QSAR for toxicities of polychlorodibenzofurans, polychlorodibenzo-1,4-dioxins, and polychlorobiphenyls

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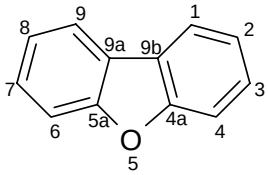
Abstract

The toxic equivalency factors (TEF values) for 12 polychlorobiphenyls (PCBs), 14 polychlorodibenzo-1,4-dioxins (PCDDs), and 24 polychlorodibenzofurans (PCDFs) have been correlated with the extent and position of chloro-substitution using a variety of molecular descriptors., with Todeschini's program Dragon 4.0. and the CODESSA program of Katritzky and coworkers.

Keywords: Polychlorodibenzofurans, polychlorodibenzodioxins, polychlorobiphenyls, toxicity, molecular descriptors, QSAR

Introduction

Among polychlorinated aromatic compounds, the most environmentally dangerous chemicals are polychlorodibenzofuran (PCDF) **1,** polychlorodibenzo-1,4-dioxin (PCDD) **2**, and. polychlorobiphenyl (PCB) derivatives **3**. Like the persistent chlorofluorocarbons that were extensively used until the discovery of their deleterious effect on the ozone layer, these polychloroaromatic compounds are harmful to the environment. Similarly to other polychlorinated compounds (used as efficient pesticides such as DDT, Aldrin and Dieldrin, which led to the "*Silent Spring*" due to bioaccumulation in fatty tissues of higher organisms), the title compounds exert a powerful toxic effect on humans (endocrine disruptors, neurotoxic, carcinogens),[1,2] and one of the polychlorodibenzo-1,4-dioxin isomers is among the most toxic organic chemicals.[2]



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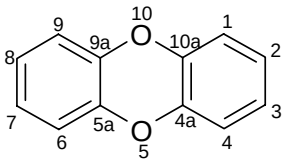

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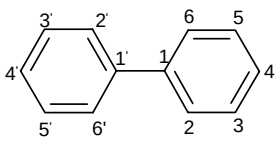

3

Results

Number of possible isomers

The number of all possible isomers of the above three classes of polychlorinated aromatic compounds can be found easily by means of Polya's Theorem. First, one has to take into account the cycle index of the molecule, depending on the automorphisms (symmetry operations involving proper axes of rotation). For PCBs, one has to consider all possible rotamers of the substituted biphenyl molecule. The cycle index leads to the figure counting series, which is a polynomial in x whose degree equals the number of hydrogen or halogen atoms in the molecule. Each subscript a for x_a indicates the order of the permutation, and each superscript b for x_a^b the number of permutations or the number of unchanged positions. Then, according to Polya's Theorem, by performing the substitution:

$$x_a^b = (y^a + 1)^b$$

one ends up with the generating function, which is a polynomial in y whose coefficients indicate the numbers of isomers. For PCBs, the possible permutations are indicated in Table 1.

Table 1. Permutations of the substituents in polychlorobiphenyls

1	2	3	4	5	6	7	8	9	10	
1	2	3	4	5	6	7	8	9	10	x^{10}
5	4	3	2	1	10	9	8	7	6	$x^2x_2^4$
1	2	3	4	5	10	9	8	7	6	$x^6x_2^2$
5	4	3	2	1	6	7	8	9	10	$x^6x_2^2$
6	7	8	9	10	1	2	3	4	5	x_2^5
10	9	8	7	6	5	4	3	2	1	x_2^5
6	7	8	9	10	5	4	3	2	1	$x_2x_4^2$
10	9	8	7	6	1	2	3	4	5	$x_2x_4^2$

Figure counting series: $(x^{10} + 2x_2^5 + 2x^6x_2^2 + 2x_2x_4^2 + x_2x_2^4)/8$.
Generating function: $y^{10} + 3y^9 + 12y^8 + 24y^7 + 42y^6 + 46y^5 + 42y^4 + 24y^3 + 13y^2 + 3y + 1$.

Therefore, there are 3 possible monochlorobiphenyls, 12 dichlorobiphenyls, 24 tri-, 42 tetra-, 46 penta-, 42 tetrachlorobiphenyls, etc. Many of the 209 possible polychlorobiphenyls have been synthesized and characterized chemically, physically, and toxicologically. Of these, fourteen have a pronounced toxic effect, similar to that of tetrachlorodibenzodioxins.[3,4]

For PCDDs, the possible permutations are shown in Table 2.

Table 2. Permutations of the substituents in polychlorodibenzo-1,4-dioxins

1	2	3	4	5	6	7	8	
1	2	3	4	5	6	7	8	x^8
4	3	2	1	8	7	6	5	x_2^4
8	7	6	5	4	3	2	1	x_2^4
5	6	7	8	1	2	3	4	x_2^4

Figure counting series: $(x^8 + 3x_2^4)/4$.
Generating function: $y^8 + 2y^7 + 10y^6 + 14y^5 + 22y^4 + 14y^3 + 10y^2 + 2y + 1$.

Therefore, there are 2 possible monochlorodibenzodioxins, 10 dichloro-, 14 tri-, 22 tetra-, 14 pentachlorodibenzodioxins, etc. Many of the 75 possible polychlorodibenzodioxins have been synthesized and characterized chemically, physically, and toxicologically. Of these, seven compounds have a high toxicity, and one of them is the most toxic.[4–7] This is the infamous and extremely toxic 2,3,7,8-tetrachlorodibenzo-1,4-dioxin or TCDD (LD_{50} = 45 μg/kg in rats), formed as a low-yield byproduct during the syntheses of 2,4,5-trichlorophenoxyacetic acid (herbicide and defoliating agent) and hexachlorophene (germicide) from chloroacetic acid and sodium 2,4,5-trichlorophenoxide. In the Seveso accident in Italy, a large amount of soil contaminated with 2,3,7,8-tetrachlorodibenzo-1,4-dioxin had to be removed at high cost. During the Vietnam War, the defoliant (Agent Orange) used by the US Army contained small amounts of 2,3,7,8-tetrachlorodibenzo-1,4-dioxin, and US veterans were compensated financially for the resulting health problems.

For PCDFs, the possible permutations are presented in Table 3.

Table 3. Permutations of the substituents in polychlorodibenzofurans

1	2	3	4	5	6	7	8	
1	2	3	4	5	6	7	8	x^8
8	7	6	5	4	3	2	1	x_2^4

Figure counting series: $(x^8 + x_2^4)/2$.
Generating function: $y^8 + 4y^7 + 16y^6 + 28y^5 + 38y^4 + 28y^3 + 16y^2 + 4y + 1$.

