RELATIONSHIPS BETWEEN ENERGY OF LUMO AND DIOXIN-LIKE ACTIVITY OF PCNs IN THE LUCIFERASE TEST

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Introduction

Polychlorinated naphthalenes (PCNs) are industrial chemicals which found numerous applications and were used world-wide since 1910. Those chemicals become a widespread environmental pollutants and recently a congener-specific data exist on their concentrations and patterns in abiotic and biotic samples from the various sites in the northern hemisphere. As reviewed recently (1) the environmental contamination with chloronaphthalenes is caused mainly due to manufacture and open use of this compounds in the past, while partly also to their presence as technical impurities in industrial mixtures of polychlorinated biphenyls (PCBs) and due to unintentional formation during various anthropogenic processes such as incineration, metal smelting or metal ore roasting *etc.*

There is a number of data available on toxicity of technical mixtures of PCNs, and mainly of the Halowax series (2). It is believed that the adverse effects associated to technical PCN exposure may be in a large part explained due to an aryl hydrocarbon receptor (AhR)- dependent mechanism of action (3-7). Nevertheless, in the case of technical PCN formulations also other dioxin-like compounds such as polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) or planar PCBs are of concern, which can co-occurrence is possible as impurities and which can act synergistically to effects caused by highly toxic congeners of chloronaphthalene.

Molecular modelling of the steric and molecular orbital parameters associated with various PCN congeners could help to elucidate the relationship between PCN structure and dioxin-like potency (8-9). The results of principal component analysis (PCA) of various physico-chemical features of all 75 chloronaphthalene congeners (10) has indicated on energy of LUMO as one of a significant descriptors of differences existing between PCNs. An attempt was taken and the model describing relationships between selected physico-chemical features of all 75 chloronaphthalene congeners and relative potencies to induce Ah receptor-mediated responses in the rat hepatoma H4IIE-Luc was created.

Key words: polychlorinated naphthalenes, PCNs, CNs, multiple regression, dioxin-like activity

Materials and Methods

The selected physico-chemical characteristics such as energy of LUMO and specific polarizability for all 75 chloronaphthalene congeners were taken from Falandysz *et al.* (9-10). The available

data on relative dioxin-like potencies of PCNs in the rat hepatoma H4IIE-Luc cell bioassay were taken from Blankenship *et al.* (4, 5) and Villeneuve *et al.* (6). The model is build up based on H4IIE luciferase induction data conducted for 11 congeners of chloronaphthalene. The multiple regression analysis (11) was applied to build a regression equation describing relationship between PCN congener activity and selected physico-chemical data.

Results and Discussion

A multiple linear regression model (Figure 1) describing the relationship between Log (1/H4IIE-Luc) and 2 independent variables is given as the equation (1):

$$\text{Log (1/H4IIE-Luc)} = 840.842 + 26.6992 \bullet \text{LUMO} - 4199.39 \bullet \text{specific polarizability} \quad (1)$$

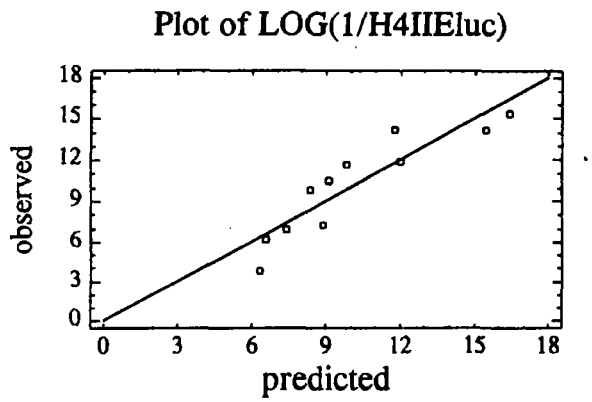

Figure 1. Relationship between observed and predicted values of Log (1/HII4E-Luc).

The p-values are less than 0.01 for each variable, the highest order term is statistically significant at the 99% confidence level (Table 1).

Table 1. Results of multiple regression analysis

Dependent variable: Log (1/H4IIE-Luc				
Independent variables:				
Parameter	Estimate	Standard error	T Statistic	p-value
Constant	840.842	119.47	7.03812	0.0001
Energy of LUMO	26.6992	6.71188	3.97791	0.0041
Specific polarizability	-4199.39	610.049	-6.88368	0.0001

Since the p-value of ANOVA (Table 2) is less than 0.01, there is a statistically significant relationship between the variables at the 99% confidence level.

Table 2. Results of analysis of variance (ANOVA)

Source	Sum of squares	Df	Mean square	F-ratio	P-value
Model	120.983	2	60.4913	25.46	0.0003
Residual	19.0109	8	2.37637		
Total (Corr.)	139.0109	10			

The R-squared statistic indicates that the model as fitted explains 86.4201% of the variability in Log (1/H4IIE-Luc). The adjusted R-squared statistic, which is more variable, is 83.0252%. The standard error of the estimate shows the standard deviation of the residuals is 1.54155. The mean absolute error (MAE) of 1.18107 is the average value of the residuals.

From the model (Figure 1) can be observed that PCN congeners with the lowest values of energy of LUMO are the most potent inducers of Ah receptor-mediated responses in the rat hepatoma HII4E-Luciferace cell bioassay. The congeners fully substituted with chlorine at the positions 1, 2, 3, 6 and 7 of the naphthalene nuclei are those with the lowest values of the energy of LUMO and they indicate the highest dioxin-like activity in the luciferase test. Next, it seems, that if only four of the positions 1, 2, 3, 6 and 7 of the naphthalene nuclei are occupied with chlorine such congeners are relatively less potent as the inducers of luciferase, and also their values of energy of LUMO are higher. And similarly, chloronaphthalene congeners, which are substituted with chlorine only at three of the five positions indicated has relatively higher values of energy of LUMO and seems to be much less potent as luciferase inducers than those with the higher substitution pattern.

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