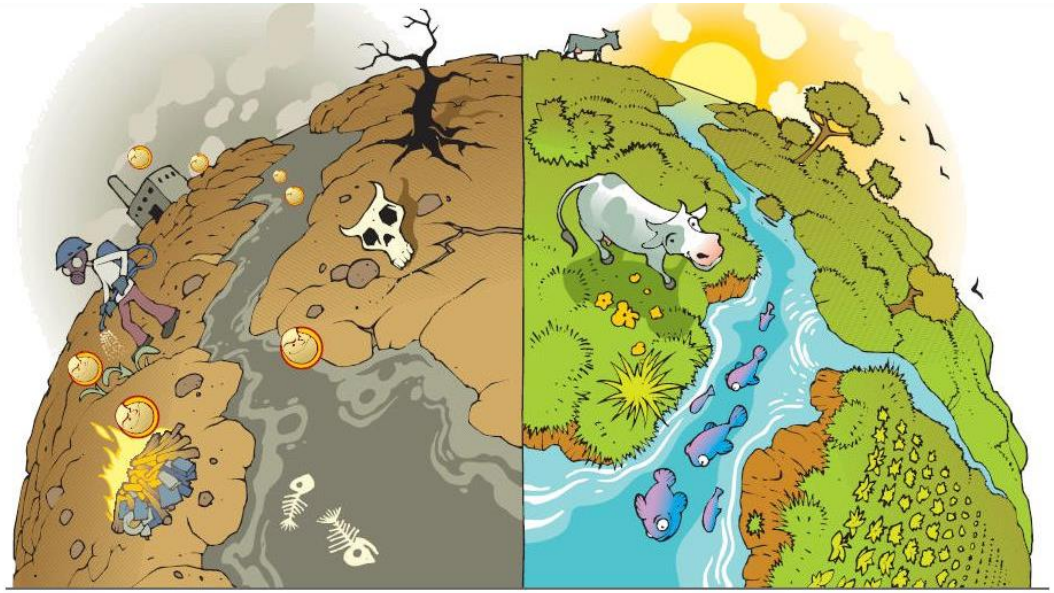
Universidade Vigo

IBER 2023

Theoretical-computational comparative study of the persistent organic pollutants: adsorption, detection and permeability



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Introduction

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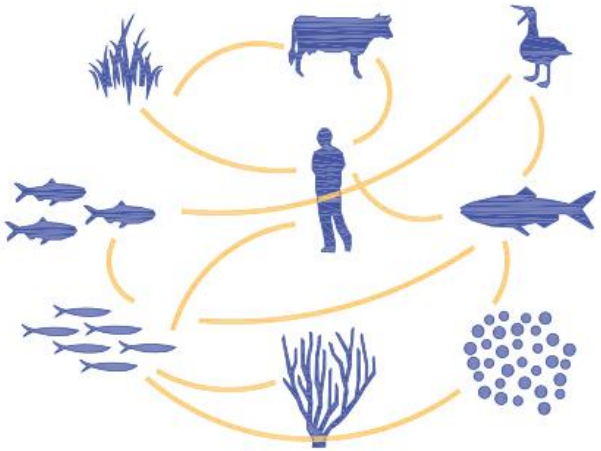
Why do persistent organic pollutants matter?

- **Persistent organic pollutants** (**POPs**) are hazardous chemicals that threaten human health and the planet's ecosystems.

Remain intact for **long periods of time**



Accumulate and magnify in living organisms through the food chain

Are **toxic** to both humans and wildlife

Become widely distributed throughout the environment

Introduction

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Why do persistent organic pollutants matter?

- **Persistent organic pollutants** (**POPs**) are hazardous chemicals that threaten human health and the planet's ecosystems.

long-term exposure even to low levels of POPs

- cancer risk
- reproductive disorders
- alteration of the immune system
- neurobehavioral impairment
- endocrine disruption
- genotoxicity
- increased birth defects.

Introduction

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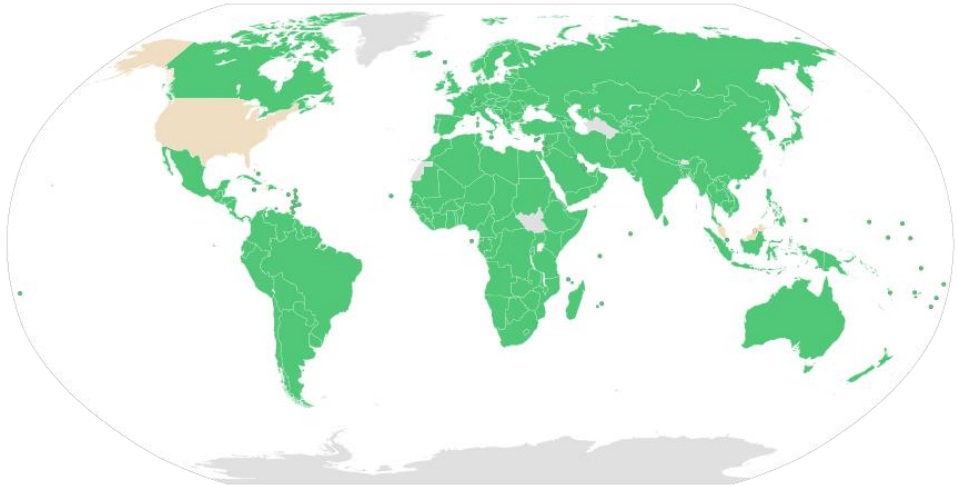
Why do persistent organic pollutants matter?

UNEP

A global treaty to protect human health and the environment from POPs

In 2004, the Stockholm Convention on persistent organic pollutants calls for reduction or elimination of releases of POPs globally.

Stockholm Convention on persistent organic pollutants (POPs)



