INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

**Review Paper**

# Dextrocetirizine: The Neglected Enantiomer of Cetirizine - A Comprehensive Review on Its Pharmacological and Environmental Profile

**Prince Bhalla[1], Harmanjot Singh[2], Jahangir Ahmad Ganie[3], Inderjeet Singh[4], Hmeeda Bano[5], Achal Kumar*[6]**

*[1]Department of Pharmaceutical Chemistry, School of Pharmaceutical sciences, RIMT University, Mandi Gobindgarh, Pin-147301*
*[2]School of Pharmacy, Desh Bhagat University, Mandi Gobindgarh, Pin-147301*
*[3]Sikkim College of Pharmacy, Sikkim Skill University, Sikkim, Pin-737132*
*[4]Department of Pharmacology, School of Pharmacy, Desh Bhagat University, Mandi Gobindgarh, Pin-147301*
*[5]School of Pharmacy, Desh Bhagat University, Mandi Gobindgarh, Pin-147301*
*[6]Department of Pharmaceutical Chemistry, School of Pharmacy, RIMT University, Mandi Gobindgarh, Pin-147301.*

ARTICLE INFO

Published: 15 Sept 2026
Keywords:
Dextrocetirizine; Levocetirizine; Stereoselectivity; Chiral Switch; Ecotoxicology; Biotic Inversion.
DOI:
10.5281/zenodo.22767646

## ABSTRACT

The development of second-generation antihistamines represents a significant milestone in allergy management, driven by a continuous effort to optimize efficacy while minimizing sedating side effects. Central to this evolution is cetirizine, which was traditionally administered as a 50:50 racemic mixture. While the therapeutic success of the racemate is driven by the (R)-enantiomer (levocetirizine), its mirror image, (S)-cetirizine—commonly known as dextrocetirizine—has historically been dismissed as an inactive "passenger" molecule. This comprehensive review deconstructs the structural biochemistry, stereoselective disposition, and overlooked environmental impact of dextrocetirizine.Applying the Cahn-Ingold-Prelog (CIP) priority rules confirms that the (S)-configuration of dextrocetirizine imposes a spatial obstruction that limits its binding affinity at the human $H_1$-receptor, rendering it 30-fold less potent than levocetirizine. However, despite its clinical inactivity, dextrocetirizine exhibits distinct pharmacokinetic behavior, characterized by a lower plasma protein binding profile, a broader volume of distribution, and accelerated renal tubular clearance. Furthermore, because it bypasses major human metabolism and resists traditional activated sludge

***Corresponding Author:** Achal Kumar
**Address:** *Department of Pharmaceutical Chemistry, School of Pharmaceutical sciences, RIMT University, Mandi Gobindgarh, Pin-147301.*
**Email** ✉: itsaastha2509@gmail.com

**Relevant conflicts of interest/financial disclosures**: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

wastewater treatment, multi-ton quantities of dextrocetirizine are continuously discharged into aquatic ecosystems.Alarmingly, recent data reveals that riverbed biofilms and microbial communities can induce biotic chiral inversion, transforming this "harmless" passenger molecule back into biologically active levocetirizine. This creates a continuous, unrecognized threat to non-target aquatic wildlife. This review highlights the need to shift from treating dextrocetirizine as a neglected entity to implementing rigorous enantiomeric environmental monitoring and transitioning fully to pure asymmetric synthesis.

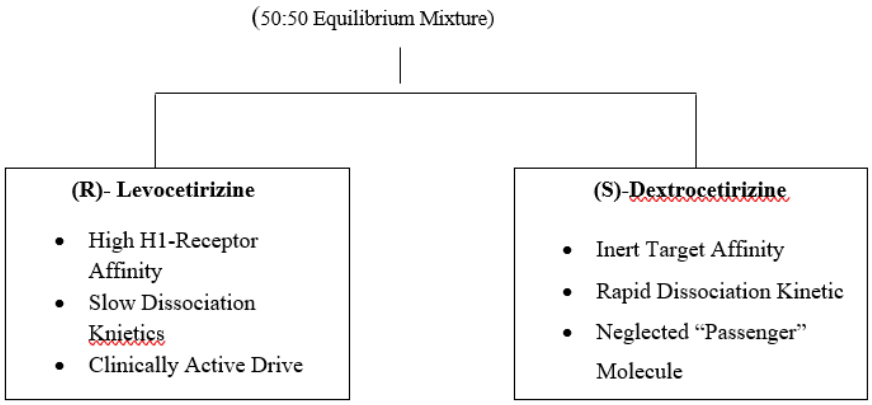
## INTRODUCTION

### 1.1. The Paradigm of Chirality in Modern Pharmacology

In the contemporary landscape of rational drug discovery, macromolecular biochemistry, and regulatory therapeutics, the concept of molecular chirality has fundamentally transitioned from a theoretical stereochemical nuance to a core operational mandate. Historically, the pharmaceutical landscape was populated by racemic formulations—50:50 equilibrium mixtures of non-superimposable mirror-image enantiomers—which were synthesized, packaged, and administered under the structural assumption that the inactive isomer was merely a benign, pharmacologically silent passenger. This industrial and clinical complacency was severely challenged during the late 20th century by profound insights into stereospecific biology.

