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QSAR modeling using a set of intermediate-duration oral NOELs

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QSAR modeling using a set of intermediate-duration oral NOELs

By Takahiro Goto

Purpose

The purpose of the project is to investigate the utility of data collected at the National Institute of Health Science in Japan for quantitative structure-activity relationship (QSAR) modeling. The hypothesis being tested is that a linear relationship exists between a chemical compound's structural and physicochemical characteristics and its no observed effect level (NOEL).

Methods

The data that was used included a set of intermediate–duration oral NOELs that are publicly accessible on the website of the National Institute of Health Science in Japan (http://www.nihs.go.jp/index-j.html). The software, Leadscope Predictive Data Miner, was used to build an associative model and to analyze the correlation between observed NOELs and calculated NOELs.

Results

The results showed that Leadscope PDM selected 117 structural characteristics (e.g., sulfonate, 1-hydoroxynaphthalen, 3-hydroxy-1-benzensulfonate, etc.) and 7 physicochemical characteristics (e.g., hydrogen bond acceptors, polar surface area, ALogP, etc.) for 218 compounds that were entered into the software. An associative model with one latent descriptor, called a PLS factor, was then developed. The Leadscope PDM program provided visualization of the correlation between observed NOELs and calculated NOELs. The R^2 was 0.35, and cross-validated R^2 was 0.21.

Conclusions

Overall, this analysis provided little evidence for utility of the data. This was because the hypothesis could not be proven with the available data and model. This project did demonstrate a good example of QSAR modeling using NOELs and Leadscope software as evidenced by the results of this study. It is anticipated that this project will facilitate further QSAR studies in the near future utilizing the data already generated.

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Table of Contents

1. INTRODUCTION

Quantitative structure-activity relationship (QSAR) is a regression of the biological activity of chemical compounds on their structural and physicochemical characteristics. Although the predictive value of the outcome is not always accurate, QSAR is a powerful method because it investigates the biological activities of large numbers of chemical compounds quickly and cost-effectively in the absence of experimental toxicological data. There are many examples of QSAR applications in public health when this method demonstrates a desired forecasting effect [1-3]. QSAR is a cross-chemical extrapolation at a level higher than Benchmark dose (BMD) modeling, chemical-specific adjustment factor (CSAF) modeling, or physiologically based pharmacokinetic (PBPK) modeling. QSAR relies on much smaller amounts of initial information than required by the other methods and, as such, it can be applied to a much larger number of substances needing health guidance values (HGVs) than BMD, CSAF, or PBPK methods can do [4].

Accuracy of toxicological QSARs has been investigated by a number of authors. For example, Rupp et al. have reported on the comparison between experimentally observed no observed adverse effect levels (NOAELs) in repetitive dose animal studies and predicted lowest observed adverse effect levels (LOAELs) obtained using TOPKAT 6.2

version 3.1 [5]. Venkatapathy et al. reported a correlation between observed LOAELs and calculated LOAELs using TOPKAT [6] and a correlation between observed tumor dose (TD_{50} - , the dose that induces tumors in half of the test animals at the end of a standard life span) and calculated the lethal dose (LD_{50} - , the dose that kills 50% of a study population [7]. Mazzatorta et al. compared oral rat chronic LOAELs with calculated LOAELs that were obtained with an in-house developed procedure that relied on partial least squares (PLS) regression. A genetic-algorithm variable selection was used as implemented in Statistics Toolbox 5.0.1 of MATLAB 7.0.1 [8]. Mombelli analyzed the predictive performance of irritant chemical compounds in three kinds of commercially available software (DEREK, HAZARDEXPERT, and TOPKAT). His conclusion was that only TOPKAT was predictive with regard to the chemicals studied [9].

When the Chemical Substances Control Law (CSCL) took effect in Japan in 1972, approximately 20,000 chemicals had already been in use, manufactured, or imported by Japanese industry in large amounts. These chemicals are called the “Existing Chemicals,” with the Japanese government being tasked by law to collect toxicological information about these substances. The data for these studied have been obtained from

animal studies. They include single dose oral toxicity study, 28-day repeated oral dose toxicity study, repeated dose and reproductive/developmental toxicity study, simple oral administration reproductive toxicity study, one-generation reproduction toxicity, and 90-day repeated dose toxicity study. Chemical compounds that emerged in Japan after the law took effect in 1972 are labeled "New Chemicals," and manufacturers and importers are required to submit data to the Japanese government about the safety of these New Chemicals. These data include toxicology, degradability, bioaccumulation, and ecological effects. The Japanese government is responsible for safety information about Existing Chemicals. Presently, only a small percent of all target Existing Chemical compounds have appropriate toxicological data due to the cost and time-consuming nature of animal experiments.

Although QSAR has not been able to completely replace the role of animal experiments (although the EU REACH legislation anticipates this), it is useful to estimate a compound's toxicity using QSAR because little time and input of information is required to provide results that are comparable with results of animal experiments. One of the useful ways to utilize QSAR is to compare the observed results in animal experiments with calculated results that QSAR generates. If the results of QSAR studies and animal

studies are comparable, the outcome of one confirms the findings of the other. Additionally, QSAR can be applicable to some compounds that do not need testing because of their low toxicity.

The hypothesis being tested is that a linear relationship exists between a chemical compound's structural and physicochemical characteristics and its no observed effect level (NOEL). The relationship between experimental and calculated NOELs is believed to be linear.

The aim of the current project is to investigate the utility of data collected at the National Institute of Health Science (NIHS) in Japan for QSAR modeling. To achieve this aim, an associative QSAR model was developed based on a set of intermediate-duration oral NOEL using the commercially available software, Leadscope Predictive Data Miner (PDM) (Leadscope Inc., Columbus, USA). Only 21 applicable publications were found using the term "Leadscope" in a search of PubMed (US National Library of Medicine, National Institutes of Health as of February 16th, 2013). The 21 publications included ones written by Arvidson [10], Cross et al. [11], Roberts et al. [12], Blower et al. [13-16], and Yang et al. [17-18]. This project, using PDM and NOELs, is expected to bring a

new aspect to QSAR modeling by providing a workable model.

2. METHODS

(1) Data Collection and Processing

The data used are a set of intermediate-duration oral NOELs that are publicly accessible on the website of the NIHS in Japan [19]. The Institute's database contains the 340 Existing Chemicals and each chemical compound was researched in a number of studies. The intermediate-duration oral NOELs studies were selected because they had the most chemical compounds and data. The availability and quality of intermediate-duration NOELs favored the use of the database. These NOELs were obtained for a: 1) 28-day repeated oral dose toxicity study for 122 compounds, 2) repeated dose and reproductive/developmental toxicity study for 85 compounds, 3) one-generation reproduction toxicity study for 1 compound, and 4) simple oral administration reproductive toxicity study for 10 compounds. The data were mainly obtained in 28-day repetitive-dose oral animal experiments in rats performed in Japan. The website also had summary pages as well as the original reports of the studies. When a difference was observed between the NOEL information in the summary pages and in the original reports, the original reports were used assuming greater accuracy. A total of two hundred twenty nine (229) chemicals with acceptable NOEL data were reported on the Institute's website and utilized for the study. These chemicals required adjustment

before they could be entered in the Leadscope program. All compounds having inorganic atoms, such as P (phosphorus), Si (silicon), or Sn (tin) were eliminated since QSAR methodology is unable to analyze data containing these compounds. The inorganic part of salts was also removed and the compounds were converted to their corresponding hydrolyzed organic forms. For example, Sodium *p*-styrenesulfonate (No. 85 in Appendix I) (a parent compound) was converted into *p*-styrensulfonic acid (a child compound). Also, the hydrates, such as Disodiumsuccinatehexahydrate (No. 128) was converted into the unhydrates form (succinic acid).

Following these adjustments, 218 NOELs remained and were used in the study. Among them, the average duration of the studies was 36.5 days with experiments for the 217 compounds being performed at 11 different institutions within Japan and one compound tested at an institution in the Netherlands.

