

Predictive Models for Aquatic Toxicity of Aldehydes Designed for Various Model Chemistries

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Received October 6, 2003

Predictive models for the aquatic toxicity of aldehydes were designed for a set of 50 aromatic or aliphatic compounds containing at least one aldehyde group, for which the acute toxicity data for the fathead minnow (*Pimephales promelas*) are available (96 h test assessing 50% lethal waterborne concentration). The molecular descriptors were based on calculations with various semiempirical or ab initio model chemistries. The resulting four-parameter models were evaluated according to the correlation coefficients R^2 . The best predictive model was obtained with the HF/STO-3G model chemistry ($R^2 = 0.868$), while the models designed for descriptors based on ab initio calculations of higher level showed a slightly worse predictivity (the HF/3-21G(d) based model $R^2 = 0.800$, the HF/6-31G(d) based model $R^2 = 0.808$, the B3LYP/6-31G(d,p) based model $R^2 = 0.812$). With the semiempirical methods a good predictivity was observed with the PM3 based model ($R^2 = 0.811$) and the AM1 based model ($R^2 = 0.791$), but the MNDO based model showed the worst predictivity ($R^2 = 0.760$). In all ab initio models and the PM3 model very similar descriptors were involved. The importance of the descriptor logarithm of the partition coefficient logP for toxicity prediction was confirmed. Additionally, the descriptors encoding the negatively charged molecular surface area, hydrogen bonding molecular surface area, and reactivity of aldehyde group were identified as essential for the toxicity prediction of aldehydes.

INTRODUCTION

The toxic burden in the environment is still increasing due to the rapid development of new compounds by the chemical industry in general and in particular by the agrochemical, petrochemical, and pharmaceutical industries. In this situation the development of tools able to assess possible hazardous effects on living species should receive high attention as pointed out in a recent European Union White Paper.¹ Information about toxicity to aquatic species is of special interest, because the probability of their exposure to a variety of chemical compounds is very high.

Although experimental (in vivo or in vitro) testing of toxicity can provide the most reliable quantitative and qualitative data about the interaction of a given compound with a biological system, it is very time and material consuming as well as being expensive, thus not suitable for the screening of large data sets of compounds. That is why the alternatives to this approach have been sought. In recent years research in the field of theoretical prediction of toxicity based on quantitative structure–activity relationships (QSAR) has become very attractive. Theoretical tools offer two real advantages when compared to experimental testing—higher speed of screening and lower costs. The main weakness of this theoretical approach is the ability to predict properties correctly only for compounds similar to the training set, i.e.,

compounds for which the prediction model was initially designed. If a solid and sufficiently diverse training set is used to design the model, then the accuracy of predictions for structurally related compounds may be highly satisfactory.

The design of predictive models takes advantage of the rapid advancements of molecular modeling and computational chemistry, which assist in various areas of research by providing a detailed description of physicochemical properties of a large variety of inorganic, organic, or biological systems. This kind of information is derived from various types of calculations, which differ in computational intensity and precision. Computational and modeling tools, with multiple methods and theories implemented, are available on a commercial basis or by free download from the Internet. To use these tools effectively, one has to be familiar with their strong and weak points, i.e., suitability and applicability to the scientific problem under the study. Ideally, the choice of a certain method and theory should be made with respect to a balanced ratio between the time (cost) and the precision of expected results.

Aldehydes are an important group of chemicals widely used in various branches of modern industry and agriculture (reagents, solvents, fragrances, flavors, pesticides). In the past there have been several efforts to design predictive models for these compounds, with biological data for multiple aquatic species (Lat. *Tetrahymena pyriformis*, *Poecilia reticulata*, *Vibrio fischeri*, *Pimephales promelas*) used for measures of response. In several studies, which differ in methodology, aldehydes were included along with compounds with completely different structural and functional

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profile in large data sets, for which general trends in toxicity prediction were sought.²⁻⁵ Aliphatic and aromatic aldehydes were studied with respect to their electrophilic mode of action, but only models with low predictivity ($R^2 = 0.6$) were found.⁶ In two studies a higher number of aliphatic aldehydes was studied along with a structurally related group of ketones.^{7,8} Some theoretical studies focused solely on aliphatic aldehydes and yielded very good predictive models, but as they were based on a small number of homologous compounds, their broader applicability is questionable.⁸⁻¹⁰ Our previous theoretical research work in the field of quantitative structure-toxicity prediction based on a small number of simple descriptors brought acceptable results in most of the studied groups of chemicals, e.g. ethers ($R^2 = 0.932$), amines ($R^2 = 0.877$), alcohols and phenols ($R^2 = 0.811$), but did not succeed in finding a well-performing predictive model for the group of aldehydes ($R^2 = 0.473$).¹¹

This study has two objectives: 1. to design predictive models on a group of 50 both aromatic and aliphatic aldehydes, for which are available the in vivo toxicity data (for aquatic organism fathead minnow, Lat. *Pimephales promelas*) and 2. to evaluate the influence of commonly used semiempirical and ab initio computational methods on the quality of descriptors and predictive models.

COMPUTATIONAL DETAILS

Selection of Compounds. A search of the U.S. EPA MED-Duluth Fathead Minnow Database¹² and Ecotox Database¹³ was performed in order to identify all data for compounds containing the aldehyde functional group. The endpoint was acute toxicity LC_{50} for Fathead minnow (96 h test assessing aqueous concentration leading to death of 50% of exposed subjects). If multiple entries were found for single compounds, the final value was calculated as a geometric mean. The search yielded 51 compounds containing at least one aldehyde group. Among the identified aldehydes propenal (acrolein) was present but was excluded from this study due to known problems in prediction of toxicity for this unique compound.^{6,7,14} All compounds with reactive (the majority according to the character of the aldehyde group), narcotic, and mixed modes of action were included. The final study set consisted of 11 aliphatic and 39 aromatic aldehydes. The toxicity values were expressed as negative of the logarithm of 50% lethal concentration LC_{50} ($-\log LC_{50}$, the concentration expressed in $\text{mmol} \cdot \text{L}^{-1}$).

