Chirality and Its Role in Environmental Toxicology

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Abstract The role of chirality is crucial in our lives as it affects various processes and phenomenon in the earth's ecosystem. The chiral pollutants are widely distributed in water, soil, sand, air, and biota. Most notorious chiral pollutants are pesticides, biphenyls, polychlorinated hydrocarbons, and some drug residues. Enantiomers of chiral xenobiotics have different toxicities, and, hence, determination of their enantioselective toxicities is essential by the environmental point of views. The toxicities of enantiomers of some chiral pollutants have been established. This chapter describes the origin, chemistry, and environmental aspects of chirality. Attempts have been made to discuss the distribution and toxicities of various chiral pollutants in the environment.

Keywords Chirality · Chiral pollutants · Distribution of the chiral pollutants · Enantioselective toxicities

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Introduction

For few decades, the environmental pollution has become the issue of focus among scientists, academicians, environmentalists, and regulatory authorities. There are many kinds of pollutants; some organic contaminants are most dangerous due to their chronic toxicities and carcinogenic nature. The most commonly found organic pollutants are pesticides, phenols, plasticizers, polychlorinated, and polycyclic aromatic hydrocarbons (PAHs) [1–4]. The presence of such pollutants in our earth ecosystem is dangerous and many methods have been reported for their monitoring. It is very important to highlight that the reported methods provide the total concentrations of pollutants but they do not distinguish which mirror images of pollutants are present and which are harmful in the case of chiral contaminants. Therefore, during the last few years, scientists and regulatory authorities are in the demand of the data on concentrations and toxicities of the chiral pollutant mirror images. This is an essential, urgent, and demanding field in the present century. For the preparation of this chapter, we have searched the literature thoroughly and observed that only few groups are working in this area. This chapter describes the role of chirality in the environment, especially the distribution and toxicities of chiral pollutants.

Origin of the Chirality

Before discussing the distribution and toxicities of chiral pollutants, it is essential to discuss some aspects of chirality so that readers can realize the importance of chirality in the environment. Basically, chirality has been derived from the Greek word *kheir* for handedness and, first of all, used by Lord Kelvin in 1883 [5]. Any molecule deprived of plane, center, and axis of symmetry exists in more than one form; these are called chiral objects or enantiomers; enantiomers that are nonsuperimposable mirror images of each other are called as chiral objects. The role of chirality is very important in our lives and still has not been fully explored. Chirality is found in a wide range of objects starting from elementary constituents of our body structure [6]. There are several examples of the chirality in our environment, i.e., burial chamber mural paintings in Egypt [5], 540 galaxies listed in *Carnegie Atlas of Galaxies* [7], and helical structures of plants and animals. Briefly, the chirality exists almost everywhere in this universe and is associated with the origin of the earth and life [8].

Chemistry of the Chirality

In 1809, Haüy [9] evolved chemical utility of the chirality, who postulated that, from crystal cleavage observations, a crystal and each constituent space-filling molecules are images of each other in overall shape. In 1848, Pasteur described the different destruction rates of *dextro* and *levo* ammonium tartrate by the mould *Penicillium glaucum* [10].

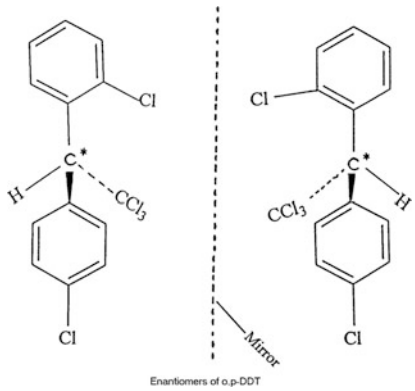

Fig. 1 Enantiomers of *o*, *p*′-DDT (1,1,1-trichloro-2-(*o*-chlorophenyl)-2-(*p*′-chlorophenyl)ethane)

The tetrahedral arrangement of carbon with different four groups makes the whole pollutant asymmetric in structure, and such pollutant differs in three dimensional configurations and exists in two forms, which are mirror images of each other (Fig. 1). These mirror images are called optical isomers, stereoisomers, enantiomers, enantiomorphs, antipodes, or chiral molecules. The phenomenon of the existence of the enantiomers is called as stereoisomerism or chirality. The 50:50 ratios of the enantiomers are called racemic mixture, which do not rotate the plane-polarized light. The number of the enantiomers may be calculated by 2^n, where n is the number of the chiral centers within the respective molecule. In the beginning, the optical isomers were distinguished with (+) and (−) signs or *d* (*dextro*) and *l* (*levo*), indicating the direction in which the enantiomers rotate the plane-polarized light. (+) or *d* stands for a rotation to the right (clockwise), whereas (−) or *l* indicates a rotation to the left (anticlockwise). The main drawback of such an assignment is that one cannot derive the number of chiral centers from it. This is possible when applying the well-known *R*/*S* notation given by Cahn and Ingold, which describes the absolute configuration (the spatial arrangement of the substituents) around the asymmetric carbon atom of the pollutant (molecule).

Environmental Aspects of the Chirality

The most notorious environmental pollutants are pesticides, which are about 25% chiral molecules [11]. Polyaromatic hydrocarbons may also be chiral pollutants. It has been observed that one of the enantiomers of the chiral pollutant may be more toxic, and, hence, both enantiomers may have different toxicities [5, 12]. This is an important information to scientists when performing environmental analyses. Biological transformation of the chiral pollutants can be stereoselective; uptake, metabolism, and excretion of enantiomers may be very different [12, 13]. Therefore, the enantiomeric composition of the chiral pollutants may be changed through these processes. Metabolites of the chiral compounds are often chiral as well. Moreover, some of the achiral

pollutants degrade into the chiral metabolites. For example, γ-hexachlorocyclohexane (γ-HCH) and atrazine degrade into γ-pentachlorocyclohexene (γ-PCCH) and 2-chloro-4-ethylamino-6-(1-hydroxy-2-methylethyl-2-amino)-1,3,5-triazine racemic mixtures, respectively. It has also been reported that the enantiomers may react at different rates with achiral molecules in the presence of chiral catalysts [4]. Since constituents of living organisms are usually chiral, there are greater chances of the chiral pollutants to react at different rates. To predict the exact chiral pollution load determination of enantioselective toxicities and concentrations of the enantiomers is thus required and an essential need.