The NOELs varied from 0.0684 to 11.89 mmol/kg/day (-2.17 to 1.08 mmol/kg/day on the log scale), and they were coded in PDM by their ID numbers. The chemical compounds' structures were converted to Simplified Molecular Input Line Entry Specification (SMILES) notation using the Online SMILES Translator and Structure File

Generator [20]. Then, a structure-data file (SDF), which has two-dimensional information about atoms, bonds, connectivity, and coordinates of molecule on each compound, was created from SMILES using the same website, and was entered in PDM along with NOELs. Also, structurally transformed compounds were entered into PDM with the child's (instead of the parent's compound) structural information. Finally, PDM had 218 compounds' ID with corresponding NOELs and structural information. General information about these compounds is shown in Appendix I.

(2) Analysis plan

Among a number of commercially available software in the area of QSAR, PDM was selected because of its ability to build an associative model. When the data about chemical compounds are entered into PDM, the software generates two kinds of their inherent information; the chemical compounds' structural characteristics (features) and physicochemical characteristics (descriptors). PDM recognizes what functional groups each chemical compound has from its SMILES. The software also automatically calculates each chemical compound's physicochemical characteristics. The structural characteristics and physicochemical characteristics of the compounds are shown below (Table 2-1 and Table 2-2). The software provided an automatic procedure for selection

of the characteristic used to build the study model.

Table 2-1: The Examples of Chemical Compounds' Structural Characteristics

Hydroxyl	1, 2-Diol / 1, 3-Diol
Amine	Carboxyl
Carboxylate	Sulfonate
1-(tert)Butylbenzene	1-Benzenesulfonate
1-Hydroxynaphthalene	1-Carbonylbenzene

Table 2-2: Chemical compounds' Physicochemical Characteristics

Physicochemical Characteristics	Definitions[a]
Molecular Weight	The sum of the atomic masses of all the atoms in the molecule
Parent Molecular Weight	The sum of the atomic masses of all the atoms in the parent molecule
Parent Atom Count	The number of all the atoms in the parent molecule
Rotatable Bonds	The number of single, non-terminal acyclic bonds
Hydrogen Bond Acceptors (HBA)	a. Any doubly bonded oxygen b. Any singly bonded oxygen, such as anion A-O- or hydroxyl A-OH c. Uncharged imine, nitrile, or aromatic N. Examples of imines include C=NH, or C=N-Ak; aromatic N includes ARO -N-ARO, where both ARO-N bonds are cyclic, aromatic d. An ether oxygen in the form C-O-C, where • neither C is substituted by a doubly-bonded N, S, or O; e.g., neither C is part of a carbonyl • at most one C is aromatic • the O is acyclic e. C-O-C is cyclic, both C are sp^3 hybridized

	f. Any doubly bonded sulfur in thioxomethyl C=S, where S has no other attachments
Hydrogen Bond Donors (HBD)	a. Any OH not part of an oxo acid (A hydroxyl of an oxo acid is considered ionized at physiological pH and will be recognized as an HBA.) b. Any NH not in a tetrazole or N-trifluoromethyl-sulfonamide
Polar surface area	Molecular polar surface area (PSA) i.e., surface attributed to polar atoms, is a descriptor that has been shown to correlate well with passive molecular transport through membranes and, therefore, allows prediction of transport of drugs.
ALogP	The octanol-water partition coefficient (log P) is the commonly used measure of lipophilicity.
Lipinski Score	Lipinski's *Rule of Five* is a simple way to assess a compound's oral bioavailability based on upper limits of the compound's logP, Molecular Weight, and the Number of Hydrogen Bond Donors and Acceptors. This score has a value between 0 – 4 and indicates the number of the following rules that are violated: a. if ALogP is greater than or equal to 5.0 – add 1; b. if Parent Molecular Weight is greater than or equal to 500 – add 1; c. if the sum of N+O atoms is greater than 10 – add 1; d. if the sum of NH + OH is greater than 5 – add 1

[a] from Leadscope User Manual [21]

Using a chemical compound's structural and physicochemical characteristics and observed NOEL, PDM generated associative models by PLS regression, and also provided a calculated NOEL derived from the model. The software also provided a correlation plot between the observed NOEL and calculated NOEL with indicators, such as R^2 and cross-validated R^2 (Q^2), which gives information about how well the calculated

NOEL correlated with the observed NOEL. R^2 is the coefficient of determination, which indicates how well the deviation of the data can be explained by the equation. Q^2 is a parameter suggesting robustness of the model to perturbations in the data.

3. RESULTS

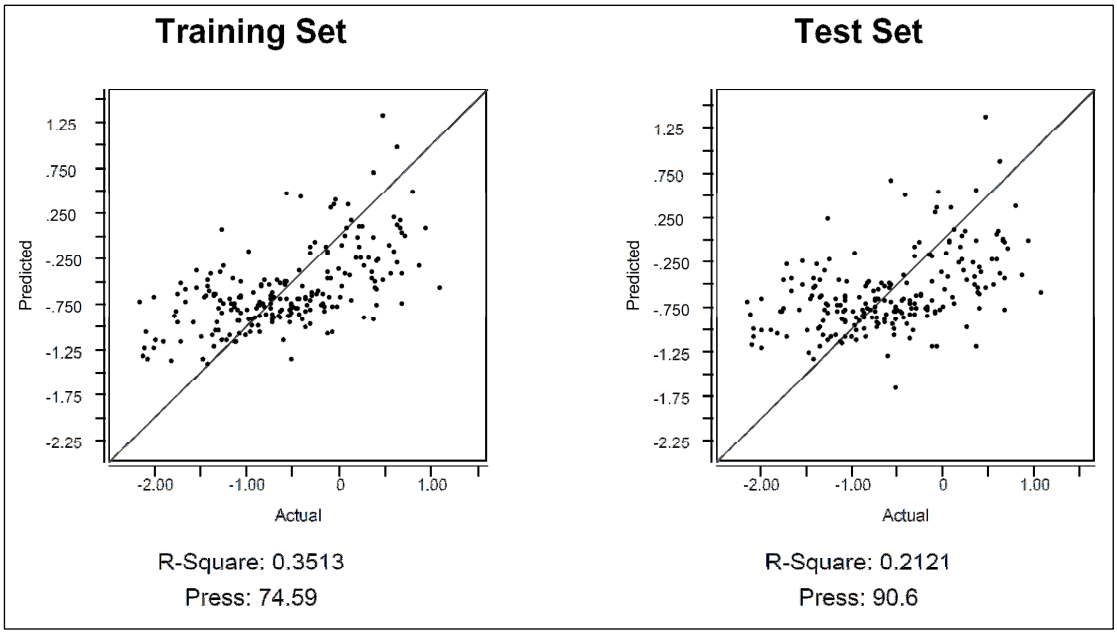
The results of the modeling in PDM showed that 218 compounds were used in the modeling as entered into PDM, and the average number of local neighbors (the compounds having similar structural characteristics) was 2.11 and the number of singletons (the compounds having no similar structural characteristics in the group of 218 compounds) was 131. Also, 117 structural characteristics (e.g., sulfonate, 1-hydoroxynaphthalen, 3-hydroxy-1-benzensulfonate, etc.) and 7 physicochemical characteristics (e.g., hydrogen bond acceptors, polar surface area, ALogP, etc.) were chosen in PDM to optimize building an associative model, and then a model (218Model) was built with one latent variable called the PLS factor (Table3-1). In the process, PDM created the PLS factor from 124 features and descriptors to avoid multicolinearity. This is because features are correlated with each other in many cases and therefore the factor analysis is used in the modeling process to deal with many like features and descriptors. Also, 2% test set (50-fold cross validation) was chosen in cross validation because of the general use for the sample size of 218 compounds. In 50-fold cross validation, the entire set of compounds is randomly divided into 50 portions. Forty-nine (49) portions are first used to build the model, while remaining one portion is used to test the model created with 49 portions. This process is repeated 50 times, using a different portion as

the test set. Also, PDM showed the correlation between observed NOELs and calculated NOELs, where observed NOELs are placed in X axis and calculated NOELs are placed in Y axis. R^2 was 0.35, and Q^2 was 0.21 (Figure 3-1). The least predicted residual error sum of square (PRESS) is 74.59 for training set and 90.6 for the test set.