To date, 185 countries have ratified the Convention

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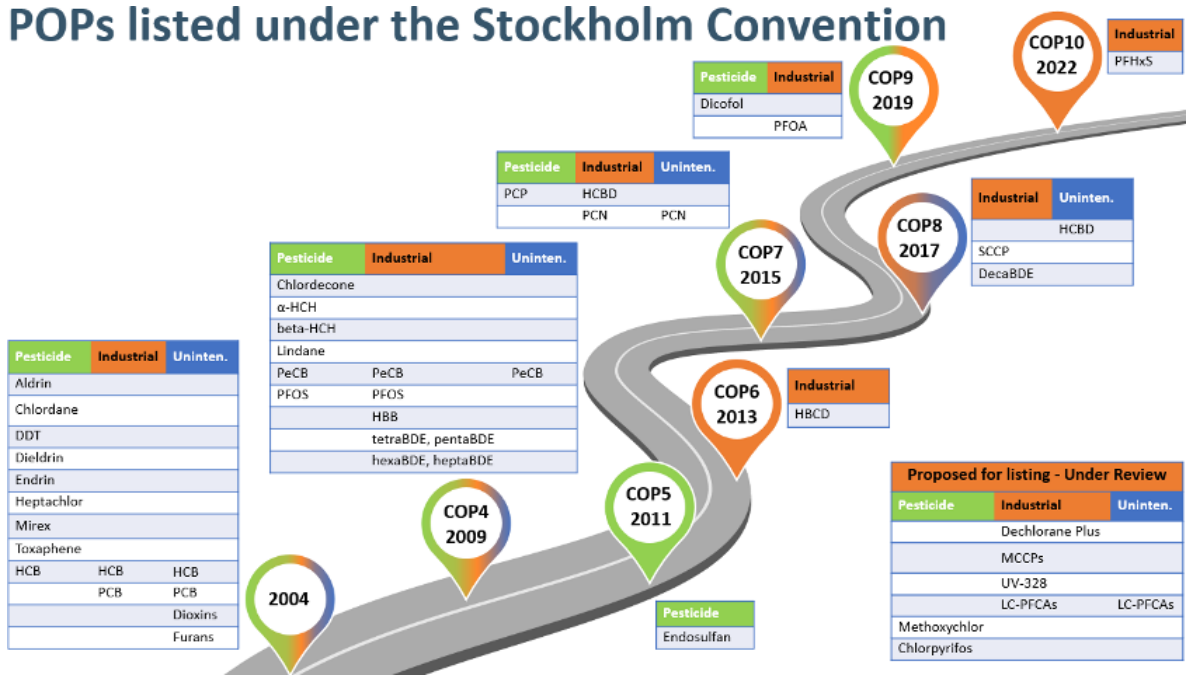
Why do persistent organic pollutants matter?



New chemicals get added regularly. 34 POPs are listed under the Convention as 17 **pesticides**, 15 **industrial chemicals**, 7 **unintentional** by-products.

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Why do persistent organic pollutants matter?

Unintentional Persistent Organic Pollutants (UPOPs) are not voluntarily produced or released into the environment but they **derive from anthropogenic sources**.

They are **emitted during incomplete combustion process** involving organic matter and chlorine or are created as **by-products of manufacturing other chemicals**.

Remarkable **decline** of unintentional POPs has been detected in all countries, which indicated that the effective implementation of the Stockholm Convention contributed to **air quality control**.

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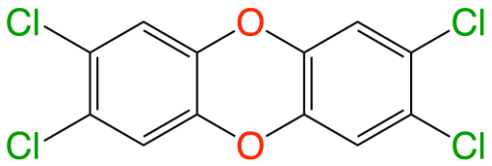
Why do persistent organic pollutants matter?

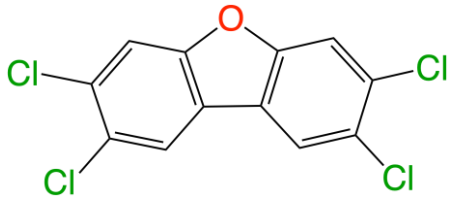
- **Polychlorinated dibenzo-p-dioxins (PCDDs)** and **dibenzofurans (PCDFs)** are the most known and the only listed as unintentional POPs.
- 75 PCDD and135 PCDF congeners
- 17 congeners substituted 2,3,7,8-positions (toxic!)

Pesticide	Industrial	Uninten.
Aldrin		
Chlordane		
DDT		
Dieldrin		
Endrin		
Heptachlor		
Mirex		
Toxaphene		
HCB	HCB	HCB
	PCB	PCB
		Dioxins
		Furans

Measures from individual toxicity assays assign a single scaling factor known as the **Toxic Equivalency Factor** (**TEF**).



2,3,7,8-tetrachloro-p-dibenzodioxin
TCDD
TEF = 1.0



2,3,7,8-tetrachlorodibenzofuran
TCDF
TEF = 0.1

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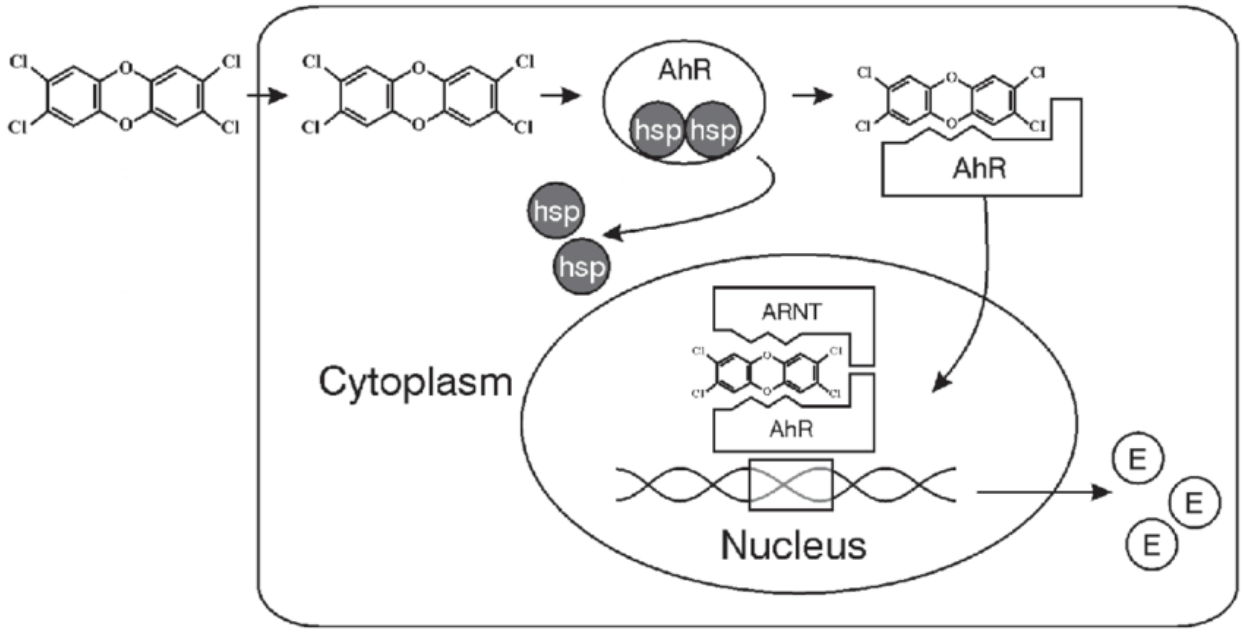
Mode of Action: Inside the cell

The binding of "dioxin-like" chemicals to the AhR is considered the initial step in the toxic effects observed in mammals.



