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Original Article

Development of QSAR models using artificial neural network analysis for risk assessment of repeated-dose, reproductive, and developmental toxicities of cosmetic ingredients

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ABSTRACT — Use of laboratory animals for systemic toxicity testing is subject to strong ethical and regulatory constraints, but few alternatives are yet available. One possible approach to predict systemic toxicity of chemicals in the absence of experimental data is quantitative structure-activity relationship (QSAR) analysis. Here, we present QSAR models for prediction of maximum "no observed effect level" (NOEL) for repeated-dose, developmental and reproductive toxicities. NOEL values of 421 chemicals for repeated-dose toxicity, 315 for reproductive toxicity, and 156 for developmental toxicity were collected from Japan Existing Chemical Data Base (JECDB). Descriptors to predict toxicity were selected based on molecular orbital (MO) calculations, and QSAR models employing multiple independent descriptors as the input layer of an artificial neural network (ANN) were constructed to predict NOEL values. Robustness of the models was indicated by the root-mean-square (RMS) errors after 10-fold cross-validation (0.529 for repeated-dose, 0.508 for reproductive, and 0.558 for developmental toxicity). Evaluation of the models in terms of the percentages of predicted NOELs falling within factors of 2, 5 and 10 of the *in-vivo*-determined NOELs suggested that the model is applicable to both general chemicals and the subset of chemicals listed in International Nomenclature of Cosmetic Ingredients (INCI). Our results indicate that ANN models using *in silico* parameters have useful predictive performance, and should contribute to integrated risk assessment of systemic toxicity using a weight-of-evidence approach. Availability of predicted NOELs will allow calculation of the margin of safety, as recommended by the Scientific Committee on Consumer Safety (SCCS).

Key words: Artificial neural network, Repeated-dose toxicity, Reproductive/developmental toxicity, QSAR model, NOEL, Cosmetic ingredients

INTRODUCTION

Many well-validated and proven *in vivo* assays are available for systemic toxicity testing. Repeated-dose toxicity refers to general toxicological effects in mammals occurring as a result of prolonged and repeated exposure to a substance, and covers a wide range of possible adverse effects, including changes in morphology, physiology, growth, development or life span. The most commonly performed animal tests for repeated-dose toxicity are 28-day and 90-day oral toxicity tests in rodents. Other major endpoints for systemic toxicity are reproductive toxicity and developmental toxicity, which refer to the adverse effects of substances on sexual function and fertility in adult males and females, and developmental toxicity in offspring (including effects on, or mediated via, lactation), respectively. In this study, we define reproductive toxicity in terms of a range of endpoints relating to impairment of male and female fertility, and we define developmental toxicity in terms of adverse effects on offspring. Studies on reproductive toxicity and developmental toxicity usually aim to identify adverse effects on various organs and tissues, and to establish the lowest dose that induces an effect (lowest observed (adverse) effect level; LO(A)EL) or the highest dose with no biologically or statistically significant effect (no observed (adverse) effect level; NO(A)EL).

Laboratory animals are generally used for toxici-

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ty testing, especially for reproductive and developmental toxicity (Jagt *et al.,* 2004; Hartung and Rovida, 2009; Spielmann and Vogel, 2006). But, according to the 7th amendment of the EU cosmetic directive, cosmetic products containing substances that have been tested in animals may no longer be sold in the EU. Nevertheless, the importance of systemic toxicity assessment for cosmetic ingredients has been highlighted in "Notes of Guidance for Testing of Cosmetic Ingredients and Their Safety Evaluation" by the Scientific Committee on Consumer Safety (SCCS) as well as in "Safety Evaluation Guidelines Edition 2014" by the The Personal Care Products Council (PCPC), which both strongly recommends calculation of the margin of safety; for this purpose, NOEL data for repeated-dose, reproductive, and developmental toxicities are required. Therefore, non-animal test methods for assessing systemic toxicity are necessary; i.e., we require methods to predict NOEL of chemicals.

At present, *in vitro* methods for predicting developmental toxicity have advanced furthest towards regulatory acceptance. Indeed, the embryonic stem cell test (EST; Spielmann *et al.,* 1997) is the only *in vitro* method that has been validated by The European Centre for the Validation of Alternative Methods (ECVAM; Brown *et al.,* 1995; Seiler and Spielmann *et al.,* 2011). However, because of the multiplicity and complexity of the processes underlying systemic toxicity, no method has yet been brought into general use.

A different approach would be to use *in silico* methods. The two major methodologies for *in silico* assessment of toxicity are (quantitative) structure-activity relationship ((Q)SAR) analysis and read-across. (Q)SAR models are built to find mathematical relationships between physicochemical or structural properties and biological activity, based on the idea that chemical structural characteristics are related to biological activity. The most widely used QSAR software for quantitative prediction of repeated-dose toxicity is Toxicity Prediction by Komputer Assisted Technology (TOPKAT; Accelrys, San Diego, CA, USA). TOPKAT is designed to predict rat chronic oral LOAEL based on a dataset of 393 chemicals collected from the U.S. Environmental Protection Agency (EPA), National Cancer Institute/National Toxicology Program (NCI/NTP), National Toxicology Program Technical Reports, Food and Drug Administration New Drug Applications, and literature reports (Mumtaz *et al.,* 1995; Venkatapathy *et al.,* 2004). Several studies (Mumtaz *et al*., 1995; Venkatapathy *et al.,* 2004; Tilaoui *et al.,* 2007; Rupp *et al.,* 2010) have found that reasonable predictions can be obtained for a range of chemicals. Another recently developed model is MolCode Toolboxes (MolCode, Ltd., Tartu, Estonia). However, both models are designed to predict LOAEL, and cannot directly predict NOEL, which is needed for calculation of the margin of safety.

For developmental or reproductive toxicity, there are some software tools based on QSAR (reviewed in Cronin and Worth, 2008; Piparo and Worth, 2010), but these were constructed to predict hazards related to developmental or reproductive toxicity (i.e., they are limited to qualitative analysis) and no quantitative model has been reported.

The aim of the present study was to construct QSAR models enabling the prediction of NOELs for repeated-dose, developmental and reproductive toxicities by combining a molecular orbital (MO) calculation method and an artificial neural network (ANN) system. Although a single model is unlikely to be sufficient for assessment of systemic toxicity, the present study indicates that prediction of NOELs using an *in silico* approach may be feasible. This would enable calculation of the margin of safety, which would be very important for safety assessment of cosmetic raw materials according to the weight of evidence approach.

MATERIAL AND METHODS

Toxicological data

NOELs of repeated-dose toxicity and developmental/ reproductive toxicity in rats were collected from the Japan Existing Chemical Data Base (JECDB; http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPage.jsp). For repeated-dose toxicity, NOELs obtained from repeated-dose 28-day (or 90-day) oral toxicity study or combined repeated-dose toxicity study and reproductive and developmental toxicity screening of 421 chemicals were collected. For reproductive toxicity, NOELs of 315 chemicals for parents were collected, while for developmental toxicity, NOELs of 156 chemicals for offspring were collected. NOELs obtained from combined repeated-dose toxicity study with reproductive and developmental toxicity screening or from reproductive and developmental toxicity screening alone were included (Table 1). However, NOEL of general toxicity obtained in reproductive and developmental toxicity screening was not used. It should be noted that 1000 mg/kg was the maximum dose in these studies. Chemicals which showed toxicity at the lowest dose of the test, i.e. NOEL was not obtained, were not included.

Extraction of descriptors

The structures of chemicals were built with Chem 3D Ultra 10.0 (CambridgeSoft Co., Cambridge, MA, USA) and modeled in their neutral forms. Geometry optimiza-

Table 1. Chemical information including *in-vivo*-determined NOEL results and MO-calculated descriptors of 245 chemicals.

CAS No.	Chemical	Sum C	Sum H	Sum O	Sum N	Sum S	Core-Core Repulsion	COSMO Area	COSMO Volume	Dipole Moment	Heat of Formation	Electronic Energy	Ionization Potential	Total Energy	Alpha Average	Beta Average	Gamma Average	MW	Repeated-dose toxicity NOEL		Reproductive toxicity NOEL		Developmental toxicity NOEL
																			male	female	male	female	
80-09-1	4,4'-Sulfonyldiphenol	-2.465	2.381	-2.382	0	2.467	15849.64	251.48	272.75	7.331	-118.0835	-83557.6	221.2863	-67708	127.584	-2.32571	23271.3	250.269	40	40	60	60	60
81-11-8	4,4'-Diamino-2,2'-stilbenedisulfonic acid	-2.896	2.972	-5.085	-0.071	5.079	21895.57	340.2	377.71	0.043	-207.1262	-121834.1	191.4584	-99938.6	217.994	-7.93001	31809.5	370.394	-	-	1000	1000	1000
87-02-5	7-Amino-4-hydroxy-2-naphthalenesulfonic acid	-1.624	1.942	-2.841	-0.038	2.560	12422.57	235.12	247.36	7.914	-146.6043	-78081.4	196.8819	-65658.8	129.682	-150.735	40505.7	239.245	1000	1000	-	-	-
88-09-5	2-Ethylbutyric acid	-0.852	1.694	-0.842	0	0	8796.081	159.87	158.64	2.347	-126.0070	-43043.6	261.7866	-34247.5	48.292	-16.0178	3001.69	116.16	10	50	250	10	50
89-04-3	1,2,4-Benzenetricarboxylic acid, trioctyl ester	-5.992	7.864	-1.873	0	0	120687.9	558.73	754.4	7.690	-194.4492	-270649.0	193.5705	-149961	284.712	-93.0711	36781.7	546.786	125	30	500	500	500
90-02-8	2-Hydroxybenzaldehyde	-0.608	1.318	-0.710	0	0	4762.566	150.69	144.94	5.245	-61.5917	-39560.1	217.6917	-34797.5	63.6156	142.388	11772.7	122.123	10	10	160	40	40
98-08-8	Trifluoromethylbenzene	-0.653	1.113	0	0	0	1534.884	156.74	153.72	3.654	-137.5508	-52915.3	234.8315	-51380.4	54.1945	-24.9613	3827.71	146.112	1	-	500	500	-
99-04-7	3-Methylbenzoic acid	-0.703	1.547	-0.845	0	0	6435.094	169.66	165.9	3.286	-81.7477	-44695.8	226.1137	-38260.7	70.0087	143.701	11636.6	136.15	300	100	1000	1000	1000
99-09-2	3-Nitrobenzenamine	-1.182	1.135	-1.340	1.387	0	5519.645	161.86	155.75	6.813	-0.4929	-45015.4	206.4274	-39495.7	70.7273	-30.861	13548.6	138.126	-	-	50	5	50
2768-02-7	Ethenyltrimethoxysilane	-1.017	1.200	-1.424	0	0	5291.604	179.21	182.85	1.984	-221.9425	-45302.6	230.7001	-40011	66.8799	47.8921	8981.76	148.234	-	-	1000	250	1000
3896-11-5	Bumetrizole	-2.634	2.902	-0.269	-0.064	0	30481.93	327.61	362.34	2.067	39.7151	-108587.8	209.8156	-78105.9	194.343	-151.071	176397	315.802	1000	1000	1000	1000	1000
4390-04-9	2,2,4,4,6,8,8-Heptamethylnonane	-3.895	3.895	0	0	0	47641.97	289.67	352.08	0.259	-88.8670	-103525.8	250.451	-55883.9	113.199	-12.2646	7264.72	226.445	-	-	1000	1000	1000
5281-04-9	D&C Red No. 7	-1.839	2.537	-5.137	-0.026	2.465	35142.58	384.19	447.31	48.242	-663.5510	-141519.5	206.0261	-106377	223.533	368.556	73689.5	424.443	100	-	1000	1000	1000
5460-09-3	Monosodium 4-amino-5-hydroxy-2,7-naphthalenedisulfonate	-1.831	1.785	-6.107	-0.066	5.220	20093.74	321.71	365.75	10.887	-444.5601	-110214.8	193.1734	-90121	152.476	167.231	51116.6	341.285	1000	1000	-	-	-
100-54-9	3-Cyanopyridine	-0.562	0.947	0	-0.385	0	2866.486	139.65	129.33	4.135	59.4995	-28131.5	237.3349	-25265	59.5976	59.4073	8908.03	104.111	5	5	-	-	-
100-69-6	2-Vinylpyridine	-1.301	1.463	0	-0.162	0	4869.672	148.5	139.8	2.294	43.2736	-30199.9	219.394	-25330.2	64.9559	-71.6521	19753	105.139	13	13	-	-	-
100-74-3	4-Ethylmorpholine	-1.191	1.613	-0.300	-0.122	0	11264.11	161.49	159.17	1.664	-53.6642	-42808.6	214.3524	-31544.5	52.1292	12.3213	3407.69	115.175	50	50	150	150	500
101-14-4	4,4'-Methylenebis(2-chloroaniline) hexahydrate	-2.073	2.040	0	-0.080	0	15211.34	274.93	296.03	2.658	18.3145	-77091.8	200.8489	-61880.5	142.312	-200.707	47509.8	267.157	2	2	50	50	50
101-72-4	N-Phenyl-N'-isopropyl-p-phenylenediamine	-3.038	3.060	0	-0.022	0	20803.88	279.54	299.08	0.638	30.8594	-75670.2	190.676	-54866.3	146.951	97.6561	74486.7	226.321	10	-	-	-	-
101-83-7	Dicyclohexylamine	-2.709	2.863	0	-0.155	0	25418.61	236.5	255.69	1.535	-49.8030	-70178.3	217.8024	-44759.7	90.2862	-8.71322	8408.81	181.32	20	20	80	40	40
102-06-7	1,3-Diphenylguanidine	-2.306	2.637	0	-0.331	0	17220.52	252.71	266.02	2.370	65.7663	-68559.9	208.1908	-51339.4	131.995	13.6582	33969.3	211.266	10	10	-	-	-
1025-15-6	1,3,5-Tris(2-propenyl) isocyanuric acid	-1.167	2.680	-1.318	-0.196	0	28412.86	280.51	311.23	0.327	-73.1303	-98057.8	239.8201	-69645	127.172	66.9761	23008.3	249.269	-	15	-	-	-
102-76-1	Glycerol triacetate	0.073	2.213	-2.286	0	0	14202.44	261.74	260.08	2.988	-276.6554	-84442.5	264.961	-70240	87.3084	25.9234	10999.5	218.206	1000	1000	1000	1000	1000
102-81-8	2-(Di-n-butylamino)ethanol	-2.355	2.850	-0.383	-0.112	0	14649.99	253.81	258.82	0.758	-91.1405	-60711.1	213.3359	-46061.1	81.3256	-1.2761	6034.41	173.298	25	25	-	-	-
103-24-2	Bis(2-ethylhexyl) nonanedioate	-4.614	6.119	-1.505	0	0	54407.06	508.32	592.34	4.520	-286.1147	-166988.0	253.5369	-112581	192.787	-12.408	18571.9	412.652	300	300	1000	300	1000
103-44-6	2-ethylhexyl vinyl ether	-2.366	2.602	-0.236	0	0	13896.17	234.34	237.08	2.039	-60.6833	-55118.5	222.6913	-41222.4	78.7481	-70.8032	6170.24	156.267	8	30	-	-	-
103-69-5	N-Ethylaniline	-1.733	1.795	0	-0.063	0	7223.324	171.84	166.32	1.569	12.1064	-36734.9	201.8806	-29511.5	71.85	-235.596	15547.6	121.182	1	1	-	-	-
103-83-3	N,N-Dimethylbenzylamine	-1.871	1.990	0	-0.119	0	12430.41	186.9	191.95	1.432	14.6029	-45382.4	214.3939	-32952	75.4356	-9.38352	7823.09	135.208	50	50	-	-	-
105-05-5	1,4-Diethylbenzene	-2.044	2.044	0	0	0	10107.18	191.83	191.66	0.062	-3.9267	-42419.6	214.9367	-32312.4	78.0304	-0.78493	11512	134.221	30	150	750	750	750
105-16-8	2-(Diethylamino)ethyl methacrylate	-1.662	2.517	-0.731	-0.124	0	16063.26	249.99	257.27	1.434	-94.6834	-67445.4	215.638	-51382.2	88.7962	102.375	14230.6	185.266	50	500	500	150	500
105-45-3	Methyl acetoacetate	-0.055	1.237	-1.183	0	0	4021.339	153.03	142.87	2.692	-136.7207	-40861.2	259.033	-36839.9	45.6861	26.4497	4769.73	116.116	1000	1000	1000	1000	1000
105-99-7	Dibutyl adipate	-1.974	3.482	-1.507	0	0	23395.55	334.53	353.75	0.615	-229.1359	-98046.6	258.1214	-74651	113.465	8.69249	11386.9	258.357	1000	1000	1000	1000	300
106-37-6	1,4-Dibromobenzene	-1.019	0.966	0	0	0	1272.832	166.75	165.04	0.001	36.5643	-35378.3	229.976	-34105.4	70.9759	-0.0334	3282.99	235.906	4	4	-	-	-