Distribution of the Chiral Pollutants in the Environment

Both point and nonpoint sources are major sources for pollution in the environment. The most commonly found chiral pollutants are given in Table 1. These compounds are widely distributed in our ecosystem. Marine water has been reported as polluted due to heptachlor *exo*-epoxide (a metabolite of heptachlor); α-, β-, and γ-HCH; toxaphene; and phenoxyalkanoic acid herbicides. There are only few papers published [5] on the ground water contamination by pesticides and other toxic organic pollutants [3]. Weigel [14] reported on the presence of several drugs in waste water. Buser *et al.* [15] identified ibuprofen, a nonsteroidal anti-inflammatory drug, in waste and river waters. Recently, Ali *et al.* [16] reviewed the literature on the distribution of drugs in the environment.

Vetter *et al.* [17] determined toxaphene in Canadian lake sediments and chloroborane congeners in the sediment from the toxaphene-treated Yukon lake [18]. Rappe *et al.* [19] reported the presence of chiral pesticides in the sediment of the Baltic Sea, and Benicka *et al.* [20] identified PCBs in sediments of a river. Wong *et al.* [21] looked into the enantiomeric ratios of eight PCB species in the sediments from selected sites in the USA. Biselli *et al.* [22] carried out a comprehensive study on the distribution of the chiral musks in sediments of various waste water plants. Moisey *et al.* [23] determined the concentrations of α-, β-, and γ-HCH isomers and enantiomers in sediments obtained from the North Sea. Aigner *et al.* [24] described the enantiomeric ratio of the pesticide chlordane in the soil of Midwestern USA. The pesticides detected in these samples were chlordane, heptachlor, and heptachlor *exo*-epoxide. Wiberg *et al.* [25] described organochlorine pesticides in 32 agricultural and 3 cemetery soils from Alabama. Lewis *et al.* [11] detected the dichlorprop pesticide in Brazilian soils, and White *et al.* [26] identified *cis*- and *trans*-chlordanes in the soil of a green house unit.

Besides water, soil, and sediments, chiral pollutants have also been detected in the atmosphere. The concentrations of chiral pollutants being found varied from place to place. Ridal *et al.* [27] detected α-HCH in air above the water surface of Ontario Lake. Ulrich and Hites [28] reported the presence of chlordane in air samples near the Great Lakes. Aigner *et al.* [24] reported enantiomeric ratios of the chlordane pesticide in the air of Midwestern USA. Similarly, Bidleman *et al.* [29] collected air samples from Corn Belt, South Carolina, and Alabama areas.

Table 1 List of some common chiral pollutants [4]

AHTN (tonalide: 1-(5,6,7,8-tetrahydro-3,5,5,6,8,8-hexamethyl-2-naphthalenyl)ethanone)
ATTI (traseolide: 1-(2,3-dihydro-1,1,2,6-tetramethyl-3-isopropyl-1*H*-inden-5-yl)ethan-1-one)
AHDI (phantolide: 1-(2,3-dihydro-1,1,2,3,3,6-hexamethyl-1*H*-inden-5-yl)ethanone)
Anatoxin-a
Acephate
Biollethrin
Bromacil
Bromocyclane (bromodan)
Bromocyclen
Chlordane (*cis*, *trans,* and other congeners)
Chlordane and metabolites
Clofibric acid
Cruformate
Crotoxyphos
Crufomate
Dialifor
o,*p*′-DDT (1,1,1-trichloro-2-(*o*-chlorophenyl)-2-(*p*′-chlorophenyl)ethane)
o,*p*′-DDD (1,1-dichloro-2-(*o*-chlorophenyl)-2-(*p*′-chlorophenyl)ethane)
α-, β-, γ-, δ-HCH (α-, β-, γ-, and δ-hexachlorocyclohexane)
DCPP (dichlorprop: 2-(2,4-dichlorophenoxy)propionic acid)
Deltamethrin
Endosulfan
Fonofos
Fenamiphos
Fensulfothion
HHCB (galaxolide: 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[*g*]-2-benzopyran)
Heptachlor
Heptachlor *exo*-epoxide
Homoanatoxin-a
Isophenphos
Isomalathion
Ibuprofen and metabolites
MCCP (2-(4-chloro-2-methylphenoxy)propionic acid)
MDCPP (methyl dichlorprop: methyl 2-(2,4-dichlorophenoxy)propionic acid)
Methamidophos
Malaxon
Malathion
Methamidophos
Naloxone
Oxychlordane
β-, γ-PCCH (β-, γ-pentachlorocyclohexene)
Photoheptachlorepoxide
Photochlordane
Profenofos
Prothiophos
PCBs (polychlorinated biphenyls)
PCB methyl sulfones ($MeSO_2$-PCBs)
Ruelene (4-*tert*-butyl-2-chlorophenylmethyl-*N*-methylphosphoramidate)
Saxitoxin
Trichloronate
4-Tolylethyl sulfoxide
Tetrodotoxin
Toxaphene
Thalidomide
Trichlorfon

Table 2 Chiral pollutants in various water resources [4]

Chiral pollutant	Water resource
Acetachlor	River water
Chlordane	River water
Clofibric acid	River water
DCPP	Sea water
Endosulfan	River water
α-HCH	Sea water
	Rain water
Heptachlor	River water
Ibuprofen	River water
Metolachlor	River water
β-PCCH	Rain water
γ-PCCH	Sea water
Polyaromatic musks	River water

The authors reported the presence of *cis*-chlordane, *trans*-chlordane, heptachlor, and heptachlor *exo*-epoxide in these samples. Other authors who described the presence of chiral pesticides in air samples are Wiberg *et al.* [30] (chlordane) and Buser and Müller [31] (heptachlor and chlordane).

Moreover, chiral xenobiotics have been routinely identified in earth's biota. Different chiral ratios of different pollutants were detected in various organs of seals, Eider ducks, polar bears, whales, pelagic zooplankton, arctic cod, sea birds, fishes, bivalves, crayfish, water snakes, barn swallows, sheep, roe deer, and even humans [32–40]. For a ready reference, Tables 2 and 3 describe the distribution of chiral pollutants in water and biota of our ecosystem. The different chiral ratios of toxaphene, *cis*- and *trans*-chlordane, and heptachlor *exo*-epoxide in air, sediment, soil, and plants are given in Tables 4–7.

Toxicities of Chiral Pollutants

Only little information is available on the enantioselective toxicity of pollutants. Basically, differences in the bioaffinity of the enantiomers to a binding site on an enzyme or receptor surface are responsible for different toxicities. Such differences may reveal in terms of distribution rates, compound's metabolism, and excretion; in antagonistic actions relative to each other; or in their individually different tissue-specific toxicological properties. The enantioselective toxicities of chiral pollutants are discussed in the following sections.