Therefore, there are 4 possible monochlorodibenzofurans, 16 dichloro-, 28 tri-, 38 tetra-, 28 pentachlorodibenzofurans, etc. Many of the 135 possible polychlorodibenzofurans have been synthesized and characterized chemically, physically, and toxicologically. Ten of them have high toxicity.[4,5,7–10]

Polyhalogenated biphenyls have been used in the past as dielectric liquids in electrical transformers, as heat transfer agents (along with polyhalogenated diphenyl ethers), as lubricating agents, and as additives for pesticides or plastics. Since 1970, however, their use has been prohibited, but owing to their persistence they are still polluting the environment.[11–18]

Toxicity of polychlorinated aromatic compounds and QSAR

Polychlorinated aromatic compounds have a high hydrophobicity and persistence.[18,19] They are therefore widespread environmental contaminants, and they accumulate in fatty tissues of animals. The biological activity of polyhalogenated aromatic compounds is characterized by their multiple effects on mammals: hepatotoxicity, porphyria, dermal lesions including chloracne, endocrine effects, immunotoxicity, gastric lesions, lung edema, thymic atrophy, body weight loss, teratogenicity, reproductive lesions, and carcinogenicity.[20–22] The in vitro induction of two enzymes has been associated with these compounds, namely aryl hydrocarbon hydroxylase (AHH) and 7-ethoxyresorufin O-deethylase (EROD). All these effects are believed to result via a specific protein complex, the intracellular cytosolic aryl hydrocarbon receptor (AhR) that is highly conserved in the evolutionary scale and acts similarly in humans and in laboratory animals. The receptor binding affinity depends on steric, electrostatic, hydrophobic, hydrogen bonding factors, with dispersion forces and electrostatic potentials playing important parts.[9,23]

Since 2,3,7,8-tetrachlorodibenzo-1,4-dioxin is the most toxic of the polychlorinated aromatic compounds, it was agreed to have it as a reference compound for the relative toxicity of such compounds.[24–30] Thus, 2,3,7,8-tetrachlorodibenzo-1,4-dioxin was assigned a toxic equivalency factor (TEF) of –9.00,[31–33] or a receptor binding affinity pEC_{50} of 8.00 (both in logarithmic units), differing by one unit in absolute values. In addition, pEC_{50}-(AHH) and pEC_{50}-(EROD) are also available. These four sets of biological activities of polychlorinated aromatic compounds are sometimes causing confusion.

Polychlorobiphenyls may have toxicities that are dioxin-like or non-dioxin-like. It was found that *ortho*-substitution decreases the toxicity, indicating that the planar polychlorobiphenyls have dioxin-like toxic effects.[34–40]

When several polychlorinated aromatic compounds appear in mixtures[41] (as they occur in the environment), and when as usual they have the same mechanism of action, their cumulated toxic effect can be found by a relationship involving partial toxicities, reminiscent of Dalton's Law of partial pressures: the total equivalent toxicity is the sum of the products of their concentration with their TEF value.[31,42,43]

In the present paper we will use the same TEF data that have recently been used by Beger and Wilkes [43] as well as by Căprioară and Diudea.[44]

Molecular Descriptors

The molecular descriptors that were tested are those included in Todeschini's Dragon 4.0 program.[46] They may be grouped according to their dimensionality from zero to three. Only representative descriptors that have nonzero values have been selected.

Zero-dimensional (0D) molecular descriptors are five constitutional data (Sp, Ss, Mv, Ms, and Mp). The 1D descriptors are grouped into three classes: functional group descriptors (nCaH, nCaR, nPhX, nHACC);[47] empirical descriptors (Ui, Hy, ARR);[47] and property descriptors (MR, PSA, MLOGP).[48–50] The 2D descriptors are 18 topological indices[51–65] (ZM1, ZM1V, ZM2,

ZM2V, Qindex, G Nar, Dz, SMTI, W, Har, w, TI1, TI2, J, SOK, Lop, BAC, VRD), 12 two-dimensional autocorrelation indices[66–68] (ATS1m, ATS2m, ATS3m, ATS1v, ATS2v, ATS3v, ATS1e, ATS2e, ATS3e, ATS1p, ATS2p, ATS3p) and 6 molecular content descriptors[69–72] (MWC01, MWC02, TWC, SRW02, SRW04, SRW06). From the 3D molecular descriptors 18 geometric indices were selected (W3D, J3D, H3D, AGDD, DDI, ADDD, G1, G2, Rgyr, SPAN, SPAM, Mecc, SPH, ASP, FDI, PJI3, L/Bw, Seig).[74–78]

Quantum-chemical descriptors were additionally chosen, namely total energy, E_t, E_{HOMO} and E_{LUMO}, calculated with the semiempirical MNDO method as implemented by the Hyperchem 7.0 program.

After computing all descriptors, they were converted into common logarithms and correlations with TEF data were explored using the Origin 6.0 program, after eliminating zero-value descriptors. In agreement with previous papers by Basak,[64,79] there are four levels of significance for molecular descriptors, conveying topostructural, topochemical, geometric, and quantum-chemical information.

Separate QSAR correlations were studied using the CODESSA program elaborated by Katritzky, Karelson, and Lobanov.[80–83] Again, hundreds of molecular descriptors (structural, topological, quantum-chemical) are used and selected for the best correlation with a specified number of descriptors.

QSAR results

The best results with the lowest numbers of molecular descriptors are presented separately for the three classes of polychloro aromatic compounds, in each case with three QSAR equations: one (A), starting with the Dragon program, and two other ones (B and C) continuing with the CODESSA program.

1. Polychlorodibenzofurans

A. Dragon program (24 compounds) (Table 4 and Figure 1)

Two PCDFs from the original set were left out.

$$\log TEF = -5.013(\pm 0.653)\cdot DP05 + 0.774(\pm 0.180)\cdot AGDD - 39.36 \quad (1A)$$

n = 24; r = 0.925; s = 0.472; F = 62.43; Q = 1.959

DP05: Randic molecular profile number 05.

AGDD: Average geometric distance degree.