Table 1. (Continued).

CAS No.	Chemical	Sum C	Sum H	Sum O	Sum N	Sum S	Core-Core Repulsion	COSMO Area	COSMO Volume	Dipole Moment	Heat of Formation	Electronic Energy	Ionization Potential	Total Energy	Alpha Average	Beta Average	Gamma Average	MW	Repeated-dose toxicity NOEL		Reproductive toxicity NOEL		Developmental toxicity NOEL
																			male	female	male	female	
106-48-9	4-Chlorophenol	-0.950	1.186	-0.283	0	0	2426.011	147.95	141.15	1.959	-32.4627	-34670.6	210.4788	-32244.6	60.4228	50.4987	12935.5	128.558	20	100	-	-	-
1066-40-6	Trimethylsilanol	-1.675	1.305	-0.544	0	0	-1560.666	137.14	130.55	1.787	-118.6646	-18704.6	229.7226	-20265.3	42.6865	-0.01572	3727.3	90.197	160	160	-	-	-
106-91-2	2,3-Epoxypropyl methacrylate	-0.557	1.620	-1.063	0	0	6947.786	189.77	181.25	2.459	-84.7486	-49914.5	243.732	-42966.8	62.7737	-4.3169	7341.83	142.154	10	30	30	30	100
107-66-4	Dibutyl phosphate	-1.620	2.292	-3.070	0	0	11444.85	256.12	263.66	4.816	-294.0350	-70066.4	246.1584	-58621.5	85.8281	56.5756	10321.4	210.209	30	30	1000	1000	300
108-39-4	3-Methylphenol	-1.226	1.514	-0.288	0	0	5213.541	147.58	140.27	1.310	-34.9947	-33959.8	214.0224	-28746.3	59.1032	11.1695	3566.96	108.14	300	100	-	-	-
108-65-6	Propylene glycol	-0.508	1.576	-1.068	0	0	7968.581	183.26	174.02	3.831	-144.1538	-48966.0	250.3841	-40997.5	54.652	-7.89089	5712.58	132.159	300	300	1000	1000	1000
108-69-0	3,5-Dimethylaniline	-1.533	1.585	0	-0.052	0	7810.477	170.59	166.88	1.401	-1.0728	-37335.2	202.0005	-29524.7	72.7049	205.904	14512.3	121.182	10	10	-	-	-
108-73-6	1,3,5-Trihydroxybenzene	-0.696	1.551	-0.855	0	0	4226.669	148.94	141.53	3.133	-121.9936	-43080.5	214.1036	-38853.9	60.2033	124.371	5270.86	126.112	300	300	-	-	-
108-80-5	Isocyanuric acid	0.963	0.652	-1.419	-0.195	0	2608.216	137.74	126.67	0.004	-140.9009	-43455.5	242.8993	-40847.2	55.8831	97.7919	5029.96	129.075	150	150	600	600	600
109-59-1	2-(1-Methylethoxy)ethanol	-0.879	1.554	-0.675	0	0	5313.807	155.79	144.34	0.421	-106.4881	-36806.0	247.0217	-31492.2	43.493	9.53204	3178.51	104.149	-	-	125	125	125
109-64-8	1,3-Dibromopropane	-0.715	1.044	0	0	0	-2158.805	145.75	137.75	2.680	-12.6383	-24495.4	260.0495	-26654.2	44.0427	23.7484	3084.59	201.888	10	10	-	-	-
109-69-3	1-Chlorobutane	-1.023	1.156	0	0	0	595.5162	136.02	124.24	1.977	-34.1326	-22052.6	247.0773	-21457.1	36.3505	-6.79077	1986.47	92.568	-	-	300	2	60
109-70-6	1-Bromo-3-chloropropane	-0.715	0.998	0	0	0	-2232.79	140.97	131.6	2.393	-22.8294	-23572.7	247.5788	-25805.5	40.405	33.3026	2828.6	157.437	20	20	-	-	-
110-02-1	Thiophene	-1.321	1.017	0	0	0.304	205.8829	113.17	101.84	0.902	29.1267	-16831.3	223.8381	-16625.4	42.0172	-26.0093	2383.51	84.136	25	25	400	25	100
110-30-5	1,2-Bis(stearoylamino)ethane	-8.331	9.542	-0.976	-0.236	0	52164.88	819.16	888.55	3.432	-276.7827	-204236.0	223.2053	-152071	290.908	-80.153	28494.3	593.031	1000	1000	-	-	-
110-63-4	1,4-Butanediol	-0.663	1.429	-0.767	0	0	1587.468	138.07	123.75	0.002	-112.7162	-29642.9	252.24	-28055.4	35.2492	-0.00911	2067.46	90.122	-	-	800	800	400
11070-44-3	Tetrahydromethy-1,3-isobenzofuranedione	-0.616	1.675	-1.059	0	0	20637.99	181.77	194.4	6.165	-127.4870	-69119.2	236.2628	-48481.2	72.3413	-22.4675	4874.57	166.176	30	100	300	300	300
110-83-8	Cyclohexene	-1.391	1.391	0	0	0	6146.697	128.6	120.35	0.210	-5.4852	-26103.0	223.7141	-19956.3	43.6566	4.84633	1797.01	82.145	50	-	500	500	500
111-03-5	2,3-Dihydroxypropyl 9-cis-octadecenoate	-3.989	5.489	-1.500	0	0	24930.23	482.82	503.14	4.547	-252.6661	-123705.7	225.1262	-98775.5	166.983	2.8972	16917	356.545	1000	1000	1000	1000	1000
111-17-1	3,3'-Thiobispropanoic acid	-0.312	2.081	-1.691	0	-0.078	2041.675	207.81	204.69	3.342	-204.4256	-53420.9	216.2728	-51379.2	69.5863	-6.2375	10022.9	178.203	200	200	100	1000	1000
111-41-1	N-(Aminoethyl)ethanolamine	-0.800	1.497	-0.381	-0.316	0	2861.75	158.68	144.32	2.789	-58.2137	-32333.1	219.6055	-29471.4	44.3307	6.4076	3230.83	104.152	60	60	-	-	-
111-82-0	Methyl dodecanoate	-2.450	3.220	-0.769	0	0	13837.01	311.28	313.17	2.364	-152.2452	-72211.7	260.6723	-58374.7	99.6993	3.12396	11285.8	214.347	1000	1000	1000	1000	1000
111-88-6	1-Octanethiol	-2.099	2.276	0	0	-0.178	6004.161	221.13	218.13	2.450	-44.6819	-38596.8	218.3487	-32592.6	68.4491	46.394	6966.68	146.29	10	10	250	50	250
1120-21-4	Undecane	-2.798	2.798	0	0	0	10769.78	255.81	253.26	0.009	-67.4338	-49417.3	260.4652	-38647.5	78.2906	-0.35859	6695.49	156.311	100	100	300	300	300
112-26-5	1,2-Bis(2-chloroethoxy)ethane	-0.872	1.660	-0.587	0	0	1942.019	222.83	215.37	0.009	-106.6072	-50764.9	247.7403	-48822.9	67.7493	0.06734	7197.87	187.066	100	50	-	-	-
112-85-6	Docosanoic acid	-4.739	5.585	-0.846	0	0	24735.57	488.9	510.07	2.396	-215.5412	-114160.5	260.3202	-89424.9	161.225	-4.914	18080	340.588	1000	1000	1000	1000	1000
115-70-8	2-Amino-2-ethyl-1,3-propanediol	-0.872	1.766	-0.739	-0.155	0	11895.41	157	160.25	2.757	-113.0709	-47495.3	228.3558	-35599.9	47.0958	35.5119	2917.26	119.163	500	1000	1000	1000	1000
115-77-5	Pentaerythritol	-0.476	1.959	-1.483	0	0	13930.55	160.24	166.02	2.215	-199.5882	-58979.4	251.7135	-45048.8	47.5938	-24.3336	2720.35	136.147	100	100	1000	1000	1000
118-69-4	2,6-Dichlorotoluene	-1.227	1.099	0	0	0	4489.471	169.34	170.46	0.772	0.8278	-40355.8	218.9725	-35866.3	72.9188	-66.412	15369.2	161.03	30	100	1000	100	300
118-79-6	2,4,6-Tribromophenol	-0.758	0.783	-0.235	0	0	2135.594	196.51	202.56	1.504	0.2758	-50811.8	222.1289	-48676.2	88.3175	42.7489	8867.5	330.801	100	100	1000	1000	300
119-06-2	Ditridecyl phthalate hydroxide tetrahydrate	-7.025	8.206	-1.020	0	0	74856.49	645.57	743.25	6.401	-190.2485	-215499.9	187.4423	-140643	275.176	-199.268	28720.1	530.83	10	10	250	50	250
119-47-1	2,2'-Methylenebis(6-tert-butyl-p-cresol)	-3.926	4.474	-0.548	0	0	56889.67	377.89	459.24	1.923	-110.1284	-144702.2	205.5757	-87812.5	187.757	-32.9763	22656.4	340.505	-	-	13	50	50
12033-89-5	Silicone nitride	0	0	0	-1.994	0	379.7994	153.36	165.18	3.133	81.8917	-20302.9	191.139	-19923.1	111.497	44.4754	50018.2	140.283	1000	1000	1000	1000	1000
121-03-9	2-Methyl-5-nitrobenzenesulfonic acid	-1.635	1.478	-3.868	1.436	2.589	10067.63	208.91	217.69	8.465	-134.4472	-73531.4	238.2038	-63463.7	91.9655	-20.274	13107	217.196	175	175	700	700	350

Table 1. (Continued).

