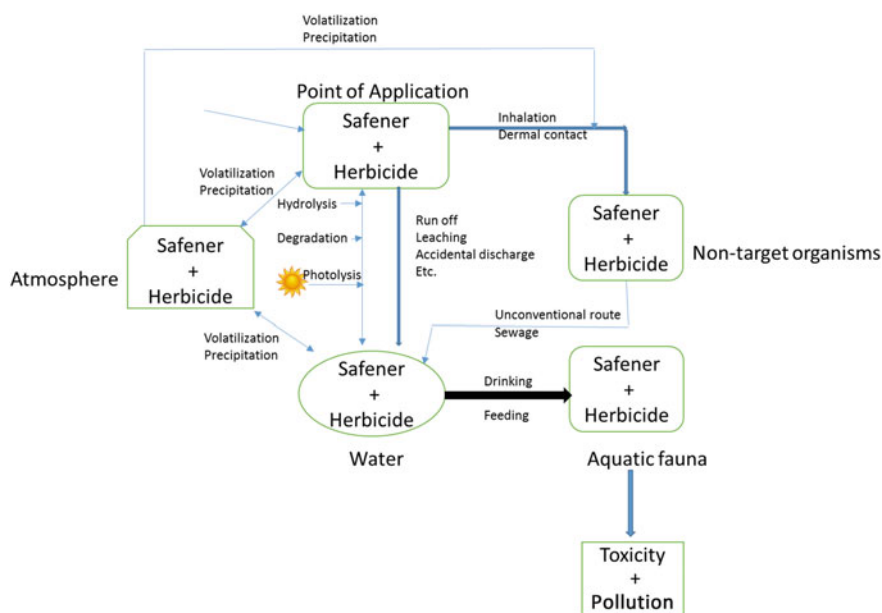


Fig. 1 Possible transportation routes and way of safeners exposure to the aquatic environment

Despite the various sorption mechanisms and degradation pathways which chemical safeners undergo, occurrence in surface waters has been observed, and remains a gap in our understanding of the exposure risks posed by these chemicals. Furilazole, benoxacor, dichlormid, and Ad-67 were detected in Midwestern US rivers between Spring and Summer 2016, with the maximum concentrations ranging from 42 to 190 ng/L (Woodward et al. 2018). In surface waters, chemical safeners are capable of producing a broad range of responses in non-target organisms (USEPA 2006), similar to their often structurally-related herbicide counterparts (Acharya and Weidhaas 2018). Most of the safeners, including benoxacor and dichlormid have *de minimis* mammalian toxicity and a high potential for bioaccumulation (Lewis et al. 2016; PPBD 2020).

There are several factors to consider when assessing our understanding of the fate and behaviour of safeners in the environment. The modes of application of safeners and herbicides and how they enter aquatic environments can affect pathways and rates of transport and dissipation. Additionally, chemistries of safeners might be different when applied together with herbicides than when used alone (Bolyard et al. 2017; Acharya and Weidhaas 2018; Su et al. 2019).

Finally, safeners can be transformed, and their transformation products should also be considered in the assessment of fate, transport, and ultimate hazard to non-target organisms. Also, routes and rates of dissipation of herbicides and safeners in the same formulation may differ. Hence, potential hazardous effects of all types of safeners (Table 1) need to be reviewed to understand the safety of this class of chemical. In this review all classes of known safeners will be discussed with respect to their fate, mobilities, and eco-toxicity. Where experimental data were not available, software and data from manufacturer safety data sheets were used. Some experimental data from our research groups were also used to corroborate some of the existing data.

2 Methods

Properties of safeners, such as Henry law's constant, bioconcentration factors (BCF), aqueous solubility, and octanol-water partition coefficient were estimated with programs within EPI Suite WEB 4.10 (USEPA 2014). The input of chemical compounds was based on the CAS number and Simplified Molecular Information and Line Entry System (SMILES) notation. These data were obtained from either ChemSpider[®] or from the Pesticide Properties Database (PPDB): University of Hertfordshire. The structures were drawn using Chemdraw[®] Ultra 12.0 (Table 1). Some data were also sourced from PubChem. For the experimental method presented in this report, see Sect. 11.

3 Leaching

Leaching is one of the primary mechanisms through which safeners and herbicides dissipate from points of application. Aqueous solubility is one important factor that determines the temporal and spatial mobility of safeners and herbicides (Acharya and Weidhaas 2018). Rates of transportation of safeners and herbicides determine their ability to protect target crops as well as the potential for exposure of non-target organisms, such as aquatic organisms. This means that if safeners and herbicides are moving at different rates, safening will not be optimized on crops (Nelson and Penner 2007). Interestingly, a recent study showed that safeners such as benoxacor and the herbicide (S-metolachlor) moved through the soil at a similar rate (Acharya et al. 2020). Unfortunately, not all chemicals move at the same rate in soil and plants. For example, the herbicide, isoxaflutole, leached faster than furilazole and thus required the use of a polymeric carrier to ensure that isoxaflutole and herbicides safeners moved at the same manner (Nelson and Penner 2007). Rates at which chemicals move depend on multiple factors, including their physical and chemical states. Hence, herbicides cannot necessarily be used to predict leaching potential of safeners. Leaching is different from other similar transportation processes, such as surface runoff and erosion, because it involves the downward movement of substances.

When new herbicides are registered, efforts are made by researchers and manufacturers to understand their potential to leach. However, little or no effort is made to understand the leaching of accompanying safeners in the academic community. Indaziflam, an emerging herbicide, was tested under simulated rain and was observed not to leach beyond 30 cm under any conditions tested (Jhala et al. 2012). This observation may not hold true for the corresponding safener and could differ under realistic field conditions, where there is a possibility that interactions between safener and herbicide can affect mobility (Bolyard et al. 2017; Acharya and Weidhaas 2018). Octanol-water partition coefficients can be used to estimate mobilities of chemicals. Smaller Log K_{OW} values indicate that the chemicals will have less potential for sediment and soil sorption, thus greater mobility. For example, the Log K_{OW} values for benoxacor and furilazole were 2.23 ± 0.16 and 1.96 ± 0.22 , respectively (Acharya and Weidhaas 2018), suggesting that furilazole will leach more readily than benoxacor, assuming hydrophobic-type interactions are dominating sorption.