Table 4. Descriptors and TEF data for polychlorodibenzofurans (Dragon)

Entry	Position of Cl	DP05	AGDD	logTEF (obs.)	logTEF (calc.)	Residual
1	2	5.63	80.90	-4.55	-5.06	0.51
2	4	5.39	80.79	-4.50	-3.97	-0.53
3	2,3	6.06	82.08	-6.33	-6.32	-0.01
4	2,8	6.06	82.00	-6.05	-6.38	0.33
5	2,3,7	6.64	83.26	-8.10	-8.33	0.23
6	2,3,8	6.48	83.18	-7.00	-7.58	0.58
7	2,6,7	6.43	83.07	-7.35	-7.41	0.06
8	2,3,4	6.16	83.06	-5.72	-6.05	0.33
9	1,2,3,6	6.38	83.81	-7.46	-6.67	-0.79
10	1,2,3,7	6.65	84.00	-7.96	-7.79	-0.17
11	1,2,4,8	6.29	83.74	-6.00	-6.20	0.20
12	2,3,4,6	6.42	84.05	-7.46	-6.59	-0.87
13	2,3,6,8	6.66	84.18	-7.66	-7.70	0.04
14	2,3,7,8	6.87	84.36	-8.60	-8.60	0.00
15	1,2,3,7,8	6.86	85.09	-8.12	-7.98	-0.14
16	1,2,3,7,9	6.66	84.73	-7.40	-7.28	-0.12
17	1,2,4,7,9	6.47	84.55	-5.70	-6.46	0.76
18	1,3,4,7,8	6.80	84.99	-7.70	-7.76	0.06
19	2,3,4,7,8	6.97	85.34	-8.82	-8.36	-0.47
20	2,3,4,7,9	6.75	84.90	-7.70	-7.54	-0.16
21	1,2,4,6,7,8	6.79	85.89	-6.08	-7.02	0.94
22	2,3,4,6,7,8	7.06	86.32	-8.33	-8.05	-0.28
23	1,2,3,4,7,8	6.97	86.07	-7.64	-7.80	0.16
24	1,2,3,6,7,8	6.98	86.07	-7.57	-7.84	0.27

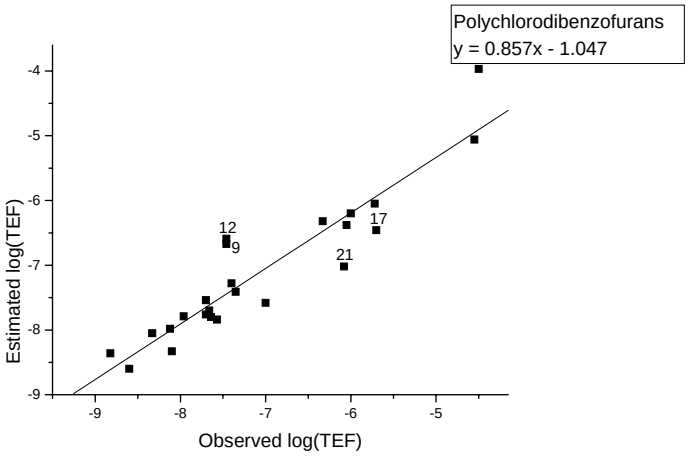

Figure 1. Experimental versus estimated TEF for PCDBFs.

B. CODESSA program with two descriptors (26 compounds) (Table 5 and Figure 2)

$$\log TEF = -3.048\cdot10^{3}(\pm3.501\cdot10^{2})\text{MinERIC} + 0.906(\pm0.094)\text{Min e–nA}_{\text{C–Cl}} - 366.\mathbf{9} \quad (1B)$$

n = 26; r = 0.919; s = 0.520; F = 63.08; Q = 1.767

MinERIC: Minimum electrophilic reactivity index for a C atom.

Min e-nAt$_{C–Cl}$: Minimum e–n attraction for a C–Cl bond.

Table 5. Two descriptors and TEF data for polychlorodibenzofurans (CODESSA)

Entry	Position of Cl	MinERIC	Min e-n$At_{C\text{-}Cl}$	logTEF (obs.)	logTEF (calc.)	Residual
1	1	$6.54\cdot10^{-5}$	397.8	-5.53	-6.32	-0.79
2	2	$4.18\cdot10^{-4}$	400.9	-4.55	-5.00	-0.45
3	4	$4.15\cdot10^{-4}$	400.6	-4.50	-4.83	-0.33
4	2,3	$2.93\cdot10^{-4}$	398.7	-6.33	-6.22	0.10
5	2,6	$4.48\cdot10^{-4}$	400.6	-4.61	-4.90	-0.29
6	2,8	$6.75\cdot10^{-4}$	400.6	-6.05	-5.69	0.36
7	2,3,4	$3.09\cdot10^{-4}$	398.9	-5.72	-6.08	-0.36
8	2,3,7	$7.99\cdot10^{-4}$	398.4	-8.10	-8.01	0.09
9	2,3,8	$4.44\cdot10^{-4}$	398.6	-7.00	-6.75	0.25
10	2,6,7	$5.73\cdot10^{-4}$	398.7	-7.35	-7.09	0.26
11	1,2,3,6	$4.38\cdot10^{-4}$	397.5	-7.46	-7.74	-0.28
12	1,2,3,7	$5.23\cdot10^{-4}$	397.5	-7.96	-7.96	0.00
13	1,2,4,8	$5.04\cdot10^{-6}$	398.1	-6.00	-5.86	0.14
14	2,3,4,6	$3.52\cdot10^{-4}$	398.8	-7.46	-6.26	1.20
15	2,3,6,8	$4.52\cdot10^{-4}$	398.5	-7.66	-6.83	0.83
16	2,3,7,8	$1.18\cdot10^{-3}$	398.6	-8.60	-9.03	-0.43
17	1,2,3,7,8	$4.42\cdot10^{-4}$	397.5	-8.12	-7.77	0.35
18	1,2,3,7,9	$3.39\cdot10^{-4}$	397.3	-7.40	-7.63	-0.23
19	1,2,4,7,9	$8.61\cdot10^{-5}$	397.3	-5.70	-6.89	-1.19
20	1,3,4,7,8	$2.49\cdot10^{-4}$	397.6	-7.70	-7.05	0.65
21	2,3,4,7,8	$1.08\cdot10^{-3}$	398.5	-8.82	-8.77	0.05
22	2,3,4,7,9	$3.15\cdot10^{-4}$	397.4	-7.70	-7.49	0.21
23	1,2,4,6,7,8	$3.89\cdot10^{-5}$	398.8	-6.08	-6.01	0.07
24	1,2,3,4,7,8	$3.34\cdot10^{-7}$	397.7	-7.64	-7.28	0.36
25	1,2,3,6,7,8	$4.32\cdot10^{-4}$	397.4	-7.57	-7.79	-0.22
26	2,3,4,6,7,8	$1.13\cdot10^{-3}$	398.8	-8.33	-8.70	-0.37

