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▶ **To cite this version:**

Valérie Forest, Jean-François Hochepied, Jérémie Pourchez. Importance of Choosing Relevant Biological End Points To Predict Nanoparticle Toxicity with Computational Approaches for Human Health Risk Assessment. Chemical Research in Toxicology, 2019, 32 (7), pp.1320-1326. 10.1021/acs.chemrestox.9b00022 . hal-02189302

HAL Id: hal-02189302
https://hal.science/hal-02189302

Submitted on 19 Jul 2019

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Importance of choosing relevant biological endpoints to predict nanoparticle toxicity with computational approaches for human health risk assessment

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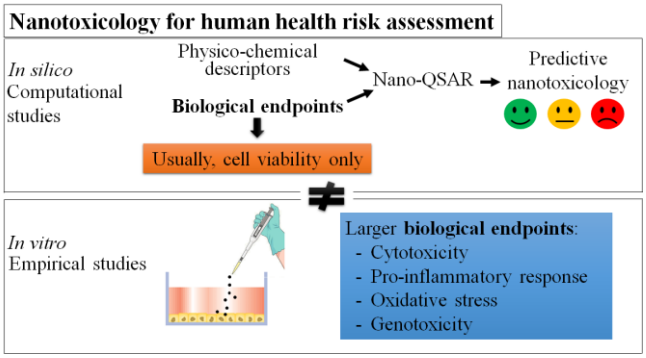
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Key-words

Nanoparticles; Cytotoxicity; *In vitro* nanotoxicology; *In silico* nanotoxicology; Predictive models; QSAR.

Table of Contents Graphic



Abstract

Because it is impossible to assess *in vitro* or *in vivo* the toxicity of all nanoparticles available on the market on a case-by-case basis, computational approaches have been proposed as useful alternatives to predict *in silico* the hazard potential of engineered nanoparticles. Despite promising results, a major issue associated with these mathematical models lies in the *a priori* choice of the physico-chemical descriptors and the biological endpoints. We performed a thorough bibliographic survey on the biological endpoints used for nanotoxicology purposes and compared them between experimental and computational approaches. They were found to be disparate: while conventional *in vitro* nanotoxicology assays usually investigate a large array of biological effects using eukaryotic cells (cytotoxicity, pro-inflammatory response, oxidative stress, genotoxicity), computational studies mostly focus on cell viability and also includes studies on prokaryotic cells. We may thus wonder the relevance of building complex mathematical models able to predict accurately a biological endpoint if this latter is not the most relevant to support human health risk assessment. The choice of biological endpoints clearly deserves to be more carefully discussed. This could bridge the gap between experimental and computational nanotoxicology studies and allow *in silico* predictive models to reach their full potential.

In the field of nanotoxicology a major aim is the investigation of the biological effects induced by engineered nanoparticles to determine their potential impact on the environment and human health. In this context, *in vivo* studies are potentially the most informative as animal models reproduce a physiological integrated response. But because of ethical issues, animal experiments are limited to follow the 3R's rule defined by Russell and Burch [1] aiming to replace, reduce and refine the use of animals for scientific purposes. This trend was followed by regulation [2] which advocates for the reduction of animal models for evaluating nanoparticles toxicity. *In vitro* models have then been developed for human risk assessment. They possess several advantages such as being inexpensive, easy and rapid to perform, but most of all they allow the high throughput screening of biological effects triggered by nanoparticles, also enabling mechanistic studies. In this context, a large panel of assays is usually carried out to determine the cytotoxicity, the pro-inflammatory response, the oxidative stress or the genotoxicity triggered by the contact of nanoparticles with eukaryotic cells [3–6] (some examples are reported in Table 1, even though there are no standardized methods and no international guidelines).

Table 1 – Biological endpoints commonly evaluated in *in vitro* nanotoxicology studies (not exhaustive).

Toxicity endpoint	**Evaluated parameter**	**Examples of assays**
Cell viability	Apoptosis induction	Caspases, TUNEL, AnnexinV
	Cell proliferation	BrdU
	Membrane damages	LDH
	Mitochondrial activity	MTT, WST-1, ATP content
Pro-inflammatory response	Cytokine production	TNF-α, interleukins (IL8, IL6, IL1α, IL1β, GM-CSF, etc.)

Oxidative stress	ROS production	Dichlorofluorescein (DCFH), dithiothritol (DTT), salicylic acid/benzoate, electron parmagnetic resonance spectroscopy (EPR), ferric reducing ability of serum (FRAS) assay, cytochrome c assay
	Antioxidant stimulation	Depletion of antioxidants: ascorbic acid, uric acid and glutathione
	Lipid peroxidation	TBARS assay
Genotoxicity	DNA damages	Comet assay Micronucleus assay 8-OHdG adducts

