Journal of Nanotoxicology and Nanomedicine
Volume 1 • Issue 1 • January-June 2016

Quasi-SMILES for Nano-QSAR Prediction of Toxic Effect of Al_2O_3 Nanoparticles

Alla P. Toropova, IRCCS, Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy

P. Ganga Raju Achary, Department of Chemistry, Institute of Technical Education and Research (ITER), Siksha 'O'Anusandhan University, Bhubaneswar, India

Andrey A. Toropov, IRCCS, Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy

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_2O_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_2O_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).

DOI: 10.4018/JNN.2016010102

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:

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

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:

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

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):

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

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

$Nmax = N_{condition} \times N_{impact} = 2 \times 3 = 6$

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

$Nmax = N_{condition} \times N_{impact} = 2 \times 5 = 10$

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:

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

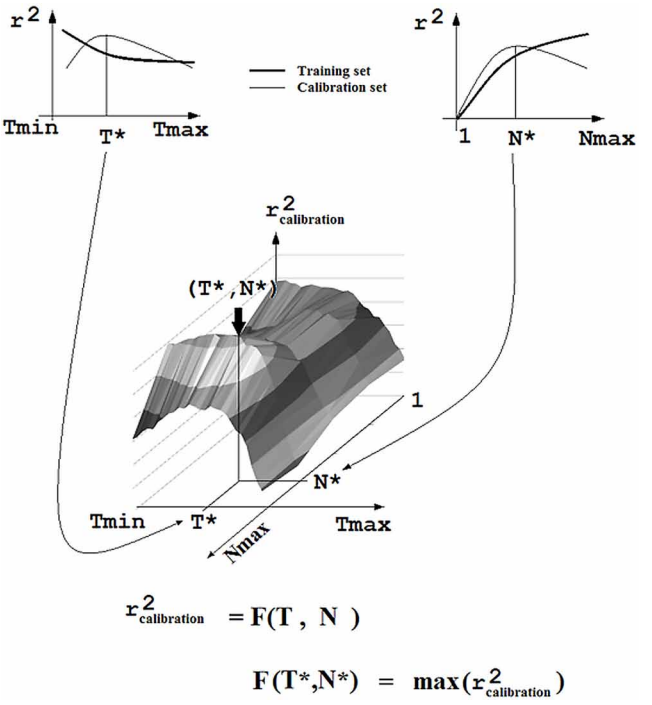
n=26, r^2=0.7382, q^2=0.6524, s=3.55, F=68 (training set)
n=9, r^2=0.7456, s=4.30 (calibration set)
n=13, r^2=0.7735, s=3.42 (validation set)

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

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)

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

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

	Split 1, Eq. 3			**Split 2, Eq. 4**			**Split 3, Eq. 5**		
C_k	$CW(C_k)$	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

	Distribution				Nanomoles of MDA per gram wet tissue			
ID	1	2	3	quasi-SMILES	Experiment	Eq.3	Eq.4	Eq.5
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).

ACKNOWLEDGMENT

We show our gratitude to EC project PROSIL funded under the LIFE program (project LIFE12ENV/IT/000154) and the EC project PeptiCAPS (Project reference: 686141).

REFERENCES

Achary, P. G. R. (2014a). QSPR modelling of dielectric constants of π-conjugated organic compounds by means of the CORAL software. *SAR and QSAR in Environmental Research*, *25*(6), 507–526. doi:10.1080/1062936X.2014.899267 PMID:24716837

Achary, P. G. R. (2014b). Simplified molecular input line entry system-based optimal descriptors: QSAR modelling for voltage-gated potassium channel subunit Kv7.2. *SAR and QSAR in Environmental Research*, *25*(1), 73–90. doi:10.1080/1062936X.2013.842930 PMID:24580100

Amenta, V., Aschberger, K., Arena, M., Bouwmeester, H., Moniz, F. B., Brandhoff, P., & Peters, R. J. et al. (2015). Regulatory aspects of nanotechnology in the agri/feed/food sector in EU and non-EU countries. *Regulatory Toxicology and Pharmacology*, *73*(1), 463–476. doi:10.1016/j.yrtph.2015.06.016 PMID:26169479