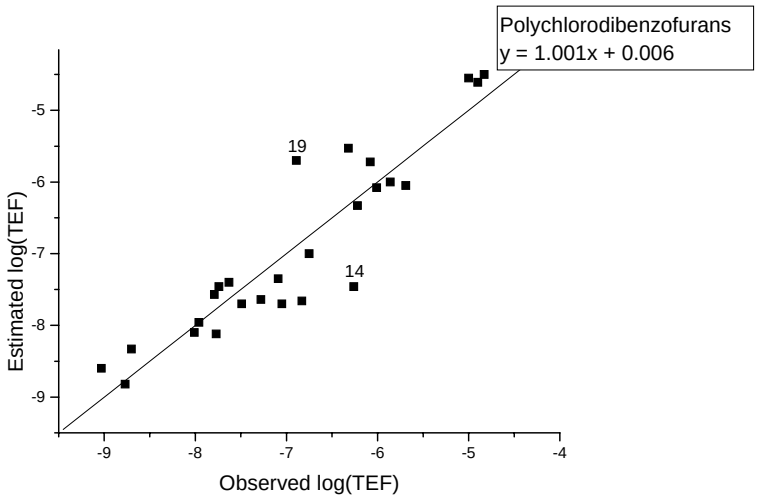

Figure 2. Experimental versus estimated TEF for PCDBFs (eq. 1B).

C. CODESSA program with three descriptors (26 compounds) (Table 6 and Figure 3)

$$\log TEF = -2.851\cdot10^{3}(\pm2.961\cdot10^{2})\text{MinERIC} + 0.826(\pm0.085)\ \text{Min e-nAt}_{C-Cl} + 2.253\cdot10^{2}(\pm66.65)\ \text{MNRIC} - 338.1 \quad (1C)$$

n = 26; r = 0.947; s = 0.431; F = 64.93; Q = 2.197
MinERIC: Minimum electrophilic reactivity index for a C atom
Min e-nAt$_{C-Cl}$: Minimum e–n attraction for a C–Cl bond
MNRIC: Maximum nucleophilic reactivity index for a C atom

Table 6. Three descriptors and TEF data for polychlorodibenzofurans (CODESSA)

No.	Position of Cl	MinERIC	Min e-nAt$_{C-Cl}$	MNRIC	logTEF (obs.)	logTEF (calc.)	Residual
1	1	$6.54\cdot10^{-5}$	397.8	0.016	-5.53	-5.84	-0.31
2	2	$4.18\cdot10^{-4}$	400.9	0.015	-4.55	-4.55	0.00
3	4	$4.15\cdot10^{-4}$	400.6	0.014	-4.50	-4.74	-0.24
4	2,3	$2.93\cdot10^{-4}$	398.7	0.016	-6.33	-5.90	0.43
5	2,6	$4.48\cdot10^{-4}$	400.6	0.017	-4.61	-5.06	-0.45
6	2,8	$6.75\cdot10^{-4}$	400.6	0.012	-6.05	-6.17	-0.12
7	2,3,4	$3.09\cdot10^{-4}$	398.9	0.016	-5.72	-5.62	0.10
8	2,3,7	$7.99\cdot10^{-4}$	398.4	0.014	-8.10	-7.92	0.18
9	2,3,8	$4.44\cdot10^{-4}$	398.6	0.015	-7.00	-6.44	0.56
10	2,6,7	$5.73\cdot10^{-4}$	398.7	0.013	-7.35	-7.20	0.15
11	1,2,3,6	$4.38\cdot10^{-4}$	397.5	0.014	-7.46	-7.73	0.27
12	1,2,3,7	$5.23\cdot10^{-4}$	397.5	0.013	-7.96	-7.98	-0.02
13	1,2,4,8	$5.04\cdot10^{-6}$	398.1	0.012	-6.00	-6.28	-0.28
14	2,3,4,6	$3.52\cdot10^{-4}$	398.8	0.013	-7.46	-6.61	0.86
15	2,3,6,8	$4.52\cdot10^{-4}$	398.5	0.014	-7.66	-6.79	0.87
16	2,3,7,8	$1.18\cdot10^{-3}$	398.6	0.013	-8.60	-9.03	-0.43
17	1,2,3,7,8	$4.42\cdot10^{-4}$	397.5	0.014	-8.12	-7.69	0.43
18	1,2,3,7,9	$3.39\cdot10^{-4}$	397.3	0.013	-7.40	-7.73	-0.33
19	1,2,4,7,9	$8.61\cdot10^{-5}$	397.3	0.015	-5.70	-6.53	-0.83
20	1,3,4,7,8	$2.49\cdot10^{-4}$	397.6	0.012	-7.70	-7.47	0.23
21	2,3,4,7,8	$1.08\cdot10^{-3}$	398.5	0.013	-8.82	-8.82	0.00
22	2,3,4,7,9	$3.15\cdot10^{-4}$	397.4	0.014	-7.70	-7.44	0.26
23	1,2,4,6,7,8	$3.89\cdot10^{-5}$	398.1	0.012	-6.08	-6.44	-0.36
24	1,2,3,4,7,8	$3.34\cdot10^{-7}$	397.7	0.012	-7.64	-7.66	-0.02
25	1,2,3,6,7,8	$4.32\cdot10^{-4}$	397.4	0.014	-7.57	-7.62	-0.05
26	2,3,4,6,7,8	$1.13\cdot10^{-3}$	398.8	0.014	-8.33	-8.68	-0.34

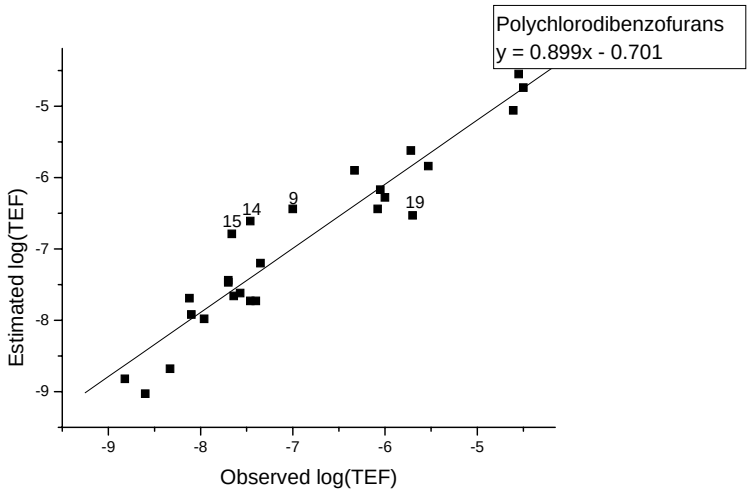

Figure 3. Experimental versus estimated TEF for PCDBFs (eq. 1C).