CAS No.	Chemical	Sum C	Sum H	Sum O	Sum N	Sum S	Core-Core Repulsion	COSMO Area	COSMO Volume	Dipole Moment	Heat of Formation	Electronic Energy	Ionization Potential	Total Energy	Alpha Average	Beta Average	Gamma Average	MW	Repeated-dose toxicity NOEL		Reproductive toxicity NOEL		Developmental toxicity NOEL
																			male	female	male	female	
121-45-9	Trimethoxyphosphine	-0.260	0.760	-1.794	0	0	2562.259	151.67	142.94	3.394	-195.9644	-37139.0	215.1452	-34576.7	54.4392	38.9042	3833.47	124.076	15	-	80	80	80
121-47-1	3-Aminobenzenesulfonic acid	-1.381	1.429	-2.568	-0.041	2.561	5651.431	181.57	180.88	5.326	-116.4768	-52897.8	204.0109	-47246.3	80.792	-159.995	9772.07	173.186	300	300	-	-	-
123-07-9	4-Ethylphenol	-1.446	1.734	-0.287	0	0	6934.9	165.68	161.58	1.622	-38.4575	-39127.6	209.6345	-32192.7	67.0192	38.9812	8472.79	122.166	100	300	-	-	-
123-11-5	4-Methoxybenzaldehyde	-0.765	1.412	-0.648	0	0	6575.747	171.75	168.06	3.163	-55.4383	-44810.1	218.7248	-38234.4	73.9398	302.599	26982.9	136.15	20	20	100	100	100
123-30-8	4-Aminophenol	-0.999	1.339	-0.289	-0.051	0	4437.8	143.43	134.99	2.172	-29.4354	-33836.7	196.1182	-29398.9	61.2941	113.973	14392.7	109.127	20	20	100	100	100
123-42-2	Diacetone alcohol	-1.007	1.802	-0.796	0	0	10735.08	158.48	160.9	3.945	-115.0998	-44971.7	253.4504	-34236.6	48.3587	-27.3017	3351.48	116.16	30	100	300	300	300
1241-94-7	2-ethylhexyl Diphenyl phosphate	-3.710	4.122	-2.793	0	0	51466.31	377.74	449.96	5.011	-214.8518	-145667.4	213.3331	-94201.1	188.583	3.46015	34338.2	362.405	20	20	-	-	-
126-30-7	2,2-Dimethyl-1,3-propanediol	-0.815	1.560	-0.745	0	0	8746.962	147.07	145.27	3.409	-112.4291	-40245.1	251.5154	-31498.1	41.6211	15.2572	1769.12	104.149	100	1000	1000	1000	1000
126-33-0	Tetrahydrothiophene-1,1-dioxide	-1.908	1.450	-1.844	0	2.301	3930.506	139.55	134.06	6.286	-92.0583	-35554.9	253.7045	-31624.4	47.8037	-6.05426	2948.81	120.166	60	200	700	200	60
126-98-7	Methacrylonitrile	-0.545	0.774	0	-0.229	0	63.5764	115.85	100.3	4.379	37.2839	-16485.1	238.9908	-16421.5	35.7899	52.3215	2838.95	67.09	8	-	30	30	30
127-68-4	Sodium 3-nitrobenzenesulfonate	-1.400	0.938	-4.515	1.432	2.545	10311.12	226.27	244.65	3.116	-298.7554	-70168.2	241.6176	-59857.1	80.9052	71.3475	7048.61	225.151	300	300	-	-	-
130-13-2	Sodium 4-amino-1-naphthalenesulfonate	-1.876	1.576	-3.175	-0.021	2.496	17262.05	248.78	277.62	6.792	-264.7291	-75979.3	198.889	-58717.2	119.419	-93.7199	17747.8	245.228	300	300	-	-	-
1321-74-0	Divinylbenzene	-1.971	1.971	0	0	0	8249.666	178.74	177.81	0.016	53.6299	-39090.2	208.5809	-30840.6	88.6409	-15.3135	19261.4	130.189	30	100	1000	300	30
1333-16-0	Methylenediphenol	-1.978	2.539	-0.561	0	0	17682.11	228.82	245.01	0.889	-50.0231	-71004.6	211.9659	-53322.5	113.295	-118.212	12442.8	200.237	40	8	-	-	-
1338-41-6	Sorbitan monooctadecanoate	-4.158	6.272	-2.114	0	0	49274.99	526.76	589.22	5.444	-357.3734	-171947.7	248.5451	-122673	190.001	24.6606	19418.2	430.624	1000	1000	-	-	-
134-62-3	N,N-Diethyl-m-toluamide acid(C12-18)ester	-1.976	2.533	-0.471	-0.086	0	21622.87	239.64	259.18	4.656	-43.9333	-70987.1	223.7032	-49364.2	103.88	-17.1485	11282.3	191.272	-	60	600	600	600
135-51-3	Sodium 2-naphthol-3,6-disulfonate	-1.877	2.130	-5.419	0	5.166	13918.43	268.24	287.98	4.674	-275.4167	-100097.1	208.6303	-86178.7	144.953	188.833	49510.3	304.289	300	300	-	-	-
13936-21-5	2-Pentylanthraquinone	-2.149	2.922	-0.773	0	0	23804.35	316.55	341.08	2.788	-50.8603	-95664.2	229.245	-71859.8	161.346	126.734	42165.6	278.35	4	15	-	-	-
140-66-9	p-tert-Octylphenol	-2.847	3.134	-0.287	0	0	23846.64	263.79	287.77	1.610	-68.6761	-76727.6	211.2234	-52880.9	110.226	-90.3808	13318.6	206.327	15	15	-	-	-
1477-55-0	1,3-Bis(aminomethyl)benzene	-1.379	1.705	0	-0.325	0	9066.819	184.98	183.25	2.852	14.1423	-42677.5	220.6653	-33610.6	74.1525	3.04504	6059.66	136.196	150	150	450	450	450
1552-42-7	3,3-Bis(p-dimethylaminophenyl)-6-dimethylaminophthalide	-3.849	4.657	-0.700	-0.108	0	60086.95	440.29	515.39	6.880	-9.2733	-166188.1	201.5612	-106101	251.546	55.1396	77567.3	415.534	120	120	1000	1000	1000
156-43-4	4-Ethoxybenzenamine	-1.411	1.685	-0.224	-0.050	0	8147.959	182.68	177.07	1.977	-25.7088	-44429.1	196.5173	-36281.1	78.9847	92.3056	21439.7	137.181	10	10	200	50	50
1570-64-5	4-Chloro-o-cresol	-1.095	1.326	-0.278	0	0	4864.519	165.18	162.09	1.801	-39.6889	-40559.3	208.9965	-35694.8	69.0589	-76.8096	13503.3	142.585	60	60	-	-	-
16219-75-3	5-Ethylidene-2-norbornene	-1.895	1.895	0	0	0	12933.07	165.96	166.32	0.289	33.4909	-41765.1	221.4247	-28832	65.1656	-22.4355	4772.8	120.194	-	20	20	20	20
1843-05-6	2-Hydroxy-4-(octyloxy) benzophenone	-3.229	4.124	-0.896	0	0	28244.2	393.71	421.8	4.605	-111.2945	-115196.5	215.5891	-86952.3	178.823	-199.257	30796.8	326.435	1000	1000	-	-	-
1879-09-0	6-tert-Butyl-2,4-xylenol heptahydrate	-2.168	2.447	-0.279	0	0	21990.75	225.22	244.38	1.832	-62.2449	-67979.2	207.3617	-45988.5	97.1837	20.9754	9513.43	178.274	6	30	150	30	30
211495-85-1	Dicyclopentylsilanediol	-2.149	2.922	-0.773	0	0	23804.35	316.55	341.08	2.788	-50.8603	-95664.2	229.245	-71859.8	161.346	126.734	42165.6	278.35	40	40	-	-	-
2216-69-5	1-Methoxynaphthalene	-1.661	1.880	-0.219	0	0	12794.08	189.73	194.21	1.658	5.2809	-53150.6	200.5581	-40356.6	98.7377	-64.1648	9077.8	158.199	30	30	-	-	-
2403-88-5	2,2,6,6-Tetramethyl-4-hydroxypiperidine	-1.949	2.474	-0.371	-0.154	0	26876.74	199.9	222.33	2.761	-85.6648	-68782.3	218.9563	-41905.5	71.4301	34.9297	4662.73	157.255	-	-	600	200	200
2416-94-6	2,3,6-Trimethylphenol	-1.518	1.793	-0.275	0	0	10733.36	178.81	180.36	1.221	-50.0599	-46380.7	210.1114	-35647.3	76.1153	69.2261	10825.2	136.193	100	100	-	-	-
2439-35-2	2-(Dimethylamino)ethyl acrylate	-0.978	1.850	-0.751	-0.121	0	10049.72	196.71	195.14	2.152	-75.6182	-51083.9	217.2314	-41034.1	65.7743	-24.1407	7643.26	143.185	4	20	100	100	100
24800-44-0	Tripropylene glycol	-1.388	2.721	-1.332	0	0	15513.57	253.85	257.7	0.273	-198.0221	-74332.8	249.0775	-58819.2	79.8014	1.94709	7080.94	192.255	200	200	1000	1000	1000
25154-52-3	Nonylphenol	-3.132	3.414	-0.281	0	0	16232.05	303.63	314.76	1.214	-74.7281	-72562.0	211.8626	-56330	116.783	-109.35	13047.2	220.354	15	60	-	-	-
25321-09-9	Diisopropylbenzene	-2.481	2.481	0	0	0	19262.82	214.23	231.47	0.522	-15.8166	-58473.1	220.9731	-39210.3	90.5334	9.46612	5708.7	162.274	30	30	750	750	750

Table 1. (Continued).