Arts, J. H. E., Hadi, M., Irfan, M.-A., Keene, A. M., Kreiling, R., Lyon, D., & Landsiedel, R. et al. (2015). A decision-making framework for the grouping and testing of nanomaterials (DF4nanoGrouping). *Regulatory Toxicology and Pharmacology*, *70*(2), S1–S27. doi:10.1016/j.yrtph.2015.03.007 PMID:25818068

Arts, J. H. E., Hadi, M., Keene, A. M., Kreiling, R., Lyon, D., Maier, M., & Landsiedel, R. et al. (2014). A critical appraisal of existing concepts for the grouping of nanomaterials. *Regulatory Toxicology and Pharmacology*, *70*(2), 492–506. doi:10.1016/j.yrtph.2014.07.025 PMID:25108058

Comelli, N. C., Ortiz, E. V., Kolacz, M., Toropova, A. P., Toropov, A. A., Duchowicz, P. R., & Castro, E. A. (2014). Conformation-independent QSAR on c-Src tyrosine kinase inhibitors. *Chemometrics and Intelligent Laboratory Systems*, *134*, 47–52. doi:10.1016/j.chemolab.2014.03.003

De Abrew, K. N., Overmann, G. J., Adams, R. L., Tiesman, J. P., Dunavent, J., Shan, Y. K., & Naciff, J. M. et al. (2015). A novel transcriptomics based in vitro method to compare and predict hepatotoxicity based on mode of action. *Toxicology*, *328*, 29–39. doi:10.1016/j.tox.2014.11.008 PMID:25475144

Diez-Ortiz, M., Lahive, E., George, S., Ter Schure, A., Van Gestel, C. A. M., Jurkschat, K., & Spurgeon, D. J. et al. (2015). Short-term soil bioassays may not reveal the full toxicity potential for nanomaterials; bioavailability and toxicity of silver ions (AgNO3) and silver nanoparticles to earthworm *Eisenia fetida* in long-term aged soils. *Environmental Pollution*, *203*, 191–198. doi:10.1016/j.envpol.2015.03.033 PMID:25910462

Filon, F. L., Mauro, M., Adami, G., Bovenzi, M., & Crosera, M. (2015). Nanoparticles skin absorption: New aspects for a safety profile evaluation. *Regulatory Toxicology and Pharmacology*, *72*(2), 310–322. doi:10.1016/j.yrtph.2015.05.005 PMID:25979643

Fourches, D., Pu, D., Tassa, C., Weissleder, R., Shaw, S. Y., Mumper, R. J., & Tropsha, A. (2010). Quantitative nanostructure - Activity relationship modeling. *ACS Nano*, *4*(10), 5703–5712. doi:10.1021/nn1013484 PMID:20857979

Guidance Document on the Validation of (Quantitative) Structure–Activity Relationship [(Q)SAR] Models. (n. d.). Retrieved from http://search.oecd.org/officialdocuments/

Hadrup, N., Sharma, A. K., Poulsen, M., & Nielsen, E. (2015). Toxicological risk assessment of elemental gold following oral exposure to sheets and nanoparticles – A review. *Regulatory Toxicology and Pharmacology*, *72*(2), 216–221. doi:10.1016/j.yrtph.2015.04.017 PMID:25929617

Long, J., Liu, C., Sun, L., Gao, H., & Liu, J. (2009). Neuronal mitochondrial toxicity of malondialdehyde: Inhibitory effects on respiratory function and enzyme activities in rat brain mitochondria. *Neurochemical Research*, *34*(4), 786–794. doi:10.1007/s11064-008-9882-7 PMID:19023656

Ma, H., Williams, P. L., & Diamond, S. A. (2013). Ecotoxicity of manufactured ZnO nanoparticles - A review. *Environmental Pollution*, *172*, 76–85. doi:10.1016/j.envpol.2012.08.011 PMID:22995930