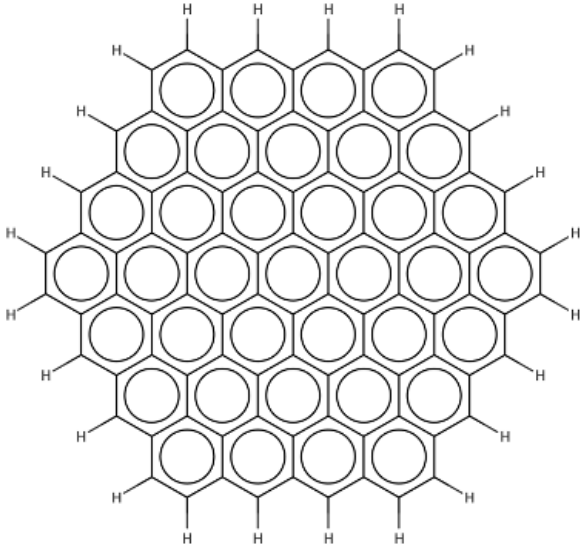
The translocation into the nucleus and the dimerization with the nuclear translocator is affected.

P. S. Ross and L. S. Birnbaum *Human and Ecological Risk Assessment* **2003**, *9*, 303

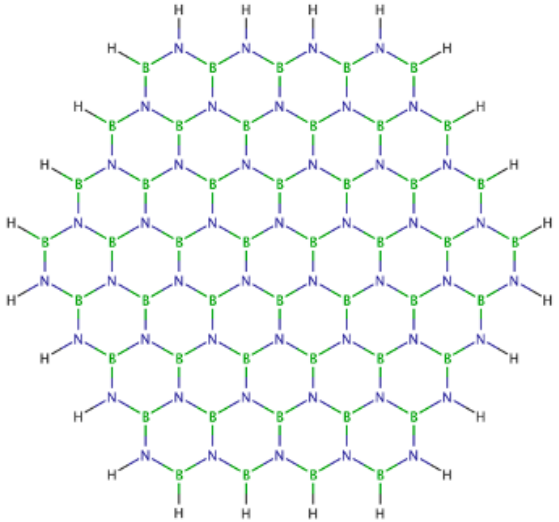
Introduction

State-of-the-Art on POPs

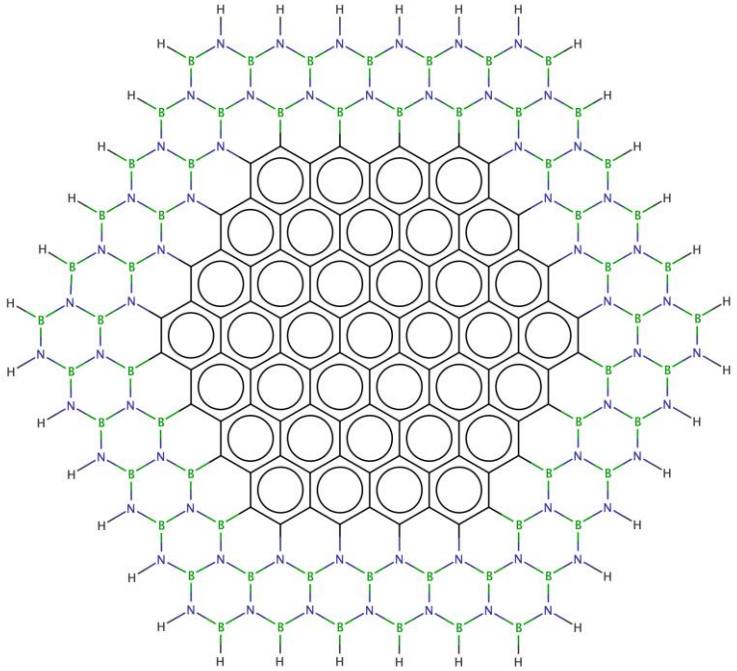
- The reduction and/or detection of “dioxins” is a priority for preventing environmental contamination and to protect living organisms from their damages.



C96



BN96

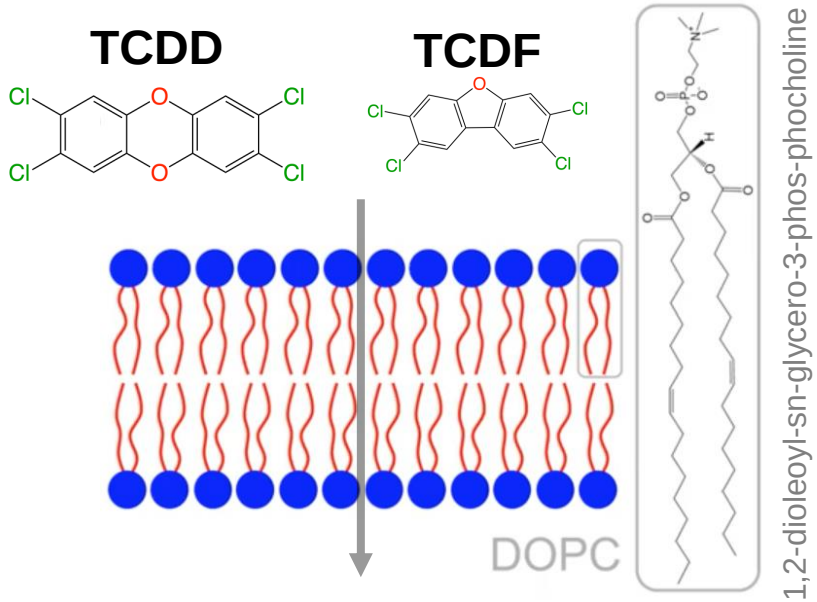


h-BNC96

The development of new substrates as chemical sensors or filters for the treatment of polluting substances involves the analysis of the affinity and stability of the complexes formed between substrates and pollutants.

State-of-the-Art on POPs

- Absorption and diffusion of dioxins through the cell membrane are the first steps of its action mechanism within cells.



The analysis of the intermolecular interactions between substances and lipid bilayers tackles the existence of storage deposits in the membranes, which become an internal source of chronic exposure to these pollutants.

Motivation

- The characterization of pollutant-membrane or pollutant-substrates interactions are key to understand involved mechanims.
- Non-covalent interaction such as dispersion (between instantaneous charges) and exchange/repulsion (due the to Pauli exclusion principle), are roughly represented in classical Force Fields.
- A energy decomposition analysis (EDA) scheme was applied in combination with Quantum Mechanics/Molecular Mechanics (QM/MM) or QM calculations.
- This theoretical research allows a **complete vision** of the problem; covering the **action**, **detection** and **treatment** of these substances.

