Quasi-SMILES for Nano-QSAR Prediction of Toxic Effect of Al$_2$O$_3$ Nanoparticles

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ABSTRACT

The level of malondialdehyde (MDA) in wet tissue of different organs is utilized as a measure of toxic effect. The numerical data on the concentration of MDA in wet tissue of liver, kidneys, brain, and heart of rat is examined as the endpoint which are impacted by different dose (mg/kg), exposure time (3 and 14 days) and single oral treatment of aluminium nano-oxide (Al$_2$O$_3$) with 30 nm or 40 nm. An attempt to develop predictive model for this endpoint has been carried out in this work. SMILES is a traditional tool to represent molecular structure for QSPRs/QSARs. In contrast to traditional SMILES, so-called quasi-SMILES can be a tool to build up quantitative features – property / activity relationships (QFPRs/QFARs) for endpoints which are not defined by solely molecular structure, but by a group of physicochemical and/or biochemical conditions. The quasi-SMILES is the representation of the above eclectic conditions whereas the QFPR/QFAR are models of endpoints which are modified under impacts of these eclectic conditions.

KEYWORDS

Al$_2$O$_3$ Toxicity, Nanoparticles, Nano-QFAR, Nano-QSAR, Quasi-SMILES, REACH, Risk Assessment, Safety Assessment

1. INTRODUCTION

The influence of various nanomaterials on the everyday life gradually increase owing to their high functional potential be very useful materials for different applications (Vanić and Škalko-Basnet, 2013; Ma et al., 2013; Singh and Gupta, 2014; Melagraki and Afantitis, 2014; Panneerselvam and Choi, 2014; Potrč et al., 2015; Sauer et al., 2015; Speck-Planche et al., 2015). However, a tool to risk assessment for nanomaterials similar to quantitative structure – property /activity relationships (QSPRs/QSARs) (Toropova et al., 2012; Yilmaz et al., 2015) as research field is in an initial phase of the development (Muthu, 2012; Oksel et al., 2015). The solution of this task for regulatory purposes in the case of nanomaterials involved in the agriculture, food, cosmetics, drug discovery, etc. needs to be reached in the near future (Arts et al., 2014; Arts et al., 2015; Filon et al., 2015; Amenta et al., 2015).

In general, different measures of danger acting of nanomaterials upon cells are known (Long et al., 2009; Prabhakar et al., 2012; Diez-Ortiz et al., 2015; Toropova et al., 2015a; Hadrup et al., 2015). In particular, the level of malondialdehyde (MDA) in wet tissue of different organs is considered as a measure of toxic effect of nanomaterials (Long et al., 2009; Prabhakar et al., 2012).

Attempts which are aimed to build up models for such acting of nanomaterials using the traditional QSPR/QSAR approaches (De Abrew et al., 2015), as rule, are impossible excepting the cases of acting of small molecules together with a nanomaterial (Fourches et al., 2010; Toropov et al., 2013).

In the case of traditional materials where the molecular structure represented by SMILES is available to mathematical and computational analyses, the QSPR/QSAR is a tool to more or less satisfactory prediction of different endpoints (Veselinović et al., 2013; Achary, 2014a, 2014b; Comelli et al., 2014; Nesmerak et al., 2014; Worachartcheewan et al., 2014; Toropova and Toropov, 2014; Veselinović et al., 2015).

A possible way to build up such models can be expressed by paradigm: "Endpoint = f(SMILES)". In the case of nanomaterials where weak variation of molecular structure accompanied by intensive variation of conditions more appropriate paradigm is "Endpoint = f(Eclectic data)".

The quasi-SMILES can be the representation of eclectic data (Toropov and Toropova, 2015). The quasi-SMILES are analogies of traditional SMILES, but symbols involved in the quasi-SMILES are representations of features and/or conditions that are not representation of features of the molecular architecture only. (Toropova and Toropov, 2013; Toropov and Toropova, 2014; Toropova et al., 2015b).

The aim of this work is to build up models for level of MDA in wet tissue of different organs of rat under different action of Al_2O_3 nanoparticles.