However, because of the multitude and variety of engineered nanoparticles we are increasingly exposed to it is impossible to assess empirically (*in vitro* or *in vivo*) their safety [7]. To avoid long, complex and costly experimental assays, computational modeling has been proposed as a useful alternative to predict *in silico* the hazard potential of engineered nanoparticles to human health. Initially developed in the 1960s to be applied on small series of congeneric compounds using relatively simple regression methods, nowadays the computational approaches allow to analyze very large datasets comprising thousands of diverse chemical structures using a wide variety of statistical and machine learning techniques [8]. In the last decade, some computational

approaches have been applied to nanoparticles such as (Q)SAR ((Quantitative) Structure Activity Relationship) [9–13], read-across [14–17], neural network [18] or decision tree [19] classifications. These models can theoretically be built using data obtained through either *in vitro* or *in vivo* assays. But in practice, to be reliable, these models should involve a very large amount of data. And it is thus difficult to get such an amount of data with *in vivo* experiments. Indeed, while *in vivo* experiments are supposed to be closer to "real life" condition because they take into account physiological parameters, they are expensive, time-consuming and limited because of ethical issues. On the contrary, *in vitro* studies seem more suitable as they are cheaper, more rapid and easier to perform. They are thus rather useful for mechanistic studies and as screening tools as they allow to collect more information. This doesn't mean that *in vivo* studies are less qualified to help assess risks, but it argues for considering a multi-step process research. First, *in vitro* assays could be used for the screening of the nanomaterials that are worth investigating further. Based on these data predictive models could be built for risk assessment. And finally particles of interest could be further investigated using *in vivo* assays that can bring complementary information.

In silico models are the subject of intensive research and are highly topical issues. An overview of the landscape of the available computational models for nanomaterials has been very recently reported [20]. Although some of these mathematical models have produced promising results, their construction is associated with some challenges and questions. A major issue lies in the *a priori* choice of the physico-chemical descriptors and biological endpoints, which are at the core of the computational modeling. As the QSAR approach remains the most abundantly documented in the literature we will focus our discussion on it thereafter. It was originally developed for risk assessment of chemicals for which many molecular descriptors are available in chemical database or easily calculated with usual softwares. Nanoparticles, because of their specific properties, need to be described by additional parameters accurately experimentally

measured such as size, shape, surface area, surface reactivity, crystalline structure, composition of core and coating, etc. [21]. Therefore, one of the specific features of QSAR modeling for nanotoxicology purposes involves a labor-intensive, time-consuming and costly effort to obtain these "nanodescriptors". And because descriptors are mathematical representations of relevant properties of nanoparticles, nanoparticle physico-chemical features should be carefully considered, especially the parameters recommended by the ISO/TR13014:2012 standard [22]. Unfortunately, a systematic and comprehensive nanoparticle physico-chemical characterization is not always available in the proposed nanoQSAR models. Furthermore, the reality is much more complex and to take into account the "biological identity" of the nanoparticles (reflecting their complex interactions with biological environments) the presence and nature of the corona formed around the nanoparticles should be introduced in the equation [23–25].

Regarding the choice of the biological endpoints to be predicted thanks to the model, the question is even more debatable. Indeed, we observed that often, the main biological endpoints that are used in empirical nanotoxicology studies (studies without any modelling purpose) and in studies dedicated to the *in silico* prediction of the nanoparticle toxicity are different. We thus wondered why there is such a discrepancy between the two types of studies. The assays used for empirical nanotoxicology reported in Table 1 can all be a priori used for modelling. But because many other parameters are involved such as the particle type, the cell type, etc… they will not exhibit the same efficiency in their predictive potential for risk assessment. No one could predict which assays (and why) will be more predictive than others. Only the construction of the models will tell if they work or not. To exemplify this point, we performed a literature survey focused on nanoparticles (including nanomaterials and nanostructure) and QSAR model and its variants (because as mentioned before, QSAR approach is among the most abundantly documented and used computational approaches). As illustrated in Figure 1, querying the PubMed database with the search terms "(nanoparticle OR nanomaterials OR nanostructure)

AND (QSAR OR QSPR OR QNAR OR QNTR) revealed that 232 reports have been published on this topic by March 2019 (please refer to Supporting Information for further details). We thoroughly reviewed these articles focusing our attention on studies in which nanoQSAR models were built using *in vitro* toxicological data (because as mentioned before unlike *in vivo* studies, they allow to get enough data to construct reliable models). Based on these criteria, we excluded 167 papers (see Supporting Information), either because they did not include experimental data (52 papers: reviews, commentaries, book chapters, etc.) or because their topic was not directly related to our issue (115 papers with no cytotoxicity data or not related to predictive nanotoxicology for human risk assessment, or based on *in vivo* data, etc.). 65 papers were therefore included in this analysis. Among them, nanoparticle toxicity assessment was performed using prokaryotic cells in 19 papers [10,16–18,26–40], eukaryotic cells in 40 papers [9,12,41–78] or both in 6 papers [79–84]. Please note that the exclusion of some studies from this bibliographic survey doesn't question their merit or usefulness, it just means they don't match the specific criteria we had previously established.