Interaction Energies: QM Case

Supermolecule Approach

$$E_{int} = E_{AB}(AB) - \left(E_A(AB) + E_B(AB)\right)$$

How to obtain the **Energy contributions**?
Density based Energy Decomposition analysis

Expression of the total energy:

$$E = -\frac{1}{2}\int \nabla^2 \rho(\boldsymbol{r},\boldsymbol{r}')_{\boldsymbol{r}'=\boldsymbol{r}} d\boldsymbol{r} + \int \hat{v}_N \rho(\boldsymbol{r}) d\boldsymbol{r} + \frac{1}{2}\iint \frac{\rho(\boldsymbol{r}_1)\rho(\boldsymbol{r}_2)}{|\boldsymbol{r}_2 - \boldsymbol{r}_1|} d\boldsymbol{r}_1 d\boldsymbol{r}_2 + \frac{1}{2}\iint \frac{\rho_{xc}(\boldsymbol{r}_1,\boldsymbol{r}_2)}{|\boldsymbol{r}_2 - \boldsymbol{r}_1|} d\boldsymbol{r}_1 d\boldsymbol{r}_2 + \sum_{I=1}^{N-1}\sum_{J>I}^{N} \frac{Z_I Z_J}{|\boldsymbol{R}_J - \boldsymbol{R}_I|}$$

M. Mandado and J. M. Hermida-Ramón *J. Chem. Theory Comput.* **2011**, 7, 633.

EDA: QM Case

$$E_{AB}(AB)$$

Subdivide the nuclear terms as contribution of the monomers

$$E = -\frac{1}{2}\int \nabla^2 \rho(\boldsymbol{r},\boldsymbol{r}')_{\boldsymbol{r}'=\boldsymbol{r}} d\boldsymbol{r} + \int \hat{v}_N \rho(\boldsymbol{r}) d\boldsymbol{r} + \frac{1}{2}\iint \frac{\rho(\boldsymbol{r}_1)\rho(\boldsymbol{r}_2)}{|\boldsymbol{r}_2 - \boldsymbol{r}_1|} d\boldsymbol{r}_1 d\boldsymbol{r}_2 + \frac{1}{2}\iint \frac{\rho_{xc}(\boldsymbol{r}_1,\boldsymbol{r}_2)}{|\boldsymbol{r}_2 - \boldsymbol{r}_1|} d\boldsymbol{r}_1 d\boldsymbol{r}_2 + \sum_{I=1}^{N-1}\sum_{J>I}^{N} \frac{Z_I Z_J}{|\boldsymbol{R}_J - \boldsymbol{R}_I|}$$

$$\sum_{I=1}^{N_A-1}\sum_{J>I}^{N_A} \frac{Z_I Z_J}{|\boldsymbol{R}_J - \boldsymbol{R}_I|} + \sum_{K=N_A+1}^{N-1}\sum_{L>K}^{N} \frac{Z_K Z_L}{|\boldsymbol{R}_K - \boldsymbol{R}_L|} + \sum_{I=1}^{N_A}\sum_{K=N_A+1}^{N} \frac{Z_I Z_K}{|\boldsymbol{R}_K - \boldsymbol{R}_I|}, \qquad N = N_A + N_B$$

A **B** **AB**

$$\hat{v}_N = \hat{v}_{N_A} + \hat{v}_{N_B}$$

M. Mandado and J. M. Hermida-Ramón *J. Chem. Theory Comput.* **2011**, 7, 633.

EDA: QM Case

$$E_{AB}(AB)$$

Represent $\rho(\mathbf{r})$ and $\rho_{xc}(\mathbf{r}_1,\mathbf{r}_2)$ as sums of unperturbed terms of each one of the monomers plus two perturbation terms from the interaction of the two monomers

$$E = -\frac{1}{2}\int \nabla^2 \rho(\boldsymbol{r},\boldsymbol{r}')_{\boldsymbol{r}'=\boldsymbol{r}} d\boldsymbol{r} + \int \hat{v}_N \rho(\boldsymbol{r}) d\boldsymbol{r} + \frac{1}{2}\iint \frac{\rho(\boldsymbol{r}_1)\rho(\boldsymbol{r}_2)}{|\boldsymbol{r}_2 - \boldsymbol{r}_1|} d\boldsymbol{r}_1 d\boldsymbol{r}_2 + \frac{1}{2}\iint \frac{\rho_{xc}(\boldsymbol{r}_1,\boldsymbol{r}_2)}{|\boldsymbol{r}_2 - \boldsymbol{r}_1|} d\boldsymbol{r}_1 d\boldsymbol{r}_2 + \sum_{I=1}^{N-1}\sum_{J>I}^{N} \frac{Z_I Z_J}{|\boldsymbol{R}_J - \boldsymbol{R}_I|}$$

$$\rho(\boldsymbol{r}) = \rho^A(\boldsymbol{r}) + \rho^B(\boldsymbol{r}) + \Delta\rho(\boldsymbol{r})_{Pol} + \Delta\rho(\boldsymbol{r})_{Pau}$$

$$\rho_{xc}(\boldsymbol{r}_1,\boldsymbol{r}_2) = \rho^A_{xc}(\boldsymbol{r}_1,\boldsymbol{r}_2) + \rho^B_{xc}(\boldsymbol{r}_1,\boldsymbol{r}_2) + \Delta\rho_{xc}(\boldsymbol{r}_1,\boldsymbol{r}_2) + \rho_x^{AB}(\boldsymbol{r}_1,\boldsymbol{r}_2)$$

M. Mandado and J. M. Hermida-Ramón *J. Chem. Theory Comput.* **2011**, 7, 633.

EDA: QM Case

$$E_{AB}(AB)$$

Represent $\rho(\mathbf{r})$ and $\rho_{xc}(\mathbf{r}_1,\mathbf{r}_2)$ as sums of unperturbed terms of each one of the monomers plus two perturbation terms from the interaction of the two monomers

$$E = -\frac{1}{2}\int \nabla^2 \rho(\boldsymbol{r},\boldsymbol{r}')_{\boldsymbol{r}'=\boldsymbol{r}} d\boldsymbol{r} + \int \hat{v}_N \rho(\boldsymbol{r}) d\boldsymbol{r} + \frac{1}{2}\iint \frac{\rho(\boldsymbol{r}_1)\rho(\boldsymbol{r}_2)}{|\boldsymbol{r}_2-\boldsymbol{r}_1|} d\boldsymbol{r}_1 d\boldsymbol{r}_2 + \frac{1}{2}\iint \frac{\rho_{xc}(\boldsymbol{r}_1,\boldsymbol{r}_2)}{|\boldsymbol{r}_2-\boldsymbol{r}_1|} d\boldsymbol{r}_1 d\boldsymbol{r}_2 + \sum_{I=1}^{N-1}\sum_{J>I}^{N} \frac{Z_I Z_J}{|\boldsymbol{R}_J-\boldsymbol{R}_I|}$$

$$\rho(\boldsymbol{r}) = \rho^A(\boldsymbol{r}) + \rho^B(\boldsymbol{r}) + \Delta\rho(\boldsymbol{r})_{Pol} + \Delta\rho(\boldsymbol{r})_{Pau}$$

$$\rho_{xc}(\boldsymbol{r}_1,\boldsymbol{r}_2) = \rho^A_{xc}(\boldsymbol{r}_1,\boldsymbol{r}_2) + \rho^B_{xc}(\boldsymbol{r}_1,\boldsymbol{r}_2) + \Delta\rho_{xc}(\boldsymbol{r}_1,\boldsymbol{r}_2) + \rho_x^{AB}(\boldsymbol{r}_1,\boldsymbol{r}_2)$$