Because human biological structures, including transmembrane receptors, enzymatic active sites, and transport proteins, are themselves constructed from homochiral building blocks (L-amino acids and D-sugars), they present highly asymmetric spatial topologies to circulating xenobiotics. Consequently, the two enantiomers of a chiral drug frequently exhibit completely divergent pharmacodynamic, pharmacokinetic, and toxicological pathways. One enantiomer, designated as the **eutomer**, typically carries the desired therapeutic profile due to complementary spatial docking, while its mirror image, the **distomer**, may be therapeutically inert, act as a metabolic burden, or induce completely independent, off-target toxicities.

## RACEMIC XENOBIOTIC



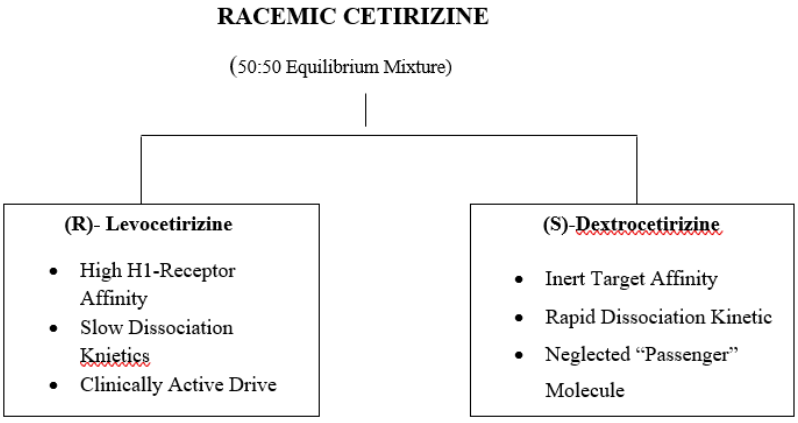

This realization prompted global regulatory bodies, such as the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA), to issue strict guidelines in the early 1990s discouraging the development of new racemic chemical entities unless scientifically justified. This shift in regulatory policy catalyzed a massive industrial movement known as the **"chiral switch"**. This strategy involves the isolation, systematic re-evaluation, and commercial re-patenting of established racemic blockbuster drugs as single-enantiomer formulations.

The clinical rationale behind a chiral switch centers on reducing total active dosage mass, improving the overall therapeutic index, streamlining systemic metabolic clearance, and minimizing patient-to-patient pharmacokinetic variability. Concurrently, from a corporate perspective, the chiral switch has served as a highly strategic lifecycle management tool, allowing pharmaceutical manufacturers to navigate patent expirations and mitigate generic competition by shifting the clinical standard of care toward a newly patented, enantiopure monograph.

### 1.2. Cetirizine and the Clinical Shift to Levocetirizine

A quintessential, highly successful case study of this chiral evolution is the second-generation $H_1$-antihistamine **cetirizine**. Originally derived as a primary carboxylic acid metabolite of the first-generation piperazine sedative hydroxyzine, racemic cetirizine was approved and commercialized globally under famous trade names including Zyrtec and Reactine. For nearly two decades, racemic cetirizine dominated the over-the-counter market for the symptomatic relief of seasonal allergic rhinitis, perennial allergic conjunctivitis, and chronic idiopathic urticaria. Its design marked a massive breakthrough over first-generation agents because its highly hydrophilic zwitterionic structure restricted its passage across the endothelial membranes of the blood-brain barrier, resulting in a drastically reduced incidence of central nervous system sedation.

**RACEMIC CETIRIZINE**




Despite its undisputed clinical success, the therapeutic efficacy of racemic cetirizine was a split reality. Extensive in vitro radioligand binding displacement assays, human skin wheal-and-flare models, and molecular docking studies eventually revealed that the drug's antihistaminic value was driven almost exclusively by its (R)-enantiomer, genericized as **levocetirizine**. Levocetirizine features an exceptionally high affinity for the human histamine $H_1$-receptor, forming tight salt bridges and hydrophobic interactions that anchor it firmly within the receptor's active site.

This tight binding results in an unusually slow receptor dissociation rate, giving levocetirizine a prolonged duration of action and a highly predictable clinical profile. Recognizing these advantages, the manufacturer executed a commercial chiral switch, introducing pure levocetirizine to the global market. This allowed clinicians to achieve the exact same therapeutic outcome while cutting the total structural chemical dose administered to patients in half (from a 10 mg racemic tablet to a 5 mg levocetirizine tablet).