Geometry Optimization Procedure. The structures of substituted aromatic compounds with highly delocalized π -electron subsystem and conjugated aldehyde group were modeled in a planar arrangement. The chains of aliphatic aldehydes were modeled in the most stable *all-trans* conformation. In situations where a multiple or strained conformation could exist, information from crystallographic structures or similar fragments was used to construct the starting geometry of the structure. In certain cases multiple minima were examined, but only the lowest energy conformation was selected for subsequent processing. The geometry of every compound was optimized using each of the following standardly used model chemistries: MNDO, AM1, PM3, HF/STO-3G, HF/3-21G(d), HF/6-31G(d), and B3LYP/6-31G(d,p). Geometry optimization and property calculations were performed by means of MOPAC 6.0¹⁵ in the case of

semiempirical methods and Gaussian 03¹⁶ in the case of ab initio methods. At each optimized geometry vibrational analysis was performed in order to ensure that the found conformation was a minimum and not a transition state. No imaginary frequencies were found, i.e., the structures represented stable gas-phase minima. Additionally, with semiempirical methods at the optimized geometry a one SCF cycle (keywords: 1SCF PREC T=80000 NOINTER VECTORS BONDS PI POLAR ENPART NOMM) property calculation and a thermochemical analysis (keywords: THERMO ROT=1) were performed. With ab initio methods Natural Bond Orbital analysis (keyword: POP=NBO), as implemented in Gaussian 03 – NBO version 3.1,¹⁷ was performed at the optimized geometry in order to calculate the charge distribution in the molecules. 3D structural information from both the Gaussian and MOPAC output files was transferred to CODESSA version 2.21¹⁸ by means of the Babel structure conversion utility. First, the Sybyl^{mol2} files were prepared, which were afterward converted to the Sybyl^{mol} files. By this procedure information about aromatic bonds of the compounds was preserved. Direct conversion of Gaussian and MOPAC outputs into Sybyl^{mol} files causes the aromatic systems to consist of a combination of single and double bonds instead of aromatic ones. The same faulty situation was observed when MOPAC output files were loaded directly into CODESSA. 3D structures are available at request.

Internal CODESSA Descriptor Calculation. 3D structures in the form of *.mol* files along with the output files from quantum chemical calculations were loaded into CODESSA. On their basis a large variety of descriptors were calculated: constitutional (number of atoms, bonds, atom types, molecular weight), topological (Wiener, Randic, Kier&Hall, and Balaban indices), geometrical (moments of inertia, shadow indices, molecular volume and surface area), electrostatic (minimum and maximum charges, polarity parameters, charged partial surface area descriptors, hydrogen bonding surface area descriptors), quantum-chemical (charge distribution, valency, and quantum mechanical energy related descriptors), thermodynamic (heat of formation, enthalpy and entropy related descriptors), and Gaussian (charge and molecular surface area related descriptors derived from Gaussian output) descriptors – internal descriptors.

External Descriptor Calculation. With semiempirical calculations in MOPAC, 3 additional descriptors were extracted from output files—the charge on the carbon atom and the oxygen atom of aldehyde group and their difference. Similarly, from Gaussian output files external descriptors HOMO and LUMO energies, and their difference (these 3 descriptors are automatically generated with MOPAC files, but not with Gaussian ones), charge on the carbon atom and the oxygen atom of aldehyde group and their difference calculated by both NBO and Mulliken population analyses were prepared. In addition to these, the theoretical values of the logarithm of the partition coefficient $\log P$ were calculated by multiple methods: *ClogP* from DayLight,¹⁹ *LogP* from Pallas version 3.0,²⁰ and *miLogP* from Molinspiration.²¹ The descriptor *Total Polar Surface Area (TPSA)* from Molinspiration was also calculated.

In total 595 (7 external) descriptors based on semiempirical and 353 (13 external) descriptors based on ab initio calculations were prepared.

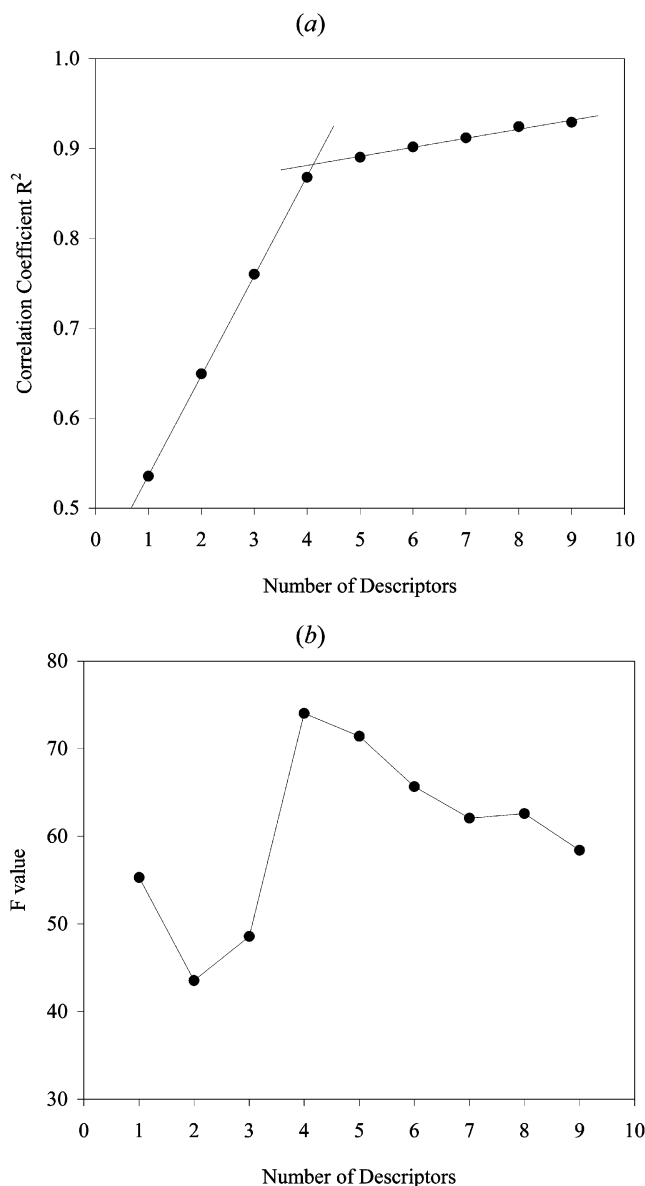


Figure 1. Plot of the correlation coefficients R^2 (a) and the Fisher criteria (b) vs the number of descriptors for the HF/STO-3G model chemistry.

Design of Predictive Models. As the total number of descriptors was too large with respect to the number of available observations, highly intercorrelated or invalid (some missing values – descriptor not defined for some compounds) descriptors were excluded from the analysis. To design rigorous models the threshold for intercorrelation was set to a strict value $R^2 = 0.6$. Finally, 370 valid descriptors for semiempirical based models and 307 for ab initio based models were used. The best predictive models were generated by the Best Multilinear Regression Analysis in a forward stepwise regression procedure implemented in CODESSA, when all compounds in the set ($n = 50$) were used to find the best fit against experimental values of toxicity ($-\log\text{LC}_{50}$, concentration in mmol.L^{-1}). The optimal number of parameters (descriptors) for the QSAR models was found by constructing a plot of the correlation coefficient R^2 values vs the number of descriptors and identifying the “break point” (Figure 1a). Adding a new descriptor behind this break point to the model increases the value of R^2 ; however, the model then becomes more complex and more difficult to explain.