Prediction software can be used to estimate chemical mobilities based on predicted Log K_{OW} . These include EPI suite (Sivey and Roberts 2012; Sivey et al. 2015; Bolyard et al. 2017), Marvin Sketch, TOXNET (TOXicology Data NETWORK) (ChemIDplus) (Acharya and Weidhaas 2018). The KOWWIN program in EPI Suite software overestimated Log K_{OW} (Table 2) compared to our experimentally measured values and the select data present in the literature of which 25 and 8% were overestimation for benoxacor and furilazole, respectively (Acharya and Weidhaas 2018). Similar overestimations by EPI Suite of 24% for benoxacor and 19% for furilazole were observed in the present study. The reason for overestimation of the EPI suite and the experiment could be attributed to a method error.

Table 2 Log K_{ow}, Log K_{oa}, and solubility of safeners determined using EPI computer simulation and PubChem

	Log K _{ow}		Log K _{ow}		Solubility		Solubility		Solubility		LogK _{oa}	
	Experimental data based match	Experimental data based match	KOWWIN v1.68 estimate	Experimental data based match	From PubChem	WSKOW v1.42	WSFragment v1.01 estimate	From PubChem	WSKOW v1.42	WSFragment v1.01 estimate	From PubChem	KOAWIN v1.10 estimate
Safeners												
Benoxacor	2.70 (2.25) ^a		2.38	20.00	0.000077	102.70	750.18	0.000077	102.70	750.18		8.21
Dichlorimid	1.84 (0.80) ^a		2.28	5000.00	0.02	1067.00	2662.20	0.02	1067.00	2662.20		6.71
Furilazole	2.12 (0.72) ^a		2.84	197	70,800	254	7,121	70,800	254	7,121		10.55
Mefenpyr-diethyl	3.83 (3.78) ^a		4.82	20	0.000054	2.40	4.45	0.000054	2.40	4.45		11.15
Cloquintocet-mexyl	5.03		5.28	0.59		0.3816	1.9566		0.3816	1.9566		12.51
Cyometrinil	–		2.52	95		196.8	467.66		196.8	467.66		3.974
Cyprosulfamido	– (0.55) ^a		2.30	–		47.7	13.94		47.7	13.94		14.44
Dicyclonon	–		1.98	–		273.1	13,826		273.1	13,826		9.074
Dietholate	3.46		3.91			27.53	17,652		27.53	17,652		5.973
Fenchlorazole-ethyl			4.54	13	0.000002	0.5799	0.3055	0.000002	0.5799	0.3055		8.916
Fenclorim	4.17		2.99	2.5	0.000011	8.883	19,424	0.000011	8.883	19,424		7.529
Fluxofenim	2.90		2.73	30	0.000097	35.96	1,6024	0.000097	35.96	1,6024		6.701
Isoxadifen-ethyl	2.01 ^b		5.66	–		0.1917	0.082283		0.1917	0.082283		10.516
Jiecaowan	–		1.22	–		5.383	46,569		5.383	46,569		–
Mephenate	2.01		1.82	–		992.7	2188.8		992.7	2188.8		8.022
Metcamifen	–		1.47	–		283.7	29,346		283.7	29,346		17.738
Naphthalic anhydride	3.24 ^b		3.24	–		5.878	592.16		5.878	592.16		7.837
Oxabetrinil	2.76		2.78	20		130.1	376.13		130.1	376.13		8.365

^adetermined by the authors in the laboratory^bfrom PubChem

The frequency and amount of rainfall affect leaching, as well as the time between rain events and application of safeners and herbicides. Greater rainfall can result in leaching of herbicides, which might result in damage of, for example, citrus tree roots, poor weed control, and groundwater contamination (Jhala et al. 2012). The presence of both herbicides and safeners in surface waters (Woodward et al. 2018) suggests we need a better understanding of leaching behaviours of these chemicals and potentially how the use and management of these herbicide/safener formulations could be optimized to minimize leaching to the environment (Chnirheb et al. 2012). Long- and short-time leaching experiments in laboratory and field trials are essential to determine leaching of both herbicides and safeners, when applied together. A recent study showed that both benoxacor and S-metolachlor leached at the same rate, which was suggested to be influenced by soil texture (Acharya et al. 2020). Leaching of chemicals to aquatic environments is problematic because some chemicals can bio-accumulate and bio-concentrate in either sediments or living organisms within the aquatic system. For example, pre-emergence application of the herbicide bromacil has been banned from use in Florida, USA, because it has been observed to leach and contaminate groundwater (Jhala and Singh 2012; Jhala et al. 2012).

The most commonly used methods for determining potential for leaching in field studies involve chemical concentrations measured in soil, water from tile drains and suction cups and dye tracer experiments (Sarmah et al. 2004). Similarly, laboratory experiments such as soil columns are common methods for qualitative and quantitative measurements of leaching of chemicals (OECD 2004).

4 Sorption

There is limited experimental data describing safener sorption to soil and sediment systems. Therefore, predicted physico-chemical properties, the few data available and data on herbicides will be used as a guide for understanding sorption of safeners. Estimates of chemical mobilities in various environments and rates of dissipation must include an understanding of sorption and desorption properties (OECD 2000). Fate and behaviour (e.g., transportation, or retention) of herbicides in soils are controlled by various factors, including rates of sorption and desorption (Mamy and Barriuso 2007), soil properties, and various processes of transformation, all of which can determine the bioavailable fraction in the environment (Davies and Jabeen 2003). Sorption of chemicals onto soil particles and their relative affinities to those soils can ultimately determine the potential for other types of dissipation.

