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OPAHs对斑马鱼胚胎的急性毒性预测

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摘要: 含氧多环芳烃(OPAHs)是化石燃料不完全燃烧或多环芳烃化学氧化、光化学氧化和生物氧化形成的一类新污染物。迄今, 已有许多 OPAHs 在环境中被检出, 一些 OPAHs 具有发育毒性、致突变性和致癌性。但是, 仍有很多 OPAHs 缺少毒性数据。定量结构-活性关系(QSAR)可以预测 OPAHs 的毒性, 以减少昂贵、耗时、费力的毒性测试。本研究基于前人报道的斑马鱼(*Danio rerio*)胚胎毒性 $\log EC_{50}$ 实验数据, 采用 B3LYP/6-31G(d,p)方法优化分子结构, 计算量子化学描述符和 Dragon 描述符, 基于多元线性逐步回归方法构建了 OPAHs 的斑马鱼胚胎急性毒性 QSAR 模型。模型包含 4 个描述符: 化学势(μ)、最大电拓扑参数(MAXDP)、Moriguchi 正辛醇-水分配系数(MLOGP)和芳香性指数(AROM), 表明 OPAHs 的得失电子能力和疏水性是影响毒性的主要原因。模型的决定系数($R^2=0.781$)、外部验证以及去一法交叉验证结果表明, 模型具有较好的预测能力和稳健性。采用 Williams 图表征了模型的应用域。该模型可以用于 OPAHs 斑马鱼胚胎急性毒性的预测, 为其生态风险评价提供数据支持。

关键词: 含氧多环芳烃; 斑马鱼胚胎; 急性毒性; QSAR; 生态风险

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Prediction of Acute Toxicity by OPAHs to Zebrafish Embryos

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Abstract: Oxygenated polycyclic aromatic hydrocarbons (OPAHs) are a new type of pollutants formed through incomplete combustion of fossil fuels or chemical oxidation, photooxidation and biological oxidation of polycyclic aromatic hydrocarbons. To date, many OPAHs have been detected in the environment, and some OPAHs have developmental toxicity, mutagenicity and carcinogenicity. However, a lot of OPAHs still lack toxicity data. Quantitative structure-activity relationship (QSAR) can be used to predict toxicity of OPAHs to reduce cost, time and labor consuming from toxicity tests. Based on reported experimental $\log EC_{50}$ values of the zebrafish (*Danio rerio*) embryos, a QSAR model of acute toxicity for OPAHs was developed by stepwise multiple linear regression method. Based on the optimized molecular structure derived from B3LYP/6-31G(d,p) method, quantum chemical descriptors and Dragon descriptors were calculated. The optimized model was comprised of four descriptors including chemical po-

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tential (μ), maximal electrotopological positive variation topological indices (MAXDP), Moriguchi octanol-water partition coefficient (MLOGP) and aromaticity index geometrical descriptors (AROM). The descriptors indicated that the ability to gain and lose electrons and hydrophobicity of OPAHs were the main contribution to toxicity. The values of model coefficient determination ($R^2=0.781$), external validation and the leave-one-out cross validation showed that the model had good predictive ability and robustness. The application domain of the model was characterized based on Williams diagram. The model developed in this study can be used to predict the acute toxicity of OPAHs to zebrafish embryos and provide data for their ecological risk assessment.

Keywords: oxygenated polycyclic aromatic hydrocarbons; zebrafish embryos; acute toxicity; QSAR; ecological risk

含氧多环芳烃(oxygenated polycyclic aromatic hydrocarbon, OPAHs)是由化石燃料不完全燃烧,或多环芳烃(polycyclic aromatic hydrocarbon, PAHs)化学氧化、光化学氧化或生物氧化形成的一类新污染物^[1-3]。OPAHs表现出致癌性、致突变性和发育毒性等毒性^[4-7]。一些 OPAHs 产生的毒性效应比母体化合物更强。例如, Mattsson 等^[7]通过人肝癌细胞实验,发现一些 OPAHs 对 DNA 的损伤显著强于 PAHs。Chibwe 等^[8]的研究表明, PAHs 污染土壤经好氧生物修复后致突变性增强,认为与 OPAHs 等转化产物的生成有关。迄今,越来越多 OPAHs 在环境中被检出^[9],但是很多 OPAHs 的毒性数据仍然缺失。