2. METHOD

2.1. Data

The experimental data on the level MDA in wet tissue (nanomoles of MDA per gram wet tissue) of liver, kidneys, brain, and heart of rat under different conditions taken in the literature (Prabhakar et al., 2012). Table 1 contains the representation of different conditions of acting Al_2O_3 nanoparticles by quasi-SMILES. These data (quasi-SMILES together with endpoint values) were three times randomly split into the training, calibration, and validation set. The length of quasi-SMILES (the number of symbols) is important indicator for possibility of a model to be successful.

It is to be noted that length 1 for quasi-SMILES is nonsense, because in this case the prevalence of each attribute is zero in the training or in calibration set (the presence in both mentioned set is impossible), i.e. for each attribute, A, one can obtain:

$$N_{training}(A) \times N_{calibration}(A) = 0$$
$$P_{training}(A) \times P_{calibration}(A) = 0$$

where $N_{training}(A)$ and $N_{calibration}(A)$ are the numbers of attribute into the training and calibration sets, respectively; $P_{training}(A)$ and $P_{calibration}(A)$ are probabilities of presence of the attribute A in the training and calibration sets, respectively.

The length 2 gives possibility to obtain at least for part of attributes:

$$N_{training}(A) \times N_{calibration}(A) \neq 0$$
$$P_{training}(A) \times P_{calibration}(A) \neq 0$$

The total number of quasi-SMILES involved in built model has significant meaning:

Length 2 …$N_{max} = N_1 \times N_2$
Length 3 …$N_{max} = N_1 \times N_2 \times N_3$
Length 4 …$N_{max} = N_1 \times N_2 \times N_3 \times N_4$

Table 1. The definition of quasi-SMILES

quasi-SMILES				Endpoint, E
Organ	Dose mg/kg	Days	Single oral treatment	Nanomoles of MDA per gram wet tissue
L=Liver K=Kidneys B=Brain H=Heart	1=2000 2=1000 3=500	X=3 days Y=14 days	T=30 nm F=40 nm	
L	1	X	T	33.6
L	2	X	T	23.4
L	3	X	T	14.5
K	1	X	T	13.4
K	2	X	T	9.95
K	3	X	T	8.73
B	1	X	T	16.7
B	2	X	T	13.1
B	3	X	T	13.2
H	1	X	T	2.8
H	2	X	T	2.2
H	3	X	T	2.8
L	1	X	F	29.8
L	2	X	F	24.1
L	3	X	F	13.7
K	1	X	F	12.2
K	2	X	F	8.93
K	3	X	F	8.51
B	1	X	F	14.4
B	2	X	F	12.7
B	3	X	F	11.0
H	1	X	F	2.43
H	2	X	F	2.14
H	3	X	F	2.38
L	1	Y	T	14.8
L	2	Y	T	10.8
L	3	Y	T	10.6
K	1	Y	T	7.2
K	2	Y	T	9.0
K	3	Y	T	8.0
B	1	Y	T	12.3
B	2	Y	T	12.0
B	3	Y	T	11.6
H	1	Y	T	2.8
H	2	Y	T	2.8
H	3	Y	T	2.6
L	1	Y	F	13.6
L	2	Y	F	10.7
L	3	Y	F	9.33
K	1	Y	F	7.7
K	2	Y	F	8.6
K	3	Y	F	8.4
B	1	Y	F	11.6
B	2	Y	F	11.6
B	3	Y	F	12.0
H	1	Y	F	2.4
H	2	Y	F	2.6
H	3	Y	F	2.7

For instance, two situations for quasi-SMILES with length 2 which are represented by a pairs of < Impact, Condition > are represented in Table 2. From practical point of view, the second situation is preferable, because 10 variables are more information about a phenomenon than 6 variables.

Using the formalism of the quasi-SMILES which are utilized to integrate eclectic data for the nanomaterials one can build up model for endpoints related to nanomaterials. Apparently, increase of length of quasi-SMILES is promoter of improving for the statistical quality of a model. In this work, the length of used quasi-SMILES is four.

