# The role of halogen and chalcogen bonds in bioactivity and remediation of endocrine disrupting pollutants

*Valentina Dichiarante*, Gabriella Cavallo and Pierangelo Metrangolo**

Laboratory of Supramolecular and Bio-Nanomaterials (SupraBioNanoLab), Department of Chemistry, Materials, and Chemical Engineering "Giulio Natta", Politecnico di Milano, via L. Mancinelli 7, Milano, Italy.

***E-mail:** valentina.dichiarante@polimi.it, pierangelo.metrangolo@polimi.it*

**Abstract**

Endocrine disrupting chemicals (EDCs) are natural or synthetic substances able to mimic, interfere with or block endogenous hormones, thus disrupting the normal function of the endocrine system. Most of them are largely applied in agriculture and industry. As a result, humans are chronically exposed to mixtures of EDCs. Their adverse effect on human health may appear long after exposure, making it difficult to assess their full impact. Thus, understanding the molecular basis of recognition of suspected EDCs by their biological targets, is fundamental to get insight in their mechanism of action. This review will focus on the role of intermolecular interactions, specifically halogen and chalcogen bonds, in EDC recognition processes, offering an overview of the latest advances in the study of disruption mechanisms.

**Keywords:** Halogen bonding, chalcogen bonding, endocrine disruptors, bisphenols, thyroid, chlorinated pesticides.

## 1. Introduction

The development of agriculture and industry has often been accompanied by the release of large amounts of environmental contaminants with consequent severe potential risks for human health. In the last decades, increasing concern was raised by a family of harmful organic chemicals of anthropogenic origin, commonly classified as Persistent Organic Pollutants (POPs) [1]. Most POPs contain C-halogen bonds, whose strength and inertness make them resistant to (photo)chemical and biological degradations and results in half-lives of years. Such environmental persistency allows POPs to be taken up by plants and animals, where they accumulate in fatty tissues due to their high lipophilicity. For these reasons, although the Stockholm Convention has restricted, or in some cases even banned, production and use of several POPs, they still represent a huge environmental and health hazard [2]. Human exposure to these contaminants may occur by ingestion, inhalation or dermal uptake. Indeed, POPs can be present in food, due to absorption from the environment by raw starting materials or to artificial contamination during processing steps. The potential sources of food contamination by POPs and the main analytical approaches to measure their levels in food samples have recently been reviewed [3-4].

Many of these pollutants have been identified as Endocrine Disrupting Chemicals (EDCs) that are able to mimic, block or interfere with hormones and induce several related diseases, like cancer, diabetes, birth defects, immune and reproductive dysfunctions [5-8]. EDCs can also bind to plasma-transporting proteins and disrupt the hormonal activity in the bloodstream, decreasing the number of available protein binding sites for endocrine-signaling molecules, and even altering their homeostasis

[9]. Their adverse effects may display after long latency periods (up to years), or in the offspring of exposed subjects, making it difficult to assess their full impact on humans, although it is generally acknowledged that developing fetus and infants are the most vulnerable to endocrine disruption [10]. EDCs include different classes of compounds, among which the most common are phthalates, polychlorinated biphenyls (PCBs), polycyclic aromatic hydrocarbons (PAHs), dioxins, polybrominated diphenyl ethers (PBDEs), pesticides, nonylphenols, bisphenol derivatives, and perfluorinated chemicals. Most of them are added to hundreds of daily use products, such as plastic packages, children's toys, food, cosmetics, medical devices, detergents, textiles, and flame retardants, among others. As a result, humans are chronically exposed to mixtures of EDCs. Disinfection byproducts are another group of derivatives that may bind to various human serum proteins. Such byproducts are formed by the reaction of disinfectants used for water treatment (like chlorine, chlorine dioxide, chloramine, or ozone) with natural organic matter and mostly consist of halogenated phenols, benzaldehydes, or benzoic acids [11]. Selected representative molecular structures and main application fields or sources of EDCs are reported in Figure 1.

Given the long-term persistence and high bioaccumulation tendency of ED pollutants, several efforts are devoted to establish highly selective and sensitive analytical approaches for the detection of trace amounts of such contaminants, in order to support and complement classical methods based on chromatography and mass spectrometry. Recent advances in the development of specific sensors and biosensors, as well as in the application of nanostructured materials (*e.g.*, metal-organic frameworks, molecular imprinted polymers, carbon nanotubes, graphene, polymer nanocomposites, metal oxides, quantum dots) to the detection of EDCs in different sample matrices have been extensively reviewed [12-16]. In this context, understanding the molecular basis of recognition of suspected EDCs by their biological targets, might help the design of novel biomimetic platforms for sensing ED pollutants. This review will focus on the role exerted by halogen and chalcogen bonding in ED recognition processes, and will offer an overview of the latest advances in the study of disruption mechanisms, as well as their potential exploitation as EDC detection tools.