CAS No.	Chemical	Sum C	Sum H	Sum O	Sum N	Sum S	Core-Core Repulsion	COSMO Area	COSMO Volume	Dipole Moment	Heat of Formation	Electronic Energy	Ionization Potential	Total Energy	Alpha Average	Beta Average	Gamma Average	MW	Repeated-dose toxicity NOEL		Reproductive toxicity NOEL		Developmental toxicity NOEL
																			male	female	male	female	
2579-20-6	1,3-Cyclohexanedimethanamine	-1.747	2.082	0	-0.335	0	16169.94	195.38	202.85	3.025	-32.3636	-51948.5	221.6474	-35778.6	66.8087	-20.4165	4826.22	142.244	60	60	300	300	300
2581-34-2	3-Methyl-4-nitrophenol	-1.275	1.464	-1.622	1.433	0	7837.875	172.22	170.2	6.438	-49.6788	-53456.4	226.2477	-45618.6	74.85	271.394	24316.9	153.137	-	-	300	300	300
26444-49-5	Diphenyl cresyl salt	-3.036	3.384	-2.721	0	0	44188.2	333.59	394.5	4.261	-152.9964	-132055.9	210.72	-87867.7	192.132	25.6857	61141.5	340.315	12	12	60	300	300
26630-87-5	Disperse Red 206	-3.817	4.971	-1.412	-0.135	0.317	63844.66	548.45	644.24	5.991	16.1048	-213616.4	179.2417	-149772	387.23	2020.72	65557.3	580.057	-	250	-	-	-
26898-17-9	Dibenzyltoluene	-3.699	3.699	0	0	0	27727.39	320.74	358.72	0.348	49.1624	-92202.5	217.1786	-64475.1	165.268	21.1719	20517.6	272.389	20	100	-	-	-
26967-76-0	Tris(p-cumenyl)phosphate	-4.780	5.098	-2.698	0	0	110781.4	399.49	566.82	6.169	-199.3739	-226239.4	210.6741	-115458	241.198	15.0998	40807.8	452.529	8	40	-	-	-
27676-62-6	1,3,5-Tris(3,5-di-tert-butyl-4-hydroxybenzyl)isocyanuric acid	-7.314	9.865	-2.164	-0.387	0	302365.3	609.87	961.39	8.459	-169.3597	-509885.3	203.9726	-207520	404.068	22.1708	51000.8	784.09	1000	1000	-	-	-
28575-17-9	Diethylbiphenyl	-2.927	2.927	0	0	0	17748.74	266.82	280.43	0.003	18.9079	-67867.7	209.4067	-50118.9	134.892	0.28373	46770.4	210.318	60	60	-	-	-
2867-47-2	2-(Dimethylamino)ethyl	-1.156	2.019	-0.738	-0.125	0	10921.68	218.23	217.07	1.483	-84.3676	-55407.6	217.0984	-44485.9	73.403	22.3468	11410.7	157.212	40	200	1000	200	200
298-06-6	O,O'-Diethyl dithiophosphate	-0.777	1.418	-1.085	0	-1.467	2679.414	210.41	213.77	1.950	-114.4156	-42479.5	229.0732	-39800.1	90.3667	-59.437	15580.7	186.223	-	-	30	300	100
3048-65-5	3a,4,7,7a-Tetrahydro-1H-indene phosphate	-1.915	1.915	0	0	0	13327.16	162.57	166.01	0.223	16.4986	-42176.2	223.825	-28849	62.6397	-17.7703	3822.54	120.194	-	67	600	200	200
3209-22-1	1,2-Dichloro-3-nitrobenzene	-1.082	0.717	-1.328	1.430	0	5005.242	178.5	180.41	6.043	-3.8740	-54290.8	220.903	-49285.6	78.8823	47.6557	23583.1	192.001	5	5	100	100	100
3319-31-1	Tris(2-ethylhexyl) 1,2,4-benzenetricarboxylate	0.602	0.643	-4.245	0	0	7161.697	212.89	218.02	7.178	-533.9983	-73769.8	224.8795	-66608.1	87.7645	36.1798	7293.23	207.119	1000	1000	1000	1000	1000
3452-97-9	3,5,5-Trimethylhexan-1-ol	-2.046	2.427	-0.381	0	0	18803.3	201.92	219.32	1.830	-96.7848	-57325.9	249.3635	-38522.6	66.4184	7.96644	3542.03	144.256	12	12	300	60	12
3586-14-9	3-Phenoxytoluene	-2.197	2.355	-0.157	0	0	15564.05	225.72	233.05	1.401	8.0635	-62096.7	213.4051	-46532.6	113.271	41.6355	22792.2	184.237	100	20	400	400	100
3648-21-3	Diheptyl phthalate	-4.114	5.296	-1.183	0	0	56642.28	408.37	493.46	4.259	-108.1280	-155887.7	209.9837	-99245.4	184.642	39.7125	18236.4	362.508	63	250	300	300	300
3846-71-7	2-(2'-Hydroxy-3',5'-di-tert-butylphenyl)benzotriazole	-3.404	3.750	-0.273	-0.074	0	45745.7	356.06	410.82	4.135	27.4188	-127249.0	217.8213	-81503.3	193.25	82.0959	42361.5	323.437	-	3	-	-	-
38640-62-9	Bis(1-methylethyl)naphthalene	-2.946	2.946	0	0	0	30476.13	251.41	286.92	0.599	6.3297	-81314.8	204.7966	-50838.7	129.933	39.8523	19634	212.334	30	-	-	-	-
4016-24-4	Sodium 1-methoxycarbonylpentadecane-2-sulfonate	-3.734	4.183	-3.911	0	2.462	38769.47	432.94	497.61	18.983	-441.5093	-135369.7	229.4841	-96600.2	149.01	8.67897	17177.1	372.494	20	20	300	300	300
4130-42-1	2,6-Bis(1,1-dimethylethyl)-4-ethylphenol	-3.094	3.355	-0.261	0	0	36963.16	284.21	326.63	1.805	-75.2312	-96736.6	206.6988	-59773.4	125.838	23.6933	13403.1	234.381	15	15	-	-	-
4189-44-0	Thiourea dioxide	-0.781	-0.102	-1.716	2.436	0.163	-942.0785	125.42	113.71	8.301	37.7515	-28425.9	225.0324	-29367.9	40.6187	83.8384	3580.96	108.115	4	20	100	20	20
4286-23-1	4-(1-Methylethenyl)phenol	-1.594	1.878	-0.285	0	0	8039.708	176.46	175.87	1.327	-18.1043	-42947.9	205.0878	-34908.2	79.6903	141.63	28661.8	134.177	30	30	60	60	60
4457-71-0	3-Methyl-1,5-pentanediol	-1.146	1.910	-0.763	0	0	7096.152	168.99	164.81	0.784	-122.9705	-42047.8	248.2266	-34951.6	49.3288	22.1875	2901.76	118.175	300	300	1000	1000	1000
4461-52-3	Methoxymethanol dodecyl ester, sodium salt	-0.053	0.768	-0.715	0	0	13.7869	98.84	80.33	3.265	-98.9952	-21169.5	245.0755	-21155.7	21.6884	4.65916	971.735	62.068	12	60	300	300	60
461-58-5	Cyanoguanidine	0.089	0.515	0	-0.604	0	-506.1776	120.92	104.56	8.837	36.8459	-21333.2	222.3775	-21839.4	48.8053	23.4355	2296.4	84.08	-	-	1000	1000	1000
4979-32-2	N,N-Dicyclohexyl-2-benzothiazolesulfenamide	-4.023	3.803	0	-0.215	0.435	45212.9	358.99	422.34	1.263	16.6494	-122459.0	210.8403	-77246.1	196.045	-445.92	58369.5	346.548	25	25	400	100	100
5039-78-1	(Methacryloyloxyethyl) trimethylammonium chloride	-5.467	1.064	-0.728	0.138	0	20600.43	242.19	257.26	3.003	-203.8436	-76299.7	216.0466	-55699.3	83.5625	10.5092	9279.96	207.7	1000	1000	-	-	-
50957-96-5	Phosphoric acid,	-2.706	3.145	-3.851	0	0	17232.34	368.2	396.56	6.204	-496.2603	-89500.1	241.91	-72267.8	109.262	53.0469	13077	288.299	125	63	1000	1000	1000
5124-25-4	Disperse Yellow 42	-3.543	3.259	-3.154	1.024	2.414	27939.57	359.4	401.51	7.127	-18.0400	-124973.2	204.6808	-97033.6	223.358	397.814	99151.4	369.394	300	300	-	-	-
51-28-5	2,4-Dinitrophenol	-1.024	1.047	-2.917	2.894	0	7457.085	184.76	182.72	8.101	-59.2698	-66499.8	233.7039	-59042.7	79.1633	82.4367	17382.2	184.108	10	10	30	30	10
526-73-8	1,2,3-Trimethylbenzene	-1.739	1.739	0	0	0	9596.08	169.06	169.39	0.603	-3.5671	-38465.1	218.1776	-28869.1	70.8865	23.7475	7549.73	120.194	30	30	-	-	-
526-78-3	2,3-Dibromosuccinic acid	0.395	1.123	-1.529	0	0	6054.54	177.41	184.13	1.702	-189.4500	-61841.4	241.999	-55786.9	61.4735	-46.9972	3887.36	275.881	1000	1000	-	-	-
536-90-3	3-Methoxybenzenamine	-1.170	1.441	-0.224	-0.047	0	6928.999	162.76	156.58	1.526	-21.8446	-39763.3	202.7795	-32834.3	70.0314	39.8844	9429.58	123.154	-	-	300	60	60
538-75-0	Dicyclohexylcarbodiimide	-2.492	2.832	0	-0.340	0	22890.06	264.45	281.65	2.615	-0.4202	-73730.2	228.5098	-50840.2	116.329	-0.07341	13047.9	206.33	100	100	-	-	-

Table 1. (Continued).

CAS No.	Chemical	Sum C	Sum H	Sum O	Sum N	Sum S	Core-Core Repulsion	COSMO Area	COSMO Volume	Dipole Moment	Heat of Formation	Electronic Energy	Ionization Potential	Total Energy	Alpha Average	Beta Average	Gamma Average	MW	Repeated-dose toxicity NOEL		Reproductive toxicity NOEL		Developmental toxicity NOEL
																			male	female	male	female	
5392-40-5	Citral	-1.815	2.251	-0.437	0	0	8479.969	220.2	220.95	4.538	-46.5168	-48273.9	219.655	-39793.9	83.3722	-94.4449	13169.2	152.236	-	-	1000	1000	200
542-18-7	chlorocyclohexane 2-hydroxypropane-1,2,3-tricarboxylate	-1.353	1.495	0	0	0	8007.018	150.4	150.36	2.186	-38.3252	-35647.1	248.2593	-27640.1	50.0799	2.93549	2056.83	118.606	10	60	300	300	300
544-76-3	n-Hexadecane	-4.008	4.008	0	0	0	16811.8	356.01	362.44	0.001	-94.7365	-72701.5	260.3444	-55889.7	113.676	0.08917	11051.1	226.445	200	40	-	-	-
556-61-6	Methane, isothiocyanato-	-0.392	0.434	0	-0.001	-0.041	-2638.568	109.14	91.26	5.107	31.9051	-11906.4	216.722	-14544.9	38.1593	-77.6373	601.15	73.112	1	1	8	2	8
56539-66-3	3-Methoxy-3-methyl-1-butanol	-1.146	1.819	-0.673	0	0	12458.47	163.75	166.16	2.958	-113.1452	-47400.3	248.5958	-34941.8	49.7185	10.979	2661.82	118.175	60	250	1000	1000	1000
56-93-9	Benzyltrimethylammonium chloride	-3.280	3.517	0	0.684	0	21996.97	215.46	240.18	11.938	-7.1531	-66064.7	225.203	-44067.7	87.5489	43.7647	11994.2	185.696	30	60	-	-	-
5707-44-8	4-Ethyl-1,1'-biphenyl	-2.526	2.526	0	0	0	14133.64	230.34	238.26	0.470	31.7762	-57353.7	206.8364	-43220.1	120.324	-123.182	72585.6	182.265	20	20	300	30	30
584-03-2	1,2-Butanediol	-0.704	1.457	-0.753	0	0	4311.404	131.55	121.99	1.007	-112.1343	-32366.2	250.6714	-28054.8	35.1228	-3.02894	1479.76	90.122	1000	200	1000	1000	1000
585-07-9	tert-Butyl methacrylate	-1.144	1.894	-0.751	0	0	14828.16	194.21	199.57	2.229	-91.7389	-55220.3	241.161	-40392.1	66.5184	76.651	8555.26	142.197	20	20	-	-	-
599-64-4	4-(1-Methyl-1-phenylethyl) phenol	-2.632	2.918	-0.287	0	0	25341.07	245.43	272.71	1.864	-13.0080	-78780.7	211.6431	-53439.7	121.988	61.6909	12423.6	212.291	100	100	-	-	-
6099-57-6	1-Naphthol-4-sulfonic acid sodium salt	-1.698	1.637	-3.441	0	2.502	16663.96	245.28	272.87	4.532	-308.1986	-78055.3	207.1618	-61391.3	111.589	-56.8652	13473	246.213	1000	1000	-	-	-
6106-21-4	Disodium succinate	0.378	1.320	-1.697	0	0	1401.27	143.95	132.3	0.007	-203.9262	-41597.2	266.2088	-40195.9	40.4266	-0.01453	3806.23	118.089	100	300	1000	1000	1000
611-06-3	2,4-Dichloronitrobenzene	-1.091	0.748	-1.331	1.432	0	4145.728	181.67	182.24	5.663	-4.9023	-53432.4	226.2977	-49286.6	82.1558	533.964	50371.6	192.001	-	-	200	40	40
611-19-8	1-Chloro-2-(chloromethyl) benzene	-1.211	1.239	0	0	0	3703.669	170.46	170.99	1.408	4.2964	-39566.5	220.4089	-35862.8	70.5874	163.295	9304.06	161.03	2	10	50	50	50
6165-51-1	1,4-Dimethyl-2-(1-phenylethyl) benzene	-2.927	2.927	0	0	0	24106.38	258.56	284.76	0.175	18.8051	-74225.4	215.2593	-50119	124.938	5.57255	14584	210.318	-	50	200	200	200
61788-76-9	Alkanes, chlorinated(C11, Cl7-12)	-7.595	3.318	0	0	0	84354.92	447.08	605.09	4.714	-258.5510	-209730.9	244.3205	-125376	202.873	19.1657	14773.1	558.113	20	20	300	300	300
620-17-7	3-Ethylphenol	-1.465	1.753	-0.288	0	0	6975.333	165.44	161.36	1.265	-38.5841	-39168.2	214.1003	-32192.9	66.5915	-5.03412	4649.29	122.166	300	300	-	-	-
620-92-8	4,4'-Methylenediphenol	-1.989	2.563	-0.574	0	0	14354.35	233.42	247.18	3.134	-55.2263	-67682.0	210.4128	-53327.7	112.025	-23.7938	20413.4	200.237	60	60	-	-	-
623-26-7	1,4-Dicyanobenzene	-0.539	0.943	0	-0.404	0	3355.639	168.12	160.2	0.001	86.7063	-34065.1	234.4778	-30709.5	80.2394	-0.0197	27542.4	128.133	1	5	-	-	-
623-91-6	Diethyl fumarate	-0.288	1.774	-1.486	0	0	7580.234	221.53	212.74	0.928	-166.9057	-60803.9	261.3256	-53223.7	76.1443	15.0383	13357.1	172.18	-	-	100	100	100
626-17-5	1,3-Dicyanobenzene	-0.522	0.936	0	-0.414	0	3369.307	168	160.02	4.688	86.6408	-34078.9	235.4901	-30709.6	78.4719	-17.6186	11323.3	128.133	-	8	-	-	-
629-62-9	n-Pentadecane	-3.766	3.766	0	0	0	15594.38	335.88	340.52	0.009	-89.2767	-68035.7	260.4334	-52441.3	106.597	-0.30545	10170.9	212.418	1000	1000	-	-	-
6362-80-7	4-Methyl-2, 4-diphenyl-1-pentene diglycidyl ether	-3.849	3.849	0	0	0	23306.85	298.12	345.22	6.626	317.2905	-79306.3	166.5527	-55999.4	202.507	-104.215	73696.4	236.356	-	45	180	180	180
638-16-4	1,3,5-triazine-2,4,6(1H,3H,5H)-trithione	-0.055	0.483	0	-0.680	0.252	-713.7331	185.09	181.88	3.487	51.1699	-32636.6	226.2952	-33350.3	94.2336	-405.135	40536.4	177.257	-	-	125	125	125
6448-95-9	C.I. Pigment Red 22	-3.088	3.724	-2.080	1.445	0	42534.97	412.79	501.5	5.152	138.3877	-156339.2	210.7421	-113804	269.704	137.214	90993.3	426.431	300	300	1000	1000	1000
6505-28-8	Pigment Orange 16	-3.902	6.061	-2.100	-0.060	0	57560.25	651.57	733.94	3.275	-58.3483	-224828.2	207.5423	-167268	381.514	-368.98	268735	620.663	1000	1000	1000	1000	1000
657-84-1	Sodium p-toluenesulfonate	-1.598	1.269	-3.186	0	2.514	10824.63	217.68	234.11	6.339	-290.9456	-57259.4	230.3046	-46434.7	76.6106	-37.2566	9260.02	194.18	1000	1000	1000	1000	1000
683-10-3	N-(Carboxymethyl)-N,N-dimethyl-1-dodecanaminium, inner monomethyl ether acetate	-4.253	4.903	-1.294	0.644	0	27340.93	367.06	392.25	14.247	-140.7351	-100134.2	238.1328	-72793.3	127.904	-68.6095	14351.9	271.442	10	10	300	60	60
6846-50-0	2,2,4-Trimethyl-1,3-pentanediol diisobutyrate	-2.389	3.847	-1.458	0	0	61621.87	321.58	395.23	3.292	-227.4594	-143157.2	253.1003	-81535.3	127.453	23.5959	12069.3	286.411	30	30	750	750	750
688-84-6	2-Ethylhexyl methacrylate	-2.077	2.817	-0.739	0	0	21223.17	267.26	284.87	2.454	-115.5110	-75411.0	243.3545	-54187.8	95.3936	-10.2496	9468.85	198.305	100	30	1000	300	100
691-37-2	4-Methyl-1-pentene homopolymer	-1.590	1.590	0	0	0	5199.888	148.06	139.72	0.310	-8.1845	-25866.0	232.864	-20666.1	44.1614	10.3938	1954.02	84.161	40	200	1000	1000	200
70-55-3	4-Methylbenzenesulfonamide	-1.628	1.639	-1.818	-0.586	2.392	7372.979	190	192.73	7.642	-67.0396	-51281.1	229.9207	-43908.1	83.813	-68.9203	12333.6	171.214	-	-	300	300	300
7299-99-2	Pentaerythritol tetra(2-ethylhexanoate)	-5.885	8.772	-2.887	0	0	184278.3	641.51	878.7	4.831	-484.0339	-363885.9	252.7517	-179608	294.967	34.946	28829.4	640.939	1000	1000	1000	1000	1000