Antisymmetrization
$\psi^A\psi^B$

Interaction
ψ^{AB}

These terms are going to account for the Exchange repulsion interactions between the two monomers

These terms are going to account for the polarization interactions between the two monomers

M. Mandado and J. M. Hermida-Ramón *J. Chem. Theory Comput.* **2011**, 7, 633.

EDA: QM Case

Supermolecule Approach

$$E_{int} = E_{AB}(AB) - \left(E_A(AB) + E_B(AB)\right)$$

$$\downarrow \quad E_{AB}(AB)$$

$$E_{int} = E_{elec}(\rho^A, \rho^B) + E_{pol}(\Delta\rho_{Pol}, \Delta\rho_{xc}) + E_{pau}(\Delta\rho_{Pau}, \rho_x^{AB})$$

$$\downarrow \quad 2^{nd} \text{ order PT}$$

$$E_{int} = E_{elec} + E_{pau} + \underbrace{E_{ind} + E_{disp}}_{E_{pol}}$$

The development of new substrates as chemical sensors or filters for the treatment of polluting substances involves the analysis of the affinity and stability of the complexes formed between substrates and pollutants.

M. Mandado and J. M. Hermida-Ramón *J. Chem. Theory Comput.* **2011**, 7, 633.
N. Ramos-Berdullas, I. Pérez-Juste, C. Van Alsenoy and M. Mandado *Phys. Chem. Chem. Phys.* **2015**, 17, 575

EDA: QM/MM Case

Supermolecule Approach

$$E_{int} = E_{AB}(AB) - \left(E_A(AB) + E_B(AB)\right)$$

How to Include the **MM Potential** in the **EDA Calculations?**
MM point charges are included as **nuclear terms** in the **energy**

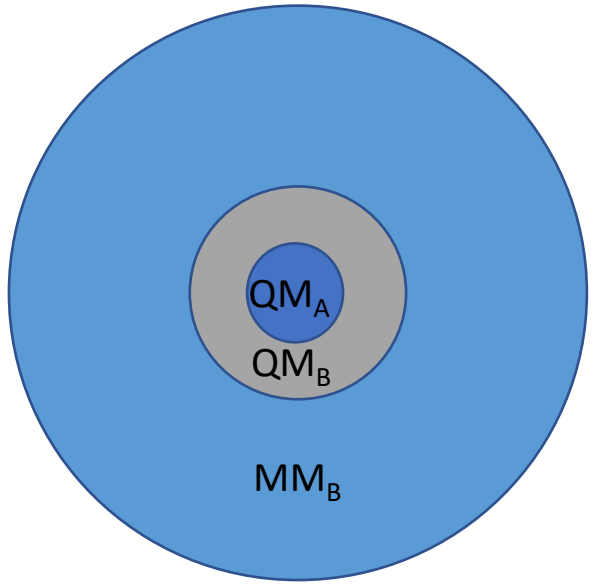
$\hat{v}_N = \hat{v}_{N_A} + \hat{v}_{N_B}$ Nuclear potential operator

$\hat{\mathbf{v}}_N = \hat{\mathbf{v}}_{N_A} + \hat{\mathbf{v}}_{N_B}^{QM/MM}$ Fragment B includes the MM region

$\hat{\mathbf{v}}_{N_B}^{QM/MM} = \hat{\mathbf{v}}_{N_B} + \hat{\mathbf{V}}_{MM}(\mathbf{r})$

Electrostatic embedding

$$\hat{\mathbf{V}}_{MM}(\mathbf{r}) = -\sum_i \frac{q_i}{|\mathbf{r} - \mathbf{R}_i|}$$



$$E_{int} = E_{elec} + E_{pau} + E_{ind} + E_{disp}$$

G. Cárdenas, Á. Pérez-Barcia, M. Mandado and J. J. Nogueira *Phys. Chem. Chem. Phys.* **2021**, 23, 20533

Chemical sensors and filters

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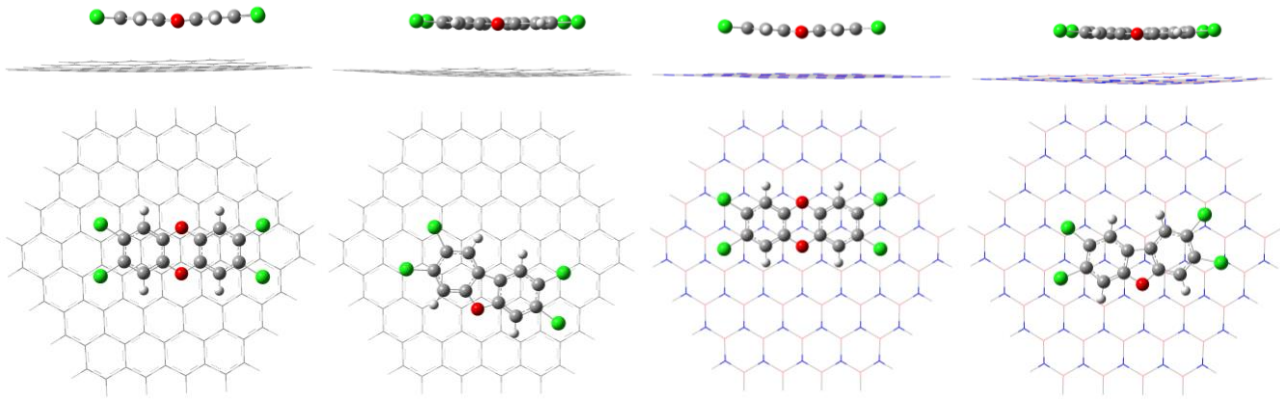
- Adsorption complexes formed between TCDD and TCDF with finite models of graphene and white graphene formed by 96 atoms (No significant differences PCBs!).
- EDA-QM scheme was applied on stacking and perpendicular complexes.
- M062X hybrid functional includes most of dispersion energy implicitly, providing a more accurate description of the density polarization.