## 2. Biological targets of ED activity

Among the major targets vulnerable to ED interference, the most often attacked ones are the nuclear receptors (NRs), such as the estrogen and androgen receptors, the pregnane X receptor (PXR), and the thyroid receptors [17].

Concerning the former, some intensively used pesticides, like glyphosate, were shown to interfere with estrogen and androgen biosynthesis or signaling [18-19]. Bisphenol compounds, as well, can bind to estrogen receptors. In particular, their diglycidyl ether derivatives - used as monomers for epoxy-resins in food packaging materials - can migrate into aqueous and acidic foodstuffs during storage, where subsequent hydrolysis of epoxy groups produces cytotoxic, mutagenic, and genotoxic compounds [20]. As for the PXR, it is the principal mediator for the xenobiotic human response, being in charge of regulating the expression of detoxifying enzymes and controlling the clearance of many endogenous and exogenous chemicals. It can bind both high molecular weight compounds or small molecules, which can act as agonists or antagonists. It has been shown that different EDCs can also be accommodated simultaneously in its binding pocket producing a synergistic effect with dramatic changes in the activities of bound ligands [21].

The latter predominant target of endocrine disrupting activity is the interaction of thyroid hormones (THs) with thyroid receptors (TRs). Natural THs, namely 3,5,3’-triiodothyronine T3 and 3,5,3’,5’-tetraiodothyronine or thyroxine T4 (Figure 2A), are essential biomolecules that play a key

role in carbohydrate and fat metabolism, protein synthesis, overall growth, and brain development. Their activity is controlled by iodothyronine deiodinases (DIs), a family of enzymes containing a seleno-cysteine residue in their active site that are able to cleave iodine atoms at specific positions of THs. The thyroid gland predominantly produces thyroxine T4 as a pro-hormone, which is converted to the active form T3 by the regioselective removal of iodine in the 5′ position on the outer ring. EDCs may interfere with the thyroid function at different levels, resulting in the disruption of synthesis, transportation, bioavailability or metabolism of THs [7].

Whereas estrogen, androgen, and PXR receptors are able to bind a wide range of structurally different ED compounds, there is a limited structural diversity among those environmentally relevant contaminants able to modulate TR activity. Thyroid receptors are highly selective for THs and show a strong preference for similar hydroxylated diphenyl core structures [22].

## 3. Role of noncovalent interactions in ED recognition

As shown in Figure 2A, THs contain several iodine atoms that facilitate their selective binding to target receptors, confirming the potential and selectivity that a single atom substitution by a heavy halogen atom can induce in biomolecules, as well as the active role of halogens as biomolecular recognition sites [23-24]. At the same time, the fact that most EDCs are poly-halogenated molecules clearly suggest a direct involvement of halogen atoms in the recognition process, together with the contribution of the selenium atom present in the DI active site, which is key to the mechanism of iodine removal.

In a recent study, for example, the affinity of halogenated phenols and bisphenols for both human and zebrafish TRs was found to increase with increasing halogen atomic mass and radius, with iodinated compounds having the highest affinity. In both cases, TR affinity also increased with the degree of halogenation [25]. Moreover, the binding potency of phenolic disinfection byproducts to human transthyretin (hTTR) was investigated by combined *in-vitro* and *in-silico* methods. hTTR is the major carrier protein of THs across the placenta and the blood-brain barrier, and so the disruption of its transport processes may bring pollutants to normally inaccessible sites and induce deleterious health effects. This study confirmed that the most potent hTTR binders, with a binding affinity similar to that of T4, were at the same time aromatic, hydroxylated, and halogenated chemicals, able to give hydrogen bonding, electrostatic, and hydrophobic interactions with this protein [11].

In addition to these classical examples of noncovalent interactions, it is of fundamental importance the establishment of peculiar directional interactions that involve compounds containing elements of groups 16-17 as electron-deficient sites, and Lewis bases. Such interactions, resulting in interatomic contacts longer than covalent single bonds, but shorter than the sum of van der Waals radii of the involved atoms, are termed halogen bonding (XB) and chalcogen bonding (ChB) according to the elements involved (Figure 3A) [26-27]. They are defined as net attractive interactions between an electrophilic region associated with a halogen (group 17) or chalcogen (group 16) atom in a molecular entity (XB or ChB donor, respectively) and a nucleophilic region in another, or the same, molecular entity (XB or ChB acceptor) [28-30]. The understanding of XB and ChB role in ED pathways requires firstly to take into consideration their directionality, strength, and nature, as well as a comprehensive analysis of their competition with other noncovalent interactions. Quantum-chemical computations combined with rotational spectroscopy have been recently proposed for the full characterization of these intermolecular interactions from both structural and energetic points of view [31]. Even though the exact nature of XB and ChB is still under debate, the main components involved include charge-transfer, electrostatic, and orbital mixing contributions. The electrostatic factor is due to the presence of

σ-holes, regions of positive electrostatic potential located on the halogen/chalcogen atom (Figure 3B-C) [32]. The strength of the bond donor atom increases descending along the two groups of elements, in accordance with the analogous polarizability trend [33-34].