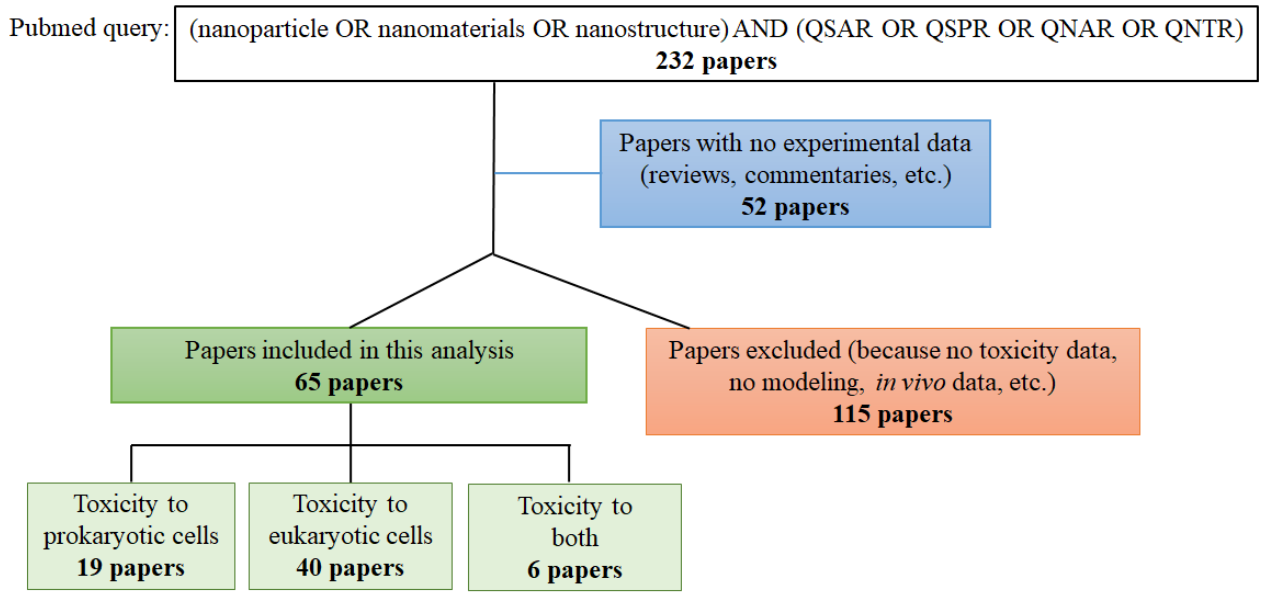


Figure 1 – Schematic summary of the literature survey performed querying the PubMed database with the search terms (nanoparticle OR nanomaterials OR nanostructure) AND (QSAR OR QSPR OR QNAR OR QNTR). Of the 232 papers found we excluded 52 papers because they didn't present experimental data and other 115 papers were excluded because they didn't match our criteria (papers with no cytotoxicity data or not related to predictive nanotoxicology for human risk assessment, or based on *in vivo* data, etc.). Of the 65 papers remaining 19 assessed toxicity on prokaryotic cells, 40 on eukaryotic and 6 on both.

When nanoparticle toxicity is investigated using prokaryotic cells, the major biological endpoint evaluated is bacteria viability (often using *Escherichia coli*) by the means of the EC_{50} measure [10,26–29,79] (half maximal effective concentration, corresponding to the nanoparticle concentration that reduces bacteria viability by 50% [17]). This cellular model and this parameter are rather useful for ecotoxicology purposes but seem less sensible to infer nanoparticle hazard to human health.

We then analyzed more closely the studies using eukaryotic cells. We especially paid attention to the quantity and quality of the data needed to build the mathematical models, 2 criteria that are commonly acknowledged to be of high importance for the construction of reliable QSAR models. In addition, we examined the number and nature of the selected biological endpoints.

Regarding the first criteria about data quantity (*i.e.* the size of the dataset), as mentioned before QSAR models were originally developed for chemicals for which data were easily available and QSAR could be built based on considerably large databases (compounds in the order of hundreds or even thousands). On the contrary, in the case of nanoparticles, due to the difficulty to gather physico-chemical and biological data in standardized conditions, datasets are often very small (units or tens, in the best case) [34]. In our bibliographic survey, we found that most of the studies used a dataset higher than 20 but at the expense of the quality of the data.

Indeed, for standard *in vitro* nanotoxicology, the ISO/TR13014:2012 standard recommends to characterize at least the 8 following nanoparticle physico-chemical features: agglomeration/aggregation state, composition, size, shape, solubility/dispersibility, specific surface area, density of surface groups and surface chemistry [22]. But in computational studies this comprehensive nanoparticle physico-chemical characterization is far from being systematic. Actually, none of the 40 papers experimentally measured these 8 crucial parameters. The nanodescriptors greatly varied depending on the studies, some considered only nanoparticle size and zeta potential while others included much more parameters calculated or experimentally assessed but none characterized the 8 parameters recommended by the ISO/TR13014:2012 standard. The lack of complete characterization may be explained by some metrological issues. First, sample preparation is not trivial for techniques requiring a good dispersion in suspensions. In addition, some questions are still open. For instance, the agglomeration/aggregation state is quite unclear. Agglomeration and aggregation are very different concepts: in agglomerates particles are just gathered by weak interactions and agglomerates size is expected to change a lot during a journey in living organisms, whereas in aggregates particles are cemented by solid bridges and will not budge. So there is a high risk that agglomerates size measurement does not make much sense, unless the medium and sample preparation is representative of biological conditions. As far as size is concerned, even in the case of well dispersed spherical particles - defined by one parameter- the correct measurement of a size distribution is all but trivial, and direct methods as TEM or indirect methods as DLS give different results. Things get even more complicated when shape is not spherical and at least a second dimensional parameter is needed to describe particles. Density of surface groups and surface chemistry may be determined in average, but locally they depend on crystal exposed faces or even edges, which supposes expensive HRTEM studies for a perfect description.

