IOCXe 2026 Conference
The 1st International Online Conference on Xenobiotics
22–23 June 2026 | Online
MDPI

Predicting the Health Effects of AhR Ligands: Bioinformatic Risk Assessment of Environmental Pollutants and Dietary Compounds

Andra-Maria Paun*, Catalina Mares, Maria Mernea, Speranta Avram
Department of Anatomy, Animal Physiology and Biophysics, University of Bucharest, Faculty of Biology, Splaiul Independentei 91-95, Bucharest, R-050095, Romania

INTRODUCTION & AIM

The **Aryl hydrocarbon receptor (AhR)** [1] acts as a key genomic defense mechanism against chemical exposure, balancing rapid detoxification processes with the maintenance of physiological homeostasis.

However,persistent environmental ligands can shift AhR activity from a protective sensor role into a systemic disruptor, potentially contributing to severe toxic effects.

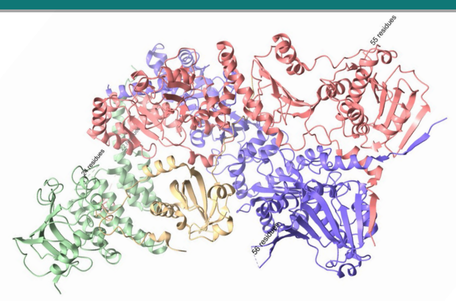

Figure 1. AhR in complex with heat shock protein HSP 90-β and ah receptor-interacting protein; PDB ID: 8QMO

The **aim** of the study is to evaluate how the structural and metabolic properties of selected AhR ligands influence environmental persistence, receptor binding characteristics, and predicted toxicological outcomes, including their potential for receptor disruption.

METHOD

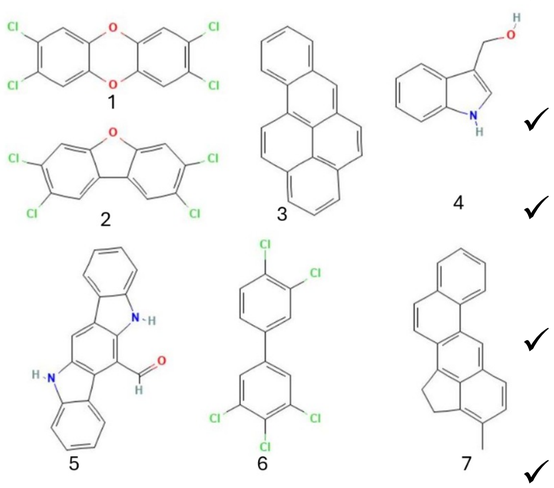

Figure 2. 2D structure of the selected ligands- 1: TCDD, 2: 2,3,7,8-TCDF, 3: Benzo[a]pyrene, 4: Indole-3-Carbinol, 5: FICZ, 6: PCB 126, 7: 3-MC

- ✓ Seven AhR ligands (TCDD, PCB 126, 2,3,7,8-TCDF, benzo[a]pyrene, 3-MC, FICZ, indole-3-carbinol) were analyzed.
- ✓ Structures and SMILES were retrieved from PubChem.
- ✓ Physicochemical properties were obtained from PubChem and ADMETlab 3.0.
- ✓ ADME, ecotoxicity, CYP450 interactions, and toxicity endpoints were predicted using Deep-PK [2] and ProTox-3.0.[3]
- ✓ Molecular docking against AhR (PDB: 8QMO, 7ZUB) was performed using AutoDock Vina [4] to evaluate binding affinity and receptor interactions.

RESULTS & DISCUSSION

TCDD, PCB126, 3-MC, and Benzo[a]pyrene showed the strongest overall toxicity profiles, with high probabilities for immunotoxicity, AhR pathway activation, and BBB-barrier toxicity.

FICZ and Indole-3-Carbinol exhibited lower toxicity signals across several endpoints, while 2,3,7,8-TCDF showed a mixed toxicity profile characterized by high immunotoxicity and BBB-barrier toxicity (*Figure 3*).