Enantioselective Toxicities of Pesticides

Möller *et al.* [41] described the different carcinogenic potencies and growth stimulation of α-HCH enantiomers in primary rat hepatocytes by reporting 100% cell death in the presence of 3.0×10^{-4} M (+)-α-HCH. Contrarily, (−)-α-HCH only induced 75% toxicity at the same concentration. By using concentrations of

Table 3 Chiral pollutants in different biota [4]

Chiral pollutant	Ecosystem component
AHTN	Rudd
	Trench liver
	Crucian carp liver
	Eel
	Mussels
trans-Chlordane	Baltic herring
	Baltic salmon
	Baltic seal
cis-Chlordane	Baltic herring
	Baltic salmon
α-HCH	Mussel
	Eider duck (liver)
	Eider duck (kidney)
	Eider duck (muscle)
	Seal liver
	Seal (blubber)
	Seal (brain)
	Seal (lung)
	Female fur seal (milk)
	Whale blubber
	Flounder (liver)
	Cod liver oil
HHCB	Rudd
	Trench liver
	Crucian carp liver
	Eel
	Mussels
Heptachlor *exo*-epoxide	Sea gulls egg
Octachlordane MC4	Baltic herring
	Baltic salmon
	Baltic seal
	Antarctic penguin
Octachlordane MC5	Baltic herring
	Baltic salmon
	Baltic seal
	Antarctic penguin
Octachlordane MC7	Baltic herring
	Baltic salmon
	Baltic seal
	Antarctic penguin
Oxychlordane	Sea gulls egg
β-PCCH	Flounder

5.0×10^{-5} M of both enantiomers, significant increases in mitosis occurred in the presence of the (+)-α-HCH enantiomer (factor 2.4) as compared with a 1.7-fold stimulation by (−)-α-HCH enantiomer. Concentration-dependent cell death rates observed in primary cultures of rat hepatocytes treated with (+)- or (−)-α-HCH and the corresponding stimulation of mitosis in these cells are depicted in Fig. 2.

Table 4 Chiral ratio of toxaphene congeners b7-1001 and b7-923 in sediments from the Canadian Hanson Lake [4]

Year of sampling	B7-1001	B6-923
1935	<1.0	0.97
1946	0.80	1.00
1954	0.81	1.01
1959	0.82	0.97
1964	0.82	1.06
1968	0.81	0.98
1973	0.78	0.98
1979	0.77	0.98
1984/7	–	0.99
1992	0.71	0.96

Table 5 Chiral ratio of *cis*- and *trans*-chlordane pesticides in soil samples [4]

Soil samples	Enantiomeric ratio of *cis*-chlordane	Enantiomeric ratio of *trans*-chlordane
Prebulk (prior to plantation)	1.22	0.861
Postbulk (after to plantation)	1.25	0.872
Near plant root	1.24	0.852

Table 6 Chiral ratio of chlordane, heptachlor, and heptachlor *exo*-epoxide in air from the Corn Belt region, South Carolina, and Alabama [4]

Location	*trans*-Chlordane	*cis*-Chlordane	Heptachlor chlordane	Heptachlor *exo*-epoxide
Alabama				
Ambient	0.98	1.01	–	–
Indoor	0.98	1.00	–	–
Corn Belt				
Above	0.74	1.11	–	–
Ambient	0.93	1.04	–	–
Indoor	0.99	0.98	–	–

Miyazaki *et al.* [42] studied the enantioselective toxicities of cyclodiene pesticides (e.g., chlordiene, chlordiene epoxide, and heptachlor *exo*-epoxide) on male German cockroach insects (*Blattella germanica*). The authors reported that (+)-chlordiene, (−)-chlordiene epoxide, and (+)-heptachlor *exo*-epoxide enantiomers exhibited stronger toxicity when compared to their corresponding antipodes (Table 8). The toxicity was expressed in percent of dead animals 24 h after the application of the compound. From the results obtained, it can be concluded that (+)-chlordiene, (−)-chlordiene epoxide, and (+)-heptachlor *exo*-epoxide are more toxic in these insects than their enantiomers. The $LD_{28.6}$ value of (+)-chlordiene was 129, while LD_{50} values of (−)-chlordiene epoxide and its racemate were 76 and 157, respectively, indicating the differences of enantioselective toxicities of these insecticides.

Furthermore, Miyazaki *et al.* [43] reported the different enantioselective toxicities of heptachlor and 2-chloroheptachlor pesticides on the same cockroach species. LD_{50} values for these pesticides were calculated after 24 h (Table 9). It has been reported that only heptachlor and 2-chloroheptachlor showed toxicities, while 3-chloroheptachlor was nontoxic. LD_{50} values for (−)-, (+)-, and (±)-heptachlor were 5.32, 3.38, and 2.64,

Table 7 Chiral ratio of *cis*- and *trans*-chlordane in different plants [4]

Plants	Enantiomeric ratio of *cis*-chlordane	Enantiomeric ratio of *trans*-chlordane
Cucumber		
Roots	0.54	0.42
Stem	0.52	0.38
Leaves	0.52	0.37
Whole fruit	0.51	0.25
Fruits peel	0.48	0.30
Fruit flesh	0.50	0.22
Lettuce		
Roots	0.55	0.46
Leaves	0.54	0.41
Pumpkin		
Roots	0.51	0.51
Stem	0.46	0.49
Leaves	0.54	0.48
Whole fruit	0.56	0.47
Fruits peel	0.55	0.47
Fruit flesh	0.56	0.47
Pepper		
Roots	0.55	0.48
Stem	0.56	0.54
Leaves	0.52	0.51
Spinach		
Roots	0.53	0.46
Leaves	0.58	0.45
Tomato		
Roots	0.55	0.37
Stem	0.59	0.30
Leaves	0.52	0.30
Zucchini		
Roots	0.55	0.42
Stem	0.58	0.36
Leaves	0.58	0.47
Whole fruit	0.60	0.46
Fruits peel	0.59	0.40
Fruit flesh	0.62	0.48

respectively. On the other hand, LD_{50} values calculated for (−)-, (+)-, and (±)-2-chloroheptachlor were 100, 50, and 20, respectively. Therefore, it may be concluded that the toxicities of the (+)-enantiomers of heptachlor and 2-chloroheptachlor are greater than that of their corresponding (−)-enantiomers. Based on these results, the theoretical LD_{50} values of the racemic mixtures of heptachlor and 2-chloroheptachlor should be 4.35 and 75.0, respectively. However, the observed LD_{50} values are lower than the theoretical values (Table 9). Therefore, it may be concluded that the toxic potency of one enantiomer is being increased due to the presence of the other.