From the molecular structures of thyroid hormones T4 and T3, it strikingly appears that they are naturally occurring XB-donors. At the same time, the pivotal role exerted by seleno-cysteine in the active site of DIs suggested the possibility of the simultaneous establishment of ChB and XB interactions [35-38]. This hypothesis has recently been reinforced by further experimental evidence, showing that PBDEs and PCBs inhibited DIs by competitively binding to their seleno-cysteine residue through XB. Density functional theory (DFT) calculations were performed using methyl selenolate ($MeSe^-$) as a small model of the DI seleno-cysteine, and confirmed that the binding strengths followed the order THs > PBDEs > PCBs, in agreement with the known XB trend. The C-I bond in THs had the best orbital overlap with the Se donor, leading to high donor-acceptor energies and the greatest activation of the C-X bond. The higher orbital energy gaps of C-Br and C-Cl bonds in PBDEs and PCBs, respectively, resulted in weaker donor-acceptor complexes and weaker C-X activation [39]. Comparison of halogen···selenium interactions suggested the existence of a threshold of noncovalent bonding strength required for dehalogenation. The fact that PBDEs binding energies were in the same range as those of THs, made these compounds effective in inhibiting DIs and undergoing debromination. On the other hand, PCBs displayed weaker Cl···Se interactions with $SeMe^-$, which was consistent with the dependence of XB strength on the size and polarizability of the halogen atom (I > Br > Cl) [28].

To shed further light on the exact molecular mechanisms of DI-catalyzed deiodination, a series of organo-chalcogen compounds (containing S, Se or Te) were synthesized, and studied as potential functional mimics of deiodinase enzymes. Experimental and theoretical investigations revealed that naphthalene-based compounds containing sulfur and/or selenium at the *peri*-positions can effectively mediate the regioselective 5-deiodination of THs, facilitating heterolytic cleavage of the C-I bond by the formation of cooperative Se/S···I and Se/S···Se contacts (Figure 2B-C). DIs might also exploit the formation of Se···I bonding for increasing the polarization of C-I bonds [40].

Although most of the reported studies focused on the mechanism of TH activation, there is some evidence that XB-related interactions might be driving forces also in the disruption of estrogen-regulated processes. Trihalogenated methyl ($CX_3$)-containing bisphenols, for instance, were reported to work as agonists for estrogen receptor ERα end antagonists for ERβ, and their biological activity was found to increase in the order F < Cl < Br, supporting the idea that the interaction of bisphenol compounds with the binding pocket of estrogen receptors is strongly influenced by XB effect of their halogen-containing core moiety [41]. This has been further confirmed by a comparative structure-activity study revealing that bisphenol C, containing a vinylidene chloride moiety in the bisphenol backbone, is the most active ligand among bisphenols examined for estrogen receptors [42], which is fully consistent with the strength order observed for organic XB-donors: $C(sp)-X > C(sp^2)-X > C(sp^3)-X$ [28].

Recent studies demonstrated that XB is also involved in the interaction of chlorinated pesticides with nuclear receptors. A molecular docking simulation revealed that chlorpyrifos (CPF), a chlorinated organophosphorus pesticide, and its metabolites enter the binding pocket of human androgen receptor (AR) forming halogen bonding through the chlorine atoms. This produces conformational changes in the AR ligand binding domain, interfering with the binding of the endogenous AR ligand. [19]. Halogen bonding is also responsible for the high binding affinity of CPF towards serum albumin [9]. The estrogenic activity of thiacloprid, another chlorinated pesticide, can be also explained considering the XB occurring between the chlorine atom and some aminoacidic residues in the binding pocket of

the ER receptor (Figure 3D) [18]. Structural studies also revealed that oxadiazon, a chlorinated herbicide, can enter the binding pocket of PXR receptor forming a network of halogen bonds and van der Waals interactions and acting as a potent PXR agonist [21].

A deeper knowledge of the molecular mechanisms involved in the recognition, transport, activation and disruption steps of endocrine processes can be extremely useful also from the analytical point of view, allowing to design selective platforms for the detection and eventual removal of ED contaminants. A very recent work, for instance, reported the synthesis of a reticulated imine-based triazine-cored covalent organic framework with several N/O functional groups (TAPT-DMTA-COF, Figure 4), that was successfully tested as solid-phase extraction adsorbent for the recovery of PBDEs from water, milk, and fish samples. An outstanding adsorption performance was achieved, with low detection limits (0.03-0.13 ng/L) and short adsorption times (10 min). Both experiments and DFT simulations showed that XB between electronegative N/O atoms of TAPT-DMTA-COF and the electropositive Br atoms of PBDEs played a major role if compared to π-π, C-H···π, and hydrophobic interactions, as further confirmed by the positive linear relation between calculated adsorption energy and bromine content [43].