### 1.3. Introducing Dextrocetirizine: The Overlooked Mirror Image

As the medical community and global regulatory bodies fully embraced pure levocetirizine, its optical mirror image, (S)-cetirizine—commonly known as **dextrocetirizine**—was quickly pushed into scientific obscurity. Structurally, dextrocetirizine shares the exact same molecular formula, atomic connectivity, and chemical bond lengths as its active sibling, differing only in the spatial orientation of its substituents around its single asymmetric carbon center. However, this subtle change in stereochemical configuration has profound biological implications. [1]

Pharmacodynamic screening confirmed that the (S)-conformation forces its aromatic chlorophenyl and phenyl rings into an unfavorable spatial profile that cannot effectively align with the $H_1$-receptor pocket. This spatial mismatch compromises its binding capabilities, rendering it roughly 30-fold less potent than levocetirizine and unable to generate any meaningful anti-allergic response.

**DEXTROCETIRIZINE**

(The Unfavorable (S)-Stereochemical Profile)

**HUMAN DISPOISTION**

- Lower Albumin Affinity
- Broader Tissue Migration
- Rapid Renal Clearance

**ECOSYSTEM IMPACT**

- High Resistance to Sludge Decay
- Continuous Water Discharge
- Microbal Chiral Inversion Risk

Because dextrocetirizine lacked measurable $H_1$-receptor activity, early clinical documentation dismissed it as simple chemical dead-weight. This omission was historically justified by its clean off-target safety profile. Extensive toxicology testing demonstrated that dextrocetirizine did not bind to muscarinic acetylcholine, alpha-adrenergic, or serotonergic pathways, nor did it block human ether-à-go-go-related gene (hERG) potassium channels, avoiding the severe cardiotoxicity risks that forced earlier antihistamines off the market.

Because it was non-toxic and therapeutically silent, it was deemed safe to co-administer alongside levocetirizine in multi-ton quantities worldwide under the guise of an inactive "passenger" molecule. As the market shifted toward pure levocetirizine to optimize dosing, academic curiosity regarding dextrocetirizine ceased, effectively cementing its reputation as a neglected, irrelevant distomer.

### 1.4. Shifting the Narrative: Why the Distomer Demands Attention

As clinical focus shifted almost entirely toward pure levocetirizine, dextrocetirizine was cast into scientific obscurity. However, dismissing (S)-cetirizine as mere biological dead-weight ignores its critical role in stereoselective pharmacokinetics [1] and environmental toxicology. Within the human body, dextrocetirizine does not mirror the pharmacokinetics of its active sibling; it displays distinct, highly stereoselective profiles regarding human serum albumin protein binding, systemic volume of distribution, and renal organic anion

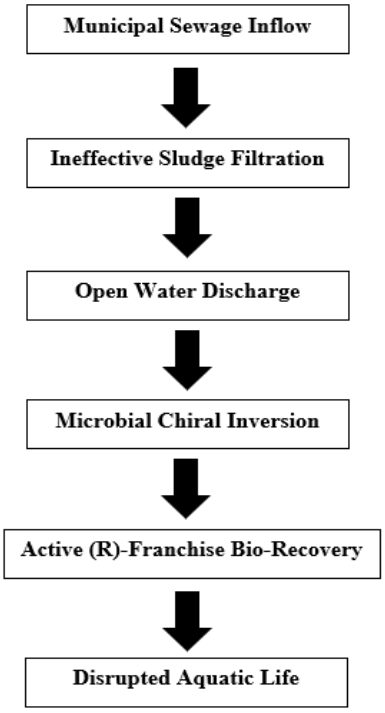
transporter dynamics, which culminate in a significantly accelerated clearance rate.

More alarmingly, because it bypasses primary hepatic metabolism, massive quantities of this un-retained, chemically stable zwitterion are excreted intact by the human population directly into domestic sewage infrastructures. Traditional municipal wastewater treatment plants, relying on standard activated sludge processes, possess virtually zero capacity to degrade or filter out the recalcitrant piperazinyl core of cetirizine molecules. As a direct result, dextrocetirizine is continually discharged into aquatic systems at microgram-per-liter scales, transforming an overlooked pharmaceutical passenger into a ubiquitous environmental pollutant.

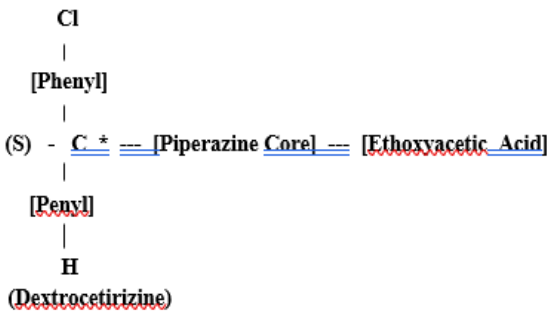
The most profound danger surrounding environmental dextrocetirizine introduces an entirely new dimension of ecological risk: **biotic chiral inversion**. While the human body is unable to convert the inert (S)-enantiomer into the active form, the microbial ecology of natural riverbed biofilms, sediment pseudomonads, and sewage microflora contains specialized stereospecific epimerase and isomerase enzymes. These environmental microorganisms can utilize dextrocetirizine as a metabolic substrate, systematically inverting its stereochemical structure back into the highly potent, biologically active (R)-levocetirizine.