At a molecular level, sorption is driven and controlled by diffusion, which is a relatively slow and first-order process. Thus, sorption and desorption are often rate-limiting steps in overall dissipation in soils. Desorption rates of chemicals can be used as an estimate of overall dissipation rates and of potential for non-point sources of contamination, for example in groundwaters (El Boukili et al. 2018). A chemical that remains strongly sorbed to the soil will not readily reach ground or surface waters through leaching or runoff. For example, the Freundlich constant for

benoxacor and furilazole are 6.4 and 3.4 $(\text{mg/g}) \times (\text{mg/L})^{(1/n)}$ in granulated activated charcoal (GAC) (Acharya et al. 2020). This suggested that benoxacor sorbed more readily to GAC than furilazole. Similarly, the Freundlich constants for furilazole and dichlormid had been reported to be 0.79–3.5 and 0.25–0.65 $(\text{mg/g}) \times (\text{mg/L})^{(1/n)}$, respectively (Carr 1990; Subba-Rao 1990). Hence, dichlormid, furilazole, and benoxacor did not sorb to any great extent on agricultural soil (Carr 1990; Subba-Rao 1990; Acharya et al. 2020). Consequently, the sorption of benoxacor and furilazole was found to be reversible (40–90%) (Acharya et al. 2020). Therefore, this class of safeners can be readily leached through the soil.

Characteristics such as pH, texture, cation exchange capacity, crystalline lattice structure, organic matter content, amorphous iron oxides, inorganic matter complexes, temperature, and moisture (Harris and Warren 1964; Gennari et al. 2008; El Boukili et al. 2018; Wiersma et al. 2019) could potentially have large effects on sorption capacities of soils. Most herbicides and all safeners reported here have $\text{Log } K_{\text{OW}}$ values >1 , suggesting a potential to sorb to organic components of soil matrices (Cumming and Rucker 2017). Both soil organic matter and clay are significant constituents affecting the sorption of mefenpyr-diethyl in soils (El Boukili et al. 2018). Similarly, only organic carbon content and adsorption parameter (n) were found to influence adsorption of benoxacor and furilazole (Acharya et al. 2020). Thus, many soil properties might not influence adsorption of safeners.

However, some herbicides such as glyphosate have greater affinity for inorganic minerals in soils (Gennari et al. 2008). Acidic soils will generally enhance herbicide sorption (Gennari et al. 2008). Retention of chemicals by soil depends on the properties of both the soil and chemical. In some cases, retention of chemicals by soils increases/decreases, while in some other cases, it remained constant with changes in soil properties (Mamy and Barriuso 2007). Therefore, each herbicide or safeners needs to be tested to know their sorption capacity under prevailing environmental conditions, ideally through experimentation but also by software prediction, as necessary. A detailed method for quantifying sorption has been developed (OECD 2000) and can be used directly or with little modification for most chemicals.

Studies of sorption of active ingredients of herbicide formulations are common, but reports on sorption of herbicide safeners to soil are limited. Hence, predictions of these properties, including $\text{Log } K_{\text{OW}}$, aqueous solubilities, and $\text{Log } K_{\text{oa}}$, as estimated from the programs (KOAWIN v1.10) within EPI suite, are given (Table 2). These properties can be used to predict potential mobilities of safeners as their movements in soils, in part, are a function of their aqueous solubility and $\text{Log } K_{\text{OW}}$ (Acharya and Weidhaas 2018) (Table 2). The aqueous solubilities vary between 0.19 mg/L for isoxadifen-ethyl and 1,070 mg/L for dichlormid. Solubility data varies depending on the source of the data, for example PubChem lists solubility of dichlormid as 5,000 mg/L, WSKOW v1.42 lists it as 1,070 mg/L and WSFragment v1.01 estimate it as 2,662 mg/L. Safeners such as isoxadifen-ethyl, cloquintocet-mexyl, mefenpyr-diethyl, fenchlorazole-ethyl and naphthalic anhydride are less soluble or not readily soluble in aqueous medium, while dichlormid, furilazole, cytometrinail, cyprosulfamide are readily soluble in water and are thus more likely to be mobile in soil environments. For example, isoxadifen-ethyl and

Table 3 Sorption capacity of safeners to organic component of the soil

Safeners	K _{oc}	K _{oc}	K _{oc}	Remarks
	PPDB	MCI method	K _{ow} method	
Benoxacor	109.0	133.2	267.5	Moderately mobile
Dichlorimid	40	120.6	78.6	Mobile
Furilazole	199	252	91.2	Moderately mobile
Mefenpyr-diethyl	634	1,501	739.6	Non-mobile
Cloquintocet-mexyl	9,856	26,130	4,985	Non-mobile
Cyometrinil	–	709.9	1,269	Slightly mobile
Cyprosulfamide	–	10.41	39.68	Mobile
Dicyclonon	–	89.86	84.25	Mobile
Dietholate	–	–	1,543	Non-mobile
Fenchlorazole-ethyl	–	18,780	4,031	Non-mobile
Fenclorim	3,655	3,344	4,267	Slightly mobile
Fluxofenim	–	6,179	222.8	Moderately mobile
Isoxadifen-ethyl	–	81,660	9,777	Non-mobile
Jiecaowan	–	14.69	26.23	Non-mobile
Mephenate	–	–	34.54	Non-mobile
Metcamifen	–	–	233.1	Slightly mobile
Naphthalic anhydride	–	15.16	181.4	Mobile
Oxabetrinil	–	368.9	459.9	Mobile