2.2. Optimal Descriptors

The optimal descriptors are calculated as the following:

$$DCW(Threshold, N_{epoch}) = \sum CW(C_k) \tag{1}$$

where C_k is code of k-th feature (condition); $CW(C_k)$ is the correlation weight for C_k; The *Threshold* and N_{epoch} are parameters of the Monte Carlo optimization. The *Threshold* is a tool to define two classes of features (conditions): rare (noise) and not rare, i.e. active. The optimal descriptors are calculated with the correlation weights of active features. Correlation weights for rare features (conditions) are fixed equal to zero, i.e. these are not involved in building up model; The N_{epoch} is the number of epochs of the Monte Carlo optimization.

The *Threshold* = T* and N_{epoch} =N* which give preferable statistical characteristics for the calibration set of quasi-SMILES should be defined by means of several runs of the Monte Carlo optimization. These parameters should be used to build up the final model for endpoint, **E** (Toropova et al., 2015a):

$$E = C_0 + C_1 \times DCW(T^*, N^*) \tag{2}$$

Table 2. Different eclectic sources for construction of the quasi-SMILES

Situation 1

	Impact 1	Impact 2	Impact 3
Condition 1	Endpoint 11	Endpoint 12	Endpoint 13
Condition 2	Endpoint 21	Endpoint 22	Endpoint 23

Nmax = N$_{condition}$ × N$_{impact}$ = 2 × 3 = 6

Situation 2

	Impact 1	Impact 2	Impact 3	Impact 4	Impact 5
Condition 1	Endpoint 11	Endpoint 12	Endpoint 13	Endpoint 14	Endpoint 15
Condition 2	Endpoint 21	Endpoint 22	Endpoint 23	Endpoint 24	Endpoint 25

Nmax = N$_{condition}$ × N$_{impact}$ = 2 × 5 = 10

Figure 1 represents the scheme of the selecting T* and N*.

The predictive potential of the model calculated with Equation 2 should be checked up with the external validation set.

All operations with quasi-SMILES are carrying out by the same algorithms which were developed for the traditional SMILES (Toropov et al., 2012a, b; Roy, 2015).

3. RESULTS AND DISCUSSION

The optimal descriptors give for three random splits the following models:

$$E = -1357.4 \ (\pm 57.96) + 344.21 \ (\pm 14.61) * DCW(1,3) \qquad (3)$$

n=26, r^2=0.7382, q^2=0.6524, s=3.55, F=68 (training set)
n=9, r^2=0.7456, s=4.30 (calibration set)
n=13, r^2=0.7735, s=3.42 (validation set)

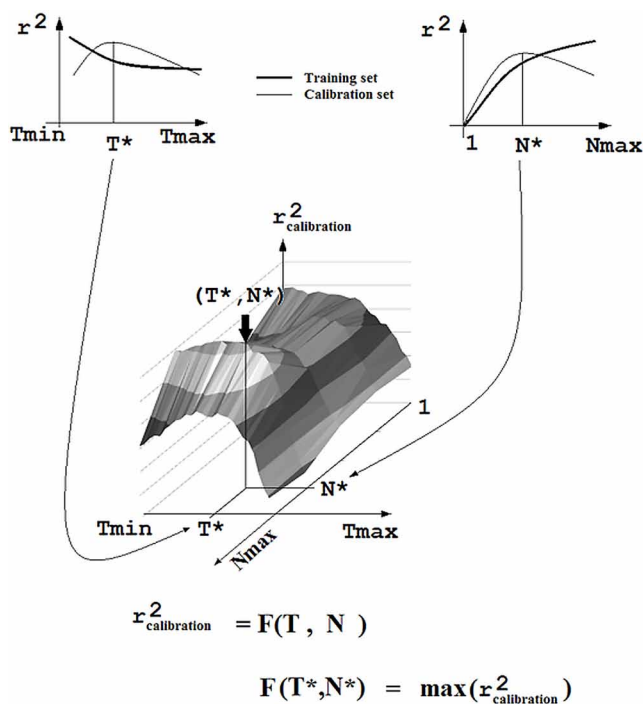$$E = -617.60 \ (\pm 17.64) + 155.21 \ (\pm 4.379) * DCW(1,3) \qquad (4)$$

n=29, r^2=0.7976, q^2=0.7479, s=3.52, F=106 (training set)
n=9, r^2=0.7711, s=3.76 (calibration set)
n=10, r^2=0.7234, s=3.51 (validation set)

$$E = -218.59 \ (\pm 7.953) + 54.172 \ (\pm 1.900) * DCW(1,3) \qquad (5)$$

Figure 1. The scheme of selecting of the T* and N*

n=28, r^2=0.7674, q^2=0.7007, s=3.76, F=86 (training set)
n=9, r^2=0.7041, s=2.71 (calibration set)
n=11, r^2=0.8254, s=4.08 (validation set)