2. Polychlorodibenzo-1,4-dioxins

A. Dragon program with three descriptors (Table 7 and Figure 4)

$$\log TEF = -22.11(\pm 13.59)\ Hy - 96.15(\pm 50.36)\cdot BLTF96 + 86.62(\pm 41.46)\cdot BLTA96 + + 6.684(\pm 1.247)\cdot GGI3 - 40.30 \quad (2A)$$

n = 14; r = 0.936; s = 0.451; F = 16.17; Q = 2.075
Hy: Hydrophilic factor
BLTF96: Verhaal model of Fish base-line toxicity from MLOGP (mmol/L)
BLTA96: Verhaal model of Algae base-line toxicity from MLOGP (mmol/L)
GGI3: Topological charge index of order 3

Table 7. Descriptors and TEF data for polychlorodibenzo-1,4-dioxins (Dragon)

Entry	Position of Cl	Hy	BLTF96	BLTA96	GGI3	logTEF (obs.)	logTEF (calc.)	Residual
1	1	-0.78	-3.88	-4.16	0.81	-5.00	-4.89	-0.11
2	2,8	-0.73	-4.10	-4.42	0.88	-6.49	-6.88	0.39
3	1,2,4	-0.69	-4.32	-4.68	1.31	-5.88	-6.25	0.37
4	2,3,7	-0.69	-4.32	-4.68	1.06	-8.15	-7.92	-0.23
5	2,3,6	-0.69	-4.32	-4.68	1.19	-7.66	-7.05	-0.61
6	1,2,3,4	-0.65	-4.53	-4.93	1.63	-6.88	-6.47	-0.41
7	1,3,7,8	-0.65	-4.53	-4.93	1.50	-7.10	-7.30	0.20
8	2,3,7,8	-0.65	-4.53	-4.93	1.25	-9.00	-8.97	-0.03
9	2,3,6,7	-0.65	-4.53	-4.93	1.38	-7.79	-8.13	0.34
10	1,2,3,4,7	-0.62	-4.74	-5.17	1.81	-6.19	-6.54	0.35
11	1,2,3,7,8	-0.62	-4.74	-5.17	1.69	-8.10	-7.38	-0.72
12	1,2,4,7,8	-0.62	-4.74	-5.17	1.69	-6.96	-7.38	0.42
13	1,2,3,4,7,8	-0.59	-4.94	-5.41	2.00	-7.55	-7.53	-0.02
14	octachloro	-0.58	-5.33	-5.88	2.75	-6.00	-6.01	0.01

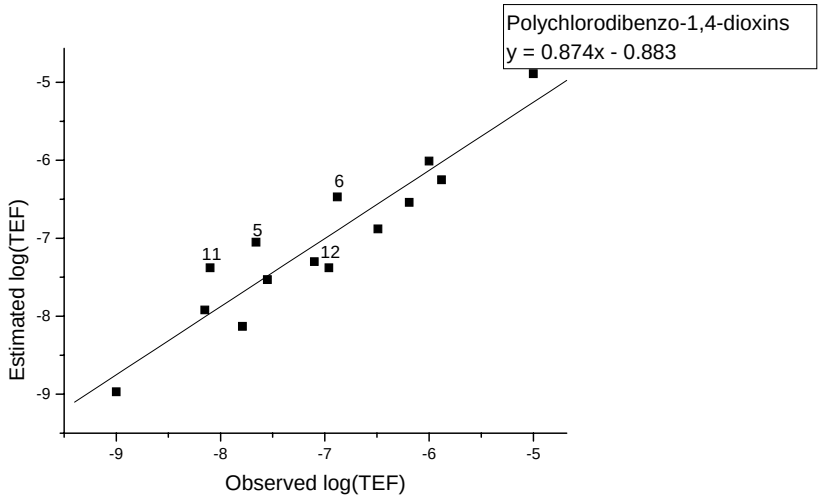

Figure 4. Experimental versus estimated TEF for PCDBDs (eq. 2A).

B. CODESSA program with two descriptors (Table 8 and Figure 5)

$$\log TEF = 6.813 \cdot 10^2(\pm 92.98)MNRIO + 6.754 \cdot 10^2(\pm 92.01)AVC - 2.667 \qquad (2B)$$

n = 14; r = 0.940; s = 0.398; F = 41.92; Q = 2.361
MNRIO: Maximum nucleophilic reactivity index for a O atom
AVC: Average valency of a C atom

Table 8. Two descriptors and TEF data for polychlorodibenzo-1,4-dioxins (eq. 2B)

Entry	Position of Cl	MNRIO	AVC	logTEF (obs.)	logTEF (calc.)	Residual
1	1	0.016	3.925	-5.00	-5.12	-0.12
2	2,8	0.015	3.923	-6.49	-6.84	-0.35
3	1,2,4	0.015	3.925	-5.88	-5.60	0.28
4	2,3,7	0.014	3.924	-8.15	-7.24	0.42
5	2,3,6	0.013	3.923	-7.66	-7.87	0.28
6	1,2,3,4	0.014	3.926	-6.88	-6.12	0.76
7	1,3,7,8	0.014	3.923	-7.10	-7.56	-0.46
8	2,3,7,8	0.013	3.924	-9.00	-7.82	-0.03
9	2,3,6,7	0.012	3.923	-7.79	-8.77	0.23
10	1,2,3,4,7	0.014	3.925	-6.19	-6.62	-0.43
11	1,2,3,7,8	0.012	3.924	-8.10	-7.97	0.13
12	1,2,4,7,8	0.013	3.924	-6.96	-7.36	-0.42
13	1,2,3,4,7,8	0.012	3.925	-7.55	-7.59	-0.04
14	octachloro	0.011	3.928	-6.00	-6.25	-0.25