McBlain and Lewin [44] reported (−)-*o*,*p*′-DDT as a more active estrogen-mimic species in rats than the (+)-enantiomer. Hoekstra *et al.* [45] described a yeast-based assay to assess the enantiomer-specific transcriptional activity of *o*,*p*′-DDT via interaction with the human estrogen receptor (hER). While the (−)-enantiomer strongly

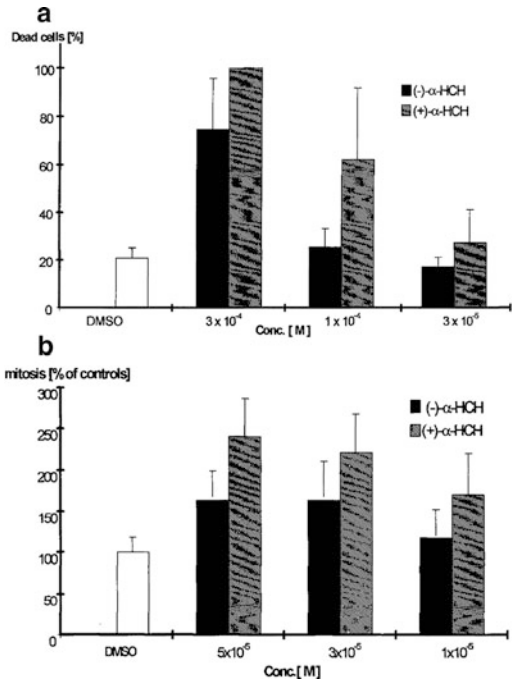

Fig. 2 Differences in the biological effects of the (+)- and (−)-enantiomers of α-HCH (α-hexachlorocyclohexane). (**a**) Toxicity in primary cultures of rat hepatocytes and (**b**) effects on the stimulation of mitosis in these cells (from [41] with reprint permission of Eco-Informa Press)

Table 8 Chiral toxicities of chlordiene, chlordiene epoxide, and heptachlor *exo*-epoxide insecticide enantiomers in the German cockroach *Blattella germanica* (% of dead animals after 24 h) (according to [42])

Insecticide	Dose (μg/g)					LD (μg/g)
	300	233	178	126	94.4	$LD_{28.6}$
(+)-Chlordiene	100	94.4	72.2	33.3	11.1	129
(±)-Chlordiene	28.6	–	–	–	–	–
(−)-Chlordiene	0	–	–	–	–	–

Insecticide	Dose (μg/g)				LD (μg/g)
	200	133.3	88.9	59.3	LD_{50}
(−)-Chlordiene epoxide	86.7	73.3	66.7	33.3	76
(±)-Chlordiene epoxide	66.7	40.0	13.3	0.0	157
(+)-Chlordiene epoxide	0	–	–	–	–

Insecticide	Dose (μg/g)					LD (μg/g)
	6.0	3.0	1.5	0.75	0.375	LD_{50}
(+)-Heptachlor *exo*-epoxide	100	86.7	46.7	33.3	6.7	1.29
(±)-Heptachlor *exo*-epoxide	93.3	80.0	33.3	13.3	0	1.82
(−)-Heptachlor *exo*-epoxide	93.3	46.7	13.3	0	0	2.98

Table 9 Chiral toxicities of heptachlor and 2-chloroheptachlor enantiomers in the German cockroach *Blattella germanica* (% of dead animals after 24 h) (according to [43])

Insecticide	Dose (μg/g)						LD_{50} (μg/g)
	18.0	10.8	6.48	3.88	2.32	1.39	
(+)-Heptachlor	93.3	66.7	43.3	0	0	0	3.38
(±)-Heptachlor	86.7	93.3	60.0	25.0	0	0	2.64
(−)-Heptachlor	90.0	46.7	36.7	0	0	0	5.32
Insecticide	Dose (μg/g)						LD_{50} (μg/g)
	200	100	50	25	12.5		
(+)-2-Chloroheptachlor	100	100	100	60	40		20
(±)-2-Chloroheptachlor	100	80	50	10	10		50
(−)-2-Chloroheptachlor	40	40	0	0	0		100

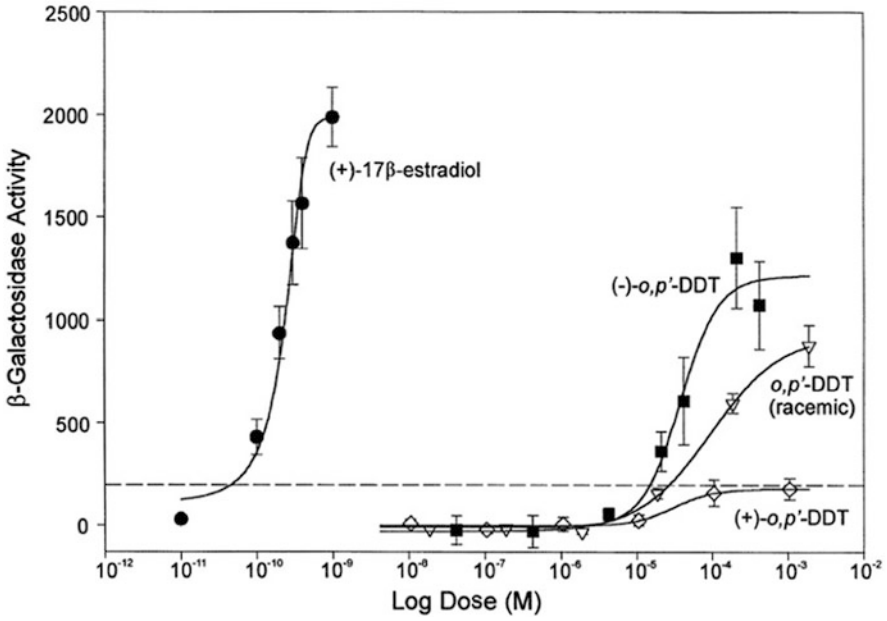

Fig. 3 Differences in enantiomer-specific transcriptional activity of *o,p′*-DDT via interaction with the human estrogen receptor (hER). Binding affinities of the (+)- and (−)-enantiomers and the racemic mixture were measured via β-galactosidase activity (from [45] with reprint permission of Elsevier)

induced measureable hER activity, the corresponding potency of the (+)-*o,p′*-DDT was negligible. However, high concentrations of the (+)-enantiomer influenced (decreased) the transcriptional activity of the (−)-*o,p′*-DDT. The dose-dependent reporter gene (β-galactosidase) activity is shown in Fig. 3.

