Int. J. Environ. Res., 10(1): 59-64, Winter 2016
ISSN: 1735-6865

Nano-QSAR: Genotoxicity of Multi-Walled Carbon Nanotubes

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Received 30 June 2015; Revised 16 Oct. 2015; Accepted 19 Oct. 2015

ABSTRACT: The study was carried out to develop an efficient approach for prediction the genotoxicity of carbon nanotubes. The experimental data on the bacterial reverse mutation test (TA100) on multi-walled carbon nanotubes (MWCNTs) was collected from the literature and examined as an endpoint. By means of the optimal descriptors calculated with the Monte Carlo method a mathematical model of the endpoint was built up. The model is represented by a function of: (i) dose (μg/plate); (ii) metabolic activation (i.e. with S9 mix or without S9 mix); and (iii) two types of MWCNTs. The above listed conditions were represented by so-called quasi-SMILES. Simplified molecular input-line entry system (SMILES) is a tool for representation of molecular structure. The quasi-SMILES is a tool to represent physicochemical and / or biochemical conditions for building up a predictive model. Thus, instead of well-known paradigm of predictive modeling "endpoint is a mathematical function of molecular structure" a fresh paradigm "endpoint is a mathematical function of available eclectic data (conditions) is suggested.

Key words: Nano-QSAR, MWCNT, Bacterial reverse mutation test, CORAL software

INTRODUCTION

Among all elements important for nanoscience and nanotechnology carbon maintains a special status (Dinadayalane and Leszczynski, 2010). In 1996 two USA and one British scientist received Nobel Prize for their discovery of fullerenes. Twenty four years later, in 2010 detection and characterization of another type of carbon nanostructure – graphene had again attracted attention of the Nobel Committee and resulted in Nobel Prize awarded to two Russian born researchers. However, there are other distinctive types of carbon nanostructure – carbon nanotubes - that were reported long time before fullerene and graphene discoveries.

Remarkably, the existence of carbon nanotubes (CNT) was described for the first time in 1952 (Monthioux and Kuznetsov, 2006). After almost quarter of Century the next paper reporting carbon nanotubes was published 1976 (Monthioux and Kuznetsov, 2006). Unfortunately, these discoveries had not significantly stimulated scientific community and only after the eminent publication of Iijima in 1991 CNTs received appropriate recognition (Iijima, 1991).

Carbon nanotubes could be divided into two distinct groups: walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs) (Iijima and Ichihashi, 1993; Bethune *et al*., 1993). It is believed that the CTNs have the most notable industrial prospects among the carbon nanostructures. By now various applications of carbon nanotubes have been developed (Baughman *et al*., 2002). One of the fastest growing areas includes their potential bio-applications and this has already attracted significant attention. Among important applications of CNTs are biosensors, drug and other delivery systems, and bioimaging (Liu *et al.,* 2011; Sinha and Yeow, 2005; Lu *et al.,* 2009; Huang *et al.,* 2011). However, there is

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another aspect of nanoaplications. The fast progress in nanoscience and nanotechnology is followed by concerns about short and long effects of nanospecies on human health and environment. This requires thoughtful studies and development of techniques that could provide desired information in fast and efficient way, before moving new nanomaterials into production lines and supermarket shells.

Quantitative structure – property / activity relationships (QSPRs/QSARs) approaches have been developed and applied to combine and take advantage of efficiency of computational methods and knowledge (sometime limited) set of experimental data. Application of such approaches opens a prospect to define and develop preferable substances to be used for solving various practical tasks (Castillo-Garit *et al.,* 2007; Afantitis *et al*., 2011; Furtula and Gutman, 2011; García *et al*., 2011; Luan *et al.*, 2014; Kleandrova et al., 2014a,b; Speck-Planche *et al.*, 2015). The QSPR/QSAR prediction of desired (or hazardous) parameters of a given substance is based on characteristics of its molecular structure. Such predictions have been successfully carried out for standard chemical compounds for almost 70 years and resulted in development of a number of new, efficient drugs.

On the other hand, predictions for an important class of species - nanomaterials have been known to create fundamental challenges for the QSPR/QSAR community. The development of systematic representation for various nanomaterials remains a complex task since the molecular architectures of these substances are very atypical, in comparison with structures of traditional substances (Leszczynski, 2010; Rallo *et al*., 2011; Dinadayalane *et al*., 2012; Roca *et al*., 2012; Liu *et al*., 2013). There are also additional barriers. The advance of traditional QSPR/QSAR analyses for nanomaterials is limited due to the absence of standardized databases for their structures, aligned together with physicochemical and biomedical endpoints. Fortunately, in the case of selected nanomaterials the data on various conditions related to the impact of these substances upon biological objects are available in the literature. This has facilitated creative modification of the standard techniques and as the consequence, the quasi-QSAR approach was introduced as an alternative to the traditional QSPR/QSAR (Toropova and Toropov, 2013; Toropova and Toropov, 2014; Toropov and Toropova, 2014). In this approach instead of the representation of a substances by molecular structure the description of the considered species by the above-mentioned available eclectic information becomes possible. In fact, the optimal descriptors calculated with so-called correlation weights of various attributes of nanomaterials could provide a tool to build up the quasi-QSAR. Since the approach is devoted to nanomaterials these quasi-QSARs can be named "nano-QSARs".