An optimal number of descriptors was confirmed by constructing the plot of the values of the Fisher criterion vs the number of descriptors (Figure 1b). The quality of models based on the 4 descriptors was evaluated by the correlation coefficient R^2 .

Validation Procedure. Two types of validation were performed. First, the leave-one-out method implemented in CODESSA was performed and is expressed by the cross-validated correlation coefficient R^2_{cv} . Second, a “leave-1/3-of-set-out” validation was performed in the following manner: the original set of 50 compounds was ordered by increasing toxicity, for training set A, and every third compound in the ordered set starting from the first compound was removed but included in the validation set A (33 compounds used for training, 17 for validation). Similarly, for the set B (33 training, 17 validation) and C (34 training, 16 validation), every third compound in the ordered set starting from the second or the third compound was removed and included in the validation sets B and C, respectively. By this procedure, every compound was twice included in the training set and once in the validation set.

RESULTS AND DISCUSSION

The resulting correlation coefficients R^2 and the cross-validated correlation coefficients R^2_{cv} along with the correlation coefficients obtained with the “leave-1/3-of-set-out” method $R^2_{\text{L1/3O}}$ of the best predictive models for each model chemistry are summarized in Table 1. For every compound the experimental and predicted values from the best model for each model chemistry are included in Table 2. These values are higher than those obtained on the first toxicity model for aldehydes ($R^2 = 0.473$; $R^2_{\text{cv}} = 0.428$).¹¹ The descriptors involved in the best models for each model chemistry are summarized in Table 1 (ordered by their significance determined by the absolute t -test value).

The model designed for the descriptors based on HF/STO-3G model chemistry showed the best correlation coefficient ($R^2 = 0.868$) and the cross-validated correlation coefficient ($R^2_{\text{cv}} = 0.840$) of all models and model chemistries. The “leave-1/3-of-set-out” validation procedure provided results consistent with the best fit obtained by CODESSA, which confirms the robustness of this model (Figure 2). The small differences are not significant. Interestingly, the models designed for descriptors based on B3LYP/6-31(d,p), HF/6-31G(d), or HF/3-21G(d) model chemistries, which are much more precise from the point of view of both theory and basis set, showed slightly lower predictivity in comparison to the relatively simple HF/STO-3G model chemistry. A comparison of the corresponding descriptors between the two best models according to the correlation coefficient R^2 , i.e., models based on ab initio the HF/STO-3G and the B3LYP/6-31G(d,p) model chemistries, revealed a good cross correlation for the descriptor encoding the partial negative surface area ($R^2 = 0.988$) and the descriptor encoding hydrogen bonding surface area ($R^2 = 0.928$). This can be explained by the fact that in general only minor differences were observed among the conformations of compounds optimized by various ab initio model chemistries. In this study the superiority of the HF/STO-3G based model is probably caused by the charge distribution resulting from

Table 1. Summary of the Results Obtained with 7 Model Chemistries on 50 Aldehydes

model chemistry	R^2	R^2_{CV}	$R^2_{L1/30}$		X^a	DX^b	t -test	descriptors used in the best predictive model
MNDO	0.760	0.707	0.671	0	3.34e+00	9.49e-01	3.515	intercept
				1	5.89e-01	5.07e-02	11.613	ClogP DayLight
				2	-1.20e+01	2.38e+00	-5.035	FNSA-3 fractional PNSA (PNSA-3/TMSA) [semi-MO PC]
				3	1.93e+00	4.91e-01	3.935	max antibonding contribution of a MO
				4	-3.40e-03	9.10e-04	-3.733	(1/2)X BETA polarizability (DIP)
AM1	0.791	0.750	0.739	0	-4.90e-01	3.46e+00	-0.142	intercept
				1	4.63e-01	4.53e-02	10.223	ClogP DayLight
				2	-1.97e+01	3.27e+00	-6.031	max bond order of a H atom
				3	1.09e-01	2.12e-02	5.144	max e-n attraction for a C atom
				4	-5.20e+01	1.36e+01	-3.833	max 1-electron react. index for a O atom
PM3	0.811	0.772	0.745	0	8.28e+00	2.54e+00	3.255	intercept
				1	3.75e-01	4.18e-02	8.961	ClogP DayLight
				2	-5.67e-02	9.94e-03	-5.707	PNSA-3 atomic charge weighted PNSA [Zefirov's PC]
				3	-6.19e-03	1.10e-03	-5.632	HBSA H-bonding surface area [semi-MO PC]
				4	-9.10e+00	2.73e+00	-3.337	min (>0.1) bond order of a H atom
HF/STO-3G	0.868	0.840	0.847	0	-4.86e+00	6.63e-01	-7.332	intercept
				1	4.30e-01	3.52e-02	12.217	ClogP DayLight
				2	-2.22e+01	2.78e+00	-7.995	FNSA-3 fractional PNSA (PNSA-3/TMSA) [Zefirov's PC]
				3	-2.14e-01	2.91e-02	-7.363	HA dependent HDCA-1 [Gaussian NBO PC]
				4	1.11e+01	1.53e+00	7.243	ΔQ_{CO} NBO
HF/3-21G(d)	0.800	0.753	0.758	0	-6.95e+00	1.33e+00	-5.236	intercept
				1	3.69e-01	4.84e-02	7.631	ClogP DayLight
				2	-2.51e+01	3.65e+00	-6.888	FNSA-3 fractional PNSA (PNSA-3/TMSA) [Zefirov's PC]
				3	-9.76e-02	1.79e-02	-5.441	HA dependent HDCA-1 [Gaussian NBO PC]
				4	-1.33e+01	2.57e+00	-5.178	Q oxygen NBO
HF/6-31G(d)	0.808	0.762	0.776	0	-3.90e+00	7.73e-01	-5.049	intercept
				1	-6.56e-02	1.00e-02	-6.533	PNSA-3 atomic charge weighted PNSA [Zefirov's PC]
				2	-9.05e-02	1.52e-02	-5.960	HA dependent HDCA-1 [Gaussian NBO PC]
				3	-8.93e+00	1.69e+00	-5.277	max net atomic charge for a O atom (Gaussian)
				4	2.60e-01	4.94e-02	5.276	ClogP DayLight
B3LYP/6-31G(d,p)	0.812	0.761	0.767	0	-4.97e+00	9.57e-01	-5.197	intercept
				1	3.89e-01	4.49e-02	8.663	ClogP DayLight
				2	-2.09e+01	3.31e+00	-6.321	FNSA-3 fractional PNSA (PNSA-3/TMSA) [Zefirov's PC]
				3	-1.16e-01	2.18e-02	-5.343	HA dependent HDCA-1 [Gaussian PC]
				4	7.49e+00	1.45e+00	5.168	ΔQ_{CO} Mulliken