Finally, on the third criteria regarding the biological endpoints, we observed that in the vast majority of the cases (29/40 papers) only one biological endpoint was considered, mainly cell viability. While as mentioned before, in standard *in vitro* nanotoxicology before concluding on the toxicity of a nanoparticle several parameters should be investigated (*i.e.* cytotoxicity, pro-inflammatory response, oxidative stress, genotoxicity, etc.). In this respect, the study from Maher *et al.* [55] was the most complete as in addition to cytotoxicity, reactive oxygen species and pro-inflammatory cytokine production were included as biological endpoints. Similarly, Le *et al.* [47] considered the oxidative stress in their computational study.

In the end, none of the 40 papers met the 3 criteria (dataset>20; physico-chemical characterization as recommended by ISO/TR13014:2012 standard; and more than one biological endpoint studied), 10 met 2, 20 only one and 10 not even one.

Therefore, there is a gap between the nanodescriptors and biological endpoints used in computational approaches and *in vitro* empirical testing for human health risk assessment. Taken together these observations argue for the need to discuss the relevance of the selected biological endpoints. Such discussion could bridge the gap between experimental and computational nanotoxicology studies to get predictive models more useful for human risk assessment. It should be also interesting to consider and include in nanoQSAR alternative biological parameters which could be more relevant to take into account nanoparticle dose-effects such as NOAEL (No Observable Adverse Effect Level, *i.e.* the highest tested nanoparticle dose at which no adverse effect is found where higher doses result in an adverse effect).

It is unanimously acknowledged that many challenges in predictive nanotoxicology are associated with the quantity and quality of the data needed to build the mathematical model. But the nature of the biological endpoints deserves better attention and should be carefully discussed to get more useful and applicable models to support human risk assessment. This

way, mathematical models could reach their full potential, able to predict nanoparticle toxicity avoiding empirical assays, saving time, money and animal experiments.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declarations of interest

The authors declare no competing financial interest.

Supporting Information

Details on the 232 publications found when querying the PubMed database with the search terms (nanoparticle OR nanomaterials OR nanostructure) AND (QSAR OR QSPR OR QNAR OR QNTR).

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Supporting Information

Table of content:

Details on the 232 publications found when querying the PubMed database with the search terms (nanoparticle OR nanomaterials OR nanostructure) AND (QSAR OR QSPR OR QNAR OR QNTR)……..….S2-S11

	Authors	Journal	Ref in the text	No experimental data (reviews, commentaries)	Papers included in our analysis and performed on:			Papers not included in our analysis for the following reasons:			
					Prokaryotic cells	Eukaryotic cells	Both	No toxicity data	No modeling	*In vivo* data	Topic not related to human risk assessment
1	Lata and Vikas.	SAR QSAR Environ Res. 2019, 30(2):109-130.	/								x
2	Shchelokov *et al.*	Langmuir. 2018	/								x
3	Choi *et al.*	Chemosphere. 2019, 217:243-249.	67			x					
4	Salahinejad and Zolfonoun.	SAR QSAR Environ Res. 2018, 29(12): 997-1009.	/								x
5	Möser *et al.*	Int J Mol Sci. 2018, 19(11), pii: E3482.	/								x
6	Ojha *et al.*	Nanotoxicology. 2018 :1-21.	68			x					
7	Dabrowska *et al.*	Int J Mol Sci. 2018, 19(10).	/								x
8	Ahmadi and Akbari.	SAR QSAR Environ Res. 2018, 29(11): 895-909.	/								x
9	Tasi *et al.*	Nanoscale. 2018, 10(44):20863-20866.	/	x							
10	Wang *et al.*	Chemosphere. 2019, 214:79-84.	/								x
11	Utembe *et al.*	Environ Toxicol Chem. 2018, 37(12): 2972-2988.	/	x							
12	Bhutto *et al.*	Talanta. 2018, 189:174-181.	/								x
13	Vracko *et al.*	SAR QSAR Environ Res. 2018, 29(8):567-577.	/					x			
14	Leone *et al.*	Chemosphere. 2018, 210:52-56.	69			x					
15	Lopalco and Denora.	Methods Mol Biol. 2018, 1800:347-365.	/	x							
16	Golbamaki *et al.*	Nanotoxicology. 2018, 9:1-17.	41			x					
17	Villaverde *et al.*	Sci Total Environ. 2018, 634:1530-1539.	/	x							
18	Wang *et al.*	Anal Bioanal Chem. 2018, 410(18):4379-4386.	/								x
19	Choi *et al.*	Sci Rep. 2018, 8(1):6110.	70			x					
20	Toropov *et al.*	Nanomaterials. 2018, 8(4). pii: E243.	/					x			
21	Zhai *et al.*	Toxicol Mech Methods. 2018, 28(6):440-449.	30		x						