In Equations 3-5, the n is the number of quasi-SMILES in a set (i.e. training set, calibration set, or validation set); the r^2 is the correlation coefficient; the q^2 is leave-one-out cross-validated r^2; the s is root-mean squared error; and the F is Fischer F-ratio.

Table 3 contains the correlation weights $CW(C_k)$ for split 1 (Equation 3), split 2 (Equation 4) and split 3 (Equation 5) together with frequencies of C_k in the training and calibration sets.

Table 4 contains quasi-SMILES together with the numerical data on E for the models.

The third distribution into the training set, the calibration set, and the validation set should be estimated as the worst since attribute of quasi-SMILES "L" is absent in the calibration set. However, even for this distribution the prediction for the endpoint characterized by quite satisfactory statistical quality.

The mechanistic interpretation of a QSPR/QSAR model is important principle of building up predictive model (OECD, 2007; REACH 2011). The mechanistic interpretation for models similar to ones suggested in this work can be defined as the following. Having the numerical data on the correlation weights of features obtained in several runs of the Monte Carlo optimization, one can classify the features as promoters of endpoint increase (if the correlation weight of a feature every time is large) and promoters of endpoint decrease (if the correlation weight of a feature every time is small). In the examined dataset (Table 3), one can select doses ('1' and '2') together with the liver ('L') as promoters of increase the endpoint. Only heart ('H') is the promoter of the endpoint decrease. It can be interpreted as the following: the high doses (2000 and 1000 mg/kg) give increase of nanomoles of MDA per gram in wet tissue, liver accumulates the MDA more intensively than other organs, and heart accumulates the MDA less intensively than other organs.

Thus, the thesis that optimal descriptor can be a translator of eclectic data into endpoint prediction is confirmed.

Table 3. Correlation weights of quasi-SMILES attributes (conditions) for calculation of the DCW(1,3) for split 1, 2, and 3; T and C are frequencies of C_k in the training set and calibration set, respectively

C_k	Split 1, Eq. 3			Split 2, Eq. 4			Split 3, Eq. 5		
	$CW(C_k)$	T	C	$CW(C_k)$	T	C	$CW(C_k)$	T	C
1	1.00499	6	5	1.10609	12	3	1.09869	10	2
2	1.00071	10	3	1.09139	9	3	1.03604	11	2
3	0.99649	10	1	1.07653	8	3	1.02655	7	5
B	0.99828	8	2	0.98928	7	1	1.10572	6	2
F	0.98857	11	6	0.99074	15	6	1.07396	14	4
H	0.96721	7	1	0.92433	8	3	0.90153	8	2
K	0.98800	3	5	0.97011	7	2	1.04558	7	5
L	1.00881	8	1	1.03275	7	3	1.20953	7	0
T	0.99670	15	3	0.99545	14	3	1.09827	14	5
X	0.99518	12	7	0.99811	15	4	1.08228	10	6
Y	0.98255	14	2	0.97300	14	5	0.99005	18	3

Table 4. Distributions into the training (T), calibration (C), and validation (V) sets for splits 1, 2, and 3; together with experimental and calculated level ADM in wet tissue of rats