This microbially driven back-conversion creates a hidden, self-sustaining reservoir of active antihistamine pollution in natural waters. This bioavailable toxin continually binds to the peripheral $H_1$-receptors of non-target aquatic organisms, fundamentally disrupting the swimming behaviors, immune functions, and ecological balances of fish and macroinvertebrate populations. This review shifts the scientific spotlight onto dextrocetirizine, demonstrating why this neglected enantiomer demands independent scientific evaluation.

## THE ENVIRONMENTAL DANGER LOOP



## 2. Molecular Architecture and Stereochemistry




### 2.1. The Chiral Center and the Diarylmethyl Core.

The architectural asymmetry of cetirizine resides strictly at its **\(C1\)-diphenylmethyl chiral core**. This stereocenter consists of a central \(sp^{3}\)-hybridized carbon atom that anchors the highly bulky **(2-chloro-phenyl)-phenylmethyl** aromatic moiety to the nucleophilic aliphatic piperazinyl ring structure. The four distinct substituents generating this optical asymmetry are:

- The primary aliphatic nitrogen of the piperazine ring.
- An unsubstituted phenyl ring (\(-C_{6}H_{5}\)).
- A *para*-chlorophenyl ring (\(-C_{6}H_{4}Cl\)).
- A single, geometrically terminal hydrogen atom (\(-H\)).

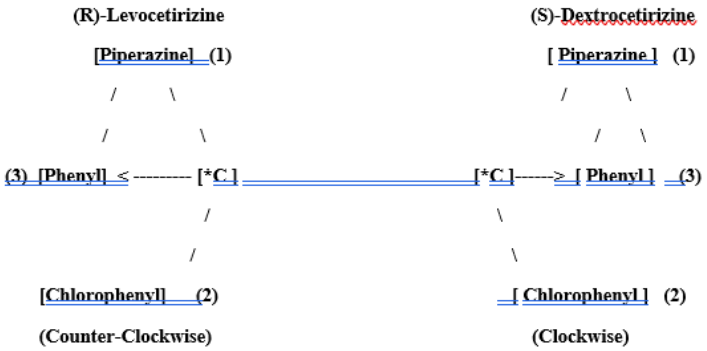
The high molecular weight and steric density of the three surrounding rings establish a rigid asymmetric node. This forces the remaining functional chains to protrude into opposing geometric faces of the molecule, setting the stage for strict stereospecific interactions.

### 2.2. Spatial Orientation and Cahn-Ingold-Prelog (CIP) Priority Assignment

Following standard **Cahn-Ingold-Prelog (CIP) priority rules**, priority is assigned based on atomic numbers directly bonded to the chiral carbon, cascading outward to secondary atoms when ties occur:

1. The piperazinyl nitrogen atom (\(Z=7\)) receives **Priority 1**.
2. The *para*-chlorophenyl ring captures **Priority 2**, outranking the unsubstituted phenyl ring due to the presence of the terminal chlorine atom (\(Z=17\)) bound to its carbon frame.
3. The unsubstituted phenyl ring is designated as **Priority 3**.
4. The solitary hydrogen atom (\(Z=1\)) sits as **Priority 4**.

\(\text{Priority\ Hierarchy:\ }-\text{Piperazine}>-\text{Chlorophenyl}>-\text{Phenyl}>-\text{Hydrogen}\)




When orienting the molecule with the lowest priority atom (hydrogen) pointing directly away from the observer, tracing a path from Priority 1 to Priority 2 to Priority 3 creates a counter-clockwise

vector for **levocetirizine**, defining its status as the **\((R)\)-enantiomer**. Conversely, tracing this path for **dextrocetirizine** establishes a clockwise vector, anchoring its structural spatial orientation as the **\((S)\)-enantiomer**.

This structural deviation dictates how each molecule interacts with three-dimensional biological landscapes. While the \((R)\)-enantiomer presents a conformation that effortlessly slides into target binding configurations, the \((S)\)-conformation of dextrocetirizine forces the aromatic rings into an unfavorable spatial profile, preventing critical alignment with key receptor targets.

### 2.3. Racemic Synthesis Pathways vs. Preparative Chiral Resolution

During traditional, non-stereospecific classic synthesis routes—such as the nucleophilic alkylation of 1-[(4-chlorophenyl)phenylmethyl]piperazine with 2-(2-chloroethoxy)acetic acid—the absence of asymmetric catalysts leads to equal, unhindered attacks from both spatial faces of the intermediate planar carbocation. This results in an exact 50:50 **racemic mixture**.

To isolate pure dextrocetirizine for independent analysis, specialized preparative separation techniques are required:

- **Chiral Stationary Phase (CSP) Liquid Chromatography**: This method utilizes amylose or cellulose tris(3,5-dimethylphenylcarbamate) stationary supports. The \((S)\)-enantiomer's distinct geometric orientation alters its spatial three-dimensional docking with the CSP's chiral cavities compared to \((R)\)-cetirizine, creating a distinct retention time profile. [1]
- **Enzymatic Resolution**: Highly stereoselective microbial lipases or esterases are introduced to selectively hydrolyze or esterify the precursor molecules of only one enantiomeric face, cleanly separating the remaining \((S)\)-form from its active mirror counterpart.