22	Vracko *et al.*	Curr Comput Aided Drug Des. 2018, 14(1):2-4.	/	x							
23	Gupta and Bassant.	Chemosphere. 2018, 201:361-369.	/								x
24	Roh *et al.*	Mol Cell. 2018, 69(6):993-1004.e3.	/								x
25	Titma T.	Toxicol In Vitro. 2018, 50:11-21.	/						x		
26	Trinh *et al.*	Chem Res Toxicol. 2018, 31(3):183-190.	71			x					
27	Gajewicz *et al.*	Nanotoxicology. 2018,12(1):1-17.	/							x	
28	Shin *et al.*	SAR QSAR Environ Res. 2017, 28(11):875-888.	42			x					
29	Rajput *et al.*	Nucleic Acids Res. 2018, 46(D1):D894-D900.	/								x
30	Wang *et al.*	ACS Nano. 2017, 11(12):12641-12649.	72			x					
31	Mikolajczyk *et al.*	Beilstein J Nanotechnol. 2017, 8:2171-2180.	31		x						
32	Sizochenko *et al.*	Nanomaterials (Basel). 2017, 7(10). pii: E330.	/							x	
33	Zhao *et al.*	ACS Appl Mater Interfaces. 2017, 9(41):35740-35748.	/								x
34	Puzyn *et al.*	Food Chem Toxicol. 2018, 112:478-494.	/	x							
35	Concu *et al.*	Nanotoxicology. 2017, 11(7):891-906.	80				x				
36	Johnson *et al.*	Small. 2017, 13(42).	/								x
37	Bañares *et al.*	Nanotoxicology. 2017, 11(7):839-845.	21	x							
38	Kovalishyn *et al.*	Food Chem Toxicol. 2018, 112:507-517.	/	x							
39	Chen *et al.*	Int J Mol Sci. 2017, 18(7), pii: E1504.	/	x							
40	Helma *et al.*	Front Pharmacol. 2017, 8:377.	43			x					
41	Burello E.	Toxicol Sci. 2017, 159(2):339-353.	/							x	
42	Boukhvalov and Yoon.	Chem Res Toxicol. 2017, 30(8):1549-1555.	/								x
43	Lai *et al.*	Environ Sci Pollut Res Int. 2018, 25(4):3060-3077.	/	x							
44	Gajewicz A.	Nanoscale. 2017, 9(24):8435-8448.	16		x						
45	Wang *et al.*	Expert Opin Drug Discov. 2017, 12(8):769-784.	/	x							

46	Savastano *et al.*	Molecules. 2017, 22(5). pii: E816.	/								x
47	Liu *et al.*	ACS Appl Mater Interfaces. 2017, 9(22):18626-18638.	/								x
48	Urbaszek *et al.*	Beilstein J Nanotechnol. 2017, 8:752-761.	/								x
49	Al Faouri *et al.*	J Appl Toxicol. 2017, 37(11):1346-1353.	/								x
50	Manganelli and Benfenati.	Methods Mol Biol. 2017, 1601:275-290.	/	x							
51	Kim *et al.*	J Biomol Struct Dyn. 2018, 36(5):1360-1368.	/								x
52	Barrick *et al.*	Environ Toxicol Chem. 2017, 36(7):1704-1714.	/	x							
53	Meunier *et al.*	Int J Pharm. 2017, 526(1-2):157-166.	/								x
54	González-Durruthy *et al.*	J Chem Inf Model. 2017, 57(5):1029-1044.	/							x	
55	Luan *et al.*	Food Chem Toxicol. 2018, 112:571-580.	73			x					
56	Fjodorova *et al.*	Nanotoxicology. 2017, 11(4):475-483.	18		x						
57	Basant and Gupta.	Nanotoxicology. 2017, 11(3):339-350.	81				x				
58	Toropova *et al.*	Ecotoxicol Environ Saf. 2017, 139:404-407.	32		x						
59	Richarz *et al.*	Adv Exp Med Biol. 2017, 947:303-324.	/	x							
60	Brehm *et al.*	Adv Exp Med Biol. 2017, 947:257-301.	/	x							
61	Oksel *et al.*	Adv Exp Med Biol. 2017, 947:103-142.	/	x							
62	Cassano *et al.*	Altern Lab Anim. 2016, 44(6):533-556.	74			x					
63	Toropova and Toropov.	J Theor Biol. 2017, 416:113-118.	44			x					
64	Miljanić *et al.*	Anal Bioanal Chem. 2017, 409(9):2285-2295.	/								x
65	Choi and Park.	Drug Des Devel Ther. 2016, 11:17-26.	/								x
66	Huang *et al.*	Anal Chem. 2017, 89(1):666-672.	/								x
67	Santi *et al.*	Bioconjug Chem. 2017, 28(2):471-480.	/								x
68	Basant and Gupta.	Nanotoxicology. 2017, 11(1):20-30.	45			x					
69	Szefler *et al.*	Int J Mol Sci. 2016, 17(11), pii: E1796.	/								x
70	Wyrzykowska *et al.*	Nanotechnology. 2016, 27(44):445702.	/					x			
71	Jagiello *et al.*	J Nanopart Res. 2016, 18(9):256.	/								x