采用实验方法获取 OPAHs 的毒性数据需要消耗大量的人力、经费和时间。为了减少动物实验和高效地获取毒性数据,计算模拟方法被越来越多地用于化学品的毒性预测。其中,定量构效关系(QSAR)方法可以通过揭示有机化合物分子结构和毒性之间联系,已经被成功用于多种有机污染物(如 PAHs、呋喃、二噁英以及多氯联苯等)的毒性预测^[10-12]。目前,关于 OPAHs 急性毒性的预测模型还鲜有报道。

本研究参照经济合作与发展组织(OECD)关于 QSAR 模型构建和评估的导则^[13],基于 Knecht 等^[4]通过斑马鱼胚胎急性毒性实验得到的 32 种 OPAHs 的毒性数据($\log EC_{50}$)(表 1),采用多元线性逐步回归法筛选 OPAHs 的描述符,建立 OPAHs 斑马鱼胚胎急性毒性的 QSAR 模型,验证其预测能力,表征了模型的应用域,为 OPAHs 的生态风险评估提供数据支持。

1 材料与方法 (Materials and methods)

基于 B3LYP/6-31G(d,p)方法,使用 Gaussian 09 软件^[14]优化分子结构,并计算了 19 种包含前线轨道能量、可极化率性、偶极矩以及部分原子电荷等在

量子化学描述符。借助 Dragon 6^[15]得到 4 885 种描述符,移去常数、近似常数和缺失值的描述符,得到可用的 2 629 种描述符。从美国环境保护局(US EPA)开发的 EPI SuiteTM 软件^[16]数据库中查询出正辛醇-水分配系数($\log K_{ow}$)。将毒性实验数据以 7:3 的比例划分为训练集(22 个 OPAHs)和验证集(10 个 OPAHs)进行模型构建和外部验证^[17],采用 IBM SPSS Statistic 21 中的多元线性逐步回归法构建了 OPAHs 的急性毒性模型。采用 Matlab 8.0 软件计算了模型的决定系数(R^2)、预测相关系数(Q^2)和表征模型随机误差的分散程度的均方根误差(RMSE)以评价模型的拟合优度和预测能力^[18]。基于 Hat-matrix 方法计算得到杠杆值的 Williams 图表征应用域,识别离群点^[19-20]。使用 Weka 3.0 软件进行去一法内部交叉验证,采用预测相关系数平方(Q^2_{cv})和均方根误差(RMSE_{cv})表征模型的稳健性^[21]。

2 结果 (Results)

2.1 模型的建立

本研究分别采用 Dragon 描述符、量子化学描述符以及综合以上 2 类描述符建立了 3 个 QSAR 模型(表 2)。基于 2 629 种 OPAHs Dragon 描述符,采用多元线性逐步回归法筛选出模型(1)的 R^2 为 0.524,表明模型的拟合优度不高。使用多元线性逐步回归法筛选量子化学描述符和 $\log K_{ow}$,建立了模型(2)的 R^2 为 0.436,模型的拟合优度也不高。本研究综合了量子化学描述符和 Dragon 描述符,得到模型(3),统计学参数表明,模型(3)的拟合优度较好,筛选出 4 种描述符包括化学势(μ)、最大电拓扑参数(MAXDP)、Moriguchi 正辛醇-水分配系数(MLOGP)和芳香性指数(AROM),说明量子化学描述符和 Dragon 描述符可以从不同的角度表征 OPAHs 的分子属性,更有利于揭示分子结构与其毒性的关联。由于模型