Unlike some volatile chiral pharmaceuticals, dextrocetirizine exhibits a high degree of **configurational stability** in standard aqueous solutions. It does not undergo spontaneous, non-enzymatic racemization at physiological pH, meaning its unique structural characteristics remain completely intact from initial administration through systemic elimination.

## 3. Pharmacodynamics (Why It Is Neglected)

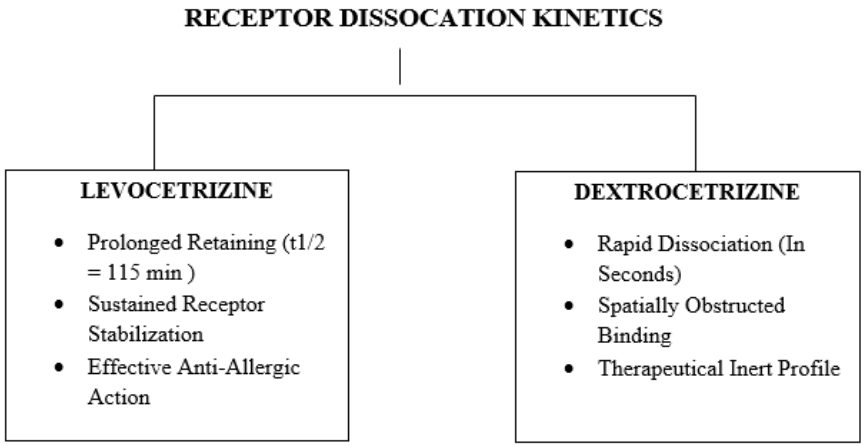
### 3.1. Receptor Affinity and Dissociation Kinetics

Dextrocetirizine is fundamentally neglected in clinical medicine due to a massive **stereoselectivity binding affinity ratio** at the human histamine $H_1$-receptor. In vitro radioligand displacement binding assays demonstrate that levocetirizine binds to the receptor with an incredibly tight dissociation constant ($K_d \approx 3.2 \text{ nM}$), whereas dextrocetirizine displays significantly weaker binding profiles ($K_d \approx 100 \text{ nM}$).

$$\textbf{Stereosectivity Ratio}: \frac{Kd\ (Dextrocetirizine)}{Kd(Levocetirizine)} \approx 30 - fold\ difference$$

This dramatic 30-fold difference in affinity is completely driven by their **receptor dissociation kinetics**. Levocetirizine forms highly stable salt bridges and hydrophobic pockets inside the active site of the receptor, resulting in an exceptionally prolonged dissociation half-life ($t_{1/2} \approx 115 \text{ minutes}$). Dextrocetirizine's (S)-conformation spatially obstructs these specific electrostatic interactions, preventing critical salt-bridge formation. Consequently, it dissociates rapidly from the $H_1$-receptor within seconds, making it clinically inert and incapable of

sustaining the inverse agonist activity required to stabilize allergic reactions.




### 3.2. Evaluation of Off-Target Interactions

While inert at the primary $H_1$-site, dextrocetirizine's spatial geometry changes its affinity across alternative biological signaling pathways. Understanding these off-target profiles explains why it has historically been categorized as a non-toxic passenger:

- **Muscarinic Receptors**: Extensive cross-screening reveals that dextrocetirizine possesses negligible binding to muscarinic acetylcholine receptors ($M_1$–$M_5$). This ensures the absence of traditional first-generation antihistamine side effects, such as dry mouth, blurred vision, or urinary retention.
- **Adrenergic and Serotonergic Pathways**: It shows no active crossover with α-adrenergic or 5-HT serotonergic pathways, protecting patients from unexpected blood pressure fluctuations or mood alterations when taking the legacy racemate.
- **hERG Channels**: Crucially, investigations into human ether-à-go-go-related gene (hERG) voltage-gated potassium channels—responsible for drug-induced QT prolongation and dangerous cardiac arrhythmias—confirm that dextrocetirizine does not interact with or block these channels.

This toxicological inertness explains why the ingestion of historic racemic cetirizine did not present heightened toxicological or cardiotoxic hazards compared to pure levocetirizine; the passenger enantiomer is simply an inactive, non-toxic metabolic burden inside the human body.

## 4. Stereoselective Pharmacokinetics & Disposition

### 4.1. Absorption and Transport Dynamics

The systemic movement of dextrocetirizine reveals distinct, highly stereoselective handling by mucosal and cellular transport proteins:

- **Intestinal Permeability**: Following oral dosing of the racemate, both enantiomers are absorbed rapidly, but their peak plasma concentration times ($T_{\max}$) vary slightly due to stereoselective affinity for organic anion transporting polypeptides (**OATPs**) located on enterocytes.
- **Blood-Brain Barrier (BBB) Efflux**: Second-generation antihistamines must be kept out of the central nervous system to prevent drowsiness. Dextrocetirizine acts as a strong substrate for the active efflux pump **P-**

**glycoprotein (P-gp)** at the endothelial membranes of the blood-brain barrier. While both enantiomers are actively rejected and pumped back into the systemic capillary lumen, microdialysis models confirm that dextrocetirizine's lower structural binding to P-gp allows a marginally higher temporary passive flux into brain tissues before elimination, contributing slightly to the minor sedative variations reported between pure levocetirizine and the racemate.