## 4. Outlook and perspectives

The accumulation of endocrine-disrupting compounds in the environment and in living tissues is strongly related to the occurrence of critical health problems in humans and animals, including neurological and developmental deficits, cancer, and reproductive disorders. For this reason, a deeper understanding of the exact mechanisms behind proper functioning of the endocrine system has significant environmental and toxicological implications. Cooperative halogen and chalcogen bonding between thyroid hormones and iodothyronine deiodinases appear to be of fundamental importance for the disruption of thyroid functioning, and similar halogen bond-based interactions seem to be at play also in the inhibition of estrogen receptors. Further research on these topics would allow not only the design of mimics that target specific binding proteins, but also “artificial receptors” for the recognition of hormone structural analogues with ED properties, or selective adsorption tools for environmental remediation.

## Conflict of interest statement

Nothing to declare.

## Acknowledgements

Authors are grateful for the financial support provided by the European Research Council (ERC) under the projects FOLDHALO (no. 307108) and MINIRES (no. 789815).

## References

Papers of particular interest, published within the period of review, have been highlighted as:
* of special interest
* * of outstanding interest


1. Ballschmiter K, Hackenberg R, Jarman WM, Looser R: **Man-made chemicals found in remote areas of the world: the experimental definition for POPs**. *Environ Sci Pollution Res* 2002, **9**:274.
2. Stockholm Convention. http://chm.pops.int/TheConvention/ThePOPs/tabid/673/Default.aspx (accessed 1 March 2021).
3. Guo W, Pan B, Sakkiah S, Yavas G, Ge W, Zou W, Tong W, Hong H: **Persistent organic pollutants in food: contamination sources, health effects and detection methods**. *Int J Environ Res Public Health* 2019, **16**:4361.
4. Chormey DS, Zaman BT, Kasa NA, Bakırdere S: **Liquid phase microextraction strategies and their application in the determination of endocrine disruptive compounds in food samples**. *Trends Anal Chem* 2020, **128**:115917.
5. Gonsioroski A, Mourikes VE, Flaws JA: **Endocrine disruptors in water and their effects on the reproductive system**. *Int J Mol Sci* 2020, **21**:1929.
6. Predieri B, Bruzzi P, Bigi E, Ciancia S, Madeo SF, Lucaccioni L, Iughetti L: **Endocrine disrupting chemicals and type 1 diabetes**. *Int J Mol Sci* 2020, **21**:2937.
7. Yilmaz B, Terekeci H, Sandal S, Kelestimur F: **Endocrine disrupting chemicals: exposure, effects on human health, mechanism of action, models for testing and strategies for prevention**. *Rev Endocr Metab Disord* 2020, **21**:127.
8. Nowak K, Jabłońska E, Ratajczak-Wrona W: **Immunomodulatory effects of synthetic endocrine disrupting chemicals on the development and functions of human immune cells.** *Environ Int* 2019, **125**:350.
9. Dahiya V, Anand BG, Kar K, Pal S: **Analyzing organophosphate pesticide-serum albumin binding interaction: a combined STD NMR and molecular docking study**. *J Biomol Struct Dyn* 2020, DOI: 10.1080/07391102.2020.1745280.
10. Street ME, Bernasconi S: **Endocrine-disrupting chemicals in human fetal growth**. *Int J Mol Sci* 2020, **21**:1430.
11. Yang X, Ou W, Xi Y, Chen J, Liu H: **Emerging polar phenolic disinfection byproducts are high-affinity human transthyretin disruptors: an in vitro and in silico study**. *Environ Sci Technol* 2019, **53**:7019.
12. Lu X, Sun J, Sun X: **Recent advances in biosensors for the detection of estrogens in the environment and food**. *Trends Anal Chem* 2020, **127**:115882.
13. Azzouz A, Kumar Kailasa S, Kumar P, Ballesteros E, Kim KH: **Advances in functional nanomaterial-based electrochemical techniques for screening of endocrine disrupting chemicals in various sample matrices**. *Trends Anal Chem* 2019, **113**:256.
14. Huang K, Wang X, Zhang H, Zeng L, Zhang X, Wang B, Zhou Y, Jing T: **Structure-directed screening and analysis of thyroid-disrupting chemicals targeting transthyretin based on molecular recognition and chromatographic separation**. *Environ Sci Technol* 2020, **54**:5437.

15. Wang H, Li J, Shi H, Xie S, Zhang C, Zhao G: **Enhanced photoelectrocatalytic reduction and removal of atrazine: effect of co-catalyst and cathode potential**. *ACS Appl Mater Interfaces* 2019, **11**:38663.

16. Araiza- Olivera D, Gutierrez-Aguilar M, Espinosa-García AM, García-García JA, Tapia-Orozco N, Sánchez-Pérez C, Palacios-Reyes C, Escárcega D, Villalón-López DN, García-Arrazola R: **From bench to bedside: biosensing strategies to evaluate endocrine disrupting compounds based on epigenetic events and their potential use in medicine**. *Environ Toxicol Pharmacol* 2020, **80**:103450.