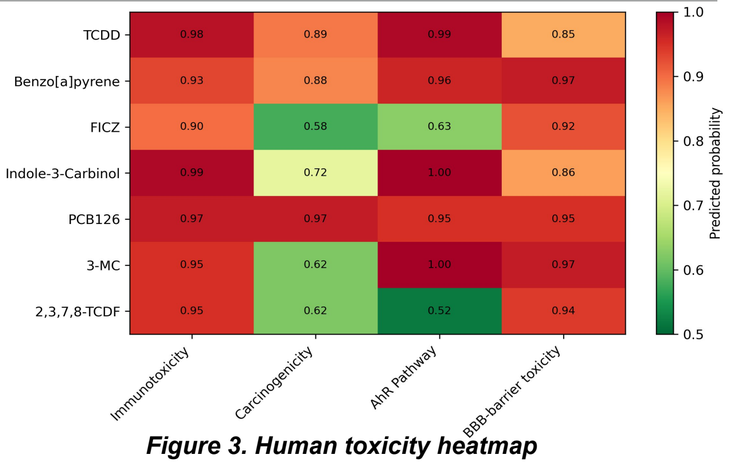

Figure 3. Human toxicity heatmap

TCDD, benzo[a]pyrene, PCB126, 3-MC) showed high environmental toxicity; Indole-3-Carbinol and FICZ exhibited significantly lower ecotoxic impact -*Table 1.*

Table 1. Ecotoxicity and predicted CNS Permeability of the selected ligands (BF-Bioconcentration Factor)

Compound	BF	Bio-degradation	Aquatic Toxicity	Bee Toxicity	Crustacean Toxicity	*Fathead Minnow* Toxicity	*T. Pyriformis*	Ecotoxicity	Predicted CNS Permeability
TCDD	3.54	Safe	Toxic	Toxic	Toxic	5.33	6.72	Active/ 0.75	Yes
Benzo[a]pyrene	2.44	Toxic	Toxic	Safe	Toxic	5.44	4.1	Active/ 0.91	Yes
FICZ	0.11	Safe	Non-Toxic	Safe	Toxic	4.93	2.04	Active/ 0.68	Yes
Indole-3-Carbinol	0.57	Safe	Non-Toxic	Safe	Safe	3.55	2.26	Inactive/ 0.59	Yes (limited)
PCB 126	4.67	Safe	Toxic	Safe	Toxic	5.3	6.09	Active/ 0.82	Yes
3-MC	2.95	Safe	Toxic	Safe	Toxic	5.48	6	Active/ 0.81	Yes
2,3,7,8-TCDF	3.69	Safe	Toxic	Safe	Toxic	5.49	6.38	Active/ 0.71	Yes

Table 2. In Silico Binding Affinities of the selected ligands

Ligand	8QMO Energy (kcal/mol)	7ZUB Energy (kcal/mol)
3-MC	-14.4	-14.4
Benzo[a]pyrene	-14.1	-14.1
FICZ	-13.5	-12.9
2,3,7,8-TCDF	-10.5	-10.2
PCB 126	-10.2	-10.3
TCDD	-10	-10.1
Indole-3-Carbinol	-7.5	-7.3
Positive control	-10.2	-10.7
Negative control	-9.2	-8.4

Blind docking consistently targeted the AhR PAS-B ligand-binding cavity, with stable results across both receptor conformations (7ZUB and 8QMO). Binding patterns remained consistent between the two structures, indicating methodological robustness.

3-MC and benzo[a]pyrene showed the strongest predicted receptor interactions, forming contacts with multiple core binding pocket residues. Indole-3-carbinol showed the weakest binding interactions, consistent with its smaller molecular size and reduced interaction surface.

Docking performance was validated using apigenin as a positive control, which effectively engaged key residues, while agathisflavone served as a negative control due to binding at an alternative site with limited interaction in the core pocket.