Let us summarize the novel features of this approach. One recognizes that the innovative, possible way to build up predictive model related to nanomaterials is application of the new paradigm: "**Endpoint = F (Available eclectic data)",** instead of traditional paradigm: "**Endpoint = F (Molecular structure)".**

The aim of the present work is the investigation of the application of optimal descriptors as possible contributions towards building up predictive model for genotoxicity of multi-walled carbon nanotubes (MWCNTs). Various conditions (concentration, presence / absence of S9 mix, different types of MWCNTs) are represented by quasi-SMILES (Toropov and Toropova, 2015). These quasi-SMILES are basis to build up predictive model according to paradigm "**Endpoint = F (Available eclectic data)"**, by means of the CORAL software (Toropova and Toropov, 2014).

MATERIALS & METHODS

The experimental data on the genotoxic potential of two products of multi-walled carbon nanotubes (coded as N-MWCNTs, diameter of 44 nm/BET surface area of 69 m^2/g and MWNT-7, diameter of 70 nm/BET surface area of 23 m^2/g) were taken from the literature (Ema *et al*., 2012). Table 1 contains experimental data related to genotoxicity of MWCNTs. Various codes, related to the conditions which were considered for building up nano-QSAR models, are provided in the Table 2. The details of calculations are given in the Table 3. This table contains specifics of three random distributions of the experimental information. The experimental data was divided into the training, calibration, and validation sets.

Each of the data sets has an important function. The training set contains data which are directly involved in building up models. Data from the calibration set serve to avoid the overtraining. The data from validation set is used at the end of calculations to test predictive potential of the developed models models.

The optimal descriptors used in this study are calculated as follows:

$$DCW(T,N) = \Sigma CW(S_k) + \Sigma CW(SS_k) = \Sigma CW(A_k) \quad (1)$$

Where S_k and SS_k are fragments of quasi-SMILES which contain one and two symbols, respectively; A_k is a code of an attribute of MWCNTs (Table 2); the $CW(S_k)$ and $CW(SS_k)$ are correlation weights of the above-mentioned quasi-SMILES attributes. The correlation weights of attributes are calculated with optimization carried out by the Monte Carlo

Table 1. Experimental data and conditions on bacterial reverse mutation tests on multi-walled carbon nanotubes (Ema *et al.*, 2012).

Test substance	Concentration, μg/plate	S9Mix	The average number of revertant colonies / plate, TA100
N-MWCNTs	0.78	-	120
	1.56	-	109
	3.13	-	119
	6.25	-	116
	12.5	-	114
	25.0	-	109
	50.0	-	114
	100.0	-	117
N-MWCNTs	0.78	+	105
	1.56	+	115
	3.13	+	114
	6.25	+	127
	12.5	+	133
	25.0	+	120
	50.0	+	125
	100.0	+	128
MWNT-7	0.78	-	111
	3.13	-	118
	6.25	-	122
	12.5	-	123
	25.0	-	118
	50.0	-	121
	100.0	-	121
MWNT-7	0.78	+	126
	3.13	+	114
	6.25	+	135
	12.5	+	124
	25.0	+	124
	50.0	+	108
	100.0	+	134

Table 2. List of attributes (conditions) related to the genotoxicity of multi-walled carbon nanotubes (MWCNTs)

Attribute	Codes of attributes (S_k) and their meaning
Test substance	1 = N-MWCNTs 2 = MWNT-7
Mix S9	+ = with Mix S9 - = without Mix S9
Concentration (μg/plate)	A = 0.78 B = 1.56 C = 3.13 D = 6.25 E = 12.5 F = 25.0 G = 50.0 H = 100.0

technique. The correlation weights should provide maximal value of the correlation coefficient between the *DCW(T,N)* and experimental TA100. The T and N are parameters of the optimization: T (threshold) is coefficient for classification of attributes into two categories: rare and not rare. Correlation weight for rare impact is fixed equal to zero. Therefore rare attribute are not involved in building up a model. The N is the number of epochs of the Monte Carlo optimization. There are T* and N* parameters which give preferable statistics for the calibration set (Toropova and Toropov, 2014). These values are used to build up model.