(1)和(2)不能满足预测的参数要求,下文重点对模型(3)进行了详细讨论。OPAHs 的斑马鱼胚胎急性毒性实验数据(logEC₅₀)和最优模型的预测数据以及筛选出 4 种描述符的具体数值分别如表 1 和表 2 所示。

表 1 OPAHs 的 logEC₅₀ 实验值与预测值及模型筛选出的分子描述符计算值
Table 1 The experimental and predicted values of logEC₅₀ for OPAHs and molecular descriptors values

序号 No.	OPAHs	logEC ₅₀		μ	MAXDP	MLOGP	AROM
		实验值 ^[4]	预测值				
		Experimental ^[4]	Predicted				
1	氧杂蒽酮 Xanthone	2.00	2.39	-0.148	5.03	2.44	0.984
2	1,2-苯并蒽醌 Aceanthrenequinone	1.95	1.55	-0.159	5.14	3.32	0.952
3	1,2-二羟基蒽醌 1,2-dihydroxyanthraquinone	2.27	1.78	-0.168	5.20	2.30	0.981
4	4,5-亚菲基酮 4,5-phenanthrylene ketone	1.48	1.49	-0.156	5.19	3.76	0.957
5	9-芴酮 9-fluorenone	2.40	1.57	-0.156	4.89	3.32	0.767
6	2,7-二羟基萘 2,7-dihydroxynaphthalene	2.30	1.71	-0.115	3.14	2.02	0.956
7	1,6-二羟基萘 1,6-dihydroxynaphthalene	1.78	2.24	-0.111	3.38	2.02	0.956
8	2-羟基-9-芴酮 2-hydroxy-9-fluorenone	1.50	2.42	-0.147	4.93	2.71	0.768
9	5,12-萘并萘醌 5,12-naphthacenequinone	1.72	1.57	-0.164	5.54	3.73	0.963
10	2,3-二羟基萘 2,3-dihydroxynaphthalene	1.78	1.73	-0.116	3.17	2.02	0.953
11	1,5-二羟基萘 1,5-dihydroxynaphthalene	1.87	2.34	-0.110	3.38	2.02	0.955
12	1,8-二羟基蒽醌 1,8-dihydroxyanthraquinone	2.30	1.82	-0.168	5.22	2.30	0.976
13	萘嵌苯酮 Perinaphthenone	1.08	0.828	-0.158	4.58	3.32	0.963
14	11h-苯并[a]芴-11-酮 11h-benzo[a]fluorene-11-one	1.70	2.03	-0.151	5.50	4.18	0.829
15	2-羟基蒽醌 2-hydroxyanthraquinone	1.11	1.46	-0.172	5.14	2.32	0.987
16	1,4-二羟基蒽 1,4-dihydroxyanthraquinone	2.70	2.32	-0.157	5.20	2.30	0.976
17	菲醌 Phenanthrene-quinone	0.301	0.743	-0.176	4.83	2.89	0.767
18	1,2-萘醌 1,2-naphthoquinone	0.301	-0.00100	-0.181	4.22	1.94	0.986
19	1,4-苯醌 1,4-benzoquinone	0	-0.0755	-0.200	3.28	0.411	0
20	1,4-蒽醌 1,4-anthraquinone	0.301	0.425	-0.173	4.64	2.89	0.955
21	9-羟基苯并[a]芘 9-hydroxybenzo[a]pyrene	0.301	0.646	-0.122	3.83	4.80	0.949
22	1,4-萘二酮 1,4-naphthoquinone	-1.00	-0.508	-0.190	4.19	1.94	0.989
23	12-羟基苯并[a]芘 12-hydroxybenzo[a]pyrene	1.98	1.52	-0.122	4.44	4.80	0.949
24	1,3-二羟基萘 1,3-dihydroxynaphthalene	2.30	2.33	-0.110	3.39	2.02	0.956
25	2,6-二羟基萘 2,6-dihydroxynaphthalene	1.84	1.81	-0.113	3.14	2.02	0.955
26	蒽醌 Acenaphthenequinone	1.65	0.910	-0.165	4.53	2.43	0.964
27	1-羟基-9-芴酮 1-hydroxy-9-fluorenone	1.74	1.57	-0.159	4.95	3.22	0.767
28	苯并[c]菲[1,4]醌 Benzo[c]phenanthrene-1,4-dione	1.15	0.949	-0.169	5.25	3.73	0.946
29	7,12-苯并蒽醌 Benz[a]anthracene-7,12-dione	0.845	1.57	-0.169	5.71	3.73	0.958
30	苯并蒽酮 1,9-benz-10-anthrone	2.36	2.03	-0.151	5.49	4.18	0.830
31	芘-4,5-二酮 Pyrene-4,5-dione	0.301	0.849	-0.171	5.09	3.32	0.955
32	1,4-菲醌 Phenanthrene-1,4-dione	0.176	0.478	-0.176	4.81	2.89	0.952