Table 1. (Continued).

CAS No.	Chemical	Sum C	Sum H	Sum O	Sum N	Sum S	Core-Core Repulsion	COSMO Area	COSMO Volume	Dipole Moment	Heat of Formation	Electronic Energy	Ionization Potential	Total Energy	Alpha Average	Beta Average	Gamma Average	MW	Repeated-dose toxicity NOEL		Reproductive toxicity NOEL		Developmental toxicity NOEL
																			male	female	male	female	
75-50-3	Trimethylamine	-0.872	1.005	0	-0.133	0	2696.328	110.75	97.62	1.400	-13.0026	-17846.6	215.8833	-15150.3	28.2179	-25.2378	1365.61	59.111	40	40	200	200	200
7550-35-8	Lithium bromide	0	0	0	0	0	-3725.345	88.93	72.91	9.573	-63.5073	-4655.1	271.7462	-8380.44	3.97283	45.808	1652.57	86.844	5	5	5	5	80
75-59-2	Tetramethylammonium hydroxide	-2.826	2.472	-0.569	0.922	0	7310.877	147.96	144.43	6.200	-28.5865	-33358.6	181.1889	-26047.8	42.4307	-15.681	7693.31	91.153	-	5	-	-	-
75-66-1	2-Propanethiol, 2-methyl-	-1.079	1.274	0	0	-0.195	4030.921	134.58	131.61	2.605	-20.9860	-22827.9	221.6377	-18796.9	40.0229	-53.793	1524.7	90.183	-	10	200	200	50
7580-85-0	2-tert-Butoxyethanol No.7	-1.142	1.813	-0.671	0	0	9429.543	169.69	165.65	0.289	-112.0642	-44370.3	246.1791	-34940.7	50.1703	4.332	3080.82	118.175	4	4	100	100	100
760-23-6	3,4-Dichloro-1-butene	-0.918	1.125	0	0	0	588.1206	144.59	139.65	3.141	-8.4939	-28256.2	243.7733	-27668.1	45.9343	-29.4716	1764.42	124.997	2	10	50	50	50
7647-17-8	Cesium chloride	0	0	0	0	0	-1442.55	201.2	268.36	6.417	-168.8116	-6042.3	300.6367	-7484.89	0	0	0	168.358	-	10	-	-	-
76-83-5	Triphenylchloromethane	-3.140	3.249	0	0	0	35591.47	285.29	329.84	2.076	69.5774	-100104.0	225.3239	-64512.5	159.48	19.9224	16272.1	278.781	12	12	-	-	-
7756-94-7	Triisobutylene	-2.892	2.892	0	0	0	28767.06	229.31	262.74	0.425	-40.7503	-70123.7	227.0845	-41356.6	86.2544	-13.5985	6651.93	168.322	30	30	-	-	-
77-73-6	Dicyclopentadiene	-2.076	2.076	0	0	0	18827.27	165.55	173.2	0.214	41.2357	-50387.4	222.8216	-31560.1	66.7795	-11.8992	4202.27	132.205	-	20	100	20	20
77-85-0	1,1,1-Tris(hydroxymethyl) ethane	-0.668	1.819	-1.151	0	0	11962.01	151.35	153.74	3.993	-159.7404	-50239.2	250.5326	-38277.2	44.6717	13.3144	2045.59	120.148	300	300	1000	1000	1000
77-99-6	2-Ethyl-2-hydroxymethyl-1,3-propanediol	-0.953	2.057	-1.103	0	0	15604.67	166.2	175.32	2.219	-164.2637	-57329.4	252.1895	-41724.7	51.4855	-5.15822	2729.08	134.175	200	200	800	800	800
7803-57-8	Hydrazine monohydrate	0	0.830	-0.453	-0.378	0	-3875.015	99.45	72.92	1.931	-40.2397	-12513.6	210.1488	-16388.6	14.8918	-0.22225	353.244	50.06	3	3	18	6	2
78-42-2	Tris(2-ethylhexyl) phosphate	-5.366	5.916	-2.909	0	0	50387.89	535.77	609.26	1.688	-356.2569	-164159.5	245.9471	-113772	204.016	57.7967	23522.3	434.638	100	100	-	-	-
78-51-3	Tris(2-butoxyethyl) phosphate	-3.094	4.524	-3.842	0	0	42429.45	442.37	514.23	4.968	-421.2979	-155803.5	243.6658	-113374	174.671	37.6132	17320.1	398.476	100	100	-	-	-
78-67-1	2,2-AzRobis(2-methylpropionitrile)	-1.218	1.734	0	-0.516	0	12889.93	221.6	228.26	0.184	75.1190	-53934.7	235.4334	-41044.8	81.4607	0.80184	7175.87	164.21	-	2	50	10	10
78-97-7	2-Hydroxypropanenitrile	-0.274	0.852	-0.371	-0.207	0	-167.6278	111.29	95.42	5.369	-26.2614	-20313.4	267.1736	-20481	28.6853	5.08975	1597.13	71.079	6	6	30	30	30
79-27-6	Tetrabromoethane	-0.574	0.565	0	0	0	-1877.236	158.65	164.01	1.536	5.8203	-36921.0	243.2567	-38798.3	60.1227	-25.5182	3642.37	345.654	6	6	-	-	-
793-24-8	N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine	-3.748	3.755	0	-0.007	0	29392.48	330.07	366.79	0.662	15.3894	-94603.2	189.9035	-65210.7	169.251	28.4693	82587.2	268.401	4	4	100	100	100
79-39-0	Methacrylamide	-0.418	1.014	-0.520	-0.076	0	2219.235	128.66	116.92	4.725	-39.9748	-26157.5	227.9045	-23938.3	40.9821	17.5627	2815.49	85.105	30	-	50	50	50
79-94-7	4,4'-Isopropylidenebis(2,6-dibromophenol)	-1.956	2.376	-0.547	0	0	50566.54	301.03	383.37	2.878	-13.3918	-141949.3	214.8682	-91382.8	174.407	0.89823	14741.4	543.875	1000	1000	-	-	-
80-43-3	Dicmylperoxide	-3.316	3.625	-0.309	0	0	47934.61	304.9	361.05	0.407	9.7681	-118412.3	225.3246	-70477.6	149.425	9.01302	13722.8	270.371	60	60	-	-	-
80-51-3	4,4'-Oxybis(benzenesulfonylhydrazide)	-2.375	2.711	-3.795	-1.349	4.808	22528.87	339.23	374.02	6.428	-91.1157	-117643.1	216.4617	-95114.2	182.36	-134.137	69347.5	358.386	10	10	30	30	30
81-16-3	2-Amino-1-naphthalenesulfonic acid	-1.914	1.971	-2.531	-0.060	2.533	15655.94	216.72	231.64	5.451	-91.4480	-74527.8	201.3186	-58871.8	121.582	221.457	21058.5	223.246	200	200	1000	1000	1000
82-45-1	1-Aminoanthraquinone	-0.987	1.800	-0.777	-0.035	0	18828.66	232.65	250.44	2.715	-22.5127	-77546.3	205.8034	-58717.7	132.572	-251.331	39532.9	223.231	-	-	1000	-	-
824-78-2	p-Nitrophenol sodium salt	-1.015	0.872	-2.300	1.443	0	7182.009	200.63	208.39	16.326	-202.5742	-49182.5	205.1966	-42000.5	69.0611	486.631	32095.1	161.092	160	400	400	400	400
83-32-9	Acenaphthene	-1.856	1.856	0	0	0	14121.32	187.48	193.32	0.731	36.4480	-50450.8	202.5507	-36329.4	98.5131	-87.679	21094.9	154.211	12	12	-	-	-
839-90-7	1,3,5-Tris(2-hydroxyethyl)-1,3,5-triazine-2,4,6-(1H,3H,5H)-trione	0.025	2.558	-2.419	-0.164	0	28340.74	267.36	294	0.367	-275.1789	-110175.6	239.3395	-81834.8	109.315	107.611	15302.5	261.234	1000	1000	1000	1000	1000
840-65-3	Dimethyl 2,6-naphthalenedicarboxylate	-0.660	2.109	-1.448	0	0	19057.25	264.14	281.61	0.024	-133.5094	-88662.6	215.5224	-69605.4	134.172	1.00092	39853.4	244.246	1000	1000	1000	1000	1000
842-18-2	Potassium 7-hydroxy-1,3-naphthalenedisulfonate	-1.924	2.159	-5.398	0	5.163	14547.04	267.6	289.28	5.647	-273.4550	-100723.7	213.2035	-86176.7	141.633	-437.464	36294.9	304.289	300	100	-	-	-
84-51-5	2-Ethylanthraquinone	-1.428	2.201	-0.773	0	0	20095.53	257.5	276.8	2.711	-34.3870	-81609.9	229.0275	-61514.4	138.79	100.11	35147.2	236.27	-	10	-	-	-
85-41-6	Phthalimide hydrate	-0.122	1.111	-0.840	-0.149	0	7170.94	165.27	162.55	3.930	-53.4684	-48090.2	234.1439	-40919.3	78.1106	-90.7751	9575.64	147.133	1000	500	1000	250	250
86-87-3	1-Naphthylacetic acid	-1.321	2.017	-0.696	0	0	15851.53	216.11	224.62	2.151	-45.6643	-65726.7	208.1688	-49875.1	108.68	25.037	15690.2	186.21	25	25	-	-	-

Table 1. (Continued).