N. Ramos-Berdullas, I. Pérez-Juste, C. Van Alsenoy and M. Mandado *Phys. Chem. Chem. Phys.* **2015**, 17, 575

R. Alvarado, N. Ramos-Berdullas and M. Mandado *Int. J. Quantum Chemistry* **2021**, 121, e26591.

Chemical sensors and filters

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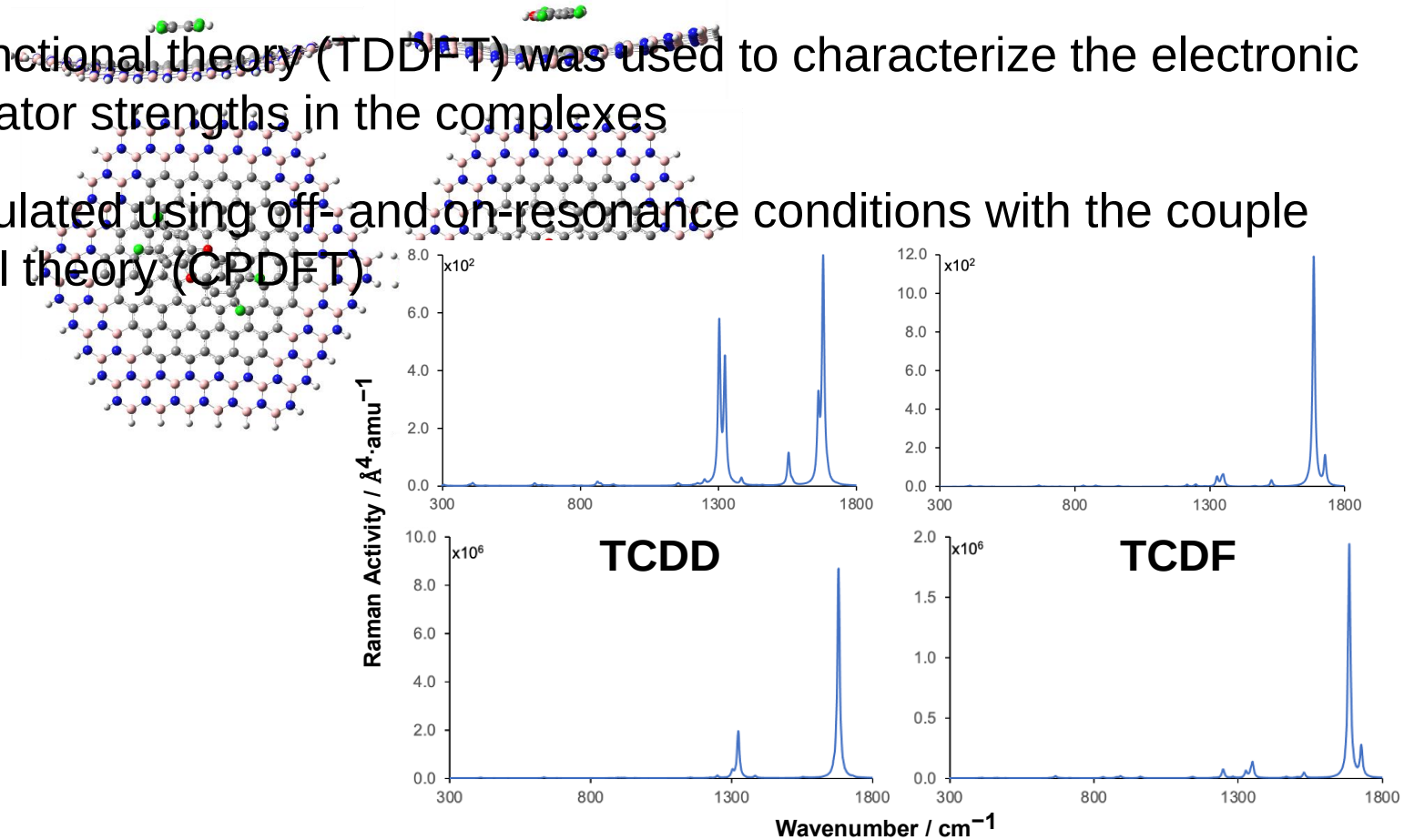
- Strong confinement of the electromagnetic response within the carbon domains
- High modulation of the resonance wavelengths in the visible and/or UV region (SERS).
- Time-dependent density functional theory (TDDFT) was used to characterize the electronic transitions with larger oscillator strengths in the complexes
- Raman Activities were calculated using off- and on-resonance conditions with the couple perturbed density functional theory (CPDFT)



M. Mandado and N. Ramos-Berdullas *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy* **2022**, *266,* 120451.

R. Alvarado, N. Otero, M. Mandado and N. Ramos-Berdullas *Chemosensors* **2023**, 11, 266.

Chemical sensors and filters

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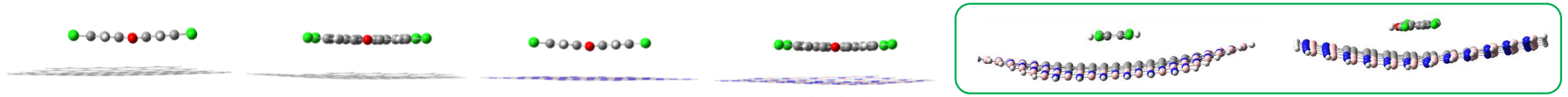
	TCDD			TCDF		
	C96	BN96	BNC96	C96	BN96	BNC96
Electrostatic	-21.3	-22.8	-21.1	-19.6	-18.8	-19.0
Pauli	52.5	55.4	51.2	48.7	47.6	46.9
Induction	-5.0	-18.1	-5.1	-4.2	-16.4	-4.3
Dispersion	-59.5	-45.0	-59.7	-56.2	-39.2	-55.9
Total	-33.4	-30.6	-34.7	-31.4	-26.9	-32.3

The dispersion energy is the dominant contribution in all the complexes, but some important differences explain the trends observed in the total interaction energies.

The induction energy is significant in white graphene (BN96) due to the presence of polar B-N bonds.

External borazine rings have little influence on the interaction of the pollutants



R. Alvarado, N. Ramos-Berdullas and M. Mandado *Int. J. Quantum Chemistry* **2021**, 121, e26591.
R. Alvarado, N. Otero, M. Mandado and N. Ramos-Berdullas *Chemosensors* **2023**, 11, 266.