Table 3-1. Modeling method summary

Method used:	Partial Least Squares Regression	
Final predictors used:	Total:	124
Structural features:		hierarchy features(116), dynamic features(1)
Calculated descriptors:		Leadscope calculated properties(7)
Number of PLS factors:	1	
Cross-validation:	2% test set	

Figure 3-1. Model summary



Note: R-Square in Training Set (0.3513) is R^2 and R-Square in Test Set (0.2121) is Q^2.

Also, out of 124, the 10 best features and descriptors that contributed to the model more than others are shown in Table 3-2 (e.g., hydrogen bond acceptors and polar surface area). Because features that have smaller residuals (shown as % Feature Residuals) are a better contributor to the model, the features are in the order of smaller residuals. Loadings are the correlation coefficients between the features and the PLS factor. Features that have larger absolute total loadings and larger total weight are generally better contributors.

Table 3-2. Top10 most significant features and descriptors

Name	Total Loadings	Total (+) Loadings	Total (-) Loadings	Total Weight	% Feature Residuals
Hydrogen Bond Acceptors	0.285	0.285	0.0	0.259	50.9
Polar Surface Area	0.27	0.27	0.0	0.229	56.0
sulfonate	0.253	0.253	0.0	0.219	61.4
1-benzene-sulfonate	0.249	0.249	0.0	0.239	62.7
sulfonyl group	0.228	0.228	0.0	0.155	68.6
benzene, 1-sulfonyl-	0.228	0.228	0.0	0.168	68.6
2-naphthalene-sulfonate	0.18	0.18	0.0	0.113	80.5
naphthalene, 1-hydroxy-	0.173	0.173	0.0	0.169	82.1
1-benzene-sulfonate, 3-hydroxy-	0.16	0.16	0.0	0.128	84.5
benzene, 1-(alkyl, acyc)-	-0.152	0.0	-0.152	-0.101	86.0

The residuals in the 218Model suggested that there might be a weak positive correlation between NOELs and residuals (Figure 3-2). The histogram of the frequency of the residuals demonstrated that the residuals were reasonably normally distributed (Figure

3-3).

Figure 3-2. The Residuals in the 218Model

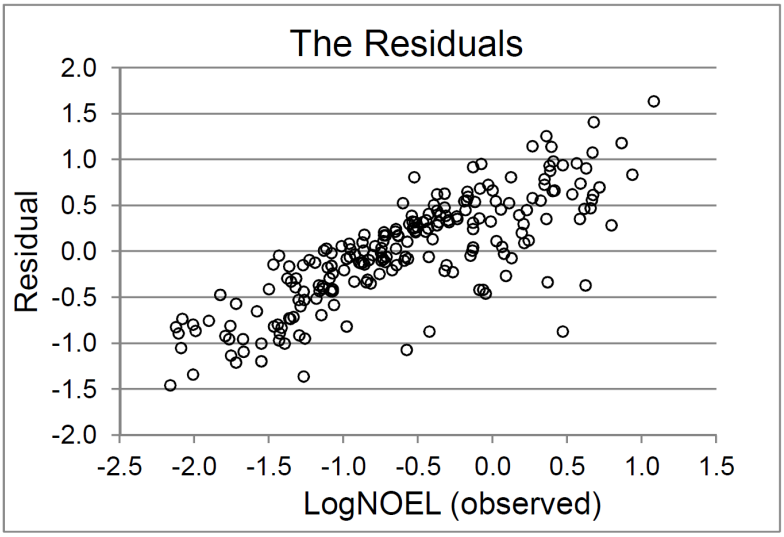
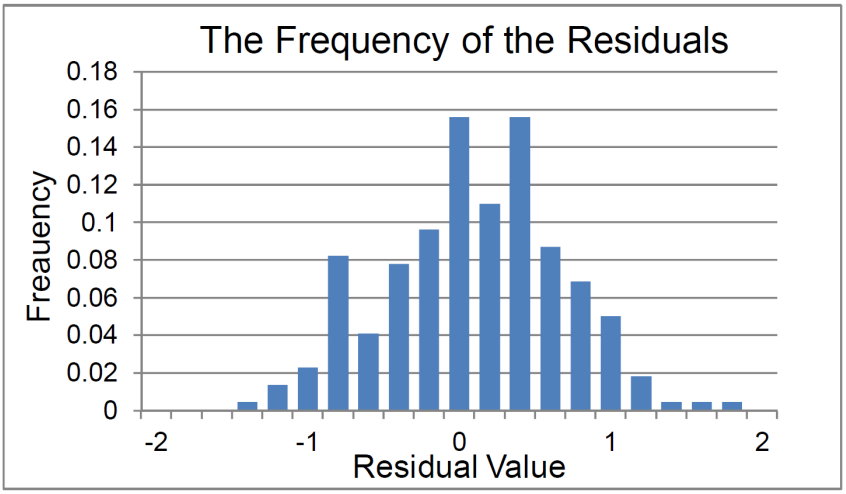


Figure 3-3. The Frequency of the Residuals in the 218Model



Next, the average of observed NOELs was compared with calculated NOELs from each

institution. Out of all 12 institutions, 8 institutions conducted studies on more than one compound. Among these 8 institutions, the average in each institution turned out to be reasonably close to each other, and the relative difference did not exceed 33% (Table 3-3).

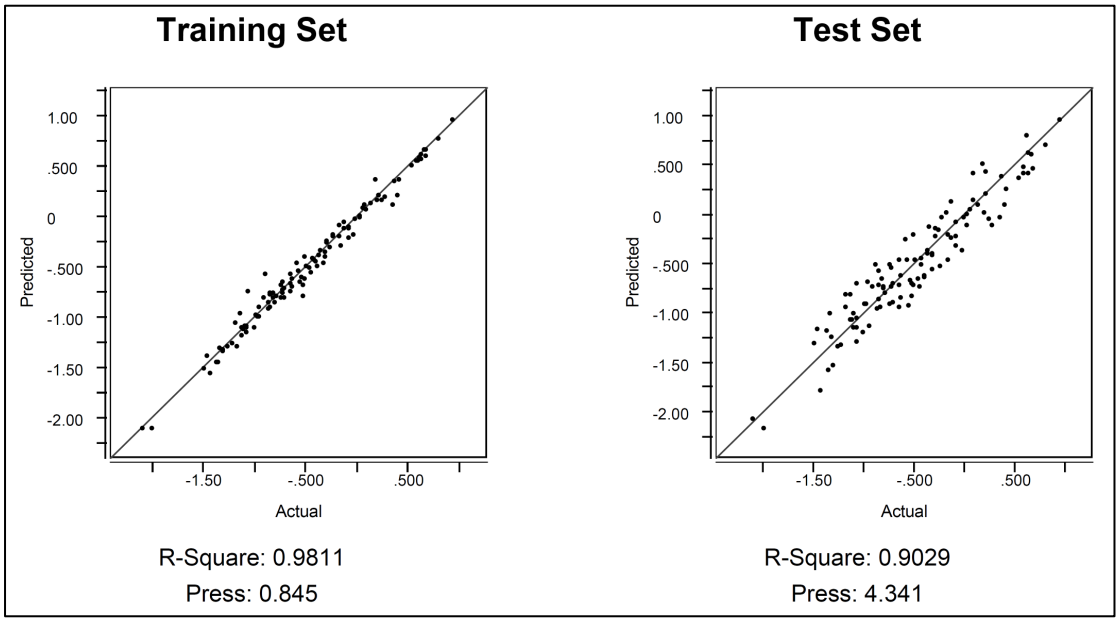
Table 3-3. The average of observed NOELs and that of calculated NOELs in 8 institutions