Melagraki, G., & Afantitis, A. (2014). Enalos InSilicoNano platform: An online decision support tool for the design and virtual screening of nanoparticles. *RSC Advances*, *4*(92), 50713–50725. doi:10.1039/C4RA07756C

Muthu, M. S. (2012). Focus on the development of computer-aided nanomedicine design. *Nanomedicine (London)*, *7*(10), 1471–1473. doi:10.2217/nnm.12.116 PMID:23148536

Nesmerak, K., Toropov, A. A., & Toropova, A. P. (2014). SMILES-based quantitative structure-retention relationships for RP HPLC of 1-phenyl-5-benzylsulfanyltetrazoles. *Structural Chemistry*, *25*(1), 311–317. doi:10.1007/s11224-013-0293-2

OECD environment health and assessment No. 69. (2007).

Oksel, C., Ma, C. Y., Liu, J. J., Wilkins, T., & Wang, X. Z. (2015). (Q)SAR modelling of nanomaterial toxicity: A critical review. *Particuology*, *21*, 1–19. doi:10.1016/j.partic.2014.12.001

Panneerselvam, S., & Choi, S. (2014). Nanoinformatics: Emerging databases and available tools. *International Journal of Molecular Sciences*, *15*(5), 7158–7182. doi:10.3390/ijms15057158 PMID:24776761

Potrč, T., Baumgartner, S., Roškar, R., Planinšek, O., Lavrič, Z., Kristl, J., & Kocbek, P. (2015). Electrospun polycaprolactone nanofibers as a potential oromucosal delivery system for poorly water-soluble drugs. *European Journal of Pharmaceutical Sciences*, *75*, 101–113. doi:10.1016/j.ejps.2015.04.004 PMID:25910438

Prabhakar, P. V., Reddy, U. A., Singh, S. P., Balasubramanyam, A., Rahman, M. F., Indu Kumari, S., & Mahboob, M. et al. (2012). Oxidative stress induced by aluminum oxide nanomaterials after acute oral treatment in Wistar rats. *Journal of Applied Toxicology*, *32*(6), 436–445. doi:10.1002/jat.1775 PMID:22161306

REACH. (2011). Retrieved from http://ec.europa.eu/environment/chemicals/nanotech/pdf/report_ripon1.pdf

Toropov, A.A., Toropova, A.P., Benfenati, E., Nicolotti, O., Carotti, A., Nesmerak, K., … Leszczynski, J. (2015). QSPR/QSAR analyses by means of the CORAL software: Results, challenges, perspectives. In K. Roy (Ed.), Quantitative Structure-Activity Relationships in Drug Design, Predictive Toxicology, and Risk Assessment (pp. 560-585). Hershey, PA, USA: IGI Global.

Sauer, U. G., Aumann, A., Ma-Hock, L., Landsiedel, R., & Wohlleben, W. (2015). Influence of dispersive agent on nanomaterial agglomeration and implications for biological effects in vivo or in vitro. *Toxicology In Vitro*, *29*(1), 182–186. doi:10.1016/j.tiv.2014.10.011 PMID:25458487

Singh, K. P., & Gupta, S. (2014). Nano-QSAR modeling for predicting biological activity of diverse nanomaterials. *RSC Advances*, *4*(26), 13215–13230. doi:10.1039/c4ra01274g

Speck-Planche, A., Kleandrova, V. V., Luan, F., & Cordeiro, M. N. D. S. (2015). Computational modeling in nanomedicine: Prediction of multiple antibacterial profiles of nanoparticles using a quantitative structure-activity relationship perturbation model. *Nanomedicine (London)*, *10*(2), 193–204. doi:10.2217/nnm.14.96 PMID:25600965

Toropov, A. A., & Toropova, A. P. (2014). Optimal descriptor as a translator of eclectic data into endpoint prediction: Mutagenicity of fullerene as a mathematical function of conditions. *Chemosphere*, *104*, 262–264. doi:10.1016/j.chemosphere.2013.10.079 PMID:24246220