17. Toporova L, Balaguer P: **Nuclear receptors are the major targets of endocrine disrupting chemicals.** *Mol Cell Endocrinol* 2020, **502:**110665.

18. Zhang C, Schilirò T, Gea M, Bianchi S, Spinello A, Magistrato A, Gilardi G, Di Nardo G: **Molecular basis for endocrine disruption by pesticides targeting aromatase and estrogen receptor**. *Int J Environ Res Public Health* 2020, **17**:5664.

19. Hazarika J, Ganguly M, Borgohain G, Sarma S, Bhuyan P, Mahanta R: **Disruption of androgen receptor signaling by chlorpyrifos (CPF) and its environmental degradation products: a structural insight.** *J Biomol Struct Dyn* 2021, DOI: 10.1080/07391102.2021.187588.

20. Zhang J, Lv C, Li Z, Guan T, Wang Y, Li T, Zhang T: **Interactions of bisphenol diglycidyl ether with estrogen receptors α: fluorescence polarization, reporter gene, and molecular modeling investigations**. *Toxicol Lett* 2020, **332**:14.

21. Delfosse V, Huet T, Harrus D, Granell M, Bourguet M, Gardia-Parège C, Chiavarin B, Grimaldi M, Le Mével S, Blanc P, Huang D, Gruszczyk J, Demeneix B, Cianférani S, Fini JB, Balaguer P, Bourguet W: **Mechanistic insights into the synergistic activation of the RXR–PXR heterodimer by endocrine disruptor mixtures.** *PNAS* 2021, **118**:e2020551118 e2020551128.

22. Paul-Friedman K, Martin M, Crofton KM, Hsu CW, Sakamuru S, Zhao J, Xia M, Huang R, Stavreva DA, Soni V, Varticovski L, Raziuddin R, Hager GL, Houck KA: **Limited chemical structural diversity found to modulate thyroid hormone receptor in the Tox21 chemical library**. *Environ Health Persp* 2019, **127**:097009.

23. European Research Council, Final Report Summary - FOLDHALO (Folding with Halogen Bonding). https://cordis.europa.eu/project/id/307108/reporting (accessed 1 March 2021).

24. Pizzi A, Pigliacelli C, Bergamaschi G, Gori A, Metrangolo P: **Biomimetic engineering of the molecular recognition and self-assembly of peptides and proteins via halogenation**. *Coord Chem Rev* 2020, **411**:213242.

25. * Kollitz EM, De Carbonnel L, Stapleton HM, Ferguson PL: **The affinity of brominated phenolic compounds for human and zebrafish thyroid receptor β: influence of chemical structure**. *Toxicological Sci* 2018, **163**:226.

* This study demonstrated that the binding affinity of common brominated phenolic compounds for human and zebrafish thyroid receptor TRβ increases with increasing halogen size and decreasing electronegativity, as well as increasing the degree of halogenation.

26. Desiraju GR, Ho PS, Kloo L, Legon AC, Marquardt R, Metrangolo P, Politzer P, Resnati G, Rissanen K: **Definition of the halogen bond (IUPAC Recommendations 2013)**. *Pure Appl Chem* 2013, **85**:1711.

27. Aakeroy CB, Bryce DL, Desiraju GR, Frontera A, Legon AC, Nicotra F, Rissanen K, Scheiner S, Terraneo G, Metrangolo P, Resnati G: **Definition of the chalcogen bond (IUPAC Recommendations 2019)**. *Pure Appl Chem* 2019, **91**:1889.

28. Cavallo G, Metrangolo P, Milani R, Pilati T, Priimagi A, Resnati G, Terraneo G: **The halogen bonding**. *Chem Rev* 2016, **4**:2478.

29. Metrangolo P, Resnati G: **Type II halogen···halogen contacts are halogen bonds.** *IUCrJ* 2014, **1**:5.

30. Vogel L, Wonner P, Huber SM: **Chalcogen bonding: an overview**. *Angew Chem Int Ed* 2019, **58**:1880.

31. Puzzarini C, Spada L, Alessandrini S, Barone V: **The challenge of non-covalent interactions: theory meets experiment for reconciling accuracy and interpretation**. *J Phys Condensed Matter* 2020, **32**:343002.

32. Politzer P, Murray JS, Clark T: **Halogen bonding and other σ-hole interactions: a perspective.** *Phys Chem Chem Phys* 2013, **15**:11178.

33. Berger G, Frangville P, Meyer F: **Halogen bonding for molecular recognition: new developments in materials and biological sciences**. *Chem Commun* 2020, **56**:4970.

34. Biot N, Bonifazi D: **Chalcogen-bond driven molecular recognition at work**. *Coord Chem Rev* 2020, **413**:213243.

35. Metrangolo P, Resnati G: **Halogen and chalcogen team up**. *Nature Chem* 2012, **4**:437.

36. Albers WM, Milani R, Tappura K, Munter T, Resnati G, Metrangolo P: **Self-Assembly of Pyridine-Modified Lipoic Acid Derivatives on Gold and Their Interaction with Thyroxine (T4).** *Int J Mol Sci* 2013, **14**:3500.