^a X — regression coefficient. ^bDX — regression coefficient mean square error.

a different treatment of orbitals by this method (Slater Type Orbitals) when compared to other ab initio and DFT methods (Gaussian type orbitals), because a worse correlation ($R^2 = 0.773$) was observed with the descriptor encoding the difference of charge on the oxygen atom and the carbon atom of aldehyde group. This is a quite controversial observation, because the DFT methods are known to realistically reproduce the charge distribution. Although a certain trend of improvement of the correlation coefficient R^2 can be observed with an increasing level of theory and an enlarging basis set from HF/3-21G(d) toward B3LYP/6-31G(d,p), the contribution from more sophisticated methods is not substantial, while the time required to optimize the structures and calculate the physicochemical properties is obviously much higher (for a comparison of absolute and relative computational costs see Table 3).

Models designed for descriptors based on semiempirical PM3 or AM1 model chemistries showed a good predictivity. The PM3 based model is comparable to the best models designed for descriptors based on ab initio model chemistries. The least predictive model was designed for descriptors based on semiempirical MNDO calculations, which could be explained by the rather poor geometries produced by this method (e.g. an aldehyde group not coplanar with a phenyl ring, bad treatment of intramolecular hydrogen bonds).

Clearly, a direct comparison of semiempirical and ab initio model chemistries on the design of predictive models cannot be done, because the number and the character of the

descriptors generated by CODESSA and used for the design is not completely equal (see Table 4). Despite the fact that with semiempirical model chemistries a much higher number of descriptors (especially quantum-chemical and thermodynamic) was generated and used, no model with a higher predictivity compared to the ab initio based ones was found. This observation suggests a slight superiority of ab initio model chemistries over semiempirical ones in terms of the quality of descriptors, which is in contrast with a previous study on nitrobenzenes, which showed that the semiempirical (AM1) results are more reliable than those obtained with a low-level ab initio model chemistry (HF/STO-3G).²²

Descriptors Involved in the Best Model. The descriptor LogP not only describes the ability of a certain compound to passively penetrate through biomembranes, but it is also a valuable descriptor of a thermodynamic property—entropy, which is related to the desolvation of the molecular surface upon exiting from the water phase into the oil phase. A number of previous studies proved the importance of the logarithm of the partition coefficient logP for the correct prediction of toxicity.^{2,3,6–8,14} In this study the descriptor logarithm of the partition coefficient ClogP was present in all of the best predictive models. LogP alone is the most “powerful” descriptor, because in the series of models based on only one descriptor, the one based on ClogP from DayLight showed the highest correlation coefficient $R^2 = 0.535$ ($R^2 = 0.492$ on *miLogP* from Molinspiration; $R^2 = 0.458$ on *LogP* from Pallas).

Table 2. Experimental and Predicted Values for the Best Model for Each Mode Chemistry