No.	Institution	The average of observed log-NOELs	The average of calculated log-NOELs	Absolute error	Relative error, %	The number of studies
1	Safety Research Institute for Chemical Compounds Co., Ltd.	-0.509	-0.582	0.073	14	28
2	Research Institute for Animal Science in Biochemistry and Toxicology	-0.789	-0.612	0.177	22	34
3	Food and Drug Safety Center, Hatano Research Institute, Japan	-0.471	-0.513	0.042	9	41
4	Mitsubishi Chemical Medience Corporation	-0.703	-0.680	0.023	3	33
5	Public Interest Incorporated Foundation BioSafety Research Center	-0.476	-0.632	0.156	33	28
6	Bozo Research Center	-0.604	-0.628	0.024	4	21

7	Panapharm Laboratories Co., Ltd.	-0.744	-0.558	0.186	25	13
8	Nihon Bioresearch Inc.	-0.550	-0.624	0.074	13	16

Finally, a number of chemical compounds were placed in groups to improve the model. By dividing 218 compounds into two or more groups, it was believed that a better associative model could be developed. In order to achieve this, a model with a high Q^2 was created. The 218Model was created with one compound that had the largest residual in the results being removed. Then another associative model was created with the remaining 217 compounds and again removing one compound with the largest residual. This procedure was repeated until the model achieved a 0.9 or larger Q^2. When 104 compounds were removed, a Q^2 of the model was 0.9029 with 114 compounds left (114Model) (Figure 3-4). Also, all compounds that were included in the 114Model are shown in Appendix I. In the construction of the 114Model, 115 structural characteristics and 8 physicochemical characteristic were used and the model was created with 10 PLS factors.

Figure 3-4. Model summary in the 114 Model



4. DISCUSSION

It is difficult to develop a definition of a good associative predictive model. However, large R^2 is considered an acceptable norm. Venkatapathy et al. have reported 0.31 as R^2 in a correlation between observed TD_{50} and LD_{50} calculated using TOPKAT. The authors considered this correlation value to be low [7]. Mazzatorta et al. have reported 0.54 as R^2 in the comparison of oral rat chronic LOAELs with calculated LOAELs obtained with an in-house developed procedure that relied on PLS with a genetic-algorithm variable selection. The study was implemented using Statistics Toolbox 5.0.1 of MATLAB 7.0.1 [8]. In the present project, the results showed that the model created had a relatively small R^2 value (0.35). Future work will be initiated to determine the underlying reason for the relatively small R^2 derived from the models that were created and to make improvements on subsequent models.

(1) Duration

First, emphasis was placed on the duration of the studies from which 218 NOELs were obtained. One hundred twenty two (122) NOELs out of 218 NOELs were obtained in the 28 day experiments, but the other NOELs were not. Average duration was 36.5 days (±10.5 days of one standard deviation), while the longest duration was 98 days (each

duration is shown in appendix II). An associative model was built using the 122 NOELs that were obtained in the 28 day study. The model did not suggest any improvement. The model demonstrated a smaller R^2 than the 218Model, and the correlation between the observed NOELs and the calculated NOELs looked more scattered than the 218Model (results not shown).

(2) Variance among 12 institutions

Second, the 218 experiments were conducted in 12 different facilities. A variance among the facilities was expected. Not all facilities complied with the same guideline that the Japanese government had issued. Some complied, some did not. The effect of variance among facilities was analyzed using SAS (SAS 9.3 TS Level 1M0 W32_7PRO platform, SAS Institute Inc., Cary, North Carolina) with the command of "proc mixed." Eight (8) institutions were entered into SAS rather than the 12 institution because 4 institutions conducted only one experiment. All institutions are shown in appendix II. The results demonstrated that: 1) "Fit statistics" is 165.3 for -2 Res Log Likelihood, 167.3 for AIC (Akaike Information Criterion), 167.4 for AICC (AIC with a correction for finite sample sizes), and 167.4 for BIC (Bayesian Information Criterion), 2) p-value of "Solution for Fixed Effects" is less than 0.0001 for both intercept and observed, 3)

Solution for Random Effects are 0 for all eight institutions , and 4) p-value of Type 3 Tests of Fixed Effects was less than 0.0001. Therefore, the results of "proc mixed" suggested that there were no random effects among the institutions, meaning that the results of the correlation between the observed NOELs and the calculated NOELs were not dependent on the variance of the institutions.

Also, as shown in table 3-3, the result may suggest that there is a signal in at least some of the institutions rather than noises, but it is not very helpful to perform further analysis with stratified data, because the number of studies in each institution is not very large (13 to 41).

(3) Grouping the compounds

Finally, the 114Model was created in order to develop better associative models. This was done by dividing 218 compounds into groups (Figure 3-4). No useful chemical structural relationship among the selected 114 compounds or among the removed 104 compounds was found. No structural commonality was found in the 114 compounds (e.g., the number of benzene rings or the size of the compounds), nor did there seem to be any structural commonality in the removed 104 compounds. Although an effort was

made to predict the NOELs by the removal of 104 compounds using the 114Model, the results showed that the 114Model failed to predict. The reason this did not occur was because the 114 compounds were “cherry-picked” compounds according to the residuals. A model with the 104 compounds did not show good associative relationship. The model had small R^2, and correlation between observed NOELs and calculated NOELs seemed to be scattered. If the model had shown useful relationship, the results would have suggested that there existed two proper chemical compounds groups in the 218 compounds. Although the 114Model suggests that there may be some signal involving some of 218 compounds, the noise that caused the distorted relationship could not be identified and thus removed.

In data mining, how to remove the noise is a common issue. Julian-Ortiz et al. report interesting results [22]. At first, they built the model of chronic LOAEL by means of a multilinear regression (MLR) with 229 compounds that were originated from the U.S. Environmental Protection Agency (EPA) and the National Toxicology Program (NTP) database. They suggested that the model did not show great correlation between observed LOAEL and calculated LOAEL. However, when they used 86 compounds that originated from EPA (but not NTP) and built a model, the model showed a great

improvement compared with the original model with all 229 compounds as 1) the residuals got smaller; 2) heteroscedasticity (dependence of the variance on the value of the experimental datum) disappeared; 3) the standard error of the estimates reduced; 4) correlation was improved; and 5) Fisher-Snedecor parameter *F* rose. Interestingly, they added a model with compounds that originated from NTP but this did not show useful improvement. They concluded that only data obtained from EPA could be properly modeled by means of MLR, while data obtained from NTP database introduced noise and did not provide good models by themselves or in combination with the EPA data. Also, they stated that better models could be built by using only reliable data.

5. CONCLUSION

In this project, the utility of the NOELs of the 218 compounds was tested by building models using QSAR modeling technique with PDM. The results suggested that although the model showed some association between observed NOELs and calculated NOELs, the model provided little evidence for good utility of the data. Also, the reason why the model could not achieve good associative relationship between the observed NOELs and calculated NOELs was considered, and the results analyzed with SAS. An effort was made to group the chemical compounds. The results suggest that, perhaps, both the "signal" and "noise" are present in the analyzed data, but efforts to filter out the noise was not successful. Once only the signal-contacting data are left, the model can be significantly improved. This work will be undertaken by the author in the future. In this respect, the present project will help to further the study of the QSAR methodology.