CAS No.	Chemical	Sum C	Sum H	Sum O	Sum N	Sum S	Core-Core Repulsion	COSMO Area	COSMO Volume	Dipole Moment	Heat of Formation	Electronic Energy	Ionization Potential	Total Energy	Alpha Average	Beta Average	Gamma Average	MW	Repeated-dose toxicity NOEL		Reproductive toxicity NOEL		Developmental toxicity NOEL
																			male	female	male	female	
868-77-9	2-Hydroxyethyl methacrylate	-0.379	1.506	-1.127	0	0	5439.966	175.09	166.18	4.101	-123.5859	-45709.7	241.8683	-40269.8	56.0264	-15.8403	7130.65	130.143	-	30	1000	1000	1000
87-59-2	2,3-Dimethylaniline	-1.523	1.574	0	-0.052	0	8791.726	165.52	164.23	1.565	1.1843	-38314.2	200.9946	-29522.5	72.2296	-54.7444	9952.45	121.182	12	-	-	-	-
87-62-7	2,6-Dimethylaniline	-1.497	1.556	0	-0.059	0	8686.853	165.28	163.08	1.627	1.1094	-38209.4	200.5828	-29522.5	71.9522	155.987	12326	121.182	10	10	250	50	50
87-84-3	Chloropentabromocyclohexane	-1.289	1.056	0	0	0	26663.39	219.66	269	2.971	-21.5562	-93300.4	232.6683	-66637	103.323	-178.215	11288.2	513.086	140	1000	-	-	-
88-18-6	2-tert-Butylphenol	-1.861	2.132	-0.271	0	0	17179.35	189.93	202.48	1.160	-42.4766	-56262.1	211.37	-39082.7	79.9841	40.6262	6514.48	150.22	20	20	-	-	-
88-19-7	o-Toluenesulfonamide	-1.637	1.651	-1.812	-0.582	2.380	9279.97	183.56	190.37	7.238	-62.2265	-53183.3	225.8971	-43903.3	82.6053	44.3345	6559.7	171.214	20	20	100	100	100
882-33-7	Diphenyl disulfide	-2.287	2.221	0	0	0.066	9386.834	242.35	258.18	4.272	60.6308	-54285.8	220.6999	-44898.9	143.536	-0.46312	95259.2	218.331	-	1	30	30	30
88-44-8	2-Amino-5-methylbenzenesulfonic acid	-1.555	1.606	-2.564	-0.060	2.572	8540.744	196.05	199.26	4.935	-121.2418	-59234.8	200.6663	-50694.1	90.4292	82.8175	7665.44	187.213	300	300	1000	1000	1000
88-53-9	2-Amino-5-chloro-4-methyl-benzenesulfonic acid	-1.511	1.476	-2.559	-0.048	2.581	8744.868	211.49	220.46	5.377	-127.2045	-66388.7	201.4485	-57643.9	100.713	46.4924	14610.3	221.658	1000	1000	-	-	-
88-60-8	6-tert-Butyl-m-cresol	-2.043	2.329	-0.286	0	0	19186.27	208.21	223.37	1.789	-55.0331	-61724.6	212.0035	-42538.3	88.8817	70.5979	11070.8	164.247	13	13	60	13	13
88-85-7	2-sec-Butyl-4,6-dinitrophenol	-1.853	1.883	-2.926	2.896	0	21287.12	247.76	267.21	5.272	-79.4760	-94122.0	229.8007	-72834.9	109.065	153.549	17136	240.215	-	-	2	2	2
88-89-1	2,4,6-Trinitrophenol	-1.033	0.866	-4.170	4.337	0	11185.26	211.76	215.33	1.895	-70.7635	-87097.1	244.115	-75911.8	92.3008	-108.433	21491.4	229.106	4	4	45	45	45
89-61-2	1,4-Dichloro-2-nitrobenzene	-1.075	0.742	-1.327	1.431	0	4128.109	181.75	182.15	5.963	-4.5944	-53414.4	219.114	-49286.3	80.8073	-22.5232	28285.8	192.001	-	-	200	20	60
89-72-5	o-sec-Butylphenol	-1.872	2.144	-0.272	0	0	16360.03	193.8	205.09	1.272	-44.4412	-55444.7	211.2444	-39084.7	79.9323	58.1393	6363.05	150.22	12	60	300	300	300
89-83-8	Thymol aluminium salt	-1.832	2.116	-0.284	0	0	14279.58	195.97	202.95	1.656	-52.3283	-53372.2	212.3598	-39092.6	81.7912	55.7181	10265.8	150.22	8	8	200	200	40
91-15-6	1,2-Dicyanobenzene	-0.552	0.922	0	-0.371	0	3976.072	165.28	160.09	7.876	88.6234	-34683.7	235.8434	-30707.6	77.4385	66.669	9501.52	128.133	6	1	30	6	6
91-76-9	2,4-Diamino-6-phenyl-s-triazine	-0.630	1.592	0	-0.961	0	10964.39	217.51	217.61	1.022	46.6910	-57460.3	218.0376	-46495.9	121.288	412.164	52829.2	187.204	4	4	100	4	20
923-26-2	2-Hydroxypropyl methacrylate	-0.692	1.805	-1.113	0	0	8237.37	195.15	190.08	3.544	-132.7692	-51959.3	243.5376	-43721.9	62.9171	-1.02619	7434.14	144.17	300	300	1000	1000	1000
92-88-6	4,4'-Biphenyldiol	-1.732	2.301	-0.569	0	0	11230.3	214.03	220.26	0.003	-50.6597	-61110.4	198.3305	-49880.1	116.724	-0.69716	94598.9	186.21	8	8	200	200	200
93-68-5	o-Acetoacetotoluidide	-1.367	2.246	-0.838	-0.040	0	14373.68	229.18	239.55	6.332	-74.7204	-66351.8	211.7614	-51978.1	101.859	112.845	22579.8	191.229	25	25	250	250	250
941-69-5	N-Phenylmaleimide	-0.859	1.661	-0.763	-0.039	0	11057.61	193.27	196.85	2.355	-23.9291	-58126.2	212.0807	-47068.6	94.3666	-156.026	19093	173.171	3	-	20	20	20
95-31-8	N-tert-butyl-2-benzothiazolesulfenamide	-2.380	2.217	0	-0.271	0.434	15842.26	262.29	285.75	1.135	31.5146	-66943.9	212.497	-51101.6	138.355	304.856	47335.5	238.365	-	40	200	200	200
95-32-9	2-(4-Morpholinyldithio) benzothiazole	-2.018	2.085	-0.292	-0.236	0.462	15023.17	284.73	310.61	2.710	16.8271	-76461.0	214.8297	-61437.8	171.799	473.608	76925	284.409	300	100	1000	1000	1000
95-33-0	N-Cyclohexyl-2-benzothiazolesulfenamide	-2.703	2.535	0	-0.269	0.438	18495.67	287.28	310.77	1.094	28.5058	-75779.2	213.4994	-57283.5	152.537	265.532	46094.3	264.403	80	80	-	-	-
95-50-1	o-Dichlorobenzene	-1.064	0.901	0	0	0	1977.886	153.66	150.17	1.898	9.6116	-34392.4	217.7731	-32414.5	64.073	-156.024	9981.01	147.004	20	20	-	-	-
95-57-8	2-Chlorophenol	-0.953	1.160	-0.277	0	0	3119.95	146.87	140.55	2.696	-31.3515	-35363.4	212.7271	-32243.5	59.7256	-170.949	9745.26	128.558	40	40	-	-	-
95-63-6	1,2,4-Trimethylbenzene	-1.725	1.725	0	0	0	9096.855	172.9	171.91	0.315	-5.3555	-37967.7	214.2915	-28870.8	71.2148	-2.83538	9034.9	120.194	100	100	-	-	-
95-64-7	3,4-Dimethylaniline	-1.520	1.572	0	-0.052	0	8235.141	167.37	164.86	1.391	-0.3751	-37759.2	199.1814	-29524	73.2986	169.588	15457.6	121.182	10	10	-	-	-
95-73-8	2,4-Dichloro-1-methylbenzene	-1.223	1.097	0	0	0	3652.63	172.64	172.09	1.473	0.1518	-39519.6	215.7657	-35867	73.845	-104.9	16859.3	161.03	-	-	79	79	79
96-29-7	Ethyl methyl ketoxime	-0.874	1.323	-0.310	-0.139	0	2622.619	132.87	121.18	1.453	-18.8873	-27246.4	237.1643	-24623.8	41.1532	2.19171	1180.17	87.121	4	4	100	30	100
96-45-7	2-Imidazolidinethione	-0.654	1.063	0	0.055	-0.464	1846.464	131.86	120.94	9.065	11.6947	-23955.7	218.4308	-22109.3	52.2088	-206.61	-2148.1	102.154	1	1	-	-	-
96-69-5	4,4'-Thiobis(6-tert-butyl-m-cresol)	-3.981	4.406	-0.555	0	0.130	52921.71	365.46	457.79	4.786	-97.1568	-141575.1	204.4124	-88653.4	200.132	7.04127	43832.9	358.538	15	15	-	-	-
96-76-4	2,4-Di-tert-butylphenol	-2.668	2.939	-0.271	0	0	30363.62	252.54	288.35	1.242	-65.6615	-83241.5	208.1748	-52877.9	109.803	38.8728	8739.86	206.327	75	20	-	-	-
97-39-2	1,3-Bis(2-methylphenyl) guanidine	-2.663	2.972	0	-0.309	0	20942.99	282.18	301.86	4.152	51.8045	-79182.3	203.9627	-58239.3	149.822	173.919	53605.3	239.319	15	8	50	50	20

Table 1. (Continued).

CAS No.	Chemical	Sum C	Sum H	Sum O	Sum N	Sum S	Core-Core Repulsion	COSMO Area	COSMO Volume	Dipole Moment	Heat of Formation	Electronic Energy	Ionization Potential	Total Energy	Alpha Average	Beta Average	Gamma Average	MW	Repeated-dose toxicity NOEL		Reproductive toxicity NOEL		Developmental toxicity NOEL
																			male	female	male	female	
97-52-9	4-Nitro-o-anisidine	-1.148	1.291	-1.572	1.430	0	8999.581	189.89	188.2	7.045	-38.5268	-58708.1	204.4633	-49708.5	88.7992	461.598	40968	168.152	30	30	200	200	40
97-88-1	Butyl methacrylate	-1.142	1.881	-0.739	0	0	9661.939	203.61	200.21	2.277	-96.3012	-50058.6	243.307	-40396.7	66.0445	-11.5941	6205.19	142.197	30	300	1000	300	1000
97-99-4	Tetrahydrofurfuryl alcohol	-0.773	1.455	-0.682	0	0	7183.75	139.96	132.22	2.848	-102.8350	-37965.1	243.9017	-30781.4	40.4442	-25.9622	1723.36	102.133	40	40	150	50	50
98-51-1	p-tert-Butyltoluene	-2.231	2.231	0	0	0	16314.39	202.1	213.59	0.092	-10.5607	-52076.4	217.3587	-35762	83.9326	-51.7549	10495.8	148.247	2	5	5	5	2
98-54-4	p-tert-Butylphenol	-1.865	2.152	-0.287	0	0	14986.19	194.23	205.08	1.609	-47.5435	-54074.0	211.263	-39087.8	80.4192	-89.0869	9522.37	150.22	60	60	60	60	200
98-83-9	1-Methylethenylbenzene	-1.790	1.790	0	0	0	7489.826	165.72	162.83	0.206	29.4343	-35618.7	212.44	-28128.9	73.2166	-11.3543	18348.3	118.178	40	40	1000	200	200
99-71-8	4-(1-Methylpropyl)phenol	-1.884	2.172	-0.288	0	0	14258.57	197.54	207.06	1.600	-48.8329	-53347.7	210.7735	-39089.1	80.5016	-72.0653	9687.7	150.22	100	100	-	-	-
99-88-7	4-(1-Methylethyl)aniline	-1.806	1.858	0	-0.051	0	10893.69	185.38	188.19	1.433	-0.9290	-43861.2	200.2648	-32967.6	79.1518	228.764	18827.4	135.208	6	6	60	60	20
99-94-5	4-Methylbenzoic acid	-0.714	1.561	-0.847	0	0	6402.783	169.72	166.21	3.383	-82.0490	-44663.8	227.8503	-38261	70.8625	219.615	19828.3	136.15	300	300	100	100	1000
99-96-7	4-Hydroxybenzoic	-0.347	1.478	-1.131	0	0	4969.953	160.93	155.93	2.620	-120.8696	-46558.6	220.494	-41588.6	67.7967	298.326	21741.7	138.123	40	40	1000	1000	1000

CAS No.; Chemical Abstract Service number.

tion was performed and then molecular-orbital descriptors were calculated using the PM3 Hamiltonian of a semi-empirical MO package (MOPAC2002). The calculated descriptors (listed in Table 1) are: Sum of charges of carbon, hydrogen, oxygen, nitrogen, sulphur (Sum C, Sum H, Sum O, Sum N, Sum S), core-core repulsion, COSMO area, COSMO volume, dipole moment, heat of formation, electronic energy, ionization potential, total energy, average of polarizability α, β, γ (alpha, beta, gamma average), and molecular weight (MW).

These descriptors were grouped by correlation coefficient (*r* value; results for the repeated-dose toxicity model are shown in Table 2 as an example), and independent descriptors showing a statistically significant correlation with NOEL (Tables 3-5) were chosen to be used as the input layer for further analysis.

Artificial neural network (ANN) analysis

Calculated molecular descriptors and *in-vivo*-determined NOELs obtained from the database were correlated using an artificial neural network. A typical ANN consists of an input layer, a hidden layer, and an output layer, as previously reported (Hirota *et al.,* 2013; Fig. 1). In this study, two hidden layers were used for repeated-dose toxicity and reproductive toxicity, while a single hidden layer was used for developmental toxicity. *In-vivo*-determined NOEL was the output layer, and the descriptors used for the input layer were correlated with it using the neural network. All calculations were performed using QwikNet Ver.2.23. In ANN learning, an online back-propagation algorithm was used for network training, with values of the learning rate and momentum parameter of 0.02 and 0.7, respectively. The range of weights was set to be -6 to 6 (weight perturbation; 50%).

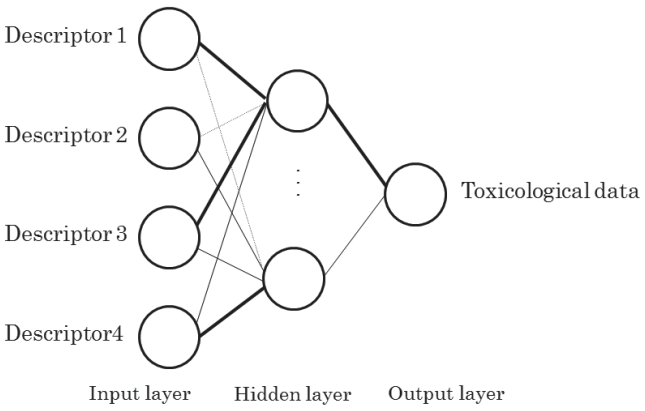

Fig. 1. Schematic representation of a 3-layered neural network.