Having data on optimal correlation weights, one can (i) calculate DCW(T*,N*) for all fullerene C60 nanoparticles; (ii) calculate (with data on the training set) a model for TA100:

$$TA100 = C_0 + C_1 \times DCW\ (T^*, N^*) \quad (2)$$

The model should give preferable statistical quality for the calibration set (i.e best quality for a preliminary external test set); and (iii) predictive potential of the model should be checked up with an external validation set. The MWCNTs of the validation set are not involved in building up model.

RESULTS & DISCUSSION

The statistical quality of models for TA100 calculated by the Monte Carlo technique (using the CORAL software, http://www.insilico.eu/coral) is the following:

Split 1

$$TA100 = 82.40\ (\pm 2.325) + 7.543\ (\pm 0.482) * DCW(2,9) \quad (3)$$

$n=20$, $r^2=0.5340$, $s=6.02$, $F=21$ (training set)

$n=5$, $r^2=0.6586$, $R_m^2=0.556$, $s=9.9$ (calibration set)

$n=5$, $r^2=0.6131$, $s=3.94$ (validation set)

Table 3. Three distributions of available experimental data into the training (T), calibration (C), and validation (V) sets; quasi-SMILES representing genotoxicity by MWCNTs, experimental and predicted TA100 values (average number of revertant colonies / plate)

ID	Distribution			quasi-SMILES	TA100			
	1	2	3		Experiment	Eq. 3	Eq. 4	Eq. 5
01	C	V	T	1-A	120	107.59	115.07	114.86
02	T	T	T	1-B	109	103.41	108.99	108.07
03	C	T	T	1-C	119	108.72	113.66	118.91
04	V	T	C	1-D	116	117.71	118.03	121.21
05	T	C	T	1-E	114	116.04	122.16	117.56
06	T	V	C	1-F	109	111.70	117.18	108.07
07	T	C	T	1-G	114	114.70	119.83	116.95
08	V	T	V	1-H	117	117.76	120.14	120.02
09	T	T	T	1+A	105	116.85	115.58	116.04
10	V	T	V	1+B	115	108.56	115.00	122.78
11	V	V	T	1+C	114	113.87	119.67	114.69
12	V	V	C	1+D	127	122.86	136.40	135.92
13	T	T	T	1+E	133	128.01	128.17	128.93
14	C	C	V	1+F	120	112.71	123.19	122.78
15	T	T	T	1+G	125	116.91	116.47	117.05
16	C	T	V	1+H	128	122.91	130.72	134.73
17	T	C	T	2-A	111	113.26	117.07	116.31
18	T	V	C	2-C	118	114.40	115.66	120.35
19	T	T	T	2-D	122	123.39	120.03	122.66
20	T	C	T	2-E	123	121.72	124.17	119.00
21	T	T	C	2-F	118	117.38	119.18	109.52
22	T	T	T	2-G	121	120.38	121.83	118.39
23	T	V	T	2-H	121	123.43	122.14	121.46
24	T	T	T	2+A	126	120.34	115.43	114.98
25	T	T	T	2+C	114	117.36	119.52	113.64
26	T	T	T	2+D	135	126.35	136.24	134.86
27	T	V	T	2+E	124	131.49	128.02	127.87
28	C	T	V	2+F	124	116.20	123.04	121.73
29	T	T	T	2+G	108	120.39	116.31	115.99
30	T	T	T	2+H	134	126.39	130.56	133.67

Split 2

TA100 = 102.1 (± 0.93) + 6.652 (± 0.255) * DCW(2,33) (4)

n=18, r^2=0.6270, s=5.37, F=27 (training set)

n=5, r^2=0.7898, R_m^2=0.5269, s=6.11 (calibration set)

n=7, r^2=0.5289, s=6.25 (validation set)

Split 3

TA100 = 87.82 (± 1.0481) + 9.832 (± 0.2644) * DCW(2,33) (5)

n=20, r^2=0.6395, s=5.14, F=32 (training set)

n=5, r^2=0.7306, R_m^2=0.5304 s=6.80 (calibration set)

n=5, r^2=0.5662, s=5.66 (validation set)

The R_m^2 is criterion of predictive potential of a model according to the literature (Roy et al., 2009): a model has predictive potential if $R_m^2$is larger than 0.5.

Unfortunately, the total number of experimental data available for the nano-QSAR analysis is limited to 30. As the result, the statistical quality of the model is not high for the training set. However, even with this limitation each model has the predictive potential, since the range of correlation coefficients for validation sets spans from 0.52 to 0.61. It is expected that the application of the approach for similar data with n>30 would provide improved statistics.