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APPENDICES

I. General Information for the 218 Chemical Compounds (Parent compounds)

No.	Name	Compound ID[a]	SMILES	MW[b]	Formula	[c]
1	4-Vinylpyridine	Taka100-43-6	C1=NC=CC(=C1)C=C	105.14	C_7H_7N	1
2	3-Cyanopyridine	Taka100-54-9	C1=CC(=CN=C1)C#N	104.12	$C_6H_4N_2$	1
3	2-Vinylpyridine	Taka100-69-6	C1=C(C=C)N=CC=C1	105.15	C_7H_7N	1
4	4-Ethylmorpholine	Taka100-74-3	N1(CCOCC1)CC	115.18	$C_6H_{13}NO$	1
5	4,4'-Methylenebis(2-chloroaniline)	Taka101-14-4	C2=C(CC1=CC(=C(N)C=C1)Cl)C=CC(=C2Cl)N	267.15	$C_{13}H_{12}Cl_2N_2$	
6	Dicyclohexylamine	Taka101-83-7	C2C(NC1CCCCC1)CCCC2	181.32	$C_{12}H_{23}N$	1
7	1,3-Diphenylguanidine	Taka102-06-7	C1=CC=CC=C1NC(N)=NC2=CC=CC=C2	211.26	$C_{13}H_{13}N_3$	1
8	Glyceroltriacetate	Taka102-76-1	C(C(OC(=O)C)COC(C)=O)OC(C)=O	218.20	$C_9H_{14}O_6$	1
9	2-(Di-n-butylamino)ethanol	Taka102-81-8	N(CCCC)(CCCC)CCO	173.30	$C_{10}H_{23}NO$	
10	Bis(2-ethylhexyl)nonanedioate	Taka103-24-2	C(OC(=O)CCCCCCCC(OCC(CCCC)CC)=O)C(CCCC)CC	412.66	$C_{25}H_{48}O_4$	1
11	2-ethylhexylvinylether	Taka103-44-6	C(OC=C)C(CCCC)CC	156.27	$C_{10}H_{20}O$	
12	N-Ethylaniline	Taka103-69-5	C1=C(NCC)C=CC=C1	121.20	$C_8H_{11}N$	
13	N,N-Dimethylbenzylamine	Taka103-83-3	c1(ccccc1)CN(C)C	135.23	$C_9H_{13}N$	1
14	1,4-Diethylbenzene	Taka105-05-5	c1(ccc(CC)cc1)CC	134.22	$C_{10}H_{14}$	1
15	2-(Diethylamino)ethylmethacrylate	Taka105-16-8	C(N(CC)CC)COC(C(C)=C)=O	185.27	$C_{10}H_{19}O_2N$	1
16	Methylacetoacetate	Taka105-45-3	C(C(OC)=O)C(C)=O	116.12	$C_5H_8O_3$	1
17	Dibutyladipate	Taka105-99-7	C(C)CCOC(CCCCC(OCCCC)=O)=O	258.40	$C_{14}H_{26}O_4$	1
18	1,4-Dibromobenzene	Taka106-37-6	C1=C(C=CC(=C1)Br)Br	235.92	$C_6H_4Br_2$	
19	4-Chlorophenol	Taka106-48-9	C1=C(C=CC(=C1)Cl)O	128.56	C_6H_5ClO	1
20	2,3-Epoxypropylmethacrylate	Taka106-91-2	C(OC(C(C)=C)=O)C1CO1	142.17	$C_7H_{10}O_3$	
21	3-Methylphenol	Taka108-39-4	C1=C(C)C=CC=C1O	108.14	C_7H_8O	1
22	Propyleneglycolmonomethyletheracetate	Taka108-65-6	C(OC)C(OC(C)=O)C	132.16	$C_6H_{12}O_3$	1
23	3,5-Dimethylaniline	Taka108-69-0	C1=C(C)C=C(C=C1C)N	121.20	$C_8H_{11}N$	1

24	1,3,5-Trihydroxybenzene	Taka108-73-6	C1=C(O)C=C(O)C=C1O	126.11	$C_6H_6O_3$	
25	Isocyanuricacid	Taka108-80-5	O=C1NC(NC(N1)=O)=O	129.09	$C_3H_3N_3O_3$	
26	4-Methylpyridine	Taka108-89-4	C1=CN=CC=C1C	93.10	C_6H_7N	
27	1,3-Dibromopropane	Taka109-64-8	C(CBr)CBr	201.89	$C_3H_6Br_2$	
28	1-Bromo-3-chloropropane	Taka109-70-6	C(CCl)CBr	157.44	C_3H_6BrCl	1
29	Thiophene	Taka110-02-1	C1=CC=CS1	84.14	C_4H_4S	1
30	1,2-Bis(stearoylamino)ethane	Taka110-30-5	C(NC(CCCCCCCCCCCCCCCCC)=O)CNC(CCCCCCCCCCCCCCCCC)=O	593.02	$C_{38}H_{76}N_2O_2$	
31	Tetrahydromethy-1,3-isobenzofuranedione	Taka11070-44-3	CC12C(=CCCC1)C(OC2=O)=O	166.18	$C_9H_{10}O_3$	1
32	3,3'-Thiobispropanoicacid	Taka111-17-1	C(C(O)=O)CSCCC(O)=O	178.21	$C_6H_{10}O_4S$	1
33	N-(Aminoethyl)ethanolamine	Taka111-41-1	N(CCN)CCO	104.15	$C_4H_{12}N_2O$	1
34	Methyldodecanoate	Taka111-82-0	C(C)CCCCCCCCCC(OC)=O	214.35	$C_{13}H_{26}O_2$	1
35	1-Octanethiol	Taka111-88-6	C(CCCCS)CCC	146.30	$C_8H_{18}S$	
36	Undecane	Taka1120-21-4	C(C)CCCCCCCCC	156.31	$C_{11}H_{24}$	
37	1,2-Bis(2-chloroethoxy)ethane	Taka112-26-5	C(OCCCl)COCCCl	187.07	$C_6H_{12}Cl_2O_2$	1
38	Docosanoicacid	Taka112-85-6	C(CCCCCCCCCCCCCCC)CCCCCCC(=O)O	340.59	$C_{22}H_{44}O_2$	
39	2-Amino-2-ethyl-1,3-propanediol	Taka115-70-8	C(C(N)(CO)CO)C	119.16	$C_5H_{13}NO_2$	1
40	Pentaerythritol	Taka115-77-5	C(C(CO)(CO)CO)O	136.17	$C_5H_{12}O_4$	
41	2,6-Dichlorotoluene	Taka118-69-4	C1=CC=C(C(=C1Cl)C)Cl	161.03	$C_7H_6Cl_2$	1
42	2,4,6-Tribromophenol	Taka118-79-6	c1(c(cc(Br)cc1Br)Br)O	330.80	$C_6H_3Br_3O$	
43	4,4'-Methylenebis(2,6-di-tert-butylphenol)	Taka118-82-1	C(c1c(c(C(C)(C)C)cc(c1)Cc1cc(C(C)(C)C)c(O)c(c1)C(C)(C)C)O)(C)(C)C	424.65	$C_{29}H_{44}O_2$	
44	Ditridecylphthalate	Taka119-06-2	C1=CC(=C(C=C1)C(OCCCCCCCCCCCCCC)=O)C(OCCCCCCCCCCCCCC)=O	530.83	$C_{34}H_{58}O_4$	
45	2,2'-Methylenebis(6-tert-butyl-p-cresol)	Taka119-47-1	C1=C(C=C(C(=C1C(C)(C)C)O)CC2=CC(=CC(=C2O)C(C)(C)C)C)C	340.51	$C_{23}H_{32}O_2$	1
46	2-Methyl-5-nitrobenzenesul	Taka121-03-9	C1=C(C=CC(=C1[S](O)(=O)=O)C)	217.20	$C_7H_7NO_5S$	1