compound	CAS no.	-log LC ₅₀							
		exp	predicted						
			MNDO	AM1	PM3	HF/STO-3G	HF/3-21G(d)	HF/6-31G(d)	B3LYP/6-31G(d,p)
4-hexyloxy-2-methoxybenzaldehyde	10015	1.9470	1.9428	1.6649	1.8385	1.7311	1.828	1.8506	1.6471
5-bromo-4-hydroxy-3-methoxy-2-nitrobenzaldehyde	10026	0.5759	0.6669	0.7954	0.6220	0.8698	0.9951	0.8962	1.2890
hexanal	66251	0.7577	0.7740	1.0401	0.8662	1.0891	0.8007	0.7895	0.9799
4-phenoxybenzaldehyde	67367	1.6344	1.1772	1.8636	1.6702	1.8827	1.8783	1.8776	1.8162
ethanal	75070	0.1151	0.0986	0.4182	0.1372	0.4756	0.1284	0.0686	0.3846
2-hydroxybenzaldehyde	90028	1.7251	1.6376	1.4454	1.5718	1.6638	1.7062	1.6278	1.5073
3,5-dibromo-2-hydroxybenzaldehyde	90595	2.5176	2.2868	2.4215	2.6243	2.6450	2.4638	2.4443	2.4221
2,4-dihydroxybenzaldehyde	95012	1.0230	1.6517	1.4276	0.6983	0.8912	0.7921	0.8246	0.8195
2-methylbutanal	96173	0.9365	0.7618	0.7548	0.7462	0.8624	0.754	0.7847	0.9395
4-(dimethylamino)benzaldehyde	100107	0.5138	1.1384	0.8780	0.9951	0.8290	0.8574	0.9105	0.6545
benzaldehyde	100527	1.0315	0.8590	0.9027	0.7837	0.9812	0.9961	1.0862	0.9941
4-chlorobenzaldehyde	104881	1.8055	1.5963	1.9899	1.4504	1.6257	1.7191	1.6998	1.6563
pentanal	110623	0.8246	0.6817	0.7952	0.6623	0.9221	0.661	0.6490	0.7941
4-(diethylamino)benzaldehyde	120218	0.8702	1.3410	1.3464	1.3695	1.0495	1.0334	1.0830	1.0920
3-ethoxy-4-hydroxybenzaldehyde	121324	0.2781	0.8183	0.6665	0.6204	0.3888	0.601	0.6668	0.5917
3-methoxy-4-hydroxybenzaldehyde	121335	0.2590	0.6474	0.4629	0.3817	0.2241	0.4226	0.4897	0.3254
4-isopropylbenzaldehyde	122032	1.3500	1.4003	0.9974	1.3070	1.3039	1.4439	1.5024	1.2971
2-methylpentanal	123159	0.7265	0.9121	0.9730	0.9239	1.0220	0.8813	0.9433	1.1027
butanal	123728	0.6907	0.5543	0.5546	0.4717	0.7312	0.5502	0.4924	0.6583
2-hydroxy-3-methoxybenzaldehyde	148538	1.8021	1.4089	1.1537	1.5822	1.4135	1.248	1.2737	1.2492
2-chloro-6-fluorobenzaldehyde	387451	1.2266	1.9306	1.8035	1.6996	1.6360	1.6829	1.7769	1.7622
2-fluorobenzaldehyde	446526	1.9635	1.4664	1.6855	1.1719	1.4328	1.5586	1.5527	1.4560
α,α,α -3-trifluoromethylbenzaldehyde	454897	2.2752	2.3794	1.3657	1.7906	1.9698	1.9664	2.0305	1.9619
2-methylbenzaldehyde	529204	0.3563	1.1834	0.7451	0.9589	0.9089	1.0348	1.0792	0.9729
2-nitrobenzaldehyde	552896	1.0210	1.1891	1.1153	1.3632	1.1874	1.3826	1.0722	1.4496
4-nitrobenzaldehyde	555168	1.1750	0.9765	1.0382	1.1295	1.1301	1.0485	1.1256	1.1568
3-methylbutanal	590863	1.4233	0.5996	0.7586	0.7120	0.9284	0.7279	0.7365	0.9109
2,4-dimethoxybenzaldehyde	613456	0.9174	1.0451	0.9840	1.0483	1.0218	1.2722	1.2714	1.0645
5-chloro-2-hydroxybenzaldehyde	635938	2.3082	2.0507	1.8934	2.2303	2.3859	2.1417	2.0478	2.1746
pentafluorobenzaldehyde	653372	2.2510	1.8082	2.5634	2.4616	2.5383	2.4239	2.5242	2.6416
4,6-dimethoxy-2-hydroxybenzaldehyde	708769	1.8324	1.3699	1.5604	1.8616	1.8013	1.7416	1.8187	1.6199
2,4-dichlorobenzaldehyde	874420	1.9878	2.0883	2.3318	2.0451	2.0792	2.365	2.2021	2.2341
5-bromo-2-hydroxybenzaldehyde	1761611	2.1893	1.9961	2.0409	2.1933	2.3183	2.1743	2.0015	2.1136
3-bromo-4-hydroxy-5-methoxybenzaldehyde	2973764	0.8877	1.0925	0.8701	0.8092	0.5760	0.5824	0.7724	0.5997
2,3-dimethylpentanal	3944761	0.8535	1.0928	1.1861	1.1669	1.2381	1.2013	1.1901	1.4066
2,4,5-trimethoxybenzaldehyde	4460860	0.5981	0.9036	1.0003	0.9614	0.8825	1.1483	1.3003	0.9606
3-[4-(dimethylamino)phenyl]propenal	6203185	1.4728	1.0119	1.3067	1.1511	0.8744	0.9575	1.1301	1.0509
2-chloro-5-nitrobenzaldehyde	6361213	1.6808	1.4018	1.8273	1.7378	1.6051	1.7696	1.7180	1.6727
4-ethoxybenzaldehyde	10031820	0.7279	0.6215	0.8453	1.1270	1.0698	1.1785	1.2016	1.0458
4-(diethylamino)-2-hydroxybenzaldehyde	17754904	1.5570	1.6112	1.6124	2.0639	1.6753	1.7575	1.4849	1.6732
5-hydroxy-2-nitrobenzaldehyde	42454068	0.6008	1.0737	1.1961	0.4585	0.3651	0.605	0.3677	0.7842
3-(4- <i>tert</i> -butylphenoxy)benzaldehyde	69770236	2.8372	2.7927	2.4456	2.3839	2.3267	2.1411	2.1194	2.3137
3-(3,4-dichlorophenoxy)benzaldehyde	79124768	2.9496	2.9027	2.8261	2.7816	2.7540	2.6049	2.7591	2.6620
ethanedial	107222	-0.5687	-0.3544	-0.6303	-0.1169	-0.5974	-0.6305	-0.5447	-0.5821
pyridine-2-carboxaldehyde	1121604	0.8150	0.5247	0.6264	0.5231	0.6328	0.7526	0.9247	0.6868
2,4,6-trinitrobenzaldehyde	606348	1.6833	1.5702	1.5309	1.7149	1.6983	1.2921	1.4912	1.3289
3-nitrobenzaldehyde	99616	1.4159	1.0822	1.0308	1.0950	1.1848	1.1516	1.1100	1.1739
1,5-pentanedial	111308	1.0711	0.4420	0.3496	0.3715	0.4711	0.2077	0.2634	0.3506
2-furaldehyde	98011	0.4775	0.2684	0.6062	0.6091	0.3021	0.6169	0.6759	0.6250
methanal	50000	0.0955	0.6903	0.0990	0.3401	0.1673	0.5487	0.0021	-0.3256

In the best predictive model designed for descriptors based on the HF/STO-3G model chemistry, along with *ClogP* three additional descriptors were involved. The descriptor *FNSA-3 fractional PNSA (PNSA-3/TMSA)* [Zefirov's PC] (partial negative surface area/total molecular surface area according to charges calculated by Zefirov's method based on the Sanderson's electronegativities' equalization principle) encodes the distribution of the negative charge normalized by the total surface area of the molecule.²³ The positive contribution of this descriptor in the final QSAR eq 1 is probably related to the presence of negatively charged chlorine and fluorine atoms or hydroxy and nitro groups in the molecules, which generally increase the toxicity (all values of this descriptor have negative signs).

The descriptor *HA dependent HDCA-1 [Gaussian NBO PC]* (hydrogen bond donor charged surface area derived from NBO analysis) describes hydrogen-bonding properties of the compounds. Formation of hydrogen bonds could be linked with the toxic effect in some cases, as it facilitates the creation of the intermolecular interactions between the compound and the biological structure, but the negative contribution in eq 1 suggests that more likely here is that it characterizes the ability of a compound to penetrate through the biomembranes to/within the living organism. A higher value of this descriptor indicates lower penetration and toxicity of a compound (unlike *ClogP*).