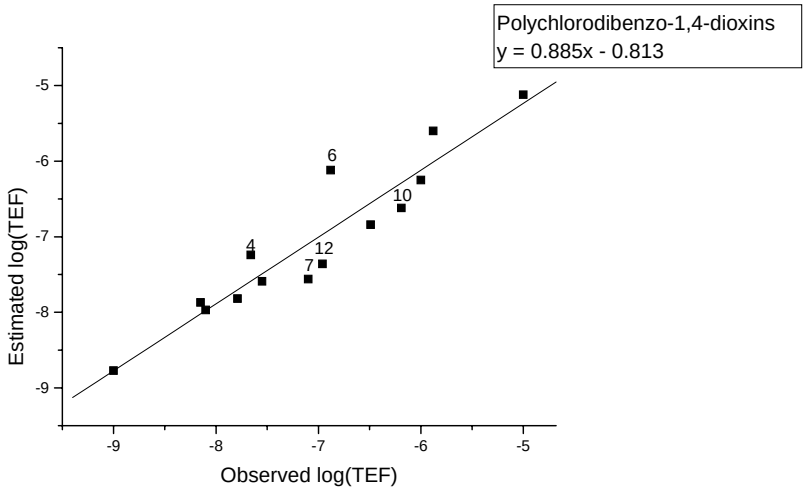

Figure 5. Experimental versus estimated TEF for PCDBDs (eq. 2B).

C. CODESSA program with three descriptors (Table 9 and Figure 6)

$$\log TEF = -4.507(\pm 0.301)AVC1 - 8.596\cdot 10^{2}(\pm 52.94)MNRIO - 1.639\cdot 10^{2}(\pm 18.54)AVO - 372.6 \quad (2C)$$

n = 14; r = 0.986; s = 0.200; F = 121.4; Q = 4.930
AVC1: Average Information content (order 1)
MNRIO: Maximum nucleophilic reactivity index for a O atom
AV: Average valency of an O atom.

Table 9. Three descriptors and TEF data for polychlorodibenzo-1,4-dioxins (eq. 2)

Entry	Position of Cl	AVC1	MNRIO	AVO	logTEF (obs.)	logTEF (calc.)	Residual
1	1	2.22	0.016	2.222	-5.00	-4.97	0.03
2	2,8	2.41	0.015	2.220	-6.49	-6.59	-0.10
3	1,2,4	2.51	0.015	2.228	-5.88	-5.72	0.16
4	2,3,7	2.51	0.014	2.225	-8.15	-7.37	0.29
5	2,3,6	2.52	0.013	2.223	-7.66	-8.02	0.13
6	1,2,3,4	2.55	0.014	2.229	-6.88	-6.91	-0.03
7	1,3,7,8	2.55	0.014	2.226	-7.10	-7.28	-0.18
8	2,3,7,8	2.55	0.013	2.226	-9.00	-7.94	-0.15
9	2,3,6,7	2.55	0.012	2.224	-7.79	-9.09	-0.09
10	1,2,3,4,7	2.51	0.014	2.230	-6.19	-6.56	-0.37
11	1,2,3,7,8	2.52	0.012	2.228	-8.10	-8.02	0.08
12	1,2,4,7,8	2.51	0.013	2.230	-6.96	-6.92	0.04
13	1,2,3,4,7,8	2.42	0.012	2.232	-7.55	-7.31	0.24
14	octachloro	1.82	0.011	2.227	-6.00	-6.05	-0.05

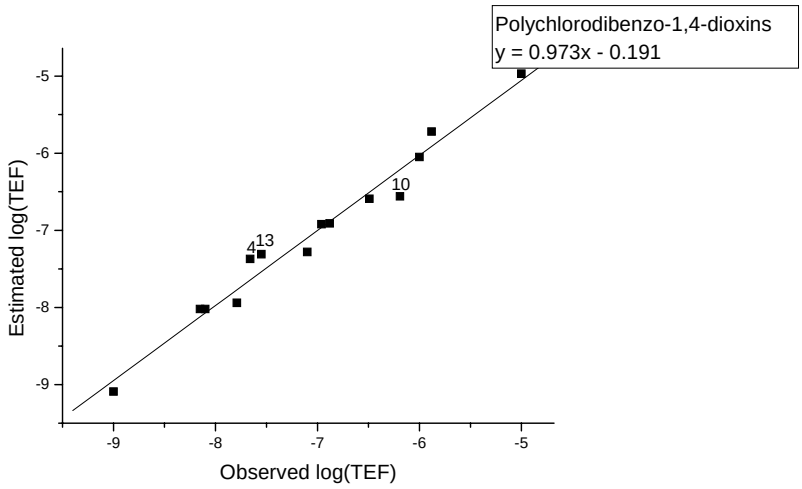

Figure 6. Experimental versus estimated TEF for PCDBDs (eq. 2C).

3. Polychlorobiphenyls

A. Dragon program with four descriptors (Table 10 and Figure 7)

$$\log TEF = -6.167(\pm 0.963)DP05 + 0.295(\pm 0.204)ATS3e - 2.130(\pm 0.920)MLOGP - 7.407(\pm 3.106)RDF015v + 83.10 \quad (3A)$$

n = 12; r = 0.927; s = 0.437; F = 10.62; Q = 2.121

DP05: Randic molecular profile number 05

ATS3e: Broto-Moreau autocorrelation of topological strucuture-lag3/weighted by atomic Sanderson

MLOGP: Moriguchi octanol-water partition coefficient (log P)

RDF015v: Radial distribution function-1.5/ weighted by atomic van der Waals volumes

Table 10. Four descriptors and TEF data for polychlorobiphenyls (eq. 3A)

Entry	Position of Cl	DP05	ATS3e	MLOGP	RDF 015v	logTEF (obs.)	logTEF (calc.)	Residual
1	2,3,4,5	6.30	49.11	6.42	6.66	-4.85	-4.27	0.58
2	2,3,4,4’	6.73	49.01	5.94	6.66	-5.55	-5.93	-0.38
3	2,2’,4,4’	6.56	48.82	6.42	6.55	-4.89	-5.14	-0.25
4	3,3’,4,4’	6.95	48.99	6.19	6.54	-7.37	-6.93	0.44
5	2,3,4,4’,5	6.87	50.36	6.42	6.55	-6.38	-6.60	-0.22
6	2,3,3’,4,4’	6.94	50.36	6.19	6.55	-6.15	-6.54	-0.39
7	3,3’,4,4’5	7.07	50.34	6.19	6.55	-7.92	-7.35	0.57
8	2,3’,4,4’,5	6.88	50.26	6.19	6.55	-6.04	-6.20	-0.16
9	2’,3’4,4’,5	6.88	50.36	5.94	6.54	-5.85	-5.57	0.28
10	2,3,3’,4,4’,5	7.06	51.82	5.94	6.54	-6.30	-6.25	0.05
11	2,2’,4,4’,5,5’	6.92	51.53	6.19	6.44	-5.10	-5.26	-0.16
12	2,3’,4,4’,5,5’	7.06	51.61	5.94	6.43	-5.80	-5.49	0.31