There is a peculiar feature of the models developed here. Interestingly, the similar, uncommon situation for QSAR approach has been noted previously for modeling carcinogenicity of organic compounds (Toropova *et al*., 2011). A group of compounds being in the "visible" training set was classified as outliers, however, the removal of these compounds leads to the decrease of the statistical quality of the model for the "invisible" validation set. The behavior of these compounds was classified as atypical (Toropova *et al*., 2011).

In the case of current study the quasi-SMILES #9, #13, #24, and #29 (Table 3) have similar atypical behavior. In fact, they are outliers even as members of the "visible" training set, however, removal of these quasi-SMILES leads to decrease of the predictive potential of the model for "invisible" validation set. Table 4 contains the correlation weights for different attributes of quasi-SMILES and lists of blocked (correlation weight is equal to zero) and active attributes (correlation weight is not equal to zero). Based on the obtained results, an ability of the applied approach to involve eclectic data to build up predictive model of genotoxicity for MWCNTs is demonstrated. The details concerning the correlation weights applied for calculation of the quasi-SMILES attributes with Eqs. 3, 4, and 5 using the Monte Carlo

Table 4. The correlation weights for quasi-SMILES attributes calculated by the Monte Carlo method for three random splits of data (Table 3) into the training, calibration, and test sets.

Attribute, A	CW(A)	Attribute, A	CW(A)	Attribute, A	CW(A)
+	1.44119	+	1.92695	+	1.61180
-	0.89420	-	1.40004	-	0.41596
1+	1.13631	1+	1.56350	1+	0.90985
1-	1.00067	1-	1.24750	1-	0.60952
1	0.89162	1	0.95046	1	1.03473
2+	1.24931	2+	1.07061	2+	0.98698
2-	1.40391	2-	1.05113	2-	0.94103
2	1.24072	2	1.40466	2	0.85008
A+	0.54591	A+	-1.00773	A+	-0.64808
A-	0.0	A-	0.0	A-	0.72822
A	0.55355	A	-0.78982	A	-0.03762
B-	0.0	B+	0.0	B-	0.0
B	0.0	B-	0.0	B	0.0
C+	0.0	B	-1.85257	C+	-1.92489
C-	0.0	C+	0.0	C-	0.0
C	0.70401	C-	0.0	C	1.10212
D+	0.0	C	-1.22743	D+	0.0
D-	0.0	D+	0.0	D-	0.0
D	1.89555	D-	-1.88531	D	1.33627
E+	1.45088	D	1.19837	E+	-0.07847
E-	0.54723	E+	0.0	E-	0.26168
E	1.12725	E-	0.0	E	0.70326
F+	0.0	E	0.0	F-	0.0
F-	0.54823	F+	0.0	F	0.0
F	0.55058	F-	0.0	G+	-0.54572
G+	0.55170	F	-0.67340	G-	0.94043
G-	0.94207	G+	-1.32532	G	-0.03795
G	0.55459	G-	0.0	H+	0.0
H+	0.0	G	-0.34880	H-	0.0
H-	0.0	H+	0.72720	H	1.21506
H	1.90176	H-	0.0		
		H	-0.29802		

Table 5. Example of calculation of the optimal descriptor for quasi-SMILES represented by symbols "1-A" for the case of split 1

Attribute, A	CW(A)
S_k	
1	0.8916
-	0.8942
A	0.5535
SS_k	
1-	1.0007
A-	0.0
$DCW(2,9)= \Sigma CW(A)=$	**3.3400**

method are provided in the Table 4. Table 5 contains an example of the calculation of the DCW(2,17) for Eq. 3 (Split 1). This representative example illustrates the applied methodology. We believe that the considered here approach has broader applications to various groups of nanomaterials.

CONCLUSIONS

This study reports development of computational models for the genotoxicity of carbon nanotubes. It is based on experimental data on the bacterial reverse mutation test (TA100) on multi-walled carbon nanotubes (MWCNTs). The approach used here resulted in semi-quantitative prediction for three different distributions of the experimental data into the visible training and calibration sets, and invisible validation set. The predictive potential of these models is different. It is noticed that in the developed models there are also quasi-SMILES (i.e. representations of combinations of conditions, Table 3) characterized by "atypical" behavior: even when included in the training set they are outliers. However the removing of those quasi-SMILES leads to decrease of predictive potential of the models.

ACKNOWLEDGEMENTS

A.A.T. and A.P.T. thank the EU project PROSIL funded under the LIFE program (project LIFE12ENV/IT/000154), R.R. thanks the EC Project MODERN (Contract 309314), D.L. and J.L. thank the National Science Foundation (NSF/CREST HRD-0833178), and EPSCoR (Award #: 362492-190200-01/NSFEPS-090378) for financial support.

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