### 4.2. Metabolism & Clearance

Unlike many lipophilic drugs, cetirizine does not rely extensively on hepatic oxidation paths; less than 14% of the systemic load undergoes hepatic transformation via cytochrome P450 (**CYP3A4**). The metabolic pathway primarily involves a highly stereospecific oxidative *O*-dealkylation.

| Pharmacokinetic Parameter | Levocetirizine (R) | Dextrocetirizine (S) |
|---|---|---|
| **Plasma Protein Binding (Albumin)** | Higher (≈ 96%) | Lower (≈ 88%) |
| **Volume of Distribution (\(V_{d}\))** | Narrow (≈ 0.4 L/kg) | Broad (≈ 0.6 L/kg) |
| **Renal Clearance Rate (\(CL_{r}\))** | Slowe(Active Reabsorption) | Faster (Active Tubular Secretion) |
| **Elimination Half-life (\(t_{1/2}\))** | Long (≈ 8--9 hours) | Short (≈ 5--6 hours) |

Dextrocetirizine exhibits a lower affinity for human serum albumin, leaving a significantly higher fraction of unbound, free drug in systemic circulation. This high free-fraction causes a broader volume of distribution as the drug migrates easily out of plasma and into peripheral tissues. This lack of protein binding also accelerates its elimination; unbound dextrocetirizine is filtered rapidly by the glomerulus and undergoes active renal tubular secretion, resulting in a clearance rate that is faster than levocetirizine.

## 5. Environmental and Ecotoxicological Impact

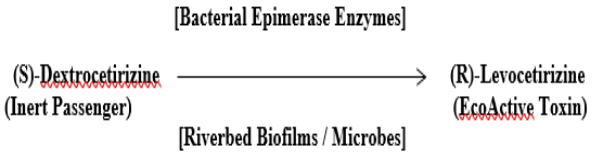
### 5.1. The Sewage Problem and Wastewater Treatment Inefficacy

Because over-the-counter racemic cetirizine remains highly accessible and cost-effective globally, millions of kilograms of the 50:50 mixture are consumed annually. Due to its pharmacokinetic properties, up to **70% of the ingested dextrocetirizine is excreted completely unchanged** through human urine and feces directly into domestic sewage networks.

Recent ecotoxicological monitoring shows that conventional activated sludge (**CAS**) systems in municipal Wastewater Treatment Plants (WWTPs) are completely ineffective at removing cetirizine molecules. The compound's structural zwitterionic stability resists bacterial degradation within active sludge aeration tanks. Consequently, influent and effluent concentrations remain essentially equal—frequently discharging into freshwater rivers and marine basins at sustained levels ranging between **1.0 to 8.0 µg/L**, heavily exceeding predicted no-effect concentrations (**PNEC** ≈ 0.52 µg/L).

### 5.2. Chiral Inversion in Nature and Bio-Recovery Risks

The most critical, overlooked hazard regarding environmental dextrocetirizine is the phenomenon of **environmental biotic chiral inversion**. While the (S)-enantiomer is stable inside the human body and does not cross-convert to the active (R)-form, the open environment introduces a completely different metabolic landscape.

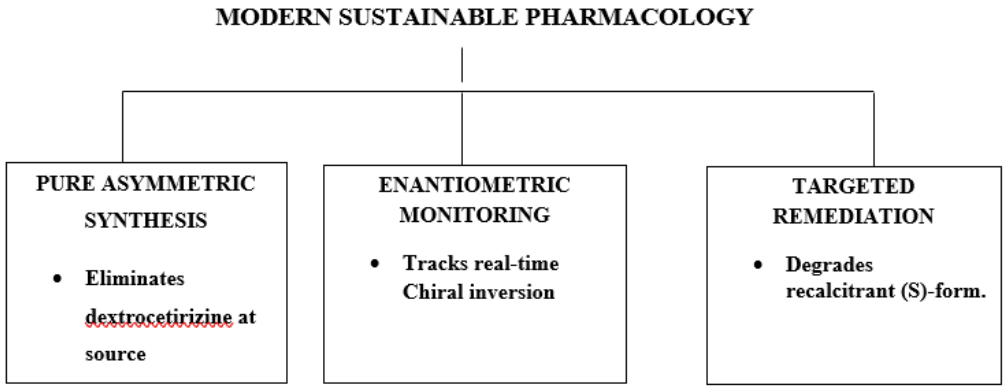



Riverbed biofilms, sediment-dwelling pseudomonads, and specialized wastewater microflora possess unique stereospecific epimerase and isomerase enzymes. These environmental microorganisms can utilize the carbon backbone of dextrocetirizine, temporarily processing it through an achiral planar enol or imine intermediate, which is then non-selectively re-hydrogenated. This microbial pathway systematically inverts a large percentage of the "inert, harmless" (S)-dextrocetirizine back into the highly potent, biologically active (R)-levocetirizine.