37. Manna D, Mugesh G: **Regioselective Deiodination of Thyroxine by Iodothyronine Deiodinase Mimics: An Unusual Mechanistic Pathway Involving Cooperative Chalcogen and Halogen Bonding** *J Am Chem Soc* 2012, **134**:4269.

38. Marsan ES, Bayse CA: **A halogen bonding perspective on iodothyronine deiodinase activity**. *Molecules* 2020, **25**:1328.

39. ** Marsan ES, Bayse CA: **Halogen bonding interactions of polychlorinated biphenyls and the potential for thyroid disruption**. *Chem Eur J* 2020, **26**:5200.

** By DFT analysis, the authors demonstrated that halogen bonding is involved in the recognition process of PCBs by iodothyronine deiodinases, and suggested the existence of a threshold of noncovalent bonding strength required for dehalogenation. PCBs do not meet this threshold and therefore act as deiodinase inhibitors by blocking their active site through a Cl···Se XB interaction.

40. Mondal S, Manna D, Raja K, Mugesh G: **Halogen bonding in biomimetic deiodination of thyroid hormones and their metabolites and dehalogenation of halogenated nucleosides**. *ChemBioChem* 2020, **21**:911.

41. ** Liu X, Suyamaa K, Shiki J, Torikai K, Nose T, Shimohigashi M, Shimohigashi Y: **Bisphenol AF: Halogen bonding effect is a major driving force for the dual ERα-agonist and ERβ-antagonist activities**. *Bioorg Med Chem* 2020, **28**:115274.

** This comparative structure-activity study demonstrated that halogen bonding is involved in the agonist/antagonist divalent function of halogenated bisphenols having trihalo-methyl substituents in their backbone.

42. * Liu X, Suyama K, Nose T, Shimohigashi M, Shimohigashi Y: **Bisphenol-C is the strongest bifunctional ERα-agonist and ERβ-antagonist due to magnified halogen bonding**. *PLoS ONE* 2021, **16**:e0246583.

* This paper showed that bisphenol C, containing a vinylidene chloride moiety in the bisphenol backbone, was an extremely active ligand for estrogen receptors, further strengthening the idea that halogen bonding drives the recognition of bisphenols derivatives by this family of receptors.

43. ** Liu L, Wang XX, Wang X, Xu GJ, Zhao YF, Wang ML, Lin JM, Zhao RS, Wu Y: **Triazine-cored covalent organic framework for ultrasensitive detection of polybrominated diphenyl ethers from real samples: experimental and DFT study**. *J Hazard Mater* 2021, **403**:123917.

** This paper reported the synthesis of a triazine-cored covalent organic framework successfully applied as solid-phase extraction adsorbent for the recovery of PBDEs from water, milk, and fish samples, with a remarkable adsorption performance. XB between electronegative N/O atoms in the COF scaffold and electropositive Br atoms of PBDEs played a major role in enhancing adsorption capacity.