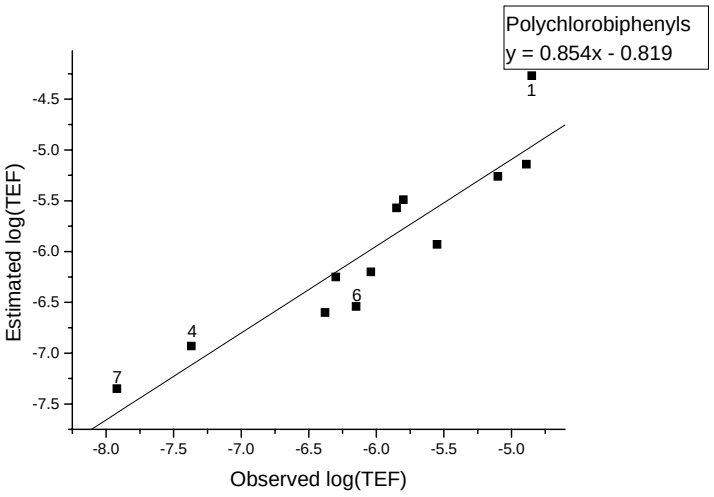

Figure 7. Experimental versus estimated TEF for PCBs (eq. 3A).

B. CODESSA program with two descriptors (Table 11 and Figure 8)

$$\log TEF = -1.778(\pm 0.311)n\text{-}nR_{C\text{-}Cl} + 1.308\cdot 10^{4}(\pm 3.399\cdot 10^{3})PMIC + 333.7 \quad (3B)$$

n = 12; r = 0.934; s = 0.366; F = 30.77; Q = 2.551
$n\text{-}nR_{C\text{-}Cl}$: Minimum n-n repulsion for a C-Cl bond
PMIC: Principal moment of inertia C / # of atoms

Table 11. Two descriptors and TEF data for polychlorobiphenyls (eq.3 B)

Entry	Position of Cl	$n\text{-}nR_{C\text{-}Cl}$	PMIC	logTEF (obs.)	logTEF (calc.)	Residual
1	2,3,4,5	192.4	$2.64\cdot 10^{-4}$	-4.85	-4.85	0.00
2	2,3,4,4’	192.3	$2.06\cdot 10^{-4}$	-5.55	-5.60	-0.05
3	2,2’,4,4’	192.2	$2.41\cdot 10^{-4}$	-4.89	-4.87	0.01
4	3,3’,4,4’	193.3	$1.77\cdot 10^{-4}$	-7.37	-7.70	-0.33
5	2,3,4,4’,5	192.4	$1.76\cdot 10^{-4}$	-6.38	-6.09	0.29
6	2,3,3’,4,4’	192.2	$1.79\cdot 10^{-4}$	-6.15	-5.70	0.45
7	3,3’,4,4’5	193.1	$1.61\cdot 10^{-4}$	-7.92	-7.51	0.41
8	2,3’,4,4’,5	192.4	$1.84\cdot 10^{-4}$	-6.04	-5.92	0.12
9	2’,3’4,4’,5	192.3	$1.76\cdot 10^{-4}$	-5.85	-5.84	0.01
10	2,3,3’,4,4’,5	192.3	$1.53\cdot 10^{-4}$	-6.30	-6.14	0.16
11	2,2’,4,4’,5,5’	192.2	$1.75\cdot 10^{-4}$	-5.10	-5.68	-0.58
12	2,3’,4,4’,5,5’	192.4	$1.60\cdot 10^{-4}$	-5.80	-6.31	-0.51

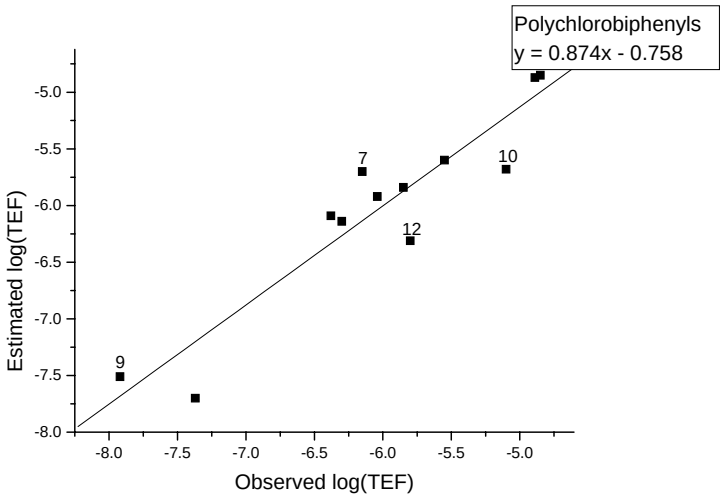

Figure 8. Experimental versus estimated TEF for PCBs (eq. 3B).

C. CODESSA program with three descriptors (Table 12 and Figure 9)

$$\log TEF = 6.798\cdot10^{3}(\pm4.993\cdot10^{3})A1eRIC - 9.318\cdot10^{2}(\pm49.28)MVC - 3.351\cdot10^{3}(\pm4.495\cdot10^{2})AERICl + 3.678\cdot10^{3} \quad (3C)$$

n = 12; r = 0.990; s = 0.146; F = 143.6; Q = 6.780
A1eRIC: Average 1-electron reactivity index for a C atom
MVC: Max valency of a C atom
AERICl: Average electrophilic reactivity index for a Cl atom.