PPDB Pesticide Properties Database: University of Hertfordshire

fenchlorazole-ethyl (Table 3) have relatively low water solubilities, therefore predicted to be less mobile in soils. Safeners with larger Log K_{OW} values are less mobile. Isoxadifen-ethyl, fenchloazole-ethyl, cloquintocet-mexyl, and mefenpyr-diethyl have Log K_{OW} values of 5.66, 4.54, 5.28, and 4.82, respectively, and are less mobile than cyprosulfamide, benoxacor, dicylonon, cyometrinil, and furilazole with Log K_{OW} values of 2.30, 2.38, 1.98, 2.52, and 2.84, respectively. Predicted K_{oc} values (Table 3), which correlate with Log K_{OW} (Table 2) in terms of mobility and sorption capacity of the chemicals to organic carbon content in soils are provided here. Assuming hydrophobic interactions are governing sorption, mobility will be inversely proportional to K_{oc}. Thus, determining solubility, Log K_{OW}, and K_{OC} properties provide fundamental information on the potential for sorption of chemical safeners to soils. Relationships exist between solubilities and adsorption capacity in one form, and adsorption capacity and molecular size in another (Acharya et al. 2020). Furilazole was determined to have lower adsorption capacity compared to benoxacor because the latter is not very soluble, while furilazole was moderately soluble. Considering their molecular structures, the smaller size of benoxacor might be the driving force for its higher adsorption capacity compared to furilazole. Therefore, both solubility and molecular size might be factors to be considered in sorption of safeners studies.

5 Volatilization

Information on volatilization of chemicals used as herbicides is required by regulatory bodies in many countries (Guth et al. 2004; Boivin and Poulsen 2017). This is because losses of these chemicals from soils, plants, and water bodies can accumulate in the atmosphere and result in long-range atmospheric transport (Dekeyser et al. 2015). Physico-chemical parameters such as Henry's law constant, soil/air and water/air distribution coefficients, and vapour pressure can be used to predict volatilization from water, soil, and plant matrices (Guth et al. 2004) (Tables 2 and 4). Vapour pressure is the best parameter to estimate volatilization of chemicals from plants, while water/air and soil/air distribution coefficients are the best parameters to predict volatilization of chemicals from water and soil, respectively (Guth et al. 2004). Compounds with vapour pressures $<10^{-3}$ to 10^{-4} Pa or Henry's law constant $<5 \times 10^{-5}$ atm-m³/mol will demonstrate negligible volatility (Guth et al. 2004), therefore safeners such as cyometrinil, and fenclorim, with Henry's law constants of 8.59×10^{-4} and 1.07×10^{-5} atm-m³/mol, respectively, may be relatively volatile. In contrast, metcamifen with a Henry's law constant of 1.32×10^{-18} atm-m³/mol would be considered non-volatile (Table 4).

Greater water content of soils normally results in greater vapour pressures of chemicals, which can therefore result in volatilization (Sarmah et al. 2004). Water can facilitate movement of safeners from soil surfaces after displacement from sorption sites. Other activities occurring within the plant, soil, or water can hasten

Table 4 Volatilization from water as estimated using EPI suite

Safeners	Henry Law's constant atm-m ³ /mol	Half-life (Lake) days	Half-life (River) Days
Benoxacor	7.58E-008	5,669	519
Dichlormid	3.29E-007	1,173	107
Furilazole	9.2E-011	4,842,000	442,200
Mefenpyr-diethyl	1.16E-009	443,200	40,630
Cloquintocet-mexyl	8.1E-010	602,100	55,190
Cyometrinil	0.000859	6	<1
Cyprosulfamide	1.78E-014	2.893E+010	2.652E+009
Dicyclonon	1.97E-009	231,300	21,200
Dietholate	7.51E-005	11.77	<1
Fenclorazole-ethyl	1.03E-006	508	46
Fenclorim	1.07E-005	43.25	3.484
Fluxofenim	3.87E-006	128	11.17
Isoxadifen-ethyl	3.41E-007	1,348	123
Jiecaowan	4.45E-008	7,872	721.2
Mephenate	2.38E-008	15,240	1,397
Metcamifen	1.32E-018	3.843E+014	3.523E+013
Naphthalic anhydride	6.19E-007	610.8	55.54
Oxabetrinil	6.08E-008	6,676	611.5

Table 5 Biodegradation of safeners: probability of rapid biodegradation (BIOWIN v4.10)

Safeners	Biowin1 (Linear Model)	Biowin2 (Non-Linear Model)	DT ₅₀ (typical) ^a	DT ₅₀ (lab @293 K) ^a
Benoxacor	0.7430	0.6339	50	–
Dichlormid	0.6359	0.2768	–	–
Furilazole	0.0712	0.0008	29	65
Mefenpyr-diethyl	0.3694	0.5283	17.5	–
Cloquintocet-mexyl	0.8198	0.9878	5	1.75
Cyometrinil	1.4015	1.0000	–	–
Cyprosulfamide	0.9114	0.9329	–	–
Dicyclonon	0.4376	0.0510		
Dietholate	1.0723	1.0000		
Fenchlorazole-ethyl	–0.1882	0.0000	2.4	2.5
Fenclorim	0.4036	0.0817	26	
Fluxofenim	–0.7974	0.0000		
Isoxadifen-ethyl	0.8534	0.9916		
Jiecaowan	–0.1409	0.0003		
Mephenate	0.5563	0.3468		
Metcamifen	0.7065	0.5242		
Naphthalic anhydride	0.6532	0.5485		
Oxabetrinil	0.3774	0.3307		

^aPPDB Pesticide Properties Database: University of Hertfordshire

volatilization. For example, cohesion, transpiration, capillary action and translocation in plants may cause the chemicals to move to parts of the plant, where volatilization may be aided (Ramanjaneyulu and Giri 2006). The data presented in Table 5 show that the half-life for volatilization from a river can be different from a lake. The half-life, as a result of volatilization in river and lake of cyometril was estimated to be <1 and 6 days, respectively, while cyprosulfamide's half-life was estimated as 2.7×10^9 and 2.9×10^{10} days, for river and lake, respectively. The proposed differences in volatilization of cyometril and cyprosulfamide could be attributed to the differences in their Henry law's constant. However, mineral components and other factors such as turbulent mixing in rivers might enhance the removal of the safeners.