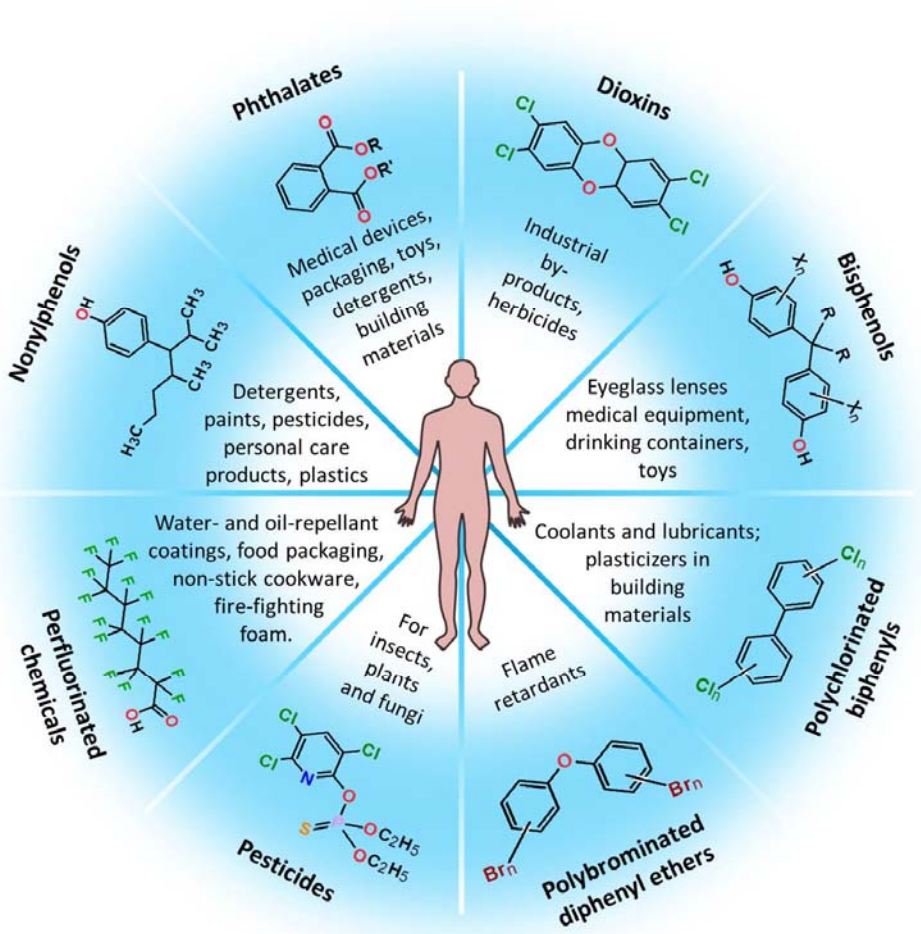


**Figure 1.** Selected classes of substances identified as endocrine disrupting chemicals and their main fields of application.

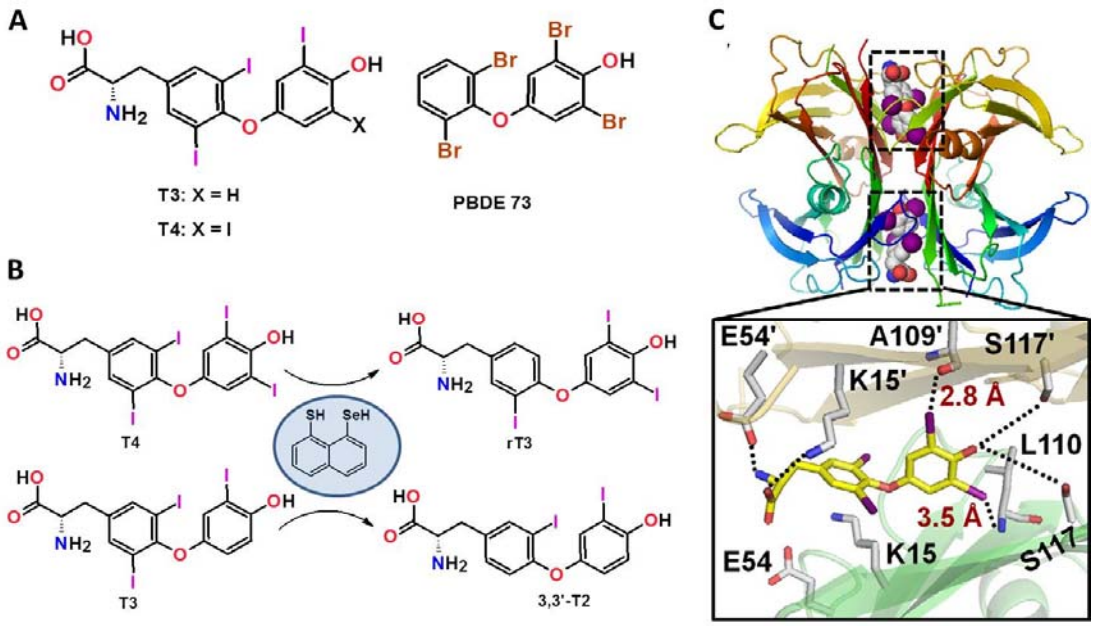


**Figure 2.** A) Molecular structures of natural thyroid hormones, T3 and T4, and poly-brominated diphenyl ether PBDE 73, highlighting their remarkable structural similarity. B) Deiodination of T4 and T3 in the presence of an iodothyronine deiodinase model compound containing a thiol and a selenol moiety at the *peri*-positions of a naphthalene ring. C) Crystal structure of the TTR·T4 complex (PDB ID: 2ROX). T4-binding sites are highlighted by boxes, with T4 shown in space-filling model. Adapted with permission from ref. 40 (Copyright 2020 John Wiley & Sons).