注:前 22 种 OPAHs 为训练集,后 10 种 OPAHs 为验证集;EC₅₀ 为半数效应浓度(μmol·L⁻¹);μ 为化学势,MAXDP 为最大电拓扑参数,MLOGP 为 Moriguchi 正辛醇-水分配系数,AROM 为芳香性指数。

Note: The former 22 kinds of OPAHs are used as the training set, and the latter 10 kinds of OPAHs are used as the test set; EC₅₀ is concentration for 50% effect to zebrafish embryos (μmol·L⁻¹); μ is the chemical potential; MAXDP is the maximal electrotopological positive variation topological indices; MLOGP is the Moriguchi octanol-water partition coefficient; AROM is the aromaticity index geometrical descriptors.

2.2 模型的解释

模型(3)的4个描述符中, μ 与 $\log EC_{50}$ 的相关性最高,相关系数为0.554。 μ 可以表征分子失电子的能力, μ 值越小,分子越不稳定,容易失去电子^[22-23]。OPAHs是一类含氧的PAHs衍生物,含氧基团的存在使得电子密度发生显著的变化(图1),也会影响其得失电子的能力^[24]。OPAHs的 μ 与 $\log EC_{50}$ 呈正相关,说明OPAHs越不稳定,其斑马鱼胚胎急性毒性

越大。MAXDP、MLOGP和AROM都为拓扑描述符。MAXDP可以表征分子的亲电性^[25],OPAHs的亲电性越强,其毒性越强。MLOGP表征分子的疏水性^[20],MLOGP与 $\log EC_{50}$ 表现出负相关,说明OPAHs疏水性越强毒性也越强。AROM表征了分子的芳香性,其值越大表明OPAHs共轭结构越稳定,其毒性越小^[26]。综上所述,OPAHs的得失电子能力和疏水性是影响其毒性的主要因素。

表2 OPAHs的 $\log EC_{50}$ QSAR模型参数

Table 2 Parameters of QSAR models for OPAHs $\log EC_{50}$ values

模型 Model	R^2	Q^2	RMSE
(1) $\log EC_{50} = -0.610 \text{ nDB} + 0.0560 \text{ DELS} + 1.32$			
训练集 Training set	0.524	0.524	0.659
验证集 Test set	0.469	0.466	0
(2) $\log EC_{50} = -9.11 \omega + 0.484 \text{ nO} - 0.271 \log K_{ow} + 1.16$			
训练集 Training set	0.436	0.0692	0.922
验证集 Test set	0.441	-0.727	1.03
(3) $\log EC_{50} = 49.1 \mu + 1.37 \text{ MAXDP} - 0.609 \text{ MLOGP} - 1.26 \text{ AROM} + 5.51$			
训练集 Training set	0.781	0.780	0.447
验证集 Test set	0.669	0.662	0.455

注: EC_{50} 为半数效应浓度; R^2 为决定系数; Q^2 为预测相关系数; RMSE 为均方根误差; nDB 为双键的个数; DELS 为分子电拓扑变化指数; ω 为亲电性指数; nO 为化合物中氧原子个数; K_{ow} 为正辛醇-水分配系数; μ 为化学势; MAXDP 为最大电拓扑指数; MLOGP 为 Moriguchi 正辛醇-水分配系数; AROM 为芳香性指数。