Miyazaki *et al*. [46, 47] reported on the enantioselective differences in the toxicities of methamidophos (*O,S*-dimethyl phosphoramidothiodate) and acetaphate (*O,S*-dimethyl-*N*-acetylphosphoramidothiodate) to houseflies. In houseflies, the (+)-enantiomers are more potent than their (−)-counterparts. By contrast, the (−)-enantiomers

were found more toxic to German cockroaches (*B. germanica*), albeit LD_{50} values were close for both enantiomers. In addition, the (−)-enantiomer resulting from sulfoxidation of propaphos was found more potently inhibiting cockroaches and—at the biochemical level—the bovine erythrocyte acetylcholinesterase (AChE) when compared with its (+)-enantiomer [47]. Furthermore, the authors studied the toxicities of these two enantiomers on houseflies and green leaf hoppers and reported only little differences in the toxicities in these insects. Phosphor-containing pesticides were introduced in the 1950s for insect control in fruits, vegetables, and other crops.

Lang *et al.* [48] described the conversion of atrazine into the racemic mixture of 2-chloro-4-ethylamino-6-(1-hydroxy-2-methylethyl-2-amino)-1,3,5-triazine by liver microsomes of rats, pigs, and humans. The authors reported on the dominance of the *R*-enantiomer in humans, while the higher concentrations of the *S*-enantiomer were observed in rats and pigs. A species-dependent enantioselective formation of this metabolite with *S*/*R* ratios of 76:24 in rats, 49:51 in pigs, and 28:72 in humans was stated. Similarly, *trans*-nonachlor, a major constituent of technical chlordane, is achiral, and the replacement of chlorine substituents by another atom or group can produce a chiral derivative. Further, malathion usually is biotransformed into racemic malaxon that exhibits anti-AChE (insecticidal) activity. For bovine erythrocyte cholinesterase, the antagonistic activity of the *R*-enantiomer is 22 times greater than for the *S*-enantiomer [49, 50].

Enantioselective Toxicities of Polychlorinated Biphenyls

Polychlorinated biphenyls (PCBs) are the most notorious class of chlorinated chiral pollutants. Although their use has been banned in many countries since the 1970s, these compounds still represent an important class of priority pollutants due to their long persistence, bioaccumulation, and toxicity [51]. About 209 PCB congeners are known, and out of them 78 are chiral in nature. Again out of these 78 PCB congeners only 19 form stable enantiomers (atropisomers) [52]. Different toxicities of these chiral PCBs have been described in terms of porphyria, teratogenicity, endocrine and reproductive malfunctions, *etc*. It has been reported that non-*ortho* coplanar PCBs exhibit the highest toxicities followed by the moderately toxic mono-*ortho* coplanar congeners, while di-*ortho*-substituted PCBs turned out to be less toxic. Ahlborg *et al.* [53] presented a toxic equivalency model to describe the toxicities of PCB congeners. The authors calculated the toxic equivalency factors (TEFs) for individual PCBs. Each PCB has been assigned a TEF value based on its toxicity relative to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), which has by definition a TEF of 1.00 (100%). Püttman *et al.* [54] reported PCB139 and PCB197 congeners as effective inducers of drug-metabolizing enzymes (e.g., cytochrome P-450 monooxygenases, CYPs; *N*-demethylase; and aldrin epoxidase). The authors described the (+)-enantiomer of PCB139 as the stronger inducer in comparison to the (−)-enantiomer. Contrarily, the racemic mixtures of PCB197 and its individual enantiomers are only weak inducers of these enzymes. Furthermore, in

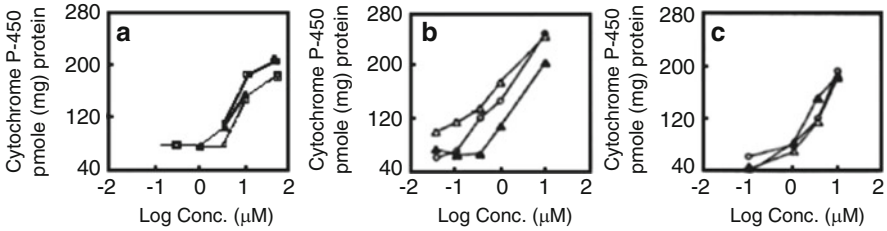

Fig. 4 Effects of the enantiomers of (**a**) PCB88, (**b**) PCB139, and (**c**) PCB197 congeners on the induction of total cytochrome P-450 enzymes (CYPs); (*triangle*) (+)-enantiomer, (*filled triangle*) (−)-enantiomer, and (*circle*) racemic mixture (from [55] with reprint permission of Elsevier)

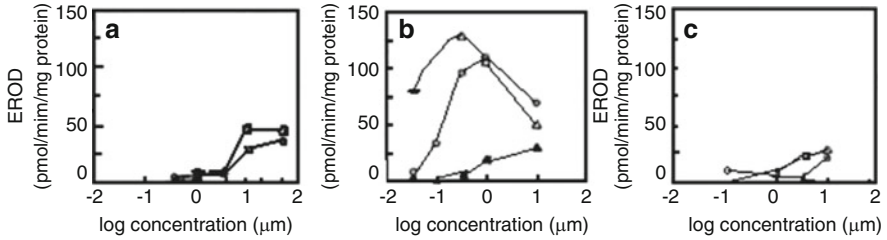

Fig. 5 Effects of the enantiomers of (**a**) PCB88, (**b**) PCB139, and (**c**) PCB197 congeners on the induction of ethoxyresorufin-*O*-deethylase (EROD) activity; (*triangle*) (+)-enantiomer, (*filled triangle*) (−)-enantiomer, and (*circle*) racemic mixture (from [55] with reprint permission of Elsevier)

1991, the same group reported activities related to the induction of CYPs, that is, the activity of ethoxyresorufin-*O*-deethylase (EROD) and benzphetamine-*N*-demethylase (BPDM) [55]. They demonstrated that EROD activity is induced to much greater extent by (+)-enantiomers of all of the congeners studied with no activities of the (−)-enantiomers of PCB88 and PCB197. The effects of the enantiomers of PCB88, PCB139, and PCB197 on the induction of total CYP enzymes and EROD and BPDM activities are shown in Figs. 4–6, respectively.