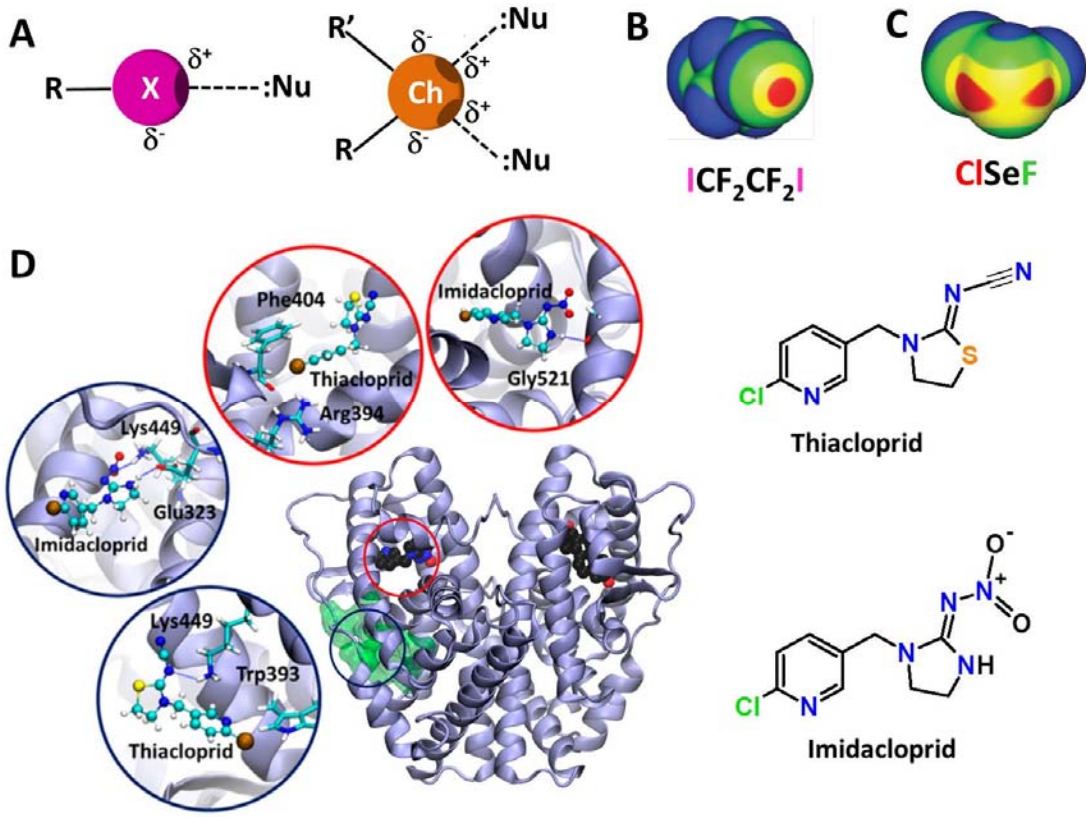


**Figure 3.** A) Schematic representation of the halogen bond (left) and chalcogen bond (right). B) Molecular surface of electrostatic potential of 1,2-diiodoperfluoroethane ($ICF_2CF_2I$) computed on the 0.001 au contour of electronic density. Iodine σ-hole is shown in red. Color code (in kcal/mol): red, > 25; yellow, between 15 and 25; green, between 0 and 15; blue, < 0 (negative). C) Molecular surface of electrostatic potential of SeFCl, computed on the 0.001 au contour of electronic density. Selenium is in the foreground, chlorine on the left and fluorine on the right. The two selenium σ-holes are shown in red. Color code (in kcal/mol): red, > 34; yellow, between 17 and 34; green, between 0 and 17; blue, < 0 (negative). Adapted with permission from ref. 32 (Copyright 2013 Royal Society of Chemistry). D) Model of the complex formed by estrogen receptor dimer (PDB ID: 1QKU) with imidacloprid and thiacloprid insecticides. The insets show a close view of docking poses of imidacloprid and thiacloprid inside the estrogen receptor binding site (red circles) and onto its recently identified allosteric pocket (blue circles). The Cl atom of thiacloprid makes halogen bonds with the guanidinium group of Arg394 and the aromatic rings of Phe404 and T393. Adapted with permission from ref. 18 (Copyright 2020 MDPI).

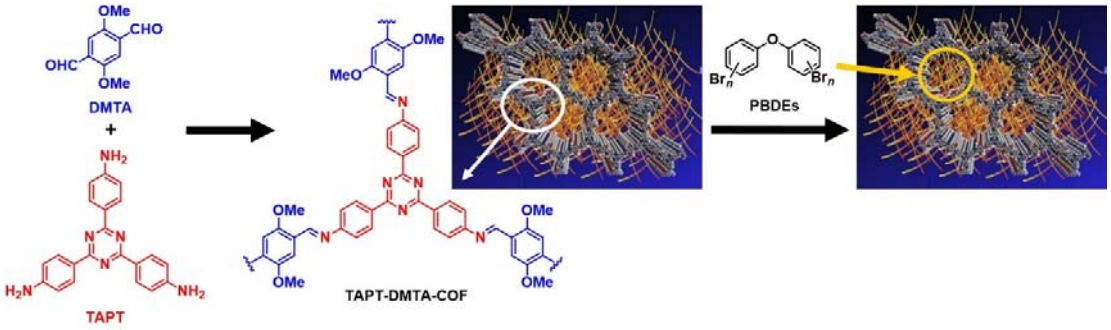


**Figure 4.** Synthesis of TAPT-DMTA-COF starting from 1,3,5-tris-(4-aminophenyl)triazine (TAPT) and 2,5-dimethoxyterephthalaldehyde (DMTA) and XB-mediated adsorption of PBDEs into its cavities. Adapted with permission from ref. 43 (Copyright 2021 Elsevier).

**Graphical abstract**