Ten-fold cross-validation

The predictive ability of the neural network model was evaluated by means of the 10-fold cross-validation method (Pasomsub *et al.,* 2010; Hirota *et al.,* 2013). This method systematically removed data successively from the training set. A network model was then constructed on the basis of this reduced data set and used to predict the removed data. This procedure was repeated for all data so that a complete set of predicted values was obtained. The goodness-of-fit was evaluated in terms of root-mean-square (RMS) error, defined as follows:

$$\text{RMS error} = \sqrt{\sum((\text{measured value} - \text{predicted value})^2) / \text{number of data}}$$

Statistical Analysis

The correlation coefficient (*r* value) was determined by the use of Pearson's correlation statistics. Multiple linear regression analysis using the forward selection method was performed by Excel Statistics 2004 software (Social Survey Research Information, Tokyo, Japan).

RESULTS

Construction and evaluation of repeated-dose toxicity model

In ANN analysis, the choice of descriptors is very important for acquiring a good-quality model. The use of a large number of descriptors to construct the model improves the predictive performance for the training data, but may impair the predictive performance for test compounds because of the increasing vulnerability of the model. Therefore, descriptors having high similarity were classified into groups, and descriptors that showed statistically significant correlations with NOEL in independent groups were chosen for the input layer of ANN analysis. Table 2 shows the simple correlation coefficients between molecular orbital (MO)-calculated descriptors. Correlation coefficients of less than -0.7 or more than 0.7 are highlighted; these are considered to be high correlations. Then, the correlation between NOEL and the selected MO-calculated descriptors (Table 3A) or the square of the descriptors (Table 3B) was confirmed. Finally, six descriptors (Sum H, Sum N, total energy, heat of formation, gamma average, and ionization potential) belonging to different groups were found to be significant correlated with NOEL, and were selected for use as the input layer of the model.

Because some chemicals have different NOEL for males and females, we used an additional descriptor with values of 0 for males and 1 for females. A preliminary

Table 2. Correlation coefficient between MO-calculated descriptors in repeated-dose toxicity model.

	Sum C	Sum H	COSMO Volume	COSMO Area	Alpha Average	Electronic Energy	Total Energy	MW	Core-Core Repulsion	Heat of Formation	Sum O	Gamma Average	Sum Cl	Ionization Potential	Dipole Moment	Beta Average	Sum S	Sum N
Sum C	**1.000**	**-0.877**	**-0.865**	**-0.855**	**-0.786**	**0.767**	**0.749**	**-0.745**	**-0.709**	0.197	0.084	-0.328	-0.297	0.216	-0.124	0.071	-0.022	0.012
Sum H	**-0.877**	**1.000**	**0.936**	**0.931**	**0.837**	**-0.868**	**-0.853**	**0.791**	**0.798**	-0.324	-0.169	0.350	-0.016	-0.096	0.123	-0.059	-0.060	-0.091
COSMO Volume	**-0.865**	**0.936**	**1.000**	**0.984**	**0.931**	**-0.939**	**-0.958**	**0.932**	**0.826**	-0.409	-0.329	0.466	0.106	-0.111	0.242	-0.003	0.065	-0.034
COSMO Area	**-0.855**	**0.931**	**0.984**	**1.000**	**0.911**	**-0.874**	**-0.934**	**0.901**	**0.724**	-0.415	-0.327	0.481	0.088	-0.094	0.224	-0.005	0.069	-0.030
Alpha Average	**-0.786**	**0.837**	**0.931**	**0.911**	**1.000**	**-0.898**	**-0.928**	**0.915**	**0.777**	-0.203	-0.307	0.669	0.070	-0.326	0.235	0.082	0.130	-0.043
Electronic Energy	**0.767**	**-0.868**	**-0.939**	**-0.874**	**-0.898**	**1.000**	**0.955**	**-0.914**	**-0.949**	0.404	0.379	-0.419	-0.120	0.119	-0.258	-0.011	-0.085	-0.005
Total Energy	**0.749**	**-0.853**	**-0.958**	**-0.934**	**-0.928**	**0.955**	**1.000**	**-0.953**	**-0.812**	0.480	0.500	-0.505	-0.122	0.110	-0.301	-0.025	-0.184	-0.059
MW	**-0.745**	**0.791**	**0.932**	**0.901**	**0.915**	**-0.914**	**-0.953**	**1.000**	**0.783**	-0.375	-0.388	0.499	0.138	-0.128	0.278	0.010	0.159	0.005
Core-Core Repulsion	**-0.709**	**0.798**	**0.826**	**0.724**	**0.777**	**-0.949**	**-0.812**	**0.783**	**1.000**	-0.283	-0.213	0.287	0.106	-0.117	0.186	-0.006	-0.029	-0.053
Heat of Formation	0.197	-0.324	-0.409	-0.415	-0.203	0.404	0.480	-0.375	-0.283	**1.000**	**0.743**	0.091	-0.115	-0.300	-0.419	0.013	-0.333	-0.040
Sum O	0.084	-0.169	-0.329	-0.327	-0.307	0.379	0.500	-0.388	-0.213	**0.743**	**1.000**	-0.177	0.030	-0.039	-0.509	-0.050	-0.697	-0.301
Gamma Average	-0.328	0.350	0.466	0.481	0.669	-0.419	-0.505	0.499	0.287	0.091	-0.177	**1.000**	-0.013	-0.372	0.136	0.033	0.141	-0.012
Sum Cl	-0.297	-0.016	0.106	0.088	0.070	-0.120	-0.122	0.138	0.106	-0.115	0.030	-0.013	**1.000**	-0.009	-0.010	-0.006	-0.024	0.003
Ionization Potential	0.216	-0.096	-0.111	-0.094	-0.326	0.119	0.110	-0.128	-0.117	-0.300	-0.039	-0.372	-0.009	**1.000**	-0.057	-0.103	-0.167	0.079
Dipole Moment	-0.124	0.123	0.242	0.224	0.235	-0.258	-0.301	0.278	0.186	-0.419	-0.509	0.136	-0.010	-0.057	**1.000**	0.151	0.374	0.189
Beta Average	0.071	-0.059	-0.003	-0.005	0.082	-0.011	-0.025	0.010	-0.006	0.013	-0.050	0.033	-0.006	-0.103	0.151	**1.000**	-0.016	0.067
Sum S	-0.022	-0.060	0.065	0.069	0.130	-0.085	-0.184	0.159	-0.029	-0.333	-0.697	0.141	-0.024	-0.167	0.374	-0.016	**1.000**	-0.012
Sum N	0.012	-0.091	-0.034	-0.030	-0.043	-0.005	-0.059	0.005	-0.053	-0.040	-0.301	-0.012	0.003	0.079	0.189	0.067	-0.012	**1.000**

Correlation coefficients of less than -0.7 or more than 0.7 are highlighted.

Table 3. Correlation coefficient between repeated-dose toxicity NOEL and MO-calculated descriptors (A) and square of MO-calculated descriptors (B).

Correlation coefficient	Sum C	Sum H	Sum O	Sum N	Sum S	Core-Core Repulsion	COSMO Area	COSMO Volume	Dipole Moment	Electronic Energy	Heat of Formation	Ionization Potential	MW	Alpha Average	Beta Average	Gamma Average	Total Energy	Log NOEL
A. Log NOEL	-0.126	0.237	-0.388	-0.061	0.233	0.199	0.301	0.288	0.065	-0.293	-0.461	0.121	0.308	0.241	0.035	0.117	-0.353	1.000
	**	**	**		**	**	**	**		**	**	*	**	**		*	**	
B. Log NOEL	0.163	0.232	0.276	-0.104	0.184	0.152	0.284	0.266	0.023	0.219	0.330	0.123	0.290	0.237	0.047	0.138	0.309	1.000
	**	**	**	*	**	**	**	**		**	**	*	**	**		**	**	

*; $p < 0.05$, **; $p < 0.01$

Table 4. Correlation coefficient between reproductive toxicity NOEL and MO-calculated descriptors.

Correlation coefficient	Sum C	Sum H	Sum O	Sum N	Sum S	Core-Core Repulsion	COSMO Area	COSMO Volume	Dipole Moment	Electronic Energy	Heat of Formation	Ionization Potential	MW	Alpha Average	Beta Average	Gamma Average	Total Energy	Log NOEL
Log NOEL	-0.090	0.230	-0.212	-0.173	0.089	0.180	0.230	0.224	0.027	-0.225	-0.357	0.150	0.213	0.176	0.014	0.076	-0.245	1.000
		**	**	**		**	**	**		**	**	**	**	**			**	

*; $p < 0.05$, **; $p < 0.01$

Table 5. Correlation coefficient between developmental toxicity NOEL and MO-calculated descriptors.

Correlation coefficient	Sum C	Sum H	Sum O	Sum N	Sum S	Core-Core Repulsion	COSMO Area	COSMO Volume	Dipole Moment	Electronic Energy	Heat of Formation	Ionization Potential	MW	Alpha Average	Beta Average	Gamma Average	Total Energy	Log NOEL
Log NOEL	-0.080	0.252	-0.267	-0.197	0.086	0.212	0.273	0.268	0.069	-0.270	-0.439	0.181	0.261	0.208	0.009	0.089	-0.295	1.000
		**	**	*		**	**	**		**	**	*	**	**			**	

*; $p < 0.05$, **; $p < 0.01$

study indicated that the ANN model with a configuration of 7-5-2-1 was optimal in terms of RMS error.

Fig. 2A shows the relationship between observed and calculated NOEL obtained by ANN analysis. The RMS error obtained for the model was 0.507. The model was then used to predict NOEL for several unknown compounds using a 10-fold cross validation procedure (Fig. 2B). The predictive RMS error for the 10-fold cross validation analysis was 0.529.

The accuracy of the predictions is shown in Table 6. 186 (44.2%) of the predicted NOELs, obtained in 10-fold cross validation, were within a factor of 2 of the *in-vivo*-determined NOELs, while over 94% of the chemicals were within a factor of 10. All chemicals were within a factor of 50 of the *in-vivo*-determined NOELs.

Construction and evaluation of reproductive toxicity model

For the reproductive toxicity model, four descriptors (Sum N, total energy, heat of formation, and ionization potential) were selected for the input layer in the same manner as described for the previous model. The correlation between NOEL and MO-calculated descriptors is shown in Table 4. Again, an additional descriptor was employed to distinguish NOELs for males and females. Here, the configuration of the ANN model was 5-5-2-1.

The RMS error obtained for the model was 0.474 (Fig. 3A) and that for the 10-fold cross-validation anal-

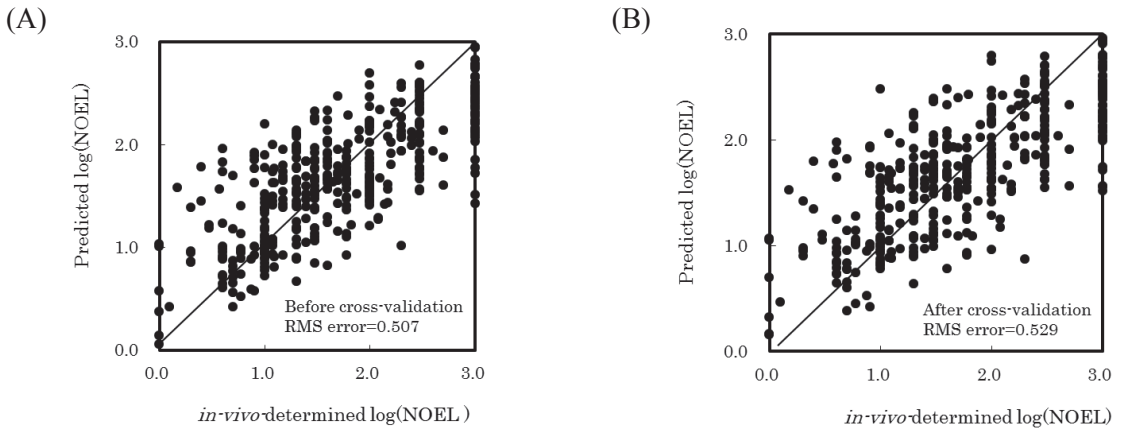

Fig. 2. Correlation between predicted and *in-vivo*-determined NOEL of repeated-dose toxicity based on MO-descriptors of the dataset of 421 chemicals. (A) Correlation before 10-fold cross validation; (B) After 10-fold cross validation. 6 descriptors selected were used as the input layer and *in-vivo*-determined NOEL were used as the output layer. The RMS errors of the ANN prediction model were 0.507 (before 10-fold cross validation; (A)) and 0.529 (after 10-fold cross validation; (B)).