The effects of the enantiomers of PCB88, PCB139, and PCB197 on the accumulation of protoporphyrin and uroporphyrin (URO) chick embryo liver cell cultures are summarized in Table 10. The results indicate that URO accumulation occurred only at high concentrations (i.e., $\geq$1.0 μM) of PCB88 and PCB197, but at low concentrations of the PCB139 congener [$\geq$0.034 μM for (+)-PCB139 and $\geq$0.34 μM for (−)-PCB139]. The strongest URO accumulation occurred with PCB139, with 64% URO generated by the (+)-enantiomer and 47% URO generated by the (−)-enantiomer at the highest concentration tested.

PCB methyl sulfones ($MeSO_2$-PCBs) are metabolites of PCBs generated via the mercapturic acid pathway. Cleavage of the sulfur–carbon bond in the cysteine moiety, methylation, and oxidation of the methyl sulfide has been described by Bakke and Gustafsson [56]. These metabolites are more persistent and less hydrophobic

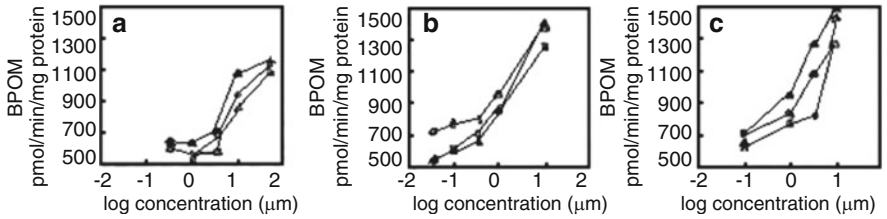

Fig. 6 Effects of the enantiomers of (**a**) PCB88, (**b**) PCB139, and (**c**) PCB197 congeners on the induction of benzphetamine-*N*-demethylase (BPDM) activity; (*triangle*) (+)-enantiomer, (*filled triangle*) (−)-enantiomer, and (*circle*) racemic mixture (from [55] with reprint permission of Elsevier)

Table 10 Concentrations of enantiomers of PCB88, PCB139, and PCB197 and induced accumulation of protoporphyrin and uroporphyrin in chick embryo liver cell culture [55]

Concentration (μM)	% Protoporphyrin		% Uroporphyrin (URO)	
	(+)-PCB88	**(−)-PCB88**	**(+)-PCB88**	**(−)-PCB88**
0.34	90.0	88.3	3.9	4.2
1.0	85.4	87.1	8.2	5.2
3.4	65.0	83.1	17.1	7.0
10.0	51.0	63.2	24.5	20.7
50.0	23.7	20.5	34.1	45.1
	(+)-PCB139	**(−)-PCB139**	**(+)-PCB139**	**(−)-PCB139**
0.034	85.7	89.6	7.0	4.1
0.1	83.5	89.1	8.6	4.1
0.34	84.8	84.6	8.5	8.0
1.0	68.3	81.5	22.1	10.7
10.0	19.8	37.9	63.5	46.6
	(+)-PCB197	**(−)-PCB197**	**(+)-PCB197**	**(−)-PCB197**
0.1	90.8	91.8	2.9	2.6
1.0	88.8	91.4	4.8	2.3
3.4	83.9	85.9	7.5	6.3
10.0	70.8	61.0	17.6	26.2

than their corresponding parents, which make them long-lasting contaminants of the biosphere. Several $MeSO_2$-PCBs have been shown to strongly induce CYP activity such as CYP2B2, 3A2, and 2C6. A study on the influence of $MeSO_2$-PCBs in the reproduction of minks (*Mustela vison*) indicated that $MeSO_2$-PCB and 1,1-dichloro-2-(*o*-chlorophenyl)-2-(*p*′-chlorophenyl)ethylene (DDE) methyl sulfone mixtures increased the litter size in these animals [57]. A strong respiratory distress and alterations in the immune status of yusho patients in Japan have been related to $MeSO_2$-PCBs [58]. There are several reports describing the toxicities of $MeSO_2$-PCBs, but, unfortunately, no report is available on the enantioselective toxicities of $MeSO_2$-PCBs. Furthermore, a Swedish and German collaborative project started in 1997 with the aim of studying enantioselective accumulation of $MeSO_2$-PCBs in the liver of humans and rats [36, 59], but data on the enantioselective toxicities are still missing.

Enantioselective Toxicities of Polycyclic Aromatic Hydrocarbons

Among the most toxic PAHs in the environment are β-naphthoflavone, benzo[*a*]-pyrene (BP), and anthracene and their derivatives. Toxicities of the racemic metabolites of PAHs are known for a long time, but only few reports are available on their enantioselective cytotoxic, mutagenic, and carcinogenic effects. In 1977, Levin *et al.* [60] studied the carcinogenic activity of *trans*-7,8-dihydroxy-7,8-dihydrobenzo[*a*]-pyrene (BP-7,8-dihydrodiol) on CD-1 mouse skin with 50, 100, and 200 nmols of each of the (+)- and (−)-enantiomers. It was observed that the (−)-enantiomer was more toxic than the (+)-enantiomer at all concentrations. The maximum tumor formation was observed after 21 weeks, with a 5–10 times higher carcinogenic activity of the (−)-enantiomer in comparison to the (+)-enantiomer. Furthermore, the same authors described the effect of BP-7,8-dihydrodiol on the skin of newborn mice, concluding the greater toxicity of the (−)-enantiomer. While the parent BP is not a carcinogen by itself, its metabolic products such as diol-epoxides are highly potent [61–66]. Two possible diastereoisomers originating from *trans*-BP-7,8-dihydrodiol were characterized [67], and one of them was shown to be an ultimate carcinogen in newborn mice [68, 69]. The diastereomer BP-7β,8α-dihydrodiol-9α,10α-epoxide (*anti*-BPDE) has been characterized as potent mutagen in bacteria and certain mammalian cells [70–72]. Wood *et al.* [73, 74] reported the (+)-enantiomer [i.e., (+)-BP-7β,8α- diol-9α,10α-epoxide, (+)-*anti*-BPDE] being four times more toxic in Chinese hamster cells than its (−)-antipode [(−)-*anti*-BPDE]. Slaga *et al.* [75] also studied the enantioselective carcinogenesis of *anti*-BPDE on mouse skin. According to the authors, the carcinogenic potency of the (+)- and (−)-*anti*-BPDE enantiomers were 60% and 2%, respectively. The results of this study are depicted in Fig. 7.