72	Chen *et al.*	J Colloid Interface Sci. 2016, 484:298-307.	/								x
73	Husin *et al.*	Molecules. 2016, 21(7). pii: E821.	/								x
74	Papa *et al.*	SAR QSAR Environ Res. 2016, 27(7):521-38.	46			x					
75	Mu *et al.*	Nanotoxicology. 2016, 10(9):1207-14.	28		x						
76	Chen *et al.*	Colloids Surf B Biointerfaces. 2016, 145:671-678.	/								x
77	Gao *et al.*	Org Biomol Chem. 2016, 14(26):6346-54.	/								x
78	Dekkers *et al.*	Regul Toxicol Pharmacol. 2016, 80:46-59.	/	x							
79	Le *et al.*	Small. 2016, 12(26):3568-77.	47			x					
80	Donkuru *et al.*	J Chromatogr A. 2016, 1446:114-24.	/								x
81	Sizochenko *et al.*	Nanoscale. 2016, 8(13):7203-8.	33		x						
82	Božič Abram *et al.*	Biochem Biophys Res Commun. 2016, 472(3):566-71.	/								x
83	Oksel *et al.*	Nanotoxicology. 2016, 10(7):1001-12.	75			x					
84	Zaboli and Raissi.	J Biomol Struct Dyn. 2017, 35(3):520-534.	/								x
85	Zhang *et al.*	ACS Appl Mater Interfaces. 2016, 8(10):6646-55.	/								x
86	Ding *et al.*	SAR QSAR Environ Res. 2016, 27(1):31-45.	/								x
87	Khan *et al.*	J Biol Inorg Chem. 2016, 21(3):295-303.	/								x
88	Lazarovits *et al.*	Chem Commun (Camb). 2015, 51(14):2756-67.	/	x							
89	Kar *et al.*	Ecotoxicol Environ Saf. 2016, 126:238-244.	82				x				
90	Winkler DA.	Toxicol Appl Pharmacol. 2016, 299:96-100.	/	x							
91	Chiu *et al.*	Langmuir. 2016, 32(1):211-20.	/								x
92	Zhao *et al.*	Anal Chem. 2016, 88(2):1412-8.	/								x
93	Fernandez *et al.*	J Chem Inf Model. 2015, 55(12):2500-6.	/								x
94	Lin *et al.*	Anal Chem. 2016, 88(1):1030-8.	/								x
95	Fourches *et al.*	Nanotoxicology. 2016, 10(3):374-83.	76			x					
96	Ying *et al.*	Nanomaterials. 2015, 5(4):1620-1637.	/	x							
97	Toropova *et al.*	Ecotoxicol Environ Saf. 2016, 124:32-36.	34		x						

98	Manganelli *et al.*	Chemosphere. 2016, 144:995-1001.	49			x					
99	Tsiliki *et al.*	J Cheminform. 2015, 7:46.	48			x					
100	Chen *et al.*	Altern Lab Anim. 2015, 43(4):221-40.	/	x							
101	Papa *et al.*	SAR QSAR Environ Res. 2015, 26(7-9):647-65.	50			x					
102	Esposito *et al.*	Toxicol Appl Pharmacol. 2015, 288(1):52-62.	77			x					
103	Zhang *et al.*	Anal Chim Acta. 2015, 880:130-5.	/								x
104	Rust *et al.*	Anal Chem. 2015, 87(14):7250-7.	/								x
105	Huang *et al.*	Chemosphere. 2015, 138:183-9.	/								x
106	Toropov and Toropova.	Chemosphere. 2015, 139:18-22.	35		x						
107	Melagraki and Afantitis.	Curr Top Med Chem. 2015, 15(18):1827-36.	/								x
108	Toropov *et al.*	Curr Top Med Chem. 2015, 15(18):1837-44.	84				x				
109	He *et al.*	Curr Top Med Chem. 2015, 15(18):1887-900.	/	x							
110	Salahinejad M.	Curr Top Med Chem. 2015, 15(18):1868-86.	/	x							
111	Liu *et al.*	Nanoscale. 2015, 7(21):9664-75.	51			x					
112	Yilmaz *et al.*	Nanomaterials. 2015, 5(2):778-791.	/					x			
113	Bygd *et al.*	Biomaterials. 2015, 56:187-97.	/							x	
114	Rabanel *et al.*	ACS Appl Mater Interfaces. 2015, 7(19):10374-85.	/								x
115	Apul *et al.*	J Hazard Mater. 2015, 295:138-44.	/								x
116	Toropov *et al.*	Comb Chem High Throughput Screen. 2015, 18(4):376-86.	/	x							
117	Liu *et al.*	Comb Chem High Throughput Screen. 2015, 18(4):365-75.	52			x					
118	Castellanos *et al.*	Nanoscale. 2015, 7(13):5654-64.	/								x
119	Galbiati E *et al.*	Bioconjug Chem. 2015, 26(4):680-9.	/								x
120	Toropova and Toropov.	Mini Rev Med Chem. 2015, 15(8):608-21.	40		x						