Permeation of POPs through Membranes

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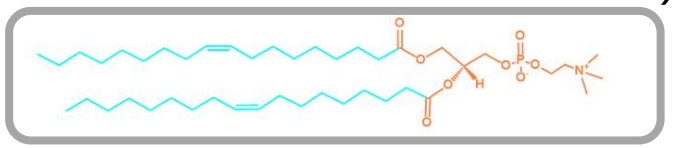
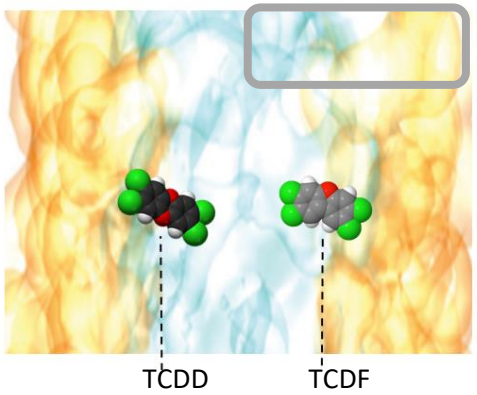
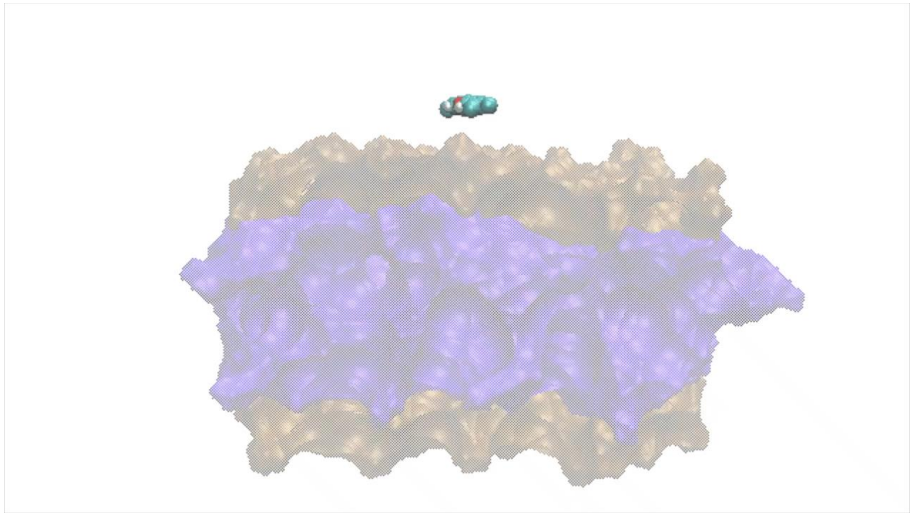
- The lipid bilayer is formed by 64 molecules of DOPC per layer with 25 Å fo water thickness
- TCDD/TCDF are placed at 32 Å from CM of the membrane
- Minimization, heating and producion by classical MD
- The permeation processes of pollutants through the lipid bilayer were simulated by means of the umbrella sampling technique.
- The reaction coordinate is divided into 65 windows separeted by 0.5 Å and CMD simulation of 20 ns was run within each window.

Dioleoylphosphocholine (DOPC)





- Is toxicity related to diffusion through the lipid bilayer?



R. Alvarado, G. Cárdenas, J. J. Nogueira, N. Ramos-Berdullas and M. Mandado *Membranes* **2023**, *13*, 28

Permeation of POPs through Membranes

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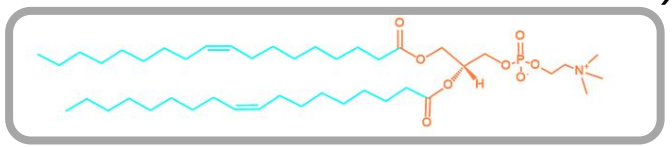
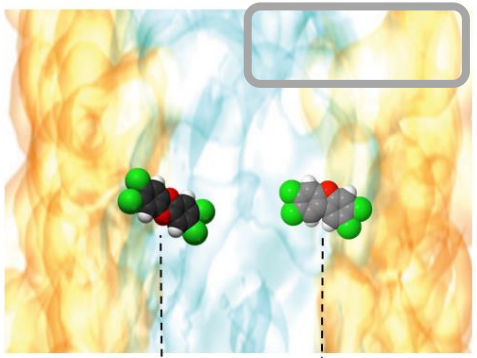
- Free energy **minimum** in the middle of the bilayer (nonpolar region)
- Free energy **maximum** close to the polar heads
- Free energy is slightly more favourable for TCDD than for TCDF
- Pollutant/lipid interactions characterized by QM/MM and EDA

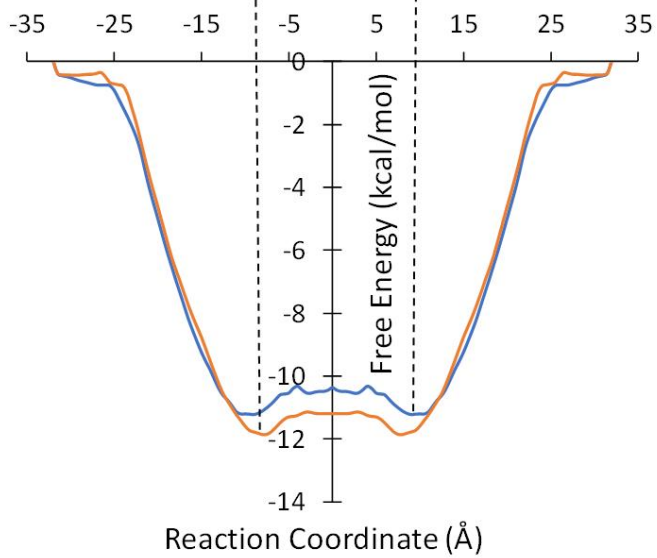
How many lipids in the QM region?

How many snapshots?

Dioleoylphosphocholine (DOPC)