The stereoselective metabolism of BP toward its ultimate carcinogen occurs as follows: BP→BP-7,8-oxide→*trans*-BP-7,8-dihydrodiol→BP-7,8-diol-9,10-epoxide (BPDE). Chang *et al.* [76] reported that the (−)-enantiomer of BP-4,5-oxide was 1.5–5.5-fold more mutagenic than the (+)-enantiomer in bacterial strains of *Salmonella typhimurium* (TA98, TA100, TA1537, TA1538) and in Chinese hamster V79 cells. The authors reported when mixtures of the enantiomers were studied in V79 cells, synergistic cytotoxic and mutagenic responses could be observed. The most cytotoxic and mutagenic effects occurred with a 3:1 mixture of the (−)- and (+)-enantiomers of BP-4,5-oxide. Levin *et al.* [77] described that the (+)-BP-7,8-oxide showed greater enantioselective toxicity in the skin of newborn mice (see Table 11). It is interesting to note that the tumor formation potencies of BP-7,8-oxide were in the order: racemic mixture > (+)-enantiomer > (−)-enantiomer. The higher toxicity of the racemic mixture might be the result of catalytic interferences between the enantiomers.

Wood *et al.* [78] studied the enantioselective toxicities of four isomers of chrysene-1,2-diol-3,4-epoxide in bacterial (histidine dependent) strains of *S. typhimurium* and in mammalian (Chinese hamster V79) cells. In strain TA98 of *S. typhimurium*, the (−)-*anti*-chyrsene-1,2-diol-3,4-epoxide was 5–10 times more toxic compared to the other three isomers. However, in strain TA100 of these bacteria and in Chinese hamster V79 cells, (+)-*anti*-chyrsene-1,2-diol-3,4-

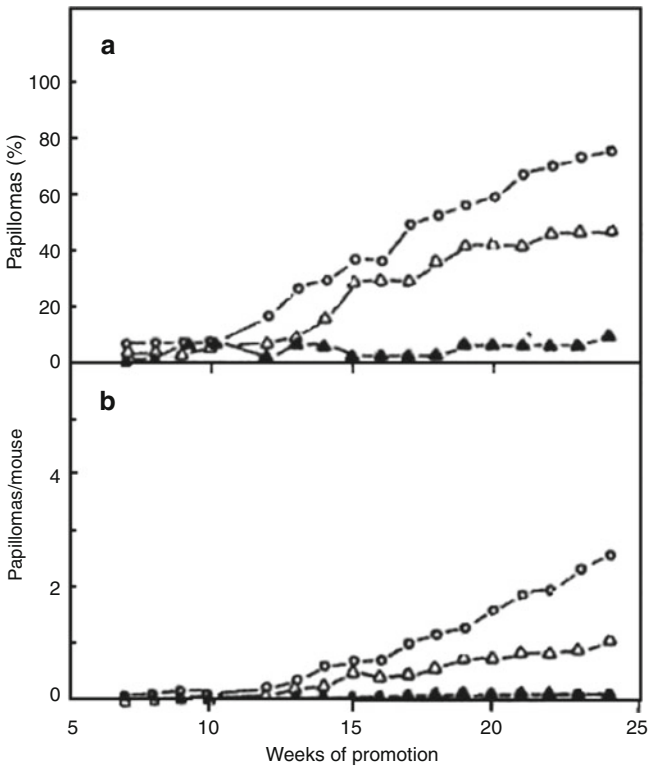

Fig. 7 Skin tumor-initiating activities of (*circle*) (+)-BP-7β,8α-diol-9α,10α-epoxide [(+)-*anti*-BPDE], (*filled triangle*) (−)-BP-7α,8β-diol-9β,10β-epoxide [(−)-*anti*-BPDE], and (*triangle*) racemic BP-7,8-diol-9,10-epoxide [(±)-*anti*-BPDE] in female CD-1 mice. A dose of 200 nmol of each compound was applied. (**a**) Percentage of papillomas; (**b**) Papillomas per mouse (from [75] with permission of American Association for Cancer Research—AACR)

Table 11 Chiral tumorigenicity of BP-7,8-oxide enantiomers (according to [77])

BP-7,8-oxide	Dose (nmol)	% of mice with tumors	No. of tumors per mouse
In adult mice			
(−)	100	11	0.11
	400	36	0.43
(+)	100	18	0.54
	400	55	1.03
(±)	100	50	0.83
	400	60	1.67
In newborn mice treated with 100, 200, and 400 nmol at the 1st, 8th, and 15th day of life			
(−)		21[a]	0.33
		20[b]	0.20
(+)		86[a]	1.82
		83[b]	2.57
(±)		93[a]	3.89
		86[b]	3.39

Female[a] and male[b] mice, respectively

Table 12 Chiral tumorigenicity of *trans*-1,2-dihydroxy-1,2-dihydrochrysene (chrysene-1,2-dihydrodiol) and *anti*-chrysene-1,2-diol-3,4-epoxide enantiomers in mouse skin (according to [79])

Compound	Dose (μmol)	% of mice with tumors	No. of tumors per mouse
(+)-Chrysene-1,2-dihydrodiol	0.4	3	0.03
	1.2	23	0.40
(−)-Chrysene-1,2-dihydrodiol	0.4	67	1.47
	1.2	83	2.77
(+)-*anti*-Chrysene-1,2-diol-3,4-epoxide	0.4	31	0.52
	1.2	60	1.47
(−)-*anti*-Chrysene-1,2-diol-3,4-epoxide	0.4	10	0.13
	1.2	23	0.33
(±)-*anti*-Chrysene-1,2-diol-3,4-epoxide	1.2	53	1.33

Table 13 Chiral pulmonary and hepatic carcinogenicity of *trans*-1,2-dihydroxy-1,2-dihydrochrysene (chrysene-1,2-dihydrodiol) and *syn*- and *anti*-chrysene-1,2-diol-3,4-epoxide enantiomers in newborn mice (according to [79])