Other parameters that affect volatility, which are frequently used in volatility experiments, include agricultural practice (rate of application of the chemical), competing processes (uptake by plants and degradation), and environmental conditions (wind speed, air humidity, soil moisture, and temperature) (Dekeyser et al. 2015). The higher the temperature and relative humidity, the higher the volatilization of chemicals. Therefore, the rate of volatilization of the same chemical in different climates will differ. Volatilization rates can be quantified by direct or indirect measurement. The indirect measurement involves conducting a complete mass balance for all relevant environmental compartments (e.g. water, soil, sediments, and plants) and determining rates of volatilization by difference. This indirect

approach will often include modelling components such as inverse modelling by the use of the dispersion model (Atmospheric modelling system, ADS) and parameterized PEARL (Pesticide Emission Assessment at Regional and Local scales) model simulation (Dekeyser et al. 2015). The direct measurement can be done by measuring the concentration of air in the treated area over a period while accounting for potential losses due to degradation. The common methods for these measurements are aerodynamic profile (ADP), energy balance (EB), relaxed eddy accumulation (REA), and plume dispersion (PD) (Dekeyser et al. 2015). Herbicides and the corresponding safeners will be present in the atmosphere of the treated sites to varying degrees based on rates of volatilization.

6 Photolysis

Photolysis of safeners is important because they are exposed directly to sunlight either in soil, on plants or crops, during transportation, and in water, if they are reaching surface waters (Balmer et al. 2000). Photolysis of chemicals is possible inside leaves and thus the mechanisms of such processes need to be studied (Schroer et al. 2017). Photodegradation could occur directly as a result of absorption of photons by a chemical or indirectly as a result of photon absorption by other constituents (photosensitizing species) in the environmental compartment (e.g. water, soil), resulting in energy transfer to the target chemical and subsequent degradation (Remucal 2014; Karpuzcu et al. 2016; Lin et al. 2019). The photochemical behaviour of chemicals can be affected by their chemical speciation and light absorption capacity (Challis et al. 2013; Remucal 2014; Karpuzcu et al. 2016). For example, in photolysis, pKa values of a chemical and the pH of the environment are important parameters because they control the chemical speciation and dictate the chemical light absorption (Calvayrac et al. 2013; Challis et al. 2013, 2014).

The pKa for benoxacor and furilazole are 12.99 and 16.44, respectively, and thus, they will be fully protonated at environmentally relevant pH values (Acharya and Weidhaas 2018). For a chemical to have both protonated and deprotonated species, it must have a pKa in the pH range relevant in the environment (i.e., pH 4–9). When this is the case, chemical speciation can have a large impact on rates of photolysis, making the study of pH dependence in photolysis experiments very important (Calvayrac et al. 2013; Challis et al. 2013; Remucal 2014). Most safeners are characterized by at least one aromatic ring, conjugated π system, with 1 or more heteroatoms (such as nitrogen, sulphur) and some functional group. All these aforementioned parameters facilitate direct absorption of solar radiation (Challis et al. 2014). However, Acharya and Weidhaas (2018) observed that both benoxacor and furilazole did not photodegrade (rate coefficient $k = -0.0031 \text{ h}^{-1}$) to any extent under UV light (Halogen S302C lamp (Thorlabs, Newton, NJ) emitting 265 mW with a maximum output = $200 \text{ W}\cdot\text{cm}^{-2}$ ($\lambda = 250\text{--}300 \text{ nm}$)). Nevertheless, Kral et al. (2019) noted that benoxacor underwent direct photolysis ($t_{1/2} \sim 10 \text{ min}$) through photo-initiated ring closure when exposed to simulated natural sunlight (1,000 W

Newport Xe arc lamp, $\lambda = 300\text{--}400$ nm, output = 8.8×10^{-3} W cm⁻²). The difference in these observations might be because of the experimental setup or the energy and wavelength output of the UV source.

Dichlormid underwent degradation in both water and methanol at 254 nm (313 kcal mol⁻¹), but did not transform under environmentally relevant UV light >290 nm due to the lower energy (Abu-Qare and Duncan 2002). Since the UV wavelength of 254 nm is more energetic than natural sunlight, such results are not directly applicable to environmental photolysis. Photodegradation rate constants determined in the lab at <290 nm usually bear little meaning to environmental photolysis rates; however, they might be of importance in a place where UV light is being employed for water treatment. Compounds that cannot absorb light at >290 nm can still undergo indirect photolysis via photo excited species such as dissolved nitrates, carbonates, iron, and dissolved organic matter, which is often abundant in natural waters, soil, and sediments. Direct photolysis quantum yields can also be measured for chemicals in order to predict photodegradation rates under any light conditions (Challis et al. 2014). Quantum yields are a characteristic property of a chemical and provide information about how efficiently a chemical degrades upon absorption of light (Remucal 2014; Challis et al. 2014; Lu et al. 2015; Lin et al. 2019). For example, benoxacor has a quantum yield of 0.14, which suggests that benoxacor is a highly photo-efficient organic micro-pollutant (Kral 2018). Hence, for photodegradation monitoring to be meaningful, efforts should be made to determine quantum yields and rate constants as a function of p*K*_a and consider exposures under both simulated and natural sunlight.

Photodegradation of the herbicide metolachlor was enhanced in the presence of benoxacor on a quartz surface and, to a lesser extent, in water, but not on a soil-simulated (kaolinite) surface (Su et al. 2019). This suggests that the reaction media and chemical mixtures can play a role in photolysis. However, an earlier study showed that dichlormid did not significantly affect s-ethyl dipropylthiocarbamate (EPTC) photodegradation at 254 nm or at >290 nm in water or methanol (Abu-Qare and Duncan 2002). Hence more study is needed to fully understand the role safeners play in the photodegradation of herbicides and potentially the role that herbicides play in the photodegradation of safeners.