Toropov, A. A., & Toropova, A. P. (2015). Quasi-QSAR for mutagenic potential of multi-walled carbon-nanotubes. *Chemosphere*, *124*, 40–46. doi:10.1016/j.chemosphere.2014.10.067 PMID:25465947

Toropov, A. A., Toropova, A. P., Puzyn, T., Benfenati, E., Gini, G., Leszczynska, D., & Leszczynski, J. (2013). QSAR as a random event: Modeling of nanoparticles uptake in PaCa2 cancer cells. *Chemosphere*, *92*(1), 31–37. doi:10.1016/j.chemosphere.2013.03.012 PMID:23566368

Toropov, A. A., Toropova, A. P., Rasulev, B. F., Benfenati, E., Gini, G., Leszczynska, D., & Leszczynski, J. (2012a). CORAL: Binary classifications (active/inactive) for liver-related adverse effects of drugs. *Current Drug Safety*, *7*(4), 257–261. doi:10.2174/157488612804096542 PMID:23062237

Toropov, A. A., Toropova, A. P., Rasulev, B. F., Benfenati, E., Gini, G., Leszczynska, D., & Leszczynski, J. (2012b). Coral: QSPR modeling of rate constants of reactions between organic aromatic pollutants and hydroxyl radical (2012). *Journal of Computational Chemistry*, *33*(23), 1902–1906. doi:10.1002/jcc.23022 PMID:22641453

Toropova, A. P., & Toropov, A. A. (2013). Optimal descriptor as a translator of eclectic information into the prediction of membrane damage by means of various TiO2 nanoparticles. *Chemosphere*, *93*(10), 2650–2655. doi:10.1016/j.chemosphere.2013.09.089 PMID:24161577

Toropova, A. P., & Toropov, A. A. (2014). CORAL software: Prediction of carcinogenicity of drugs by means of the Monte Carlo method. *European Journal of Pharmaceutical Sciences*, *52*, 21–25. doi:10.1016/j.ejps.2013.10.005 PMID:24514451

Toropova, A. P., Toropov, A. A., Benfenati, E., Korenstein, R., Leszczynska, D., & Leszczynski, J. (2015a). Optimal nano-descriptors as translators of eclectic data into prediction of the cell membrane damage by means of nano metal-oxides. *Environmental Science and Pollution Research International*, *22*(1), 745–757. doi:10.1007/s11356-014-3566-4 PMID:25223357

Toropova, A. P., Toropov, A. A., Rallo, R., Leszczynska, D., & Leszczynski, J. (2015b). Optimal descriptor as a translator of eclectic data into prediction of cytotoxicity for metal oxide nanoparticles under different conditions. *Ecotoxicology and Environmental Safety*, *112*, 39–45. doi:10.1016/j.ecoenv.2014.10.003 PMID:25463851

Toropova, A. P., Toropov, A. A., Rasulev, B., Benfenati, E., Gini, G., Leszczynska, D., & Leszczynksy, J. (2012). QSAR models for ACE-inhibitor activity of tri-peptides based on representation of the molecular structure by a graph of atomic orbitals and SMILES. *Structural Chemistry*, *23*(6), 1873–1878. doi:10.1007/s11224-012-9996-z

Vanić, Ž., & Škalko-Basnet, N. (2013). Nanopharmaceuticals for improved topical vaginal therapy: Can they deliver? *European Journal of Pharmaceutical Sciences*, *50*(1), 29–41. doi:10.1016/j.ejps.2013.04.035 PMID:23684936

Veselinović, A. M., Milosavljević, J. B., Toropov, A. A., & Nikolić, G. M. (2013). SMILES-based QSAR model for arylpiperazines as high-affinity 5-HT1A receptor ligands using CORAL. *European Journal of Pharmaceutical Sciences*, *48*(3), 532–541. doi:10.1016/j.ejps.2012.12.021 PMID:23287365