Note: EC_{50} is concentration for 50% effect; R^2 is the coefficient determination; Q^2 is the correlation coefficient of the prediction and RMSE is the root mean square error; nDB is number of double bonds constitutional indices; DELS is the molecular electrotopological variation topological indices; ω is electrophilic index, nO is the number of oxygen atoms; K_{ow} is the octanol-water partition coefficient; μ is chemical potential; MAXDP is the maximal electrotopological positive variation topological indices; MLOGP is the Moriguchi octanol-water partition coefficient; AROM is the aromaticity index geometrical descriptors.

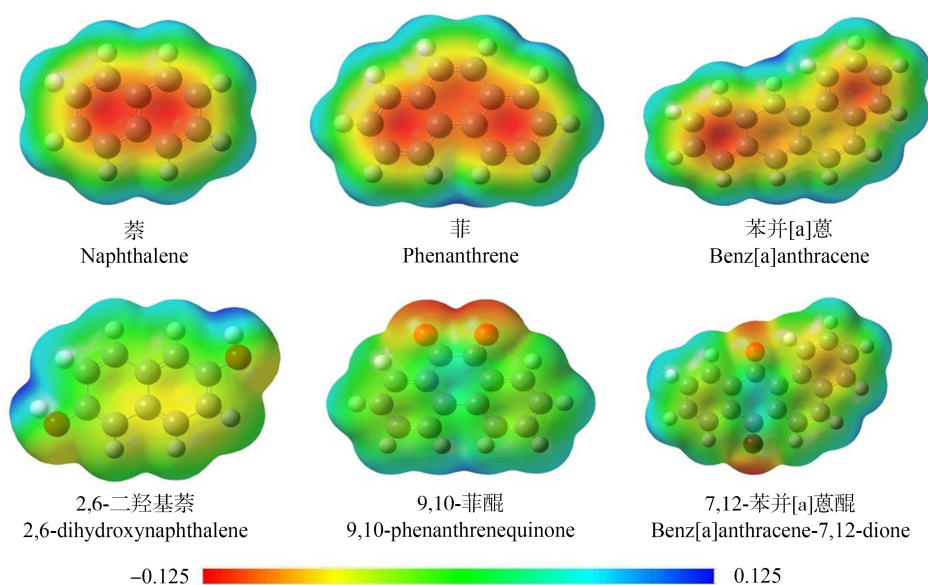


图1 含氧多环芳烃(OPAHs)特征化合物的电子密度图

Fig. 1 The electron density maps of typical oxygenated polycyclic aromatic hydrocarbon (OPAHs)

2.3 模型的验证

采用 10 种 OPAHs 的毒性实验数据作为验证集对模型的外部预测能力进行评估。结果表明,验证集的 $R^2=0.669$, $Q^2=0.662$, 说明模型(3)具有良好的预测能力。由图 2(a)可知, $\log EC_{50}$ 的实验值和预测值具有较好的一致性。如图 2(b)所示, 采用 Williams 图表征了模型的应用域, 32 种 OPAHs 标准残差的绝对值都 <3 , 模型没有离群点^[19], 说明该模型对 OPAHs 具有良好的适应性。1,4-苯醌的杠杆值为 0.704 大于警戒值 0.682, 但是 1,4-苯醌不为离群点, 说明模型(3)具有较好的延展性。去一法交叉验证结果为: $Q_{cv}^2=0.741$, $RMSE_{cv}=0.654$, Q_{cv}^2 值 >0.5 , 表明模型具有较好的稳健性。

3 讨论 (Discussion)

前人开展的 QSAR 模型研究也表明, PAHs 及其衍生物的毒性与其得失电子能力和疏水性有关。Li 等^[27]建立了 24 种羟基 PAHs 与 DNA 损伤的 QSAR 模型($R^2=0.751$), 发现羟基 PAHs 与 DNA 的静电相互作用影响二者的结合能力; 分子对接分析表明氢键、 π - π 作用会显著影响羟基 PAHs 与 DNA 的结合能力。本文所研究的化合物中除了羟基