The last descriptor involved in the best model based on HF/STO-3 model chemistry ΔQ_{Co} from NBO analysis

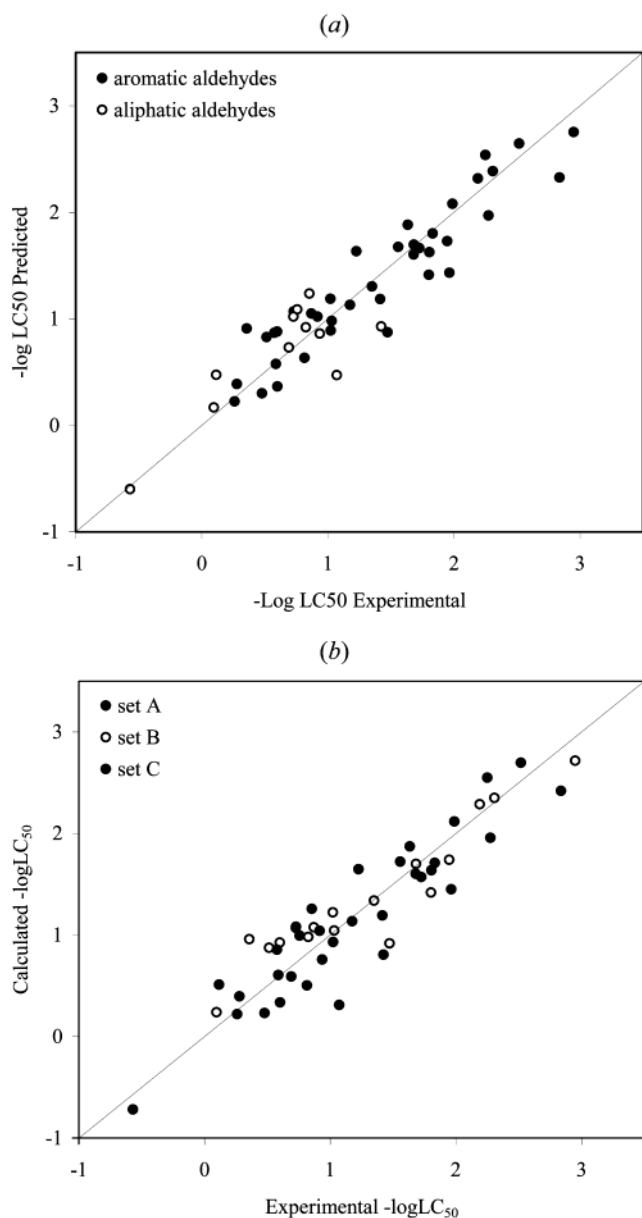


Figure 2. Graphical presentation of the best fit (a) and cross-validation by the leave-1/3-of-set-out method (b) for the best model based on the HF/STO-3G model chemistry.

Table 3. Relative Computational Costs of Model Chemistries Used Comparison of Computational Time Needed for Complete Geometry Optimization of 4-Nitrobenzaldehyde in MOPAC Version 6.0 for Semiempirical Methods and Gaussian 03W for ab Initio Methods on a Generic Intel P4@1700 MHz Machine^a

model chemistry	relative cost	time [s]
Semiempirical		
MNDO	1.38	1.82
AM1	1.71	2.36
PM3	1.00	1.38
ab Initio		
HF/STO-3G	67.40	93.00
HF/3-21G(d)	362.30	500.00
HF/6-31G(d)	2805.80	3872.00
B3LYP/6-31G(d,p)	7173.20	9899.00

^a Starting geometry was built with default structural parameters.

(difference of charges on carbon and oxygen atoms of aldehyde group derived from NBO analysis) characterizes the polarity of the C=O bond in the aldehyde group and is

Table 4. Number of Descriptors by Type in Semiempirical and ab Initio Based Models

descriptor group	semiempirical	ab initio
external	7	13
constitutional	38	38
topological	38	38
geometrical	12	12
electrostatic	81	81
quantum-chemical	382	0
thermodynamic	37	0
Gaussian	0	171
total	595	353

supposed to be directly linked with the toxic effect—reactivity with the biological structures in the living organism or cell. According to the results of previous studies, the electrophilic character of the aldehyde group is mainly responsible for the toxic effect of this group of compounds.

$$-\log LC_{50} = 0.430(ClogP) - 22.2(FNSA-3) - 0.214(HA \text{ dependent } HDCA-1) + 11.1(\Delta Q_{CO} NBO) - 4.86 \quad (1)$$

$$n = 50, R^2 = 0.868, R^2_{CV} = 0.840, F = 74.04, s^2 = 0.0826$$

Descriptors Involved in the Best Models Obtained with Other Model Chemistries. Descriptors encoding similar properties to those included in the best predictive model (HF/STO-3G based) were also found in the best models based on other model chemistries. This fact further supports the validity of the best predictive model for aldehydes. A descriptor encoding the partial negative surface area was found in four other models: descriptor *FNSA-3 fractional PNSA (PNSA-3/TMSA)* [Zefirov's PC] was present in the best models designed for descriptors based on both B3LYP/6-31G(d,p) and HF/3-21G(d) model chemistries, descriptor *FNSA-3 fractional PNSA (PNSA-3/TMSA)* [Semi-MO PC] was present in the MNDO model, while descriptor *PNSA-3 Atomic charge weighted PNSA [Zefirov's PC]* (atomic charge weighted partial negative surface area) was present in the best models designed for descriptors based on both HF/6-31G(d) and PM3 model chemistries.

Similarly, a descriptor encoding hydrogen bonding properties—descriptor *HA dependent HDCA-1* [Gaussian NBO PC]—was found in all of the best models designed for descriptors based on ab initio methods. The charge distribution calculated with a density functional theory method B3LYP/6-31G(d,p) is very precise, and the descriptor *HA dependent HDCA-1* [Gaussian PC] derived from “classical” Mulliken population analysis was used in the best model based on this model chemistry. In the model based on PM3 model chemistry the hydrogen bonding properties of aldehydes are represented by a similar descriptor *HBSA H-bonding surface area* [Semi-MO PC] (hydrogen bonding surface area).

In the best model within each model chemistry a descriptor somehow linked to the aldehyde group is present. In the model designed for descriptors based on B3LYP/6-31G(d,p) model chemistry it is the descriptor ΔQ_{CO} from Mulliken analysis (the difference of charges on carbon and oxygen atoms of aldehyde group derived from Mulliken analysis) and in the HF/3-21G(d) model the descriptor Q_O from NBO

analysis (charge on oxygen atom of aldehyde group derived from NBO analysis). In the HF/6-31G(d) model the descriptor *Max net atomic charge for an O atom (Gaussian)* describes the charge on the oxygen atom of the aldehyde group in all compounds in the set except those containing the nitro group (max net atomic charge for a O atom is then found on one of the oxygen atoms of nitro group). Similarly, in the PM3 model the descriptor *Min (>0.1) bond order of a H atom* represents the bond order of the hydrogen atom of the aldehyde group for all compounds except for those where there is an intramolecular hydrogen bond between the aldehyde group and the hydroxyl group in the *ortho* position (the min bond order is then found on the hydrogen of the hydroxyl group). With few exceptions the same situation can be observed with AM1 model chemistry, where the descriptor *Max 1-electron reactive index for an O atom* represents the physicochemical property linked with the reactivity of the oxygen atom in the aldehyde group. In the MNDO based model the electrophilic character of the studied compounds is expressed by the descriptor *(1/2)X BETA polarizability (DIP)* (the second-order molecular polarizability), because the higher order polarizabilities describe the molecule's electrophilic properties.²⁴

The descriptors *Max bond order of a H atom* and *Max e⁻n attraction for a C atom* in the AM1 based model and the descriptor *Max antibonding contribution of a MO* in the MNDO based model represent the global extremes of a given physicochemical property and occur in various structural elements in the molecules. Their interpretation in terms of toxicity is quite difficult, because they represent the local fragment reactivity rather than a linear trend within the set of studied compounds.