Table 12. Three descriptors and TEF data for polychlorobiphenyls (eq. 3C)

Entry	Position of Cl	A1eRIC	MVC	AERICl	logTEF (obs.)	logTEF (calc.)	Residual
1	2,3,4,5	$2.12\cdot10^{-4}$	3.950	$1.04\cdot10^{-3}$	-4.85	-4.81	0.04
2	2,3,4,4’	$9.87\cdot10^{-5}$	3.952	$6.21\cdot10^{-4}$	-5.55	-5.51	0.04
3	2,2’,4,4’	$-1.15\cdot10^{-7}$	3.950	$5.81\cdot10^{-4}$	-4.89	-4.76	0.13
4	3,3’,4,4’	$5.57\cdot10^{-7}$	3.953	$6.20\cdot10^{-4}$	-7.37	-7.40	-0.03
5	2,3,4,4’,5	$-1.07\cdot10^{-4}$	3.953	$7.06\cdot10^{-4}$	-6.38	-6.49	-0.11
6	2,3,3’,4,4’	$2.43\cdot10^{-5}$	3.952	$5.67\cdot10^{-4}$	-6.15	-6.39	-0.24
7	3,3’,4,4’5	$3.58\cdot10^{-6}$	3.953	$6.44\cdot10^{-4}$	-7.92	-7.70	0.22
8	2,3’,4,4’,5	$2.15\cdot10^{-4}$	3.953	$6.08\cdot10^{-4}$	-6.04	-6.05	-0.01
9	2’,3’4,4’,5	$1.10\cdot10^{-4}$	3.951	$5.56\cdot10^{-4}$	-5.85	-5.74	0.11
10	2,3,3’,4,4’,5	$3.37\cdot10^{-5}$	3.952	$7.18\cdot10^{-4}$	-6.30	-6.26	0.04
11	2,2’,4,4’,5,5’	$6.49\cdot10^{-7}$	3.950	$6.89\cdot10^{-4}$	-5.10	-5.17	-0.06
12	2,3’,4,4’,5,5’	$2.36\cdot10^{-4}$	3.953	$7.12\cdot10^{-4}$	-5.80	-5.93	-0.13

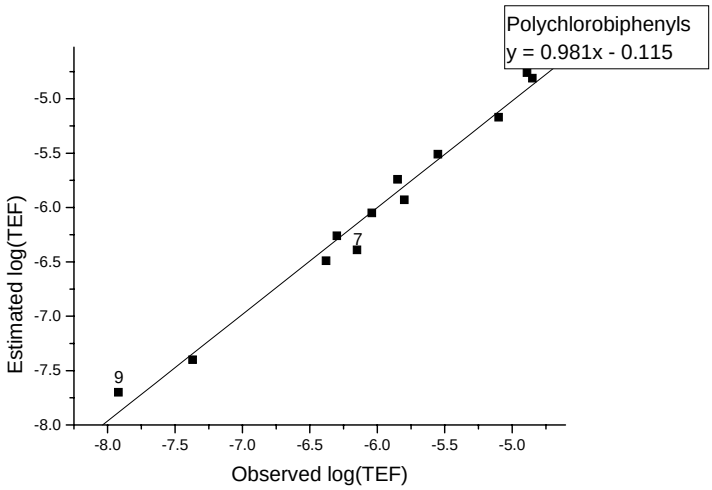

Figure 9. Experimental versus estimated TEF for PCBs (eq. 3C).

Discussion of Results

In Tables 4–12 one can see for each of the polychloroaromatic compound the parameters selected for the QSAR, the experimental and calculated logTEF values, and the difference (residual) between these two values. Diagrams presented in Figures 1–9 indicate the linear dependence between experimental and calculated TEF values, and the equation for the linear correlation that may be used for prediction within each class with the corresponding molecular descriptors.

The correlation coefficients r are satisfactory in all cases. Only two molecular descriptors appear twice: DP05 (a Randić-type molecular profile, which appears in two equations, namely eq. 1A and 3A with similar negative coefficients) and MNRIO (the nucleophilic reactivity of the oxygen heteroatom, which appears in eq. 2B and 2C). Attempts to find a unique set of up to four molecular descriptors for the combined set of all 50 or 52 polychloroaromatic compounds did not yield any correlation with $r > 0.90$.

On comparing the r values for the QSAR obtained with the Dragon and CODESSA programs, one may see that for a comparable number of descriptors the latter program yields higher r and lower s values. Of course, these two programs are based on different molecular descriptors, so that for predictions of unknown representatives from each class, one should compare the results for each of the three equations A, B, or C in the corresponding class.

Out of 209 possible PCBs, the present correlation covers only 12 (about 6%); out of the 75 possible PCDDs, equations 2A–2C include only 14 structures (about 19%); and out of the 135 possible PCDFs, we have toxicity data only for 26 compounds (also about 19%).

One can argue that the range of toxicities (3.5 for PCBs or 4 orders of magnitude for PCDDs and PCDFs) may not be large enough for all structural effects to become manifest. This is probably true for the PCBs, where out of 10 possible substitution sites only 3–6 correspond to experimentally known toxicity data. In the case of PCDD there are toxicity data for compounds from mono- to all octa-substitution sites, whereas for PCDFs out of the 8 substitution sites there are toxicity data from mono- to hexa-substituted compounds. However, many possible substitution patterns are absent from the experimental data. Therefore, till more experimental data will become available, it is still difficult to argue whether the present correlations may serve for predicting accurately toxicity values for the remaining polychloroaromatics from the three classes of compounds examined here. What can be undeniably inferred from examining the toxicity data is that no single factor or parameter is responsible for the global toxicity of these compounds. Rather, a subtle combination of electronic, steric, geometric (i. e. dihedral angle for PCBs), and hydrophobic effects are at play in determining interactions with cellular receptors that become responsible for the high toxicity of some of the polychloroaromatics.

We believe, however, that the present QSAR study can provide an informed guess about the toxicity of the many still unknown compounds from the three classes of polychloroaromatics examined here.

Conclusions

Di-, tri-, or tetra-parametric linear correlations between toxicity values (logTEF) of three classes of polychloroaromatics, namely polychlorobiphenyls (PCBs), polychlorodibenzo-1,4-dioxins (PCDDs), and polychlorodibenzofurans (PCDFs) have been presented. This QSAR study has used the Dragon program of Todeschini and the CODESSA program of Katritzky and their coworkers. The latter program was slightly superior.

Only about 6% of all possible PCBs, and 19% of all possible PCDDs and PCDFs were available with such toxicity data, but since 3.5–4 orders of magnitude of toxicities were involved, one may confidently assume that most major structural factors could manifest themselves in these data. However, many substitution patterns are not present in the experimentally available toxicity data, so that some of these patterns may escape detection.

Qualitatively, one may infer that the highest toxicity is observed with 3,3’,4,4’-tetrachlorobiphenyls (possibly with supplemental 3’ or 5’ chloro substituents) but devoid of *ortho*-chloro substituents. Apart from 2,3,7,8-tetrachloro-1,4-dibenzodioxin with the highest known toxicity of polychloroaromatics so far, any dioxin or dibenzofuran with at least one or two chlorine substituents on each benzenoid ring in positions 2,3,6,or 7 has a significant toxicity.

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