PAHs 也存在酮羰基 PAHs, 化合物的毒性除了与分子的得失电子能力有关, 还与分子的疏水性存在一定关联。Gbeddy 等^[28]建立了 30 种 PAHs 及其衍生物致癌性毒性当量因子的 QSAR 模型($R^2=0.720$), 发现分子量越大、疏水性越强, 其毒性越强。Chlebowski 等^[29]通过分子对接研究硝基取代和杂环结构的 PAHs 发育毒性, 表明疏水性更强的化合物, 如 7-硝基苯[k]荧蒽和二硝基芘, 发育毒性更强。这与本研究模型(3)筛选出的表征疏水性的 MLOGP 值与斑马鱼胚胎急性毒性呈正相关的结果一致。

综上所述, 本研究采用 B3LYP/6-31G(d,p) 方法优化 OPAHs 分子结构, 计算了量子化学描述符和 Dragon 描述符, 使用多元线性逐步回归法建立了斑马鱼胚胎 $\log EC_{50}$ 的 QSAR 模型, 发现 OPAHs 的得失电子能力和疏水性是影响 OPAHs 斑马鱼胚胎急性毒性的重要原因。所建立最优模型的 R^2 为 0.781, 内部验证和外部验证说明该模型具有较好的稳健性和预测能力。采用 Williams 图表征了模型的应用域, 表明模型具有良好的适应性和延展性, 通过模型预测的斑马鱼胚胎急性毒性可以为 OPAHs 的生态风险评价提供毒性数据支持。

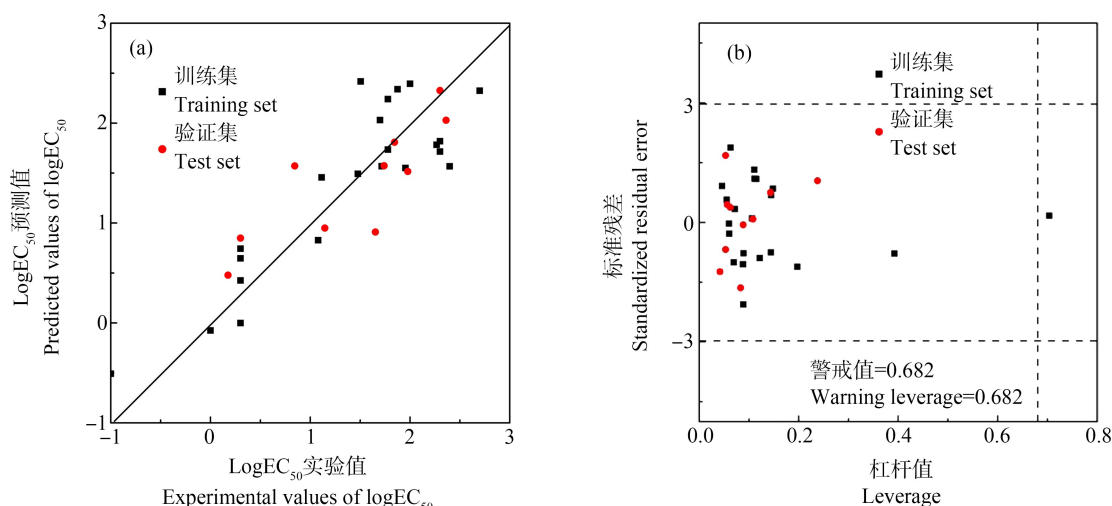


图2 OPAHs 斑马鱼胚胎 $\log EC_{50}$ 实验值和预测值的拟合 (a) 和 Williams 图表征的模型(3)应用域 (b)

Fig. 2 The fitting diagram of the experimental and predicted values of zebrafish embryos $\log EC_{50}$ for OPAHs (a) and the application domain of the model (3) based on Williams diagram (b)

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