	fonicacid		[N+](=O)[O-]			
47	3-Aminobenzenesulfonicacid	Taka121-47-1	C1=C(C=C(C=C1)N)[S](=O)(O)=O	173.20	$C_6H_7NO_3S$	1
48	4-chlorobenzoylchloride	Taka122-01-0	c1(C(=O)Cl)ccc(Cl)cc1	175.01	$C_7H_4Cl_2O$	1
49	4-Ethylphenol	Taka123-07-9	C1=C(CC)C=CC(=C1)O	122.16	$C_8H_{10}O$	1
50	4-Methoxybenzaldehyde	Taka123-11-5	C1=CC(=CC=C1C=O)OC	136.15	$C_8H_8O_2$	1
51	4-Aminophenol	Taka123-30-8	c1(ccc(O)cc1)N	109.14	C_6H_7NO	1
52	Diacetonealcohol	Taka123-42-2	C(C(C)=O)C(C)(O)C	116.18	$C_6H_{12}O_2$	
53	Paraldehyde	Taka123-63-7	C1(OC(OC(O1)C)C)C	132.16	$C_6H_{12}O_3$	
54	Azodicarboxamide	Taka123-77-3	O=C(N)N=NC(=O)N	116.08	$C_2H_4N_4O_2$	1
55	2,2-Dimethyl-1,3-propanediol	Taka126-30-7	C(C(C)(C)CO)O	104.15	$C_5H_{12}O_2$	1
56	Tetrahydrothiophene-1,1-dioxide	Taka126-33-0	O=[S]1(=O)CCCC1	120.17	$C_4H_8O_2S$	1
57	Sodium3-nitrobenzenesulfonate	Taka127-68-4	c1(cc(ccc1)[N+](=O)[O-])S(=O)(=O)[O-].[Na+]	225.15	$C_6H_4NNaO_5S$	1
58	Sodium4-amino-1-naphthalenesulfonate	Taka130-13-2	C1=CC=CC2=C(C=CC(=C12)[S](=O)(=O)[O-])N.[Na+]	245.24	$C_{10}H_8NNaO_3S$	1
59	Divinylbenzene	Taka1321-74-0	C1=CC=CC(=C1C=C)C=C	130.19	$C_{10}H_{10}$	1
60	Sorbitanmonooctadecanoate	Taka1338-41-6	[C@@H]1(OC[C@H]([C@@H]1O)O)C(O)COC(=O)CCCCCCCCCCCCCCCCC	430.62	$C_{24}H_{46}O_6$	
61	Sodium2-naphthol-3,6-disulfonate	Taka135-51-3	C1=C2C(=CC(=C1[S](=O)(=O)[O-])O)C=CC(=C2)[S](=O)(=O)[O-].[Na+].[Na+]	348.26	$C_{10}H_6Na_2O_7S_2$	
62	p-tert-Octylphenol	Taka140-66-9	C1=C(C(CC(C)(C)C)(C)C)C=CC(=C1)O	206.32	$C_{14}H_{22}O$	
63	1,3,5-Tri-tert-butylbenzene	Taka1460-02-2	C1=C(C(C)(C)C)C=C(C=C1C(C)(C)C)C(C)(C)C	246.43	$C_{18}H_{30}$	
64	1,3-Bis(aminomethyl)benzene	Taka1477-55-0	C1=C(CN)C=CC=C1CN	136.19	$C_8H_{12}N_2$	1
65	3,3-Bis(p-dimethylaminophenyl)-6-dimethylaminophthalide	Taka1552-42-7	C1=CC(=CC4=C1C(C2=CC=C(N(C)C)C=C2)(C3=CC=C(N(C)C)C=C3)OC4=O)N(C)C	415.54	$C_{26}H_{29}N_3O_2$	
66	4-Ethoxybenzenamine	Taka156-43-4	c1(ccc(N)cc1)OCC	137.18	$C_8H_{11}NO$	1

67	4-Chloro-o-cresol	Taka1570-64-5	C1=C(C(=CC(=C1)Cl)C)O	142.60	C_7H_7ClO	
68	3,4,5,6-Tetrachlorophthalimide	Taka1571-13-7	C1(=C(Cl)C(=C(C2=C1C(NC2=O)=O)Cl)Cl)Cl	284.91	$C_8HCl_4NO_2$	1
69	Perfluorooctadecanoicacid	Taka16517-11-6	O=C(C(C(C(C(C(C(C(C(C(C(C(C(C(C(C(C(C(F)(F)F)(F)F)(F)F)(F)F)(F)F)(F)F)(F)F)(F)F)(F)F)(F)F)(F)F)(F)F)(F)F)(F)F)(F)F)(F)F)(F)F)O	914.14	$C_{18}HF_{35}O_2$	1
70	4,4'-Bis(chloromethyl)-1,1'-biphenyl	Taka1667-10-3	C1=CC(=CC=C1C2=CC=C(C=C2)CCl)CCl	251.15	$C_{14}H_{12}Cl_2$	
71	Ethylcyclohexane	Taka1678-91-7	C(C)C1CCCCC1	112.21	C_8H_{16}	
72	6-tert-Butyl-2,4-xylenol	Taka1879-09-0	C1=C(C(=C(C=C1C)C(C)(C)C)O)C	178.30	$C_{12}H_{18}O$	1
73	tert-pentylbenzene	Taka2049-95-8	c1(C(CC)(C)C)ccccc1	148.24	$C_{11}H_{16}$	
74	1-Chloro-2,5-dimethoxybenzene	Taka2100-42-7	C1=C(OC)C=CC(=C1Cl)OC	172.61	$C_8H_9O_2Cl$	1
75	isobutyl2-naphthylether	Taka2173-57-1	C1=C2C(=CC=C1OCC(C)C)C=CC=C2	200.28	$C_{14}H_{16}O$	1
76	1-Methoxynaphthalene	Taka2216-69-5	C1=CC=C2C(=C1OC)C=CC=C2	158.20	$C_{11}H_{10}O$	1
77	2,3,6-Trimethylphenol	Taka2416-94-6	C1=C(C(=C(O)C(=C1)C)C)C	136.19	$C_9H_{12}O$	
78	2-(Dimethylamino)ethylacrylate	Taka2439-35-2	C(OC(C=C)=O)CN(C)C	143.21	$C_7H_{13}NO_2$	
79	Tripropyleneglycol	Taka24800-44-0	C(C(O)OCC(C)OC(CC)O)C	192.29	$C_9H_{20}O_4$	1
80	Nonylphenol	Taka25154-52-3	C1=C(C(=CC=C1)[O-])CCCCCCCCC.[K+]	220.36	$C_{15}H_{24}O$	
81	Diisopropylbenzene	Taka25321-09-9	C1=CC=CC(=C1C(C)C)C(C)C	162.27	$C_{12}H_{18}$	
82	1,3-Cyclohexanedimethanamine	Taka2579-20-6	[C@H]1(C[C@@H](CCC1)C[NH3+])C[NH3+]	142.24	$C_8H_{18}N_2$	1
83	3-Methyl-4-nitrophenol	Taka2581-34-2	C1=C([N+]([O-])=O)C(=CC(=C1)O)C	153.15	$C_7H_7NO_3$	1
84	Dibenzyltoluene	Taka26898-17-9	C1=C(C(=C(C=C1)C)CC2=CC=CC=C2)CC3=CC=CC=C3	272.38	$C_{21}H_{20}$	1
85	Sodiump-styrenesulfonate	Taka2695-37-6	C1=C([S]([O-])(=O)=O)C=CC(=C1)C=C.[Na+]	206.19	$C_8H_7NaO_3S$	
86	1,3,5-Tris(3,5-di-tert-butyl-4-hydroxybenzyl)isocyanuricacid	Taka27676-62-6	n1(Cc2cc(c(O)c(c2)C(C)(C)C)C(C)(C)C)c(=O)n(Cc2cc(C(C)(C)C)c(c(c2)C(C)(C)C)O)c(=O)n(Cc2cc(C(C)(	784.10	$C_{48}H_{69}N_3O_6$	