The identified four parameter QSAR equations of all ab initio and semiempirical PM3 model chemistries are in excellent agreement with the proposed principle, that the activity/toxicity of a compound is the sum of a compound's abilities to penetrate through (here: logP with the descriptors encoding surface and hydrogen bonding properties) and interact with biological structures (here: a descriptor encoding the reactivity of the aldehyde group).²⁵

Comparison of the Models according to the Chemical Diversity of Compounds. The used data set is quite diverse, considering both the mode of action and the presence of chemical functional groups. As indicated in "Selection of compounds", the studied compounds included chemicals classified by U.S. EPA as reactive, narcotic, or with mixed mode of action. Minor changes were observed, if 11 aliphatic aldehydes were removed from the data set. The correlation coefficients R^2 and the cross-validated correlation coefficients R^2_{CV} improved with all model chemistries. The overall trends in performance of the model chemistries remained unchanged with STO-3G giving the best results, followed by DFT, ab initio, and semiempirical model chemistries. The STO-3G based model obtained for the 39 aromatic aldehydes was built on the same 4 descriptors as the model for the complete set, except for the descriptor $\Delta Q_{CO} NBO$, which was replaced by $\Delta Q_{CO} Mulliken$. However, this model showed only a slightly higher correlation coefficient ($R^2 = 0.874$ aromatic, $R^2 = 0.868$ complete set) and a lower cross-validated correlation coefficient ($R^2_{CV} = 0.837$ aromatic, $R^2_{CV} = 0.840$ complete set) with the same aromatic outliers as the model obtained for the complete set. The toxicity of 11 aliphatic

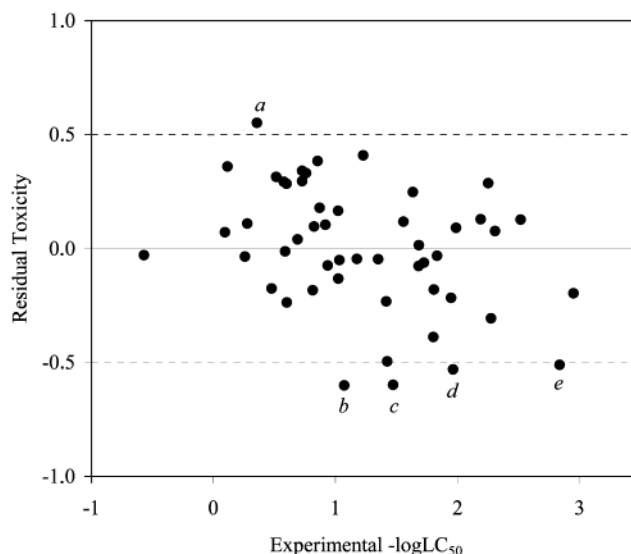


Figure 3. Graphical presentation of the outliers in the best model based on the HF/STO-3G model chemistry.

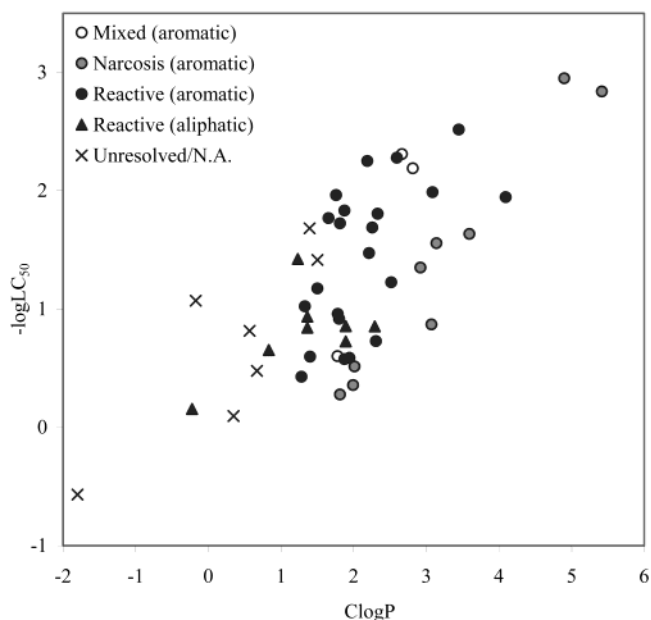


Figure 4. Plot of toxicity ($-\log LC_{50} \text{ exp}$) vs lipophilicity (ClogP) with respect to the mode of action for 50 aldehydes.

aldehydes was found to be best correlated ($R^2 = 0.834$, $n = 11$) with the descriptor *Minimum nucleophilic reaction index for a C atom* with the PM3 model chemistry. Thus the predictive model based on 4 descriptors obtained with STO-3G model chemistry for the complete data set is the most robust one with respect to the statistical performance and the structural diversity of the training set.

The narcotic mode of action of some aldehydes in the data set could be explained by a more pronounced lipophilicity (which facilitates penetration to the central nervous system) compared to the reactivity of aldehyde group, because, as can be seen on the Figure 4, the compounds with the narcotic mode of action usually exhibit higher lipophilicity than similarly toxic compounds with the reactive mode of action. The narcotic mode of action is observed with the benzaldehydes substituted at the *para* position by bulky lipophilic substituents or the dialkylamino group (e.g. 4-phenoxybenzaldehyde, 4-isopropylbenzaldehyde, 4-(diethylamino)ben-

zaldehyde), which have a minor effect on the reactivity of the aldehyde group, while multiple substitution by electron withdrawing/donating substituents (halogen atoms, methoxy, nitro and hydroxy groups) may significantly modulate the reactivity of the aldehyde group and shift the balance toward the reactive mode of action.

Based on the descriptors employed in the best models, the following general assumptions about the toxicity of aldehyde compounds could be made: those aldehydes with high values of the logarithm of the partition coefficient (O/W), which do not contain hydrophilic functional groups but are substituted by fluorine, chlorine, or bromine atoms in the positions, where it may increase the reactivity of the aldehyde functional group, are highly toxic.

Further discussion on reactive aldehydes will be addressed in the section Comparison to the Previously Published Models.