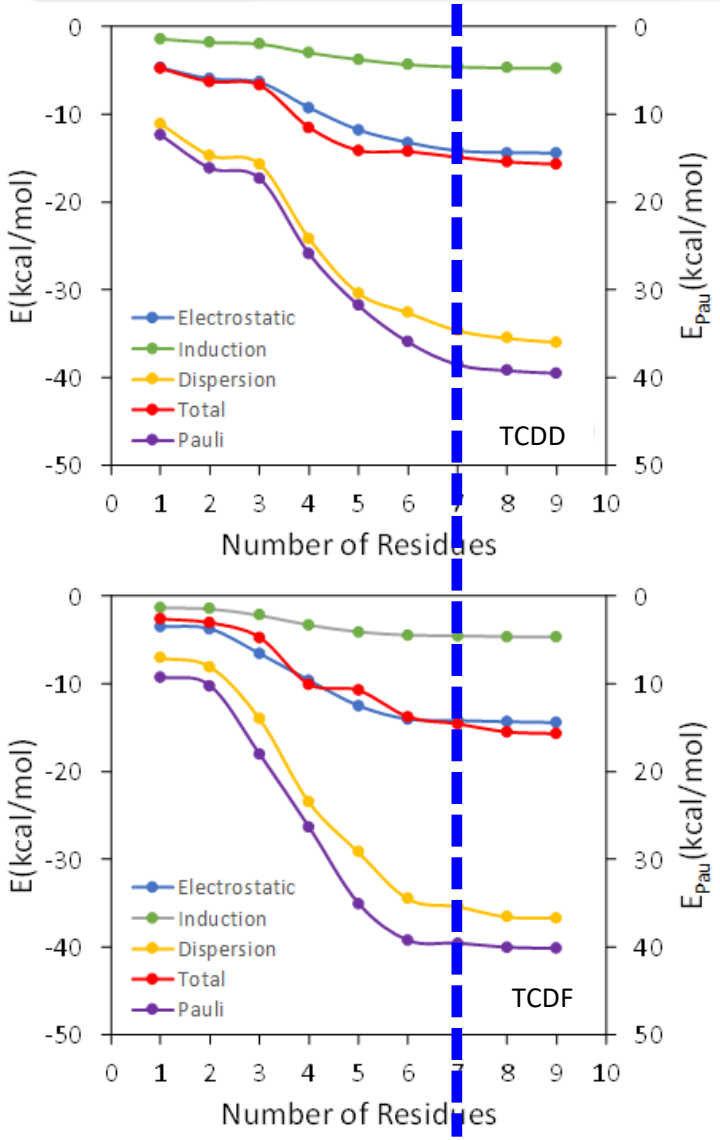






R. Alvarado, G. Cárdenas, J. J. Nogueira, N. Ramos-Berdullas and M. Mandado *Membranes* **2023**, *13*, 28

Permeation of POPs through Membranes

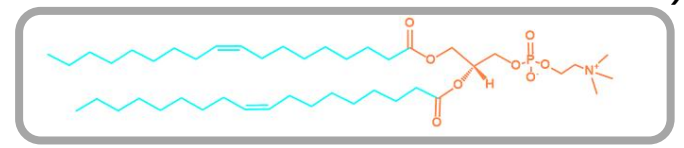


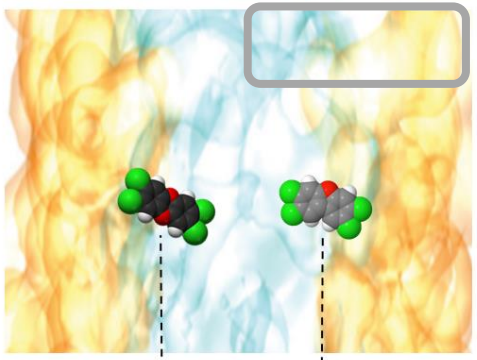
The optimal QM region must contain the pollutant and the minimum number of DOPC molecules

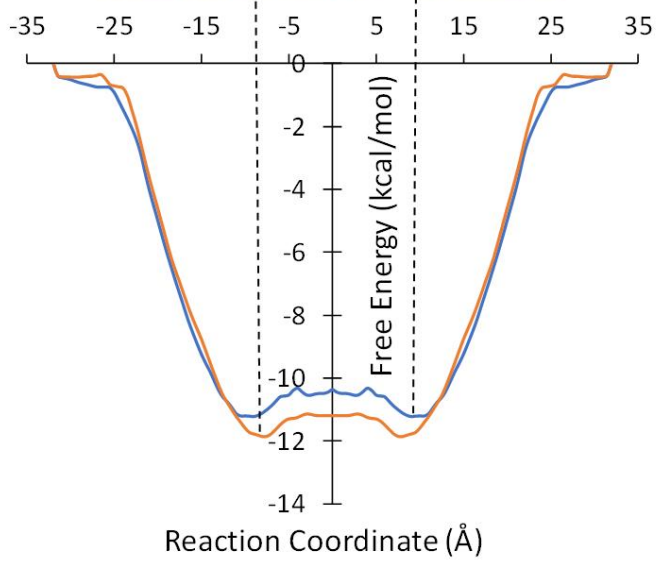
Analysis of the convergence of the interaction energy and its components as the number of the DOPC molecules increases in the minimum region

Calculations performed with 7 lipid molecules and 100 snapshots

Dioleoylphosphocholine (DOPC)







R. Alvarado, G. Cárdenas, J. J. Nogueira, N. Ramos-Berdullas and M. Mandado *Membranes* **2023**, *13*, 28

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Permeation of POPs through Membranes

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$$E_{\text{int}} = E_{\text{Pau}} + E_{\text{elec}} + E_{\text{ind}} + E_{\text{dis}}$$

	Elect	Pau	Ind	Disp	Total
TCDD	-19.6	49.7	-6.5	-41.1	-17.5
TCDF	-19.3	52.1	-6.4	-43.0	-16.5

The energy increase in the total interaction energy is significantly larger than that predicted by the CMD simulation. Good correspondence!

In both pollutants, dispersion is more than twice the electrostatic energy, whereas the induction energy has a marginal contribution.

The absorption and diffusion steps through the cell membrane do not explain the different toxicity measured for TCDD and TCDF.

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THANK YOU
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Conclusions

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- Intermolecular interactions play an important role on the mode of action, detection and treatment of pollutants
- EDA-QM scheme was applied on TCDD and TCDF with finite models of substrates
- EDA-QM/MM schem was applied on TCDD and TCDF with lipid bilayer DOPC.
- Boron nitride based materials are excellent alternatives to carbon-based adsorbents of dioxin-like pollutants
- 2D hybrid h-BNC structures could act as substrates for the Raman-enhancement of dioxins and dibenzofurans
- The permeation and diffusion steps through the cell membrane do not explain the different toxicity measured for TCDD and TCDF.

Chemical sensors and filters

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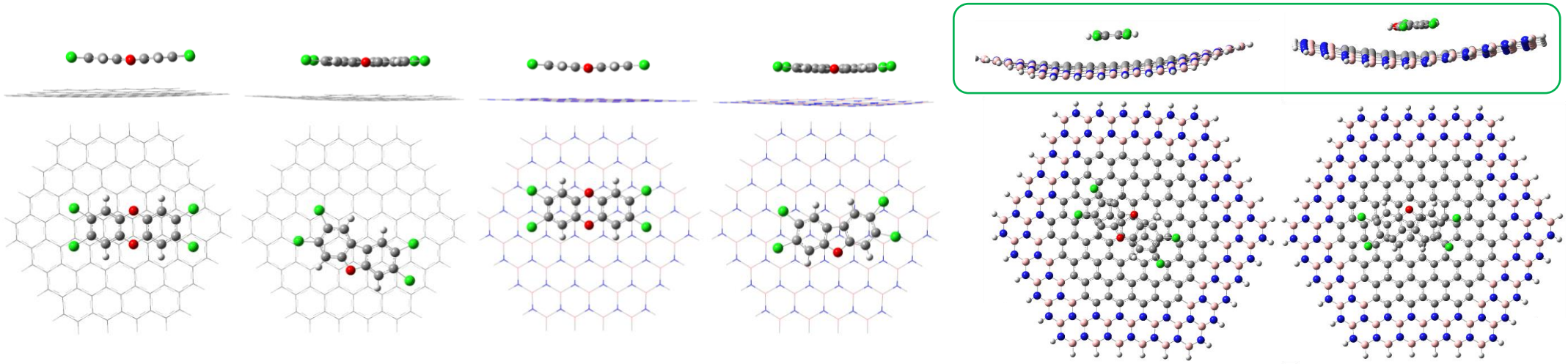
	TCDD			TCDF		
	C96	BN96	BNC96	C96	BN96	BNC96
Electrostatic	-21.3	-22.8	-21.1	-19.6	-18.8	-19.0
Pauli	52.5	55.4	51.2	48.7	47.6	46.9
Induction	-5.0	-18.1	-5.1	-4.2	-16.4	-4.3
Dispersion	-59.5	-45.0	-59.7	-56.2	-39.2	-55.9
Total	-33.4	-30.6	-34.7	-31.4	-26.9	-32.3



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