			C)C)c(c(c2)C(C)(C)C)O)c1=O			
87	Tricyclo[3.3.1.13,7]decane	Taka281-23-2	C12CC3CC(C1)CC(C2)C3	136.23	$C_{10}H_{16}$	1
88	Diethylbiphenyl	Taka28575-17-9	C1=C(C=C(C=C1)CC)C2=CC(=CC=C2)CC	210.31	$C_{16}H_{18}$	1
89	2-(Dimethylamino)ethylmethacrylate	Taka2867-47-2	C(OC(C(C)=C)=O)CN(C)C	157.24	$C_8H_{15}NO_2$	1
90	Monoisopropylnaphthalene	Taka29253-36-9	c1(cccc2ccccc12)C(C)C	170.25	$C_{13}H_{14}$	1
91	Perfluorooctane	Taka307-34-6	FC(C(C(C(F)(C(F)(F)C(C(C(F)(F)F)(F)F)(F)F)(F)F)(F)F)(F)F	438.06	C_8F_{18}	
92	1,2-Dichloro-3-nitrobenzene	Taka3209-22-1	C1=C([N+]([O-])=O)C(=C(Cl)C=C1)Cl	192.00	$C_6H_3NO_2Cl_2$	
93	Tris(2-ethylhexyl)1,2,4-benzenetricarboxylate	Taka3319-31-1	C1=C(C(=CC=C1C(OCC(CCCC)CC)=O)C(OCC(CCCC)CC)=O)C(OCC(CCCC)CC)=O	546.87	$C_{33}H_{54}O_6$	1
94	3,5,5-Trimethylhexan-1-ol	Taka3452-97-9	C(C(CCO)C)C(C)(C)C	143.26	$C_9H_{20}O$	
95	3-Phenoxytoluene	Taka3586-14-9	C2=C(OC1=CC=CC=C1)C=CC=C2C	184.25	$C_{13}H_{12}O$	1
96	Diheptylphthalate	Taka3648-21-3	c1(c(C(OCCCCCCC)=O)cccc1)C(OCCCCCCC)=O	362.51	$C_{22}H_{34}O_4$	
97	Sodium1-methoxycarbonylpentadecane-2-sulfonate	Taka4016-24-4	C(C([S]([O-])(=O)=O)C(OCC)=O)CCCCCCCCCCCCC.[Na+]	372.50	$C_{17}H_{33}NaO_5S$	
98	2,6-Bis(1,1-dimethylethyl)-4-ethylphenol	Taka4130-42-1	C1=C(C=C(C(=C1C(C)(C)C)O)C(C)(C)C)CC	234.38	$C_{16}H_{26}O$	1
99	Thioureadioxide	Taka4189-44-0	O=[S]([O-])C(N)=N	108.12	$CH_4N_2O_2S$	
100	2,2',3,3'-Tetrachloro-4,4'-diaminodiphenylmethane	Taka42240-73-3	C1=CC(=C(C(=C1CC2=CC=C(C(=C2Cl)Cl)N)Cl)Cl)N	336.04	$C_{13}H_{10}Cl_4N_2$	
101	4-(1-Methylethenyl)phenol	Taka4286-23-1	CC(=C)C1=CC=C(C=C1)O	134.18	$C_9H_{10}O$	1
102	2,2,4,4,6,8,8-Heptamethylnonane	Taka4390-04-9	C(C(CC(CC(C)(C)C)(C)C)C(C)(C)C	226.44	$C_{16}H_{34}$	
103	3-Methyl-1,5-pentanediol	Taka4457-71-0	C(C(CCO)C)CO	118.20	$C_6H_{14}O_2$	
104	Methoxymethanol	Taka4461-52-3	C(O)OC	62.07	$C_2H_6O_2$	
105	Cyanoguanidine	Taka461-58-5	C(=NC#N)(N)N	84.08	$C_2H_4N_4$	
106	N,N-Dicyclohexyl-2-benzothiazolesulfenamide	Taka4979-32-2	C1=CC=CC4=C1N=C(SN(C2CCCCC2)C3CCCCC3)S4	346.59	$C_{19}H_{26}N_2S_2$	1
107	(Methacryloyloxyethyl)trim	Taka5039-78-1	C([N+](C)(C)C)COC(C(C)=C)=O.[	207.70	$C_9H_{18}ClNO_2$	

	ethylammoniumchloride		Cl-]			
108	DisperseYellow42	Taka5124-25-4	C1=C([N+]([O-])=O)C(=CC=C1[S](=O)(=O)NC2=CC=CC=C2)NC3=CC=CC=C3	369.40	$C_{18}H_{15}N_3O_4S$	1
109	2,4-Dinitrophenol	Taka51-28-5	C1=C(C(=CC=C1[N+](=O)[O-])O)[N+](=O)[O-]	184.11	$C_6H_4N_2O_5$	
110	Ethylcarbamate	Taka51-79-6	C(OC(N)=O)C	89.03	$C_3H_7NO_2$	
111	2-Bromo-2-nitropropane-1,3-diol	Taka52-51-7	C(C([N+](=O)[O-])(CO)Br)O	199.99	$C_3H_6BrNO_4$	
112	2,3-Dibromosuccinicacid	Taka526-78-3	O=C(C(C(C(O)=O)Br)Br)O	275.88	$C_4H_4O_4Br_2$	
113	Dicyclohexylcarbodiimide	Taka538-75-0	C2C(N=C=NC1CCCCC1)CCCC2	206.33	$C_{13}H_{22}N_2$	
114	Citral	Taka5392-40-5	C(\C(=C\C=O)C)CC=C(C)C	152.23	$C_{10}H_{16}O$	
115	chlorocyclohexane	Taka542-18-7	C1(CCCCC1)Cl	118.60	$C_6H_{11}Cl$	1
116	n-Hexadecane	Taka544-76-3	C(CCCCCCCC)CCCCCCC	226.44	$C_{16}H_{34}$	
117	Monosodium4-amino-5-hydroxy-2,7-naphthalenedisulfonate	Taka5460-09-3	C1=C2C(=C(C=C1[S](O)(=O)=O)N)C(=CC(=C2)[S](=O)(=O)[O-])O.[Na+]	341.29	$C_{10}H_8NNaO_7S_2$	
118	Methane,isothiocyanato-	Taka556-61-6	S=C=NC	73.12	C_2H_3NS	
119	3-Methoxy-3-methyl-1-butanol	Taka56539-66-3	C(C(OC)(C)C)CO	118.18	$C_6H_{14}O_2$	1
120	Benzyltrimethylammonium chloride	Taka56-93-9	C1=CC=CC=C1C[N+](C)(C)C.[Cl-]	185.70	$C_{10}H_{16}ClN$	1
121	4-Ethyl-1,1'-biphenyl	Taka5707-44-8	C2=C(C1=CC=CC=C1)C=CC(=C2)CC	182.26	$C_{14}H_{14}$	
122	1,2-Butanediol	Taka584-03-2	C(C)C(CO)O	90.12	$C_4H_{10}O_2$	1
123	tert-Butylmethacrylate	Taka585-07-9	CC(OC(C(C)=C)=O)(C)C	142.20	$C_8H_{14}O_2$	1
124	4-Chloro-m-cresol	Taka59-50-7	C1=C(C(=CC=C1O)Cl)C	142.58	C_7H_7ClO	1
125	4-(1-Methyl-1-phenylethyl)phenol	Taka599-64-4	C2=C(C(C1=CC=CC=C1)(C)C)C=CC(=C2)O	212.29	$C_{15}H_{16}O$	1
126	3-Nitrophthalicacid	Taka603-11-2	C1=C(C(=C(C=C1)[N+](=O)[O-])C(=O)O)C(=O)O	211.13	$C_8H_5NO_6$	1
127	1-Naphthol-4-sulfonicacidsodiumsalt	Taka6099-57-6	C1=CC=CC2=C(C=CC(=C12)[S](=O)(=O)[O-])O.[Na+]	160.17	$C_{10}H_7NaO_4S$	1
128	Disodiumsuccinatehexahydrate	Taka6106-21-4	C(CC([O-])=O)C([O-])=O.O.O.O.O.O.O.O.[Na+].[Na+]	270.14	$C_4H_{16}Na_2O_{10}$	