121	Kleandrova *et al.*	Mini Rev Med Chem. 2015, 15(8):677-86.	/							x
122	Teske and Detweiler.	Int J Environ Res Public Health. 2015, 12(2):1112-34.	/	x						
123	Toropova *et al.*	SAR QSAR Environ Res. 2015, 26(1):29-40.	53			x				
124	Oksel *et al.*	SAR QSAR Environ Res. 2015, 26(2):79-94.	/	x						
125	Speck-Planche *et al.*	Nanomedicine (Lond). 2015, 10(2):193-204.	36		x					
126	Shahbazy *et al.*	J Photochem Photobiol B. 2015, 152(Pt A):146-55.	/							x
127	Gajewicz *et al.*	Nanotechnology. 2015, 26(1):015701.	17		x					
128	Toropov and Toropova.	Chemosphere. 2015, 124:40-6.	39		x					
129	Toropova *et al.*	Ecotoxicol Environ Saf. 2015, 112:39-45.	27		x					
130	Saleh NA.	Spectrochim Acta A Mol Biomol Spectrosc. 2015, 136 Pt C:1523-9.	/							x
131	Liu *et al.*	Chemistry. 2015, 21(2):746-52.	/							x
132	Kleandrova *et al.*	Environ Sci Technol. 2014, 48(24):14686-94.	79				x			
133	Sizochenko *et al.*	Nanoscale. 2014, 6(22):13986-93.	83				x			
134	Toropova *et al.*	Environ Sci Pollut Res Int. 2015, 22(1):745-57.	54			x				
135	Tantra *et al.*	Nanotoxicology. 2015, 9(5):636-42.	/	x						
136	Gonzalez-Diaz *et al.*	Curr Drug Metab. 2014, 15(4):470-88.	/							x
137	Liu *et al.*	Chem Commun (Camb). 2014, 50(84):12710-3.	/							x
138	Kleandrova *et al.*	Environ Int. 2014, 73:288-94.	/						x	
139	Maher *et al.*	Toxicol In Vitro. 2014, 28(8):1449-60.	55			x				
140	Yu *et al.*	ACS Nano. 2014, 8(8):7687-703.	/					x		
141	Toropova *et al.*	Ecotoxicol Environ Saf. 2014, 108:203-9.	56			x				
142	Luan *et al.*	Nanoscale. 2014, 6(18):10623-30.	57			x				
143	Liu *et al.*	Nanoscale. 2014, 6(16):9774-82.	/							x

144	Nicolotti *et al.*	Drug Discov Today. 2014, 19(11):1757-1768.	/	x							
145	Gajewicz *et al.*	Nanotoxicology. 2015, 9(3):313-25.	12			x					
146	Kar *et al.*	Ecotoxicol Environ Saf. 2014, 107:162-9.	26		x						
147	Panneerselvam and Choi.	Int J Mol Sci. 2014, 15(5):7158-82.	/	x							
148	Ehret *et al.*	Altern Lab Anim. 2014, 42(1):43-50.	58			x					
149	Putz and Ori.	Molecules. 2014, 19(4):4157-88.	/								x
150	Delbecq F.	Adv Colloid Interface Sci. 2014, 209:98-108.	/	x							
151	Ma *et al.*	ACS Comb Sci. 2014, 16(4):155-9.	/								x
152	Winkler *et al.*	SAR QSAR Environ Res. 2014, 25(2):161-72.	59			x					
153	Andriotis *et al.*	J Chem Phys. 2014, 140(9):094705.	/								x
154	Zhao *et al.*	Analyst. 2014, 139(6):1498-503.	/								x
155	Kar *et al.*	Toxicol In Vitro. 2014, 28(4):600-6.	60			x					
156	Pathakoti *et al.*	J Photochem Photobiol B. 2014, 130:234-40.	29		x						
157	Cherkasov *et al.*	J Med Chem. 2014, 57(12):4977-5010.	/	x							
158	Lubinski *et al.*	SAR QSAR Environ Res. 2013, 24(12):995-1008.	/	x							
159	Ivask *et al.*	Nanotoxicology. 2014, 8 Suppl 1:57-71.	/	x							
160	Toropov and Toropova.	Chemosphere. 2014, 104:262-4.	37		x						
161	Toropova and Toropov.	Chemosphere. 2013, 93(10):2650-5.	61			x					
162	Sayes *et al.*	Int J Nanomedicine. 2013, 8 Suppl 1:45-56.	/					x			
163	Wang *et al.*	Acc Chem Res. 2013, 46(3):761-9.	/						x		
164	Kim *et al.*	Sci Total Environ. 2014, 470-471:1553-7.	/								x
165	Ahmed *et al.*	Org Biomol Chem. 2013, 11(35):5798-808.	/								x
166	Athauda *et al.*	ACS Appl Mater Interfaces. 2013, 5(13):6237-46.	/								x

167	Leifert *et al.*	Nanoscale. 2013, 5(14):6224-42.	/	x							
168	Kwok *et al.*	ACS Nano. 2013, 7(5):4668-82.	/								x
169	Li *et al.*	J Nanosci Nanotechnol. 2013, 13(2):1399-402.	/								x
170	Toropov *et al.*	Chemosphere. 2013, 92(1):31-7.	62			x					
171	Liu *et al.*	Small. 2013, 9(9-10):1842-52.	63			x					
172	Shao *et al.*	J Chem Inf Model. 2013, 53(1):142-58.	78			x					
173	Das *et al.*	Chem Pharm Bull (Tokyo). 2013, 61(2):125-33.	/								x
174	Winkler *et al.*	Toxicology. 2013, 313(1):15-23.	/	x							
175	Muthu MS.	Nanomedicine (Lond). 2012, 7(10):1471-3.	/								x
176	Kahru and Ivask.	Acc Chem Res. 2013, 46(3):823-33.	/								x
177	Cohen *et al.*	Acc Chem Res. 2013, 46(3):802-12.	/	x							
178	Epa *et al.*	Nano Lett. 2012, 12(11):5808-12.	64			x					
179	Westerhoff and Nowak	Acc Chem Res. 2013, 46(3):844-53.	/					x			
180	Apul *et al.*	Environ Sci Technol. 2013, 47(5):2295-303.	/					x			
181	Toropov *et al.*	Chemosphere. 2012, 89(9):1098-102.	38		x						
182	Gajewicz *et al.*	Adv Drug Deliv Rev. 2012, 64(15):1663-93.	/	x							
183	Ibrahim *et al.*	Mini Rev Med Chem. 2012, 12(6):447-51.	/								x
184	Saranathan *et al.*	J R Soc Interface. 2012, 9(75):2563-80.	/								x
185	Combes *et al.*	Adv Exp Med Biol. 2012, 745:v-xiii, xv, xvii passim.	/	x							
186	Misra *et al.*	Acta Biomater. 2012, 8(5):1908-17.	/						x		
187	Avila-Salas *et al.*	J Phys Chem B. 2012, 116(7):2031-9.	/								x
188	Szymański *et al.*	Int J Mol Sci. 2012, 13(1):427-52.	/	x							
189	Le *et al.*	Chem Rev. 2012, 112(5):2889-919.	/	x							
190	Ostrowski *et al.*	J Phys Chem A. 2012, 116(1):631-43.	/								x
191	Carbó-Dorca and Besalú.	SAR QSAR Environ Res. 2011, 22(7-8):661-5.	/	x							
192	Xia *et al.*	ACS Nano. 2011, 5(11):9074-81.	/								x