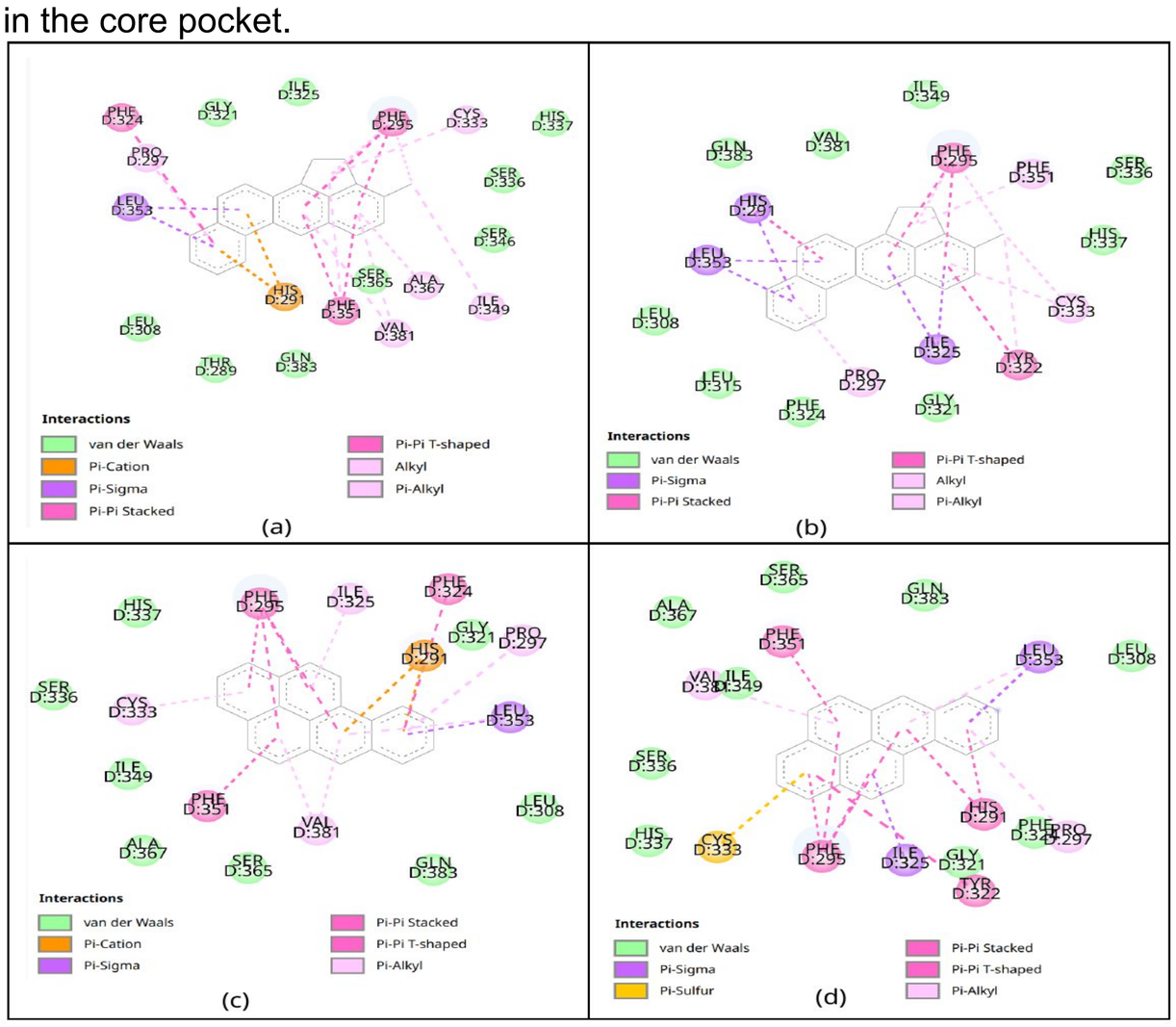

Figure 4. Ligand-Receptor Interactions; (a) 3-Methylcholanthrene with 7ZUB; (b) 3-Methylcholanthrene with 8QMO; (c) Benzo[a]pyrene with 7ZUB; (d) Benzo[a]pyrene with 8QMO

CONCLUSION

Persistent contaminants (TCDD, 2,3,7,8-TCDF, and benzo[a]pyrene) showed the strongest toxicity-related signals, while FICZ and indole-3-carbinol displayed more favorable profiles. Molecular docking confirmed stable AhR binding across receptor conformations, linking ligand persistence and binding strength to their potential biological effects.

FUTURE WORK / REFERENCES

1. Polonio, C.M. et al. Nat Rev Drug Discov 2025, 24, 610–630.
2. Myung, Y. et al. Nucleic Acids Res 2024, 52, W469–W475.
3. Banerjee, P. et al. Nucleic Acids Res 2024, 52, W513–W520.
4. Sarkar, A. et al. Results Chem 2024, 7, 101319.