In the report of Abu-Qare and Duncan (2002), the roles of singlet oxygen, hydroxyl and peroxide radicals were highlighted. Singlet oxygen is a nucleophile and thus can react with any electron-rich moiety (McNeill and Canonica 2016; Katagi 2018). For example, the furan moiety in the safener furilazole is believed to be reactive with singlet oxygen and was indicated as the major reason for the indirect photolysis of furilazole (Kral 2018; Kral et al. 2019). Other components present in natural waters can facilitate electron transfer, which will aid photodegradation of the chemicals, and might be facilitating degradation of safeners that do not absorb light above 290 nm. These indirect mechanisms are complex and more difficult to predict than direct photolysis due to the multiple ways in which some chemicals can interact with photosensitizers present in natural waters (nitrate, carbonate, dissolved organic matter) (Challis et al. 2014; Remucal 2014; McNeill and Canonica 2016).

Carbonate species are believed to contribute to photodegradation of sulphur containing compounds in natural water (Huang and Mabury 2000) as a result of abstraction of electrons from sulphur. This might play an important role in indirect photolysis of safeners such as cyprosulfamide containing sulphur moieties. Hydroxyl radicals are capable of oxidizing aromatic ring and alkyl chains (Zepp et al. 1987; Katagi 2018); therefore, this is an important oxidizing agent to consider for photolysis in natural waters. For example, indirect photolysis of furilazole and dichlormid in the presence of $\bullet\text{OH}$ radicals resulted in 30% and 20% increased decay (Kral et al. 2019). Both furilazole and dichlormid exhibited 80–90% transformation in the presence of nitrate (which is known to mediate production of $\bullet\text{OH}$) during indirect photolysis. Photodegradation products are sometimes assessed when studying photolysis kinetics and can be essential to characterize since in certain scenarios they can be more toxic than their parent chemicals. Mefenpyr-diethyl yielded four transformation products when irradiated under sunlight with a first-order rate constant of 0.580 h^{-1} (El Boukili et al. 2015). Two of these products were a result of hydrolysis (mefenpyrethyl and mefenpyr) (Hertkorn et al. 2010), suggesting that hydrolysis might be an important loss pathway in addition to photolysis (Chovelon et al. 2005).

Variability in kinetic concentration data for safeners has been reported by both Abu-Qare and Duncan (2002) and Acharya and Weidhaas (2018). Kinetic concentration data is important for allowing comparisons across studies and understanding variability in the methods, especially as it relates to rate constants and quantum yields, which can have large uncertainties when compared across studies (Challis et al. 2014). Natural sunlight exposure experiments will provide the most realistic estimation of photolysis rates at the specific latitude and sunlight conditions these experiments are conducted at. However, most researchers conduct these types of photolysis experiments under simulated sunlight using laboratory photo-reactors, which can limit their applicability to environmental systems. Additionally, light attenuation in natural systems can be significant so the result of photolysis based on test tube exposures can only be applied to near surface photolysis (Lu et al. 2015). Despite the reports of dichlormid, benoxacor, furilazole (Kral 2018), and mefenpyr-diethyl's (El Boukili et al. 2015) photolytic fate, more work is still needed on other safeners since photochemical behaviour varies greatly from chemical to chemical (Boreen et al. 2004; Chnirheb et al. 2012).

7 Chemical Reduction and Nucleophilic Substitution

Electron-rich compounds such as hydrogen sulphide may be able to reduce safeners. For example, graphite (black carbon) can aid the transfer of electrons from hydrogen sulphide to dichloroacetamide safeners through nucleophilic substitution pathways (Xu et al. 2020). This process can lead to transformation of dichloroacetamide safeners. Specifically, hydrogen sulphide has been implicated to facilitate the conversion of dichlormid, benoxacor, and AD-67 (Xu et al. 2020). Reductive

dechlorination was responsible for dichloroacetamide safener degradation when reduced by Fe (II)-amended goethite in anaerobic abiotic system (Sivey and Roberts 2012). Chemicals such as iron, manganese, and hydrogen sulphide are naturally occurring in the subsurface environment (Ricko et al. 2020).

Different chemicals generally have different abilities to reduce safeners. For example, the half-life for dichlormid was 10 h by graphite-hydrogen sulphide (Xu et al. 2020) and 50 h by Fe (II)-amended goethite (Sivey and Roberts 2012). Also, the increase in molar ratio of Fe (II) to Mn (IV) oxide increased the rate of transformation of benoxacor and furilazole (Ricko et al. 2020). This mixture of Fe (II) and Mn (IV) oxide did not cause transformation of dichlormid after 6 h of reaction. This suggested that individual safeners react differently.

However, the herbicide (S-metolachlor) and three surfactants (Triton X-100, sodium dodecyl sulphate (SDS), and Myristyltrimethylammonium bromide (MyTAB)) did not influence rates of transformation of dichloroacetamide safeners, even in the presence of $\text{Cr}(\text{H}_2\text{O})_6^{2+}$ (Ricko et al. 2020). This could be an indication that the herbicide (active ingredient) and accompany safeners may not naturally react.

Finally, since safeners can be transformed, their transformation products also need to be considered in the assessment of fate, transport, and ultimate hazard to non-target organisms. For instance, after harvest of rice, no fenoxaprop-P-ethyl or isoxadifen-ethyl was detected in straw or grain from plants, which were previously treated with a formulation containing both chemicals. However, the metabolite of fenoxaprop-P-ethyl, fenoxaprop-P was detected (Lucini and Pietro Molinari 2010, 2011). Isoxadifen-ethyl dissipated completely from the target, while fenoxaprop-P-ethyl was metabolized to a single product, which was still present as a residue.