193	Tzoupis *et al.*	J Comput Aided Mol Des. 2011, 25(10):959-76.	/								x
194	Sunshine *et al.*	Biomacromolecules. 2011, 12(10):3592-600.	/								x
195	Mavromoustakos *et al.*	Curr Med Chem. 2011, 18(17):2517-30.	/	x							
196	Chen *et al.*	J Phys Chem B. 2011, 115(13):3354-62.	/								x
197	Burello and Worth.	Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2011, 3(3):298-306	/	x							
198	Burello and Worth.	Nat Nanotechnol. 2011, 6(3):138-9.	/	x							
199	Puzyn *et al.*	Nat Nanotechnol. 2011, 6(3):175-8.	10		x						
200	Fourches *et al.*	Comb Chem High Throughput Screen. 2011, 14(3):217-25.	/	x							
201	Menard *et al.*	Environ Pollut. 2011, 159(3):677-84.	/	x							
202	Marszałł *et al.*	J Chromatogr A. 2011, 1218(2):229-36.	/								x
203	Cattaneo *et al.*	J Appl Toxicol. 2010, 30(8):730-44.	/	x							
204	Pham *et al.*	J Biol Chem. 2011, 286(1):123-30.	/								x
205	Fourches *et al.*	ACS Nano. 2010, 4(10):5703-12.	9			x					
206	Sayes and Ivanov.	Risk Anal. 2010, 30(11):1723-34.	65			x					
207	Jasinski *et al.*	Invest New Drugs. 2011, 29(5):846-52.	/								x
208	Toropova *et al.*	Mol Divers. 2011, 15(1):249-56.	/								x
209	Toropov *et al.*	Eur J Med Chem. 2010, 45(4):1387-94.	/								x
210	Ibrahim *et al.*	Spectrochim Acta A Mol Biomol Spectrosc. 2010, 75(2):702-9.	/								x
211	Cook *et al.*	J Hazard Mater. 2010, 176(1-3):367-73.	/								x
212	Huang *et al.*	Nanomedicine. 2010, 6(3):442-52.	/								x
213	Puzyn *et al.*	Small. 2009, 5(22):2494-509.	/	x							
214	Mukherjee *et al.*	Toxicol In Vitro. 2010, 24(1):169-77.	66			x					
215	Naha *et al.*	Environ Sci Technol. 2009, 43(17):6864-9.	/							x	
216	Toropov *et al.*	J Comput Chem. 2010, 31(2):381-92.	/								x
217	Schneider HJ.	Angew Chem Int Ed Engl. 2009, 48(22):3924-77.	/	x							
218	Kline *et al.*	Talanta. 2009, 78(4-5):1489-91.	/								x

219	Durdagi *et al.*	Bioorg Med Chem. 2008, 16(23):9957-74.	/								x
220	Durdagi *et al.*	Bioorg Med Chem Lett. 2008, 18(23):6283-9.	/								x
221	Chabre and Roy.	Curr Top Med Chem. 2008, 8(14):1237-85.	/	x							
222	Saliner *et al.*	IDrugs. 2008, 11(10):728-32.	/	x							
223	D'Souza *et al.*	J Drug Target. 2008, 16(7):578-85.	/								x
224	Kim *et al.*	J Am Chem Soc. 2008, 130(13):4230-1.	/					x			
225	Liu and Hopfinger.	Chem Res Toxicol. 2008, 21(2):459-66.	/					x			
226	Duffin *et al.*	Yonsei Med J. 2007, 48(4):561-72.	/	x							
227	Martin *et al.*	J Phys Chem B. 2007, 111(33):9853-7.	/								x
228	Wu *et al.*	Anal Biochem. 2007, 15;364(2):193-203.	/								x
229	Gao *et al.*	J Mol Model. 2007,13(5):573-8.	/								x
230	Song *et al.*	Comput Biol Med. 2007, 37(3):315-9.	/								x
231	Vesentini *et al.*	ScientificWorldJournal. 2005, 5:564-70.	/								x
232	Zhong *et al.*	Bioorg Med Chem. 2004, 12(15):4009-15	/								x
			Total	**52**	**19**	**40**	**6**	**9**	**4**	**7**	**95**