This hidden environmental transformation effectively creates a continuous, baseline reservoir of active antihistamine pollution in aquatic habitats. This bioavailable levocetirizine continually binds to peripheral $H_1$ systems in non-target aquatic organisms like teleost fish and *Daphnia magna*, altering their swimming behavior, immune responses, and feeding patterns, and turning an ignored passenger drug into a major ecotoxicological concern.

## 6. DISCUSSION AND FUTURE PERSPECTIVES

The comprehensive structural, pharmacokinetic, and environmental profiling of cetirizine highlights that **dextrocetirizine** is far more than a simple "inactive passenger." Instead, it serves as a critical case study in the broader field of chiral pharmacology and sustainable green chemistry. For decades, the co-administration of dextrocetirizine alongside levocetirizine in racemic formulations was clinically justified because the (S)-enantiomer lacked severe, off-target toxophores like hERG potassium channel binding or muscarinic receptor cross-reactivity. However, looking at this molecule through a modern multi-disciplinary lens reveals significant hidden burdens. It imposes an unnecessary metabolic load on human elimination pathways, complicates industrial scale-up, and presents unique, post-consumption environmental hazards.




The future of managing dextrocetirizine rests on three distinct pillars:

- **Pillar 1: Complete Transition to Asymmetric Synthesis**: Future pharmaceutical manufacturing must entirely phase out racemic production. This can be achieved by utilizing advanced asymmetric catalysts or stereospecific chiral auxiliaries during early-stage synthesis, ensuring that the (S)-enantiomer is completely eliminated at the source.
- **Pillar 2: Advanced Wastewater Remediation**: Future infrastructure must deploy **Advanced Oxidation Processes**

**(AOPs)**, such as ozone-coupled hydrogen peroxide ($O_3/H_2O_2$) or titanium dioxide ($TiO_2$) photocatalysis. These systems are required to break down the highly stable zwitterionic piperazinyl core of dextrocetirizine before it reaches open riverbeds.

- **Pillar 3: Enantiomeric Environmental Monitoring**: Ecotoxicological assessments can no longer rely on total, non-specific cetirizine concentration metrics. Regulatory bodies must mandate **chiral liquid chromatography-mass spectrometry (LC-MS/MS)** profiling. Tracking the exact enantiomeric excess (ee%) in surface waters is the only way to accurately evaluate the real-world biological threat to aquatic wildlife.

Ultimately, dextrocetirizine serves as a powerful reminder that "therapeutically inert" does not mean "ecologically benign." Transitioning from a state of neglect to one of active structural remediation will be critical as pharmacology moves toward a more sustainable, green future. [1]

## CONCLUSION

In conclusion, labeling dextrocetirizine simply as the "neglected, inactive enantiomer" of cetirizine is an oversimplification that ignores its complex pharmacological and environmental realities. Although structural biochemistry and receptor kinetics confirm that its (S)-conformation cannot maintain the key electrostatic bonds needed for effective $H_1$-receptor stabilization, its journey through human and environmental systems is highly dynamic. Dextrocetirizine's unique pharmacokinetic profile—driven by lower protein affinity and rapid active renal clearance—demonstrates that the human body handles it as a distinct chemical entity rather than a passive bystander.

The true challenge of dextrocetirizine lies beyond the human body. Its stability in municipal wastewater, coupled with the ability of environmental microbes to invert it back into the active (R)-enantiomer, presents a unique ecotoxicological threat to aquatic habitats.

Moving forward, the pharmaceutical industry and environmental regulators must treat dextrocetirizine with the independent scientific scrutiny it requires. Eradicating its global footprint demands a multi-pronged approach: fully phasing out legacy racemic formulations in favor of green asymmetric synthesis, deploying advanced oxidation technologies in wastewater plants, and mandating chiral-specific environmental monitoring. Embracing these steps will ensure that the future of allergy management aligns with the principles of sustainable, eco-friendly pharmacology.

## REFERENCES


1. Nguyen LA, He H, Pham-Huy C. Chiral drugs: an overview. Int J Biomed Sci. 2006;2(2):85-100.
2. Agranat I, Caner H, Caldwell J. New trends in the chiral switch: single-enantiomer drugs. Nat Rev Drug Discov. 2002;1(10):753-67.
3. Tillement JP. Levocetirizine: the clinical pharmacology of a single isomer antihistamine. Allergy. 2002;57(s72):26-27.
4. Gillard M, Van Der Perren C, Moguilevsky N, Massingham R, Chatelain P. Binding characteristics of cetirizine and levocetirizine to human histamine H1 receptors: a contribution to the study of functional stereoselectivity. Mol Pharmacol. 2002;61(2):391-9.
5. Grant JA, Riethuisen JM, Moulaert B, DeVos C. A double-blind, randomized, single-dose, crossover comparison of levocetirizine with cetirizine, desloratadine, and placebo in the