8 Biological Degradation

Microorganisms, such as bacteria in the soil, can also degrade organic chemicals present in their environment (McGuinness and Dowling (2009); Fenner et al. 2013; Joutey et al. 2013). Soil microorganisms will often treat organic chemicals such as herbicides and safeners as xenobiotics, and thus they can develop adaptive strategies which might result in chemical transformation. Biological degradation of pesticides has not received much attention because most pesticides are not quick to degrade (Parsek et al. 1995; Rama Krishna and Philip 2011; Fenner et al. 2013). Microorganisms initiate chemical degradation by splitting the parent chemicals, then hydrolysing it (Nakamiya et al. 2007). However, soil microorganisms might find dichloroacetamide safeners more difficult to degrade/metabolize because of the additional chlorine atom compared to chloroacetamide herbicides (Xu et al. 2020).

Predictions on biodegradation of safeners using EPI suite are reported here (Table 5). Safeners such as benoxacor are moderately biodegradable based on Biowin model predictions of 0.7430 and 0.6339, for linear and non-linear models, while fenchlorazole-ethyl has biodegradation probabilities of -0.1882 and 0.000 ,

from linear and non-linear models. In general, a half-life (DT_{50}) of a chemical in the soil below 50 days is non-persistent, between 50 and 70 is moderately persistent, $\geq 70 \leq 100$ days is persistent. Benoxacor, furilazole, mefenpyr-diethyl, cloquintocet-mexyl, fenchlorazole-ethyl, and fenclorim have measured DT_{50} values of 50, 29, 17.5, 5, 2.4, and 26 days, indicating that they are non-persistent, consistent with most of the safeners reported in Table 5.

9 Toxicity

Chemical risk assessment is one way from which concerns raised by continuous use and production of chemicals for agricultural purposes could be resolved (Joly et al. 2013). Potential impact of toxic substances including pesticides needs to be assessed by evaluating the responses of living organisms to these substances. Several studies evaluating such effects have been published to better inform the public and help researchers in further toxicity studies. A Microtox study of the effects of the safener benoxacor on bacteria (*V. fischeri*) has shown that the chemical was more toxic considering the concentration capable of inhibiting half (IC_{50}) of the population of *V. fischeri* (IC_{50} of 93 mg/L) than atrazine (IC_{50} of 197 mg/L) (Joly et al. 2013). Benoxacor has been reported to decrease growth of the freshwater algae, *S. capricornutum* (Day and Hodge 1996). Benoxacor is classified as having high toxic potency with an effective concentration (EC_{50}), exhibiting a maximal response in half of the algae population (EC_{50} of 0.63 mg/L) of freshwater algae (*S. subspicatus*) (Table 6) (European Chemical Agency 2020). Its lethal concentration (LC_{50}) that kills half of the freshwater fish species, *Ictalurus punctatus* is 1.4 mg/L, and the (LC_{50}) for *Lepomis macrochirus* is 6.5 mg/L, this is considered to be a moderately toxic potency to aquatic species (US EPA 2020; Xu et al. 2020; PPBD 2020). Furilazole has lesser toxic potency with an LC_{50} of 4.6 mg/L for freshwater fish and EC_{50} of 85.2 mg/L for algae compared to benoxacor (US EPA 2020; PPBD 2020; SDS 2020), while the LC_{50} of fluxofenim to Rainbow trout was reported to be 0.86 mg/L (SDS 2020). During chronic exposure to benoxacor, no observed effect concentrations (NOEC) of 0.31, and 0.35 mg/L were reported for *Pimephales promelas* (freshwater fish) and *Daphnia magna* (freshwater invertebrates), respectively (European Chemical Agency 2020). Benoxacor also caused a significantly reduced condition index (0.016 mg/L) of rainbow trout (European Chemical Agency 2020). Benoxacor might be moderately toxic to birds, honeybees, earthworms, and most aquatic organisms (Table 6) (European Chemical Agency 2020; PPBD 2020). Mefenpyr-diethyl and cyprosulfamide were stated as harmful to aquatic life with long-lasting effects (SDS 2020). Similarly, Isoxadifen-ethyl, fenchlorazole-ethyl, and cloquintocet-mexyl were described as very toxic to aquatic life with long-lasting effects and fenchlorazole-ethyl may cause cancer (SDS 2020). Alternatively, dichlormid might be relatively non-toxic to birds, fish, and aquatic invertebrates (considering their lethal concentration in Table 6 (PPBD 2020)). As an example of potential hazards, dichloroacetamide (a disinfection by-product) in

Table 6 Ecotoxicity of safeners on selected organisms

Safeners	Fish	D-Magna	Algae	Honeybees	Earth worm	Birds	BCF ^a
	96 h LC ₅₀	48 h EC ₅₀	72 h EC ₅₀	72 h LD ₅₀	14 days LC ₅₀	LD ₅₀	(BCFBAF v3.01)
	Mg/L	Mg/L	Mg/L	µg/bee	Mg/kg	Mg/kg	
Benoxacor	6.5	4.8	0.63	100	1,000	2,000	47.15
Dichlormid	141	161	–	–	–	>5,200	6.34
Furilazole	>6.2	>26	>85	>100	–	>2,000	6.48
Mefenpyr-diethyl	4.2	53	1.65	>700	>1,000	>2,000	30.83
Cloquintocet-mexyl	>14	>100	0.53	>100	1,000	>2,000	88.47
Cyometrinil	>5.6	–	–	–	–	–	25.84
Cyprosulfamide	>106	>102	>99.7	–	–	–	16.15
Dicyclonon	–	–	–	–	–	–	6.85
Dietholate	–	–	–	–	–	–	92.09
Fenchlorazole-ethyl	0.08	1.8	–	>300	–	>2,400	1,028
Fenclorim	0.6	2.2	20.9	20	62.5	500	701.3
Fluxofenim	0.86	0.22	–	–	–	2,000	78.69
Isoxadifen-ethyl	0.34	0.51	1.26	–	–	–	88.43
Jiecaowan	–	–	–	–	–	–	2.389
Mephenate	–	–	–	–	–	–	7.042
Metcamifen	–	–	–	–	–	–	2.718
Naphthalic anhydride	–	–	–	–	–	–	132.6
Oxabetrinil	7.1	8.5	10.7	>20	–	2,500	36.07

^aBCF bioconcentration factor

drinking water has been reported to potentially affect gut microbiota composition (Xue et al. 2019) and cause acute metabolic damage in zebrafish (Yu et al. 2015), a similar observation might be possible for dichloroacetamide safeners. Another safener, naphthalic anhydride, can cause allergic skin and eye irritation in humans (National Center for Biotechnology Information 2020a, b; SDS 2020), depending on the concentration of exposure.