Veselinović, J. B., Toropov, A. A., Toropova, A. P., Nikolić, G. M., & Veselinović, A. M. (2015). Monte Carlo method-based QSAR modeling of penicillins binding to human serum proteins. *Archiv der Pharmazie*, *348*(1), 62–67. doi:10.1002/ardp.201400259 PMID:25408278

Worachartcheewan, A., Mandi, P., Prachayasittikul, V., Toropova, A. P., Toropov, A. A., & Nantasenamat, C. (2014). Large-scale QSAR study of aromatase inhibitors using SMILES-based descriptors. *Chemometrics and Intelligent Laboratory Systems*, *138*, 120–126. doi:10.1016/j.chemolab.2014.07.017

Yilmaz, H., Novoselska, N., Rasulev, B., Toropov, A.A., Guzel, Y., Kuz'min, V., Leszczynska, D., & Leszczynski, J. (2015). Amino substituted nitrogen heterocycle ureas as kinase insert domain containing receptor inhibitors: Performance of structure - activity relationship approaches. *Journal of food and drug analysis*, 23, 168 - 175.

Alla P. Toropova (PhD) has been working in Istituto di Ricerche Farmacologiche Mario Negri Milano, Italy with Dr. Benfenati's research group. She has published about 140 papers in international journals on QSPR/QSAR analysis for inorganic and organometallic compounds, in particular, thermodynamic properties of coordination compounds of bioactive metals, and thermodynamic properties (e.g. solubility) of nano substances. She has been working over 15 years in the fields of Chemoinformatics and Nanoinformatics. She also has made scientific collaborations with many experts in the fields of Chemoinformatics and Nanoinformatics throughout the world. Dr. Toropova had taken part in development of approach of Chemoinformatics modeling based on optimal descriptors. The approach based on optimal descriptors can be useful alternative of traditional QSAR for the analyses of Nanomaterials as well as for Drug Discovery. She is one of developers of the software CORAL (http://www.insilico.eu/coral). She is a participant in the following EC projects: ORCHESTRA, ANTARES, OSIRIS, NanoBRIDGES, PreNanoTox, NanoPUZZLES.

P.Ganga Raju Achary received the MSc MPhil degrees in Chemistry from Berhampur University, Berhampur, Odisha, India, in 1997 and 2007 respectively and PhD degree in chemistry from Ravenshaw University, Cuttack, Odisha, India in 2012.In 2008, he joined the Department of Chemsitry, Institute of Technical Education and Research (ITER), Siksha O' Anusandhan University, Bhubaneswar, Odisha, India, as a Lecturer, and in 2012 became Assistant Professor. His current research include Quantitative Structure Activity Relationship (QSAR), Quantitative Structure Property Relationship (QSAR), Polymer nano-composites, computational chemistry, etc. He published more than 14 research papers in different peer reviewed journals.

Andrey A. Toropov (PhD) has been working in Istituto di Ricerche Farmacologiche Mario Milano, Italy with Dr. Benfenati's research group. The optimal (flexible) descriptors are his main scientific interest. He is developer of a recent version of the optimal descriptors named as collectors of eclectic data for a QSPR/QSAR predictions. This paradigm is especially appropriate for the cases of complex molecular systems such as nanomaterials and proteins. He had performed contributions for the development of the CORAL freeware (http://www.insilico.eu/coral). He has published about 220 papers in international journals on the QSPR/QSAR analysis: physicochemical properties, toxicity, cancirogenicity, anticancer agents, anti-HIV-1 agents, QSPR/QSAR analysis for nanomaterials. He was participant of the following EC projects: DEMETRA, CHEMPREDICT, PROSIL, ORCHESTRA, ANTARES, OSIRIS, NanoBRIDGES, PreNanoTox, NanoPUZZLES etc. He is a member of Editorial Boards of scientific journals (as a reviewer). He was visiting scientist in Jackson State University (USA, Mississippi), in 2006-2007.