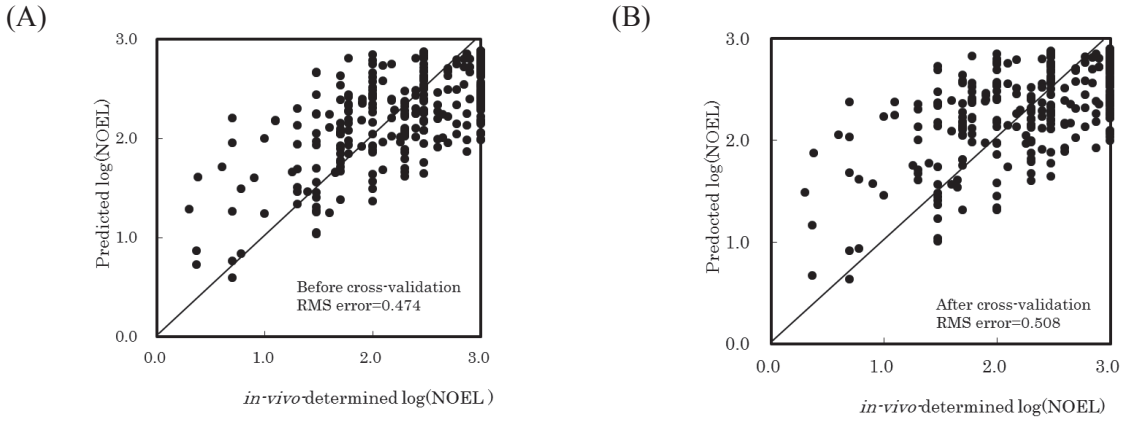

Fig. 3. Correlation between predicted and *in-vivo*-determined NOEL of reproductive toxicity based on MO-descriptors of the dataset of 315 chemicals. (A) Correlation before 10-fold cross validation; (B) After 10-fold cross validation. 4 descriptors selected were used as the input layer and *in-vivo*-determined NOEL were used as the output layer. The RMS errors of the ANN prediction model were 0.474 (before 10-fold cross validation; (A)) and 0.508 (afte r10-fold cross validation; (B)).

ysis was 0.508 (Fig. 3B). As regards accuracy, 144 (45.7%) of the predicted NOELs were within a factor of 2 of the *in-vivo*-determined NOELs, while over 95% of the chemicals were within a factor of 10. All chemicals were within a factor of 50 of the *in-vivo*-determined NOELs (Table 6).

Construction and evaluation of developmental toxicity model

For the developmental toxicity model, we selected the same four molecular descriptors (Sum N, total energy, heat formation, and ionization potential) as used in the reproductive toxicity model. The correlation between NOEL and the MO-calculated descriptors is shown in Table 5. The configuration of the ANN model was set as 4-4-1.

The RMS error obtained for the model was 0.473 (Fig. 4A) and that for the 10-fold cross-validation analysis was 0.558 (Fig. 4B). As regards accuracy, 58 (37.7%) of the predicted NOELs were within a factor of 2 of the *in-vivo*-determined NOELs, while over 94% of the chemicals were within a factor of 10 (Table 6).

DISCUSSION

The aim of the present study was to develop an *in silico* system to predict NOEL values for repeated-dose, developmental, and reproductive toxicities by using the combination of MO calculation and an ANN system. Two commercial packages, TOPKAT (Accelrys) and MolCode Toolboxes (MolCode, Ltd.), are available for predicting LOAELs, but they cannot predict NOELs, which are required for calculation of margin of safety values according to the recommendation of the Scientific Committee on Consumer Safety. Our models are the only ones so far reported that are able to predict NOEL values.

TOPKAT is the most widely used commercial QSAR software package for making quantitative toxicity predictions, and its usefulness has been examined in several studies (Lapenna *et al.,* 2010; Worth *et al.,* 2014).

Table 6. Accuracy of the three models for the prediction of NOEL.

	Number (%) of chemicals for which predicted NOELs were compared to *in-vivo*-determined NOELs					
	Factor [a)]					
	2	5	10	50	100	Total
Model						
Repeated-dose toxicity	186 (44.2)	157 (37.3)	54 (12.8)	24 (5.7)	0 (0.0)	421
Reproductive toxicity	144 (45.7)	123 (39.0)	34 (10.8)	14 (4.4)	0 (0.0)	315
Developmental toxicity	58 (37.2)	69 (44.2)	21 (13.5)	6 (3.8)	2 (1.3)	156

[a)] Factor means a range of 1/2 to 2 times, 1/5 to 5 times, 1/10 to 10 times, 1/50 to 50 times and 1/100 to 100 times.

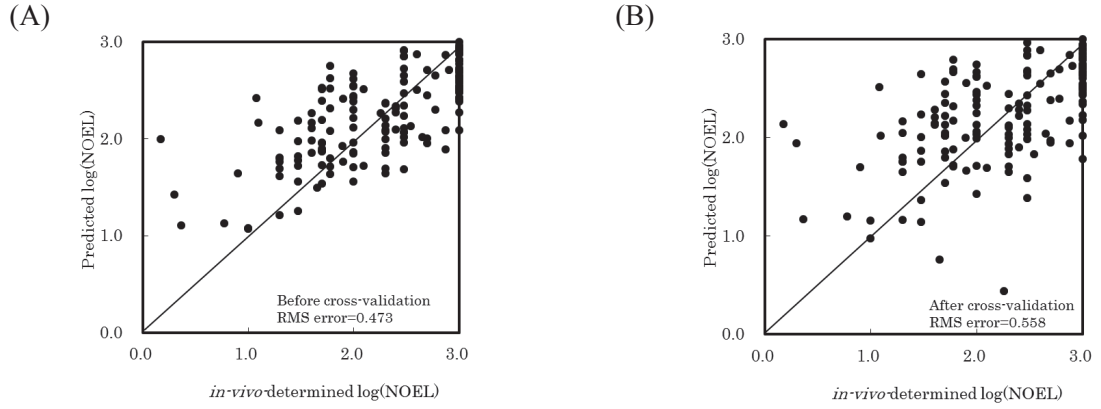

Fig. 4. Correlation between predicted and *in-vivo*-determined NOEL of developmental toxicity based on MO-descriptors of the dataset of 156 chemicals. (A) Correlation before 10-fold cross validation; (B) After 10-fold cross validation. 4 descriptors selected were used as the input layer and *in-vivo*-determined NOEL were used as the output layer. The RMS errors of the ANN prediction model were 0.473 (before 10-fold cross validation; (A)) and 0.558 (after 10-fold cross validation; (B)).

External validation is desirable to estimate the true predictive power of a QSAR model (Kubinyi *et al.,* 1998; Veerasamy *et al.,* 2011), and this was done by Venkatapathy *et al.* (2004) using a set of 160 chemicals that were not present in TOPKAT's database, collected from the U.S. EPA's Office of Pesticide Programs (OPP). The percentage of LOAELs predicted accurately to within factors of 2, 5, and 10 of the experimental values were 34, 57, and 72%, respectively and similar statistics were obtained for another set of chemicals from a different database. In the present study, we used 10-fold cross-validations to test the model, and the percentages of repeated-dose toxicity NOELs predicted accurately to within factors of 2, 5, and 10 of the experimental values were 44.2, 81.5, and 94.2%, respectively. Similar results were obtained with our reproductive toxicity and developmental toxicity models (Table 6). Since our validation method was different from that used the study in Venkatapathy *et al.* (2004) direct comparison is not appropriate, but our models appear to offer superior predictive accuracy.

It is important to note that if certain one- or two-atom fragments are missing in TOPKAT's LOAEL model substructural library for any given chemical, or if the fragments are not adequately covered by the chemicals in the model database, TOPKAT issues a warning stating that a prediction cannot be made or may be unreliable. In one of the studies by Venkatapathy *et al.* (2004),TOPKAT was unable to predict LOAEL of 134 (39%) out of 343 tested chemicals, while 53 (18%) out of 287 tested chemicals were unpredictable in the study by Tilaoui *et al.* (2007) On the other hand, our models were able to achieve similar or superior accuracy without "removing" any test chemical. Overall, our present results indicate that our models can predict NOELs of a wide range of chemicals with reasonable accuracy and high robustness.

We extracted six molecular descriptors (Sum H, Sum N, total energy, heat of formation, gamma average, and ionization potential) for the repeated-dose toxicity model and four (Sum N, total energy, heat of formation, and ionization potential) for the developmental and reproductive toxicity models. Although pathways of toxicity are complex, and the contribution of each descriptor is unclear, at least a qualitative discussion is possible. For example, liposolubility and stability are important physicochemical properties of chemicals. Liposolubility is influenced by polarizability, molecular volume and hydrogen-bonding property. Therefore, sum H, sum N, and ionization potential, which are relevant to hydrogen-bonding property, are expected to be available as descriptors of liposolubility. In turn, liposolubility influences intestinal absorption, binding affinity to proteins and receptors, and histological distribution and accumulation in general. Therefore, descriptors of liposolubility should provide information relevant to these biological processes. Further, ionization potential, heat of formation, and total energy are indicators of molecular energy, which would determine molecular stability, and this in turn would be related to metabolic degradation. Sum H, sum N and ionization potential are also related to electronegativity, and therefore to reactivity in nucleophilic and electrophilic reactions. In other words, the descriptors extracted in this study seem relevant to biological reactions that are expected to have central roles in the mechanisms and pathways of toxicity (Fig. 5).

One of the reasons for the limited success so far in developing QSAR for systemic toxicity is the lack of promising datasets that can be used to train QSAR models, as reviewed elsewhere (Piparo and Worth, 2010; Lapenna *et al.,* 2010). Since the performance of a QSAR model depends on the numerical values of the NOELs used in training the model (Leonard and Roy, 2006), training of a QSAR model for assessing the toxicity of cosmetic ingredients should ideally be done with the aid of datasets of potential or actual cosmetic ingredients (e.g. chemicals from the International Nomenclature of Cosmetic Ingredients (INCI) list). Since toxicological data for such chemicals are quite limited, all the datasets available in the JECDB were included in this study. However, among the 245 chemicals included in this study, 50 chemicals were listed in INCI. When comparison analysis was conducted with only these 50 chemicals, the percentage of repeated-dose toxicity NOELs predicted to within factors of 2, 5, and 10 of the experimental values were 33.3, 77.0, and 96.5%, respectively (Table 7). The predictions for chemicals listed in INCI compared well with those for all chemicals from JECDB (Table 6), and thus we consider that the present models are applicable to a broad range of chemicals, including cosmetic ingredients.

Another important issue is that NOELs for developmental toxicity collected in this study were obtained from toxicity tests in which observation was conducted only from the day of birth up to the 4th day. Therefore, toxicities that may appear before or after this period, which includes teratogenicity, cannot be assessed in our model. Needless to say, improvements are needed in the systemic toxicity database.

We consider that our present findings represent a proof-of-concept for prediction of NOEL of chemicals using QSAR models. This is a major step towards calculation of margin of safety values. Further, when limited data are available to estimate the toxicity of a chemical of interest, it would enable us to read across from corresponding data for suitable analogues. However, it is important

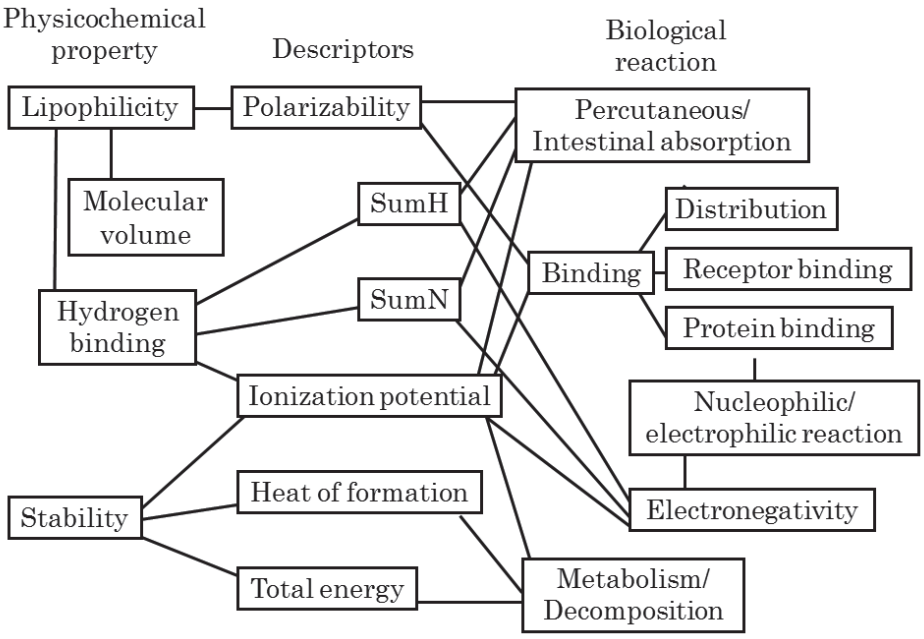

Fig. 5. Relationships between selected descriptors and toxicity-related processes.

Table 7. Accuracy of the three models for the prediction of NOEL for the subset of chemicals included in the INCI list.

	Number (%) of INCI-listed chemicals for which predicted NOELs were compared to the *in-vivo*-determined NOELs					
	Factor [a)]					
	2	5	10	50	100	Total
Model						
Repeated-dose toxicity	29 (33.3)	38 (43.7)	17 (19.5)	3 (3.4)	0 (0.0)	87
Reproductive toxicity	44 (53.7)	31 (37.8)	5 (6.1)	2 (2.4)	0 (0.0)	82
Developmental toxicity	19 (46.3)	17 (41.5)	4 (9.8)	1 (2.4)	0 (0.0)	41

[a)] Factor means a range of 1/2 to 2 times, 1/5 to 5 times, 1/10 to 10 times, 1/50 to 50 times and 1/100 to 100 times.

to realize that toxicity occurs through multiple complex mechanisms, so QSAR predictions cannot entirely replace experiments. The most promising predictive methodology may be a weight of evidence approach, combining *in silico* analysis with *in vitro* methods.

Conflict of interest---- The authors declare that there is no conflict of interest.

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