Concentrations of these safeners that are considered toxic are high compared to the amount measured in the environment (Woodward et al. 2018). Therefore there could be possibilities of lethal toxicities of this class of chemical if there were spillage to the environment. Nevertheless more work is needed on the effects of all groups of safeners to understand their various effects.

There are reports that possible synergistic effects exist between safeners and herbicides when used together (Bolyard et al. 2017; Acharya and Weidhaas 2018). However, an earlier study showed that mixtures of benoxacor and s-metolachlor did not alter the toxicity of s-metolachlor to any extent (Joly et al. 2013). The IC₅₀ of

s-metolachlor before the addition of benoxacor was 178 mg/L, and the IC_{50} of the mixture was 174 mg/L (Joly et al. 2013). More work is needed using other organisms and combinations of different safeners and herbicides to fully understand mixture toxicity of these chemicals.

10 Conclusion

Despite having biological activities, chemical safeners, which are antidotes for the effects of herbicides on target plants, have, for regulatory purposes, been classified as inert. Just as for herbicides with which they are formulated or applied with, safeners can dissipate and be transported to aquatic environments and have been detected in surface waters. However, fates and potential mobilities of safeners in the environment as well as possible adverse effects on non-target organisms, which are affected by estimates of exposure, including magnitude and duration of exposure in addition to toxic potencies have received little attention to date. Some safeners (such as benoxacor) have low aqueous solubility, are quite volatile and, based on their chemical properties, have potential for leaching to groundwater. Here, several possible routes, mechanisms, and rates of dissipation of safeners used with herbicides, including surface runoff, sorption/desorption, photodegradation, leaching and biological transformation, were reviewed. Most of the safeners can be readily leached because of their high solubilities. Laboratory experiments done in the absence of natural materials such as soil and water could not be easily used to predict what might be occurring during and after the application of safeners in the environment. Most of the safeners are not persistent in soil systems. Hazards presented by safeners were also investigated by comparing measured or predicted exposures to aquatic organisms with threshold toxic potencies for effects. It was determined that various safeners exhibit different potentials for exposure in aquatic environments and have a range of toxic potencies among organisms. Most safeners have low mammalian toxicity and moderate potential for bioaccumulation. They are moderately toxic to birds, honeybees, earthworms, and most aquatic organisms.

Considering the presence of safeners in the environment more work is needed to understand their dissipation mechanisms. Baseline information is needed on safeners from various nations of the world so that the exposure of this class of chemical can be used in risk assessment. Furthermore, various degradation products from each of the commonly used safeners should be studied. Also, aggressive efforts should be targeted towards understanding the toxicity of safeners on different organisms. The fate and toxicity of some recently synthesized safeners such as the closely related sulphonamide safeners, metcamifen and cyprosulfamide and their effects on living organisms need to be evaluated as this could help to determine their effects on impacted ecosystems and inform proper use and management of these important agrochemicals.

11 Methods for Laboratory Studies

For the determination of experimental Log K_{OW} a known volume (15 mL) of the test substance (benoxacor, mefenpyr-diethyl, cyprosulfamide, furilazole, and dichlormid) solution was added to an equal amount of octanol which had been saturated with water in a 50 mL polypropylene tube. The mixture was shaken for approximately 24 h at room temperature. Thereafter the mixture was centrifuged at 2400 rpm for 10 min and the two layers separated. Each of the phases was put into LC vials and spiked with atrazine-d5 at 50 ppb as a surrogate standard for LC-MS analysis. Then Log K_{OW} was calculated from the concentration determined by a Vanquish UHPLC and Q-ExactiveTM HF Quadrupole-OrbitrapTM mass spectrometer (Thermo-Fisher). LC separation was achieved with a Kinetex 1.7 μ m C18 LC column (100 \times 2.1 mm) (Phenomenex, Torrance, CA) using an isocratic elution of 45% H₂O: 55% methanol (each containing 0.1% formic acid) (Fisher Scientific) at a flow rate of 0.2 mL/min and column temperature of 40 °C. Samples were ionized by positive mode heated electrospray ionization (HESI) with the following source parameters: sheath gas flow = 3; aux gas flow = 1; sweep gas flow = 0; aux gas heater = 350 °C; spray voltage = 4.0 kV; S-lens RF = 80; capillary temperature = 320 °C; Aux gas heater temperature = 300 °C. A targeted-SIM and PRM (collision energy was 10, 20, 35, 15, 45, and 35 for cyprosulfamide, furilazole, benoxacor, mefenpyr-diethyl, dichlormid and atrazine, respectively) method at 60,000 resolution, AGC target = 1×10^6 , max injection time = 30 ms, and a scan range from 100–1,000 m/z was used to monitor [M+H]⁺ precursor and product ions of benoxacor (m/z 260.024 \rightarrow 149.083); mefenpyr-diethyl (m/z 373.071 \rightarrow 327.029); furilazole (m/z 300.016 \rightarrow 241.975); cyprosulfamide (m/z 375.100 \rightarrow 254.081, 135.044); dichlormid (m/z 208.029 \rightarrow 139.966) and atrazine (m/z 216.101 \rightarrow 174.054) (surrogate standard). Precursor and product ions were used for quantification and confirmation, respectively.

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Conflict of Interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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