ID	1	2	3	quasi-SMILES	Experiment	Eq.3	Eq.4	Eq.5
	Distribution				**Nanomoles of MDA per gram wet tissue**			
1	T	T	T	L1XT	33.60	21.4061	23.8192	24.5742
2	T	C	V	L2XT	23.40	19.9312	21.5384	21.1799
3	V	V	V	L3XT	14.50	18.4786	19.2317	20.6659
4	T	T	T	K1XT	13.40	14.2407	14.0967	15.6922
5	C	V	C	K2XT	9.95	12.7658	11.8160	12.2980
6	T	T	C	K3XT	8.73	11.3132	9.5093	11.7840
7	C	T	V	B1XT	16.70	17.7815	17.0711	18.9502
8	T	T	C	B2XT	13.10	16.3066	14.7903	15.5559
9	V	C	V	B3XT	13.20	14.8539	12.4837	15.0419
10	T	C	T	H1XT	2.80	7.0876	6.9908	7.8889
11	T	T	T	H2XT	2.20	5.6127	4.7101	4.4946
12	T	T	C	H3XT	2.80	4.1601	2.4034	3.9806
13	C	T	T	L1XF	29.80	18.6066	23.0881	23.2568
14	V	T	T	L2XF	24.10	17.1317	20.8074	19.8625
15	T	T	V	L3XF	13.70	15.6791	18.5007	19.3486
16	C	T	C	K1XF	12.20	11.4412	13.3657	14.3749
17	V	T	T	K2XF	8.93	9.9663	11.0849	10.9806
18	C	V	T	K3XF	8.51	8.5137	8.7782	10.4667
19	C	T	V	B1XF	14.40	14.9819	16.3401	17.6328
20	T	V	T	B2XF	12.70	13.5070	14.0593	14.2386
21	T	V	V	B3XF	11.00	12.0544	11.7526	13.7246
22	C	T	T	H1XF	2.43	4.2881	6.2598	6.5715
23	V	C	V	H2XF	2.14	2.8132	3.9790	3.1772
24	T	T	C	H3XF	2.38	1.3606	1.6724	2.6633
25	V	T	V	L1YT	14.80	17.0578	19.9210	19.5775
26	T	V	T	L2YT	10.80	15.5829	17.6403	16.1833
27	T	T	T	L3YT	10.60	14.1302	15.3336	15.6693
28	V	V	C	K1YT	7.20	9.8923	10.1986	10.6956
29	C	T	T	K2YT	9.00	8.4174	7.9178	7.3013
30	T	T	T	K3YT	8.00	6.9648	5.6111	6.7874
31	T	T	T	B1YT	12.30	13.4331	13.1730	13.9536
32	T	V	T	B2YT	12.00	11.9582	10.8922	10.5593
33	T	V	T	B3YT	11.60	10.5056	8.5855	10.0453
34	V	T	T	H1YT	2.80	2.7392	3.0927	2.8922
35	T	T	T	H2YT	2.80	1.2643	0.8119	-0.5020
36	V	V	T	H3YT	2.60	-0.1883	-1.4947	-1.0160
37	T	C	V	L1YF	13.60	14.2582	19.1900	18.2602
38	T	T	T	L2YF	10.70	12.7833	16.9092	14.8659
39	T	C	T	L3YF	9.33	11.3307	14.6026	14.3519
40	V	C	T	K1YF	7.70	7.0928	9.4675	9.3783
41	C	C	T	K2YF	8.60	5.6179	7.1868	5.9840
42	V	T	C	K3YF	8.40	4.1653	4.8801	5.4700
43	V	T	T	B1YF	11.60	10.6336	12.4419	12.6362
44	T	T	T	B2YF	11.60	9.1587	10.1612	9.2419
45	T	T	C	B3YF	12.00	7.7061	7.8545	8.7280
46	T	T	T	H1YF	2.40	-0.0603	2.3617	1.5749
47	T	T	V	H2YF	2.60	-1.5352	0.0809	-1.8194
48	V	C	T	H3YF	2.70	-2.9878	-2.2258	-2.3333

4. CONCLUSION

The suggested scheme of the prediction for level of malondialdehyde in wet tissue of rat under action of the Al_2O_3 nanoparticles (oral exposure) based on described quasi-SMILES (Table 1) gives quantitative prediction for this endpoint. Since the suggested model is validated with a group of distribution into visible the training and calibration sets and invisible validation set, the approach can be used for regulatory purposes according to OECD principles (OECD, 2007) and REACH (REACH, 2011).

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