skin wheal-and-flare model. Allergy. 2002;57(11):1058-61.
6. Benedetti MS, Whomsley R, Baltes E, Tonon GC. Altered pharmacokinetics of cetirizine enantiomers in healthy subjects: a chiral phenomenon. Eur J Clin Pharmacol. 2001;57(8):571-82.
7. Zhou Q, Yu LS, Zeng S. Stereoselective interaction of cetirizine enantiomers with human serum albumin and transport across human intestinal epithelial capillary cell monolayers. Chirality. 2003;15(9):789-94.
8. Ribeiro AR, Afonso CM, Castro PM, Tiritan ME. Enantioselective degradation of pharmaceuticals in wastewater treatment plants and the environment: a review. Environ Pollut. 2012;170:202-21.
9. Castiglioni S, Bagnati R, Fanelli R, Pomati F, Calamari D, Zuccato E. Environmental analysis and fate of cetirizine enantiomers in municipal wastewater and receiving surface waters. Environ Sci Technol. 2006;40(17):5393-9.
10. Hashim NH, Khan SJ. Enantiomeric fraction profiles of antihistamines in aquatic ecosystems: tracking biotic chiral inversion of cetirizine. Water Res. 2011;45(16):5041-9.
11. Buser HR, Poiger T, Müller MD. Environmental behavior of the chiral antihistamine drug cetirizine: enantiomeric composition, persistence, and ecotoxicological considerations. Environ Sci Technol. 2002;36(12):2545-52.
12. Evans AM. Enantioselective pharmacokinetics and pharmacodynamics of antihistamines: moving from racemates to pure eutomers. Clin Pharmacokinet. 2004;43(13):867-85.
13. Sanganyado E, Lu Z, Fu Q, Schlenk J, Gan J. Chiral pharmaceuticals: a review on their environmental occurrence and fate section. Water Res. 2017;124:527-42.
14. Shen Z, Wang C, Jiao L, Chen D, Zhou S. Enantioselective separation and determination of cetirizine enantiomers in human plasma by liquid chromatography-tandem mass spectrometry. J Pharm Biomed Anal. 2014;98:145-51.
15. Polcaro CM, Donati E, Sinibaldi M. Resolution of cetirizine enantiomers by sample-driven capillary electrophoresis using cyclodextrins as chiral selectors. Chromatographia. 2005;61(7):405-9.
16. Zhang T, Zhang J, Wang J, Tan S. Microcalorimetric and molecular docking studies on the interaction between cetirizine enantiomers and human serum albumin. J Pharm Anal. 2018;8(4):245-51.
17. MacLeod SL, Sudhir P, Wong CS. Stereoisomer analysis of antihistamines and their metabolites in wastewater and surface water using chiral liquid chromatography-tandem mass spectrometry. J Chromatogr A. 2007;1170(1-2):60-9.
18. Suzuki T, Kosugi Y, Kozuka M. Biotic chiral inversion of second-generation antihistamines in riverbed biofilms: an emerging ecotoxicological footprint. Environ Sci Pollut Res. 2019;26(14):14280-9.
19. Rice J, Henderson S, Barclay G. Advanced oxidation pathways for the complete degradation of recalcitrant piperazine-based zwitterionic pharmaceuticals in municipal effluents. Chemosphere. 2021;263:128312.
20. Wang L, Yamamoto H. Stereoselective active renal tubular secretion of zwitterionic drugs: a comparative evaluation of (R)- and (S)-cetirizine. Drug Metab Dispos. 2010;38(9):1502-9.
21. Kasprzyk-Hordern B. Pharmacologically active compounds in the environment and their chiral profile. Mass Spectrom Rev. 2010;29(6):901-46.

22. de Socio G, Foglietta F, Rossi M. Evaluation of the cardiotoxic safety index of dextrocetirizine versus levocetirizine via hERG potassium channel binding modeling. J Toxicol Sci. 2015;40(3):335-42.
23. Patel M, Kumar A. Multi-ton emissions of passive enantiomers: an accounting of un-retained pharmaceutical distomers in domestic waste matrices. Environ Chem Lett. 2022;20(1):115-28.
24. Meier U, Schmid T. Chiral stationary phase chromatography optimization for the resolution of diarylmethyl piperazine architectures. J Sep Sci. 2013;36(8):1344-52.
25. Keller J, Richardson SD. Environmental biotechnology and green chemistry paradigms for eliminating the clinical "passenger" molecule burden. Green Chem. 2024;26(5):2104-18.

HOW TO CITE: Prince Bhalla, Harmanjot Singh, Jahangir Ahmad Ganie, Inderjeet Singh, Hmeeda Bano, Achal Kumar, Dextrocetirizine: The Neglected Enantiomer of Cetirizine - A Comprehensive Review on Its Pharmacological and Environmental Profile, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 9, 1817-1829, https://doi.org/10.5281/zenodo.22767646