Compound	Dose (μmol)	Pulmonary tumor		Hepatic tumor	
		% of mice with tumors	No. of tumor per mouse	% of mice with tumors	No. of tumors per mouse
(+)-Chrysene-1,	1.4[a]	20	0.22	0	0
2-dihydrodiol	1.4[b]	16	0.54	16	0.22
(−)-Chrysene-1,	1.4[a]	89	10.62	0	0
2-dihydrodiol	1.4[b]	95	7.41	57	2.3
(±)-Chrysene-1,	1.4[a]	89	3.78	0	0
2-dihydrodiol	1.4[b]	84	3.32	26	0.68
(+)-*syn*-Chrysene-1,	0.7[a]	21	0.21	0	0
2-diol-3,4-epoxide	0.7[b]	18	0.20	3	0.03
(−)-*syn*-Chrysene-1,	0.7[a]	27	0.27	0	0
2-diol-3,4-epoxide	0.7[b]	16	0.20	0	0
(+)-*anti*-Chrysene-1,	0.7[a]	88	6.59	0	0
2-diol-3,4-epoxide	0.7[b]	91	4.34	23	0.37
(−)-*anti*-Chrysene-1,	0.7[a]	8	0.08	0	0
2-diol-3,4-epoxide	0.7[b]	14	0.16	0	0

[a]Female and male[b] mice, respectively

epoxide was the most mutagenic diol-epoxide and about 5–40 times more active than the other three optical isomers. Furthermore, the same group studied the enantioselective toxicities of *trans*-1,2-dihydroxy-1,2-dihydrochrysene (chrysene-1,2-dihydrodiol) and chrysene-1,2-diol-3,4-epoxides in two different mouse tumor models [79]. In the animals, the skin, pulmonary, and hepatic carcinogenicity of these chiral pollutants was investigated. Skin carcinogenicity is presented in Table 12. Table 13 summarizes the extent of pulmonary and hepatic tumor formation in newborn mice.

Table 12 shows that only 3% tumors were found when (+)-enantiomer of chrysene-1,2-dihydrodiol was injected, while 67% carcinogenicity was observed with the (−)-enantiomer. Contrarily, the tumor-initiating activity of (+)-, (−)-, and (±)-chrysene-1,2-diol-3,4-epoxides (at a dose of 1.2 μmol each) was 21%, 13%, and 25%,

respectively. Again, the toxicity of the racemic mixture was greater than the effects seen for (−)- and (+)-enantiomers, which might be due to the interference of both enantiomers with each other. A perusal of Table 13 indicates that again the (−)-*trans*-chrysene-1,2-dihydrodiol is more toxic than its (+)-antipode in both male and female mice.

Benz[*a*]anthracene(BA)-3,4-diol-1,2-epoxide (BADE) results from regio- and stereoselective metabolism of BA. The tumorigenic activities of the (+)- and (−)-enantiomers of *trans*-3,4-dihydroxy-3,4-dihydrobenz[*a*]anthracene (BA-3,4-dihydrodiol) and racemic diastereomers of BADE were studied in newborn Swiss-Webster mice [80]. Furthermore, Tang *et al.* determined the tumorigenic potencies of racemic *syn*- and *anti*-7,12-dimethylbenz[*a*]anthracene(DMBA)-3,4-diol-1,2-epoxides (DMBADE) via the two-stage initiation–promotion protocol in mouse skin [81]. They observed that both *syn*- and *anti*-DMBADE were active tumor initiators and that the occurrence of papillomas was dependent on the dose of carcinogen applied.

Enantioselective Toxicities of Algae Toxins

Tetrodotoxin and saxitoxin are major marine toxic chiral pollutants. The toxic effects of saxitoxin have been observed in some part of the world, and, hence, sometimes filter-feeding shell fish industries have been affected. It has also been reported that the marine environment is rich with (−)-enantiomer of saxitoxin. Other chiral neurotoxins (anatoxin, homoanatoxin, *etc.*) are produced in the aquatic environment as well [82]. Therefore, sometimes, water becomes toxic due to the presence of these compounds, and several reports have been published on the death of cattle and dogs due to intoxication [83, 84]. Accordingly, the presence of these toxic chiral pollutants may be health threatening for humans as well. Unfortunately, no reports have been published on the enantioselective toxicities of these toxins yet.

Enantioselective Toxicities of Drugs and Pharmaceuticals

A myriad of different drugs are being used by people, and among them a great part is chiral in nature. Therefore, the presence of such types of drug enantiomers in the environment may be problematic and hazardous. Weigel [14] reported on the presence of several drugs in aquatic environments at high concentrations. Kümmerer [85] reported the presence of several drugs in surface, ground, and drinking water. In 1960, thalidomide [(*R,S*)-*N*-(2,6-dioxo-3-piperidyl) phthalimide] was introduced as a sedative drug in Europe, and, unfortunately, teratogenic effects of this drug occurred in embryos due to the highly toxic *S*-enantiomer [86]. Ifosfamide is a cyclophosphamide analog, which possesses toxicity that is enantioselective in nature. Masurel *et al.* [87] studied the enantioselective toxicity of this drug in rats. The authors injected the racemate and the enantiomers separately into nontumor-

bearing rats at doses of 550–650 mg/kg. The mean weight loss (at highest dose) was 30%, 20%, and 17% for the (+)- and (−)-enantiomers and the racemic mixture of ifosfamide, respectively. Furthermore, the authors observed signs of acute bladder toxicity, as blood was reported in the urine of rats when (−)-ifosfamide was injected. Similarly, there are several other drugs whose enantiomers are selectively toxic. L-DOPA has long been introduced for the treatment of Parkinson's disease, albeit D-DOPA turned out to be toxic [88, 89]. In 1986, Domino [90] described enantioselective opioid hallucinogen interactions of *N*,*N*-dimethyltryptamine and lysergic acid *N*,*N*-diethylamide in rats.

Conclusions

It is clear from this chapter that the chirality plays an important role in environmental toxicology affecting our lives. The chiral pollutants are widely distributed. Enantioselective toxicities have been reported for several xenobiotics in the earth ecosystem. In spite of this, scientists have only rarely been attracted toward this problem, and only few groups are addressing this issue. Therefore, there is still an urgent need to more comprehensively explore the enantioselective toxicities of chiral pollutants. The existing toxicological data of pollutants, mostly pertaining to their racemic forms, must be refined in terms of enantioselective toxicities. Even achiral pollutants are sometimes metabolized into chiral follow-up products, and, therefore, the study of these chiral species is a demanding field. Analysis of the specific toxicities of the chiral pollutants is essential and may be useful for controlling certain adverse health effects and diseases. In summary, the role of chirality in environmental toxicology is a burning area and needs more attention of the world's scientists for the welfare of human beings.

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