Outliers in the Best Model. In the best predictive model 5 major outliers were identified, but they were included in the calculation of the statistics for the model. The maximum deviation was 0.6 log unit for 1,5-pentanedial. Predicted toxicity values for the compounds with a high structural similarity to the outliers should be verified by other methods and models. The graphical presentation of outlying structures is in Figure 3. In the molecule of 2-methylbenzaldehyde the close vicinity of a bulky methyl group decreases the accessibility of the aldehyde group for reaction partners and that is why its actual toxicity value is much lower than the predicted one. 1,5-Pentanedial contains two aldehyde functional groups in the molecule, and so the predictive model could underestimate its toxicity. Lower predicted toxicity for 3-[4-(dimethylamino)phenyl]propenal could be explained by the presence of a double bond in conjugation with the aldehyde group, which is responsible for the increased reactivity, resulting in higher actual toxicity of this compound than predicted. A 10-fold increase in experimental toxicity of 2-fluorobenzaldehyde compared to benzaldehyde (benzaldehyde: $-\log\text{LC}_{50} = 1.0315$, 2-fluorobenzaldehyde: $-\log\text{LC}_{50} = 1.9635$) may suggest a specific toxic action of this *ortho* halogensubstituted compound in fish. The toxicity of 3-(4-*tert*-butylphenoxy)benzaldehyde might be underestimated by the model, because this molecule does not contain any negatively charged substituents, which are important in this predictive model.

Comparison to the Previously Published Models. Most of the previous studies on small sets of structurally related aldehydes were based on a low number of descriptors, typically LogP describing lipophilicity and *Energy of the Lowest Unoccupied Molecular Orbital* (E_{LUMO}) describing the electrophilic reactivity of the aldehyde group.^{2,7,8} Despite the fact that the descriptor E_{LUMO} (as well as *Energy of the Highest Occupied Molecular Orbital* – E_{HOMO}) was included in the pool of descriptors used in this study, it did not appear in any of the best models within any of the model chemistries. Therefore the descriptor E_{LUMO} seems to be a valuable descriptor of reactivity for simple congeneric sets of aldehydes, but for more variable set of compounds other descriptors may contribute more significantly to the best predictive models.

Interestingly, a similar situation was observed with LogP. If aldehydes were studied along with compounds of different types, LogP was not always present in the best predictive

models, while other descriptors similar to the ones found in this study were employed—*Fractional Positive Surface Area* and/or *Fractional Negative Surface Area*. The authors assumed that LogP becomes less important, if the mode of action of the compounds is too different.³ On the contrary, the investigation of the *ClogP*-toxicity relationship for the 40 aldehydes with the assessed mode of the toxic action included in this study showed a very good correlation for the compounds with the narcotic mode of action ($R^2 = 0.950$, $n = 9$), while with the reactive one the correlation was much lower ($R^2 = 0.425$, $n = 31$). If these two groups of aldehydes were combined in one set, *ClogP* was found to be the most correlated descriptor ($R^2 = 0.495$, $n = 40$) and was included in all the best predictive models.

Another predictive model for a set of 45 aldehydes was designed for LogP and *Charge of the Carbonyl Oxygen* descriptor AM1 calculated,⁶ which supports the conclusion of this study, that a descriptor encoding properties of the aldehyde group is important for the design of a highly predictive model. This observation is probably linked with the prevalent reactive mode of action (via Schiff-base formation) of these compounds, due to the presence of a highly reactive aldehyde group.

The descriptors encoding hydrogen bonding properties of the aldehydes, which were used in the predictive models based on *ab initio* and PM3 model chemistries, did not appear in any of the previously published predictive models for this type of compound.

Three of the previous studies on aldehydes used fathead minnow for measures of response and are comparable to the results of this study. Both the multilinear and the neural network model designed for 397 organic chemicals, among them 7 aliphatic and 20 aromatic aldehydes, using the Group Contribution Method showed very good predictivity with the correlation coefficient $R^2 = 0.91$, the root-mean-square error RMSE = 0.37, and $R^2 = 0.90$, RMSE = 0.38.⁴ The neural network model for a group of 375 organic compounds including 6 aliphatic and 14 aromatic aldehydes based on 8 descriptors had the correlation coefficient $r = 0.82$ and RMSE of 0.83 log unit.⁵ No special models for aldehydes were designed in these two studies. Another study provided a predictive model for 8 aliphatic and 37 aromatic aldehydes based on 2 descriptors, which exhibited the correlation coefficient $R^2 = 0.6$ ($s^2 = 0.23$, $F = 31.35$, $R^2_{\text{CV}} = 0.31$).⁶ In the present study the most predictive 4-descriptor model, which has been designed for the largest set of aldehydes so far—11 aliphatic and 39 aromatic, showed a very good correlation coefficient $R^2 = 0.868$ ($s^2 = 0.083$, $F = 74.04$, $R^2_{\text{CV}} = 0.840$) comparable to the other best models and the smallest value of RMSE = 0.27 log unit of all predictive models. Furthermore, our models have been validated also using external data sets, providing similarly good results.

CONCLUSION

Predictive models for the toxicity of a group of 50 aldehydes consisting of 4 parameters (descriptors) were successfully designed and validated. The descriptors used in the best models could be rationally interpreted. Poor prediction for outliers could be explained by their structural properties. Consistent with other previous studies, the logarithm of the partition coefficient logP (O/W) was found

to be a powerful and valuable descriptor, as it was present in all of the best models. The results of this study fully support the previously proposed theory, that the logarithm of the partition coefficient and information about physico-chemical properties mapped onto the molecular surface together with descriptor(s) of the functional group mainly responsible for the toxic effects are essential for the correct prediction of toxicity.

Generally, the quality of predictions slightly improves with the increase in the quality of the model chemistry used for the calculation of descriptors, on which the models are based. The one exception to this rule is the result obtained with calculations at the HF/STO-3G level, as the model designed for descriptors based on this model chemistry showed the best predictivity of all. This fact can be explained by the differences in charge distribution produced by this model chemistry.

According to our findings the semiempirical method PM3, due to its very low computational demands, might be applied for studying big data sets with thousands of compounds with fair results. For a more precise study on a smaller set of compounds, where the highest possible precision of the prediction model is desirable, ab initio or density functional theory calculations of higher level could be recommended as a basis for the calculation of descriptors.

ACKNOWLEDGMENT

Support from European Union within Research Training Network IMAGETOX (HPRN-CT-1999-00015) is gratefully acknowledged. Authors thank to Prof. Alan Katritzky (University of Florida, Gainesville, U.S.A.) and Prof. Mati Karelson (University of Tartu, Estonia) for providing CODES-SA software.

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CI034219J