129	1-Chloro-2-(chloromethyl) benzene	Taka611-19-8	C1=CC=CC(=C1CCl)Cl	161.03	$C_7H_6Cl_2$	
130	3-Ethylphenol	Taka620-17-7	C1=C(C=CC=C1CC)O	122.16	$C_8H_{10}O$	
131	4,4'-Methylenediphenol	Taka620-92-8	c1(Cc2ccc(O)cc2)ccc(O)cc1	200.23	$C_{13}H_{12}O_2$	1
132	1,4-Dicyanobenzene	Taka623-26-7	C1=CC(=CC=C1C#N)C#N	128.14	$C_8H_4N_2$	1
133	n-Pentadecane	Taka629-62-9	C(CCCCCCC)CCCCCCC	212.41	$C_{15}H_{32}$	
134	1,3-Benzenedicarboxylicacid,5-sulfo-,monosodiumsalt	Taka6362-79-4	C1=C(C=C(C=C1[S](=O)(=O)[O-])C(O)=O)C(O)=O.[Na+]	268.18	$C_8H_5NaO_7S$	
135	Phenylurea	Taka64-10-8	C1=C(C=CC=C1)NC(N)=O	136.15	$C_7H_8N_2O$	1
136	C.I.PigmentRed22	Taka6448-95-9	C1=C2C(=CC=C1)C=C(C(=O)\C2=N/NC3=C(C=CC(=C3)[N+]([O-])=O)C)C(=O)NC4=CC=CC=C4	426.43	$C_{24}H_{18}N_4O_4$	
137	PigmentOrange16	Taka6505-28-8	C1=CC=CC=C1NC(=O)C(N=NC2=CC=C(C=C2OC)C3=CC(=C(C=C3)N=NC(C(=O)C)C(=O)NC4=CC=CC=C4)OC)C(=O)C	620.65	$C_{34}H_{32}N_6O_6$	1
138	Sodiump-toluenesulfonate	Taka657-84-1	C1=C([S](=O)(=O)[O-])C=CC(=C1)C.[Na+]	194.18	$C_7H_7NaO_3S$	
139	N-(Carboxymethyl)-N,N-dimethyl-1-dodecanaminium, innersalt	Taka683-10-3	C([N+](CCCCCCCCCCCC)(C)C)C([O-])=O.[Cl-].[Na+]	271.44	$C_{16}H_{33}NO_2$	
140	2,2,4-Trimethyl-1,3-pentanedioldiisobutyrate	Taka6846-50-0	C(C(C(C(C)C)OC(=O)C(C)C)(C)C)OC(=O)C(C)C	286.46	$C_{16}H_{30}O_4$	
141	2-Ethylhexylmethacrylate	Taka688-84-6	C(C(CCCC)CC)OC(C(C)=C)=O	198.34	$C_{12}H_{22}O_2$	1
142	4-Methyl-1-pentene	Taka691-37-2	C(C(C)C)C=C	84.16	C_6H_{12}	1
143	Pentaerythritoltetra(2-ethyl hexanoate)	Taka7299-99-2	C(OC(=O)C(CCCC)CC)C(COC(=O)C(CCCC)CC)(COC(=O)C(CCCC)CC)COC(=O)C(CCCC)CC	640.94	$C_{37}H_{68}O_8$	1
144	Trimethylamine	Taka75-50-3	N(C)(C)C	59.11	C_3H_9N	1
145	2-tert-Butoxyethanol	Taka7580-85-0	C(OC(C)(C)C)CO	118.17	$C_6H_{14}O_2$	
146	3,4-Dichloro-1-butene	Taka760-23-6	C(C(C=C)Cl)Cl	124.99	$C_4H_6Cl_2$	
147	Triphenylchloromethane	Taka76-83-5	C3=C(C(C1=CC=CC=C1)(C2=CC=CC=C2)Cl)C=CC=C3	278.78	$C_{19}H_{15}Cl$	
148	Triisobutylene	Taka7756-94-7	[C](C)(C)C	168.30	$C_{12}H_{24}$	
149	1,1,1-Tris(hydroxymethyl)e	Taka77-85-0	C(C(C)(CO)CO)O	120.15	$C_5H_{12}O_3$	1

	thane					
150	2-Ethyl-2-hydroxymethyl-1,3-propanediol	Taka77-99-6	C(C(CO)(CO)CO)C	134.17	$C_6H_{14}O_3$	1
151	2,5-Dimethyl-2,5-di(t-butylperoxy)hexane	Taka78-63-7	C(C(OOC(C)(C)C)(C)C)CC(OOC(C)(C)C)(C)C	290.44	$C_{16}H_{34}O_4$	1
152	2-Hydroxypropanenitrile	Taka78-97-7	CC(C#N)O	71.08	C_3H_5NO	
153	Tetrabromoethane	Taka79-27-6	C(C(Br)Br)(Br)Br	345.65	$C_2H_2Br_4$	
154	N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine	Taka793-24-8	C2=C(NC1=CC=CC=C1)C=CC(=C2)NC(CC(C)C)C	268.40	$C_{18}H_{24}N_2$	
155	4,4'-Isopropylidenebis(2,6-dibromophenol)	Taka79-94-7	C2=C(C(C1=CC(=C(O)C(=C1)Br)Br)(C)C)C=C(Br)C(=C2Br)O	543.87	$C_{15}H_{12}Br_4O_2$	
156	4,4'-Sulfonyldiphenol	Taka80-09-1	C2=C([S](C1=CC=C(O)C=C1)(=O)=O)C=CC(=C2)O	250.27	$C_{12}H_{10}O_4S$	
157	Dicmylperoxide	Taka80-43-3	C1=CC=CC=C1C(OOC(C2=CC=CC=C2)(C)C)(C)C	270.37	$C_{18}H_{22}O_2$	1
158	4,4'-Oxybis(benzenesulfonylhydrazide)	Taka80-51-3	C1=CC(=CC=C1[S](NN)(=O)=O)OC2=CC=C([S](NN)(=O)=O)C=C2	358.40	$C_{12}H_{14}N_4O_5S_2$	
159	2-Amino-1-naphthalenesulfonicacid	Taka81-16-3	c1(c2c(ccc1N)cccc2)S(O)(=O)=O	223.26	$C_{10}H_9NO_3S$	
160	Benzanthrone	Taka82-05-3	C1=CC=C4C3=C1C2=CC=CC=C2C(C3=CC=C4)=O	230.26	$C_{17}H_{10}O$	1
161	p-Nitrophenolsodiumsalt	Taka824-78-2	C1=CC(=CC=C1[N+](=O)[O-])[O-].[Na+]	161.09	$C_6H_4NNaO_3$	
162	Acenaphthene	Taka83-32-9	c12c3CCc1cccc2ccc3	154.22	$C_{12}H_{10}$	1
163	1,3,5-Tris(2-hydroxyethyl)-1,3,5-triazine-2,4,6-(1H,3H,5H)-trione	Taka839-90-7	C(N1C(N(C(=O)N(C1=O)CCO)CCO)=O)CO	261.23	$C_9H_{15}N_3O_6$	
164	Dimethyl2,6-naphthalenedicarboxylate	Taka840-65-3	C1=C2C(=CC=C1C(OC)=O)C=C(C(OC)=O)C=C2	244.25	$C_{14}H_{12}O_4$	1
165	Potassium7-hydroxy-1,3-naphthalenedisulfonate	Taka842-18-2	C1=C([S]([O-])(=O)=O)C=C2C(=C1[S]([O-])(=O)=O)C=C(O)C=C2.[K+].[K+]	380.48	$C_{10}H_6K_2O_7S_2$	
166	Phthalimide	Taka85-41-6	C1=CC=CC2=C1C(NC2=O)=O	147.13	$C_8H_5NO_2$	1
167	1-Naphthylaceticacid	Taka86-87-3	C1=CC=CC2=CC=CC(=C12)CC(O)=O	186.22	$C_{12}H_{10}O_2$	

168	7-Amino-4-hydroxy-2-naphthalenesulfonicacid	Taka87-02-5	C1=CC(=CC2=CC(=CC(=C12)O)[S](O)(=O)=O)N	239.25	$C_{10}H_9NO_4S$	1
169	2,6-Dimethylaniline	Taka87-62-7	C1=CC=C(C(=C1C)N)C	121.18	$C_8H_{11}N$	1
170	Chloropentabromocyclohexane	Taka87-84-3	C1(C(C(C(C(C1Br)Br)Br)Br)Br)Cl	513.09	$C_6H_6Br_5Cl$	
171	2-Ethylbutyricacid	Taka88-09-5	C(C(C(O)=O)CC)C	116.16	$C_6H_{12}O_2$	
172	2-tert-Butylphenol	Taka88-18-6	C1=CC=CC(=C1C(C)(C)C)O	150.22	$C_{10}H_{14}O$	1
173	o-Toluenesulfonamide	Taka88-19-7	c1(c(cccc1)C)S(=O)(=O)N	171.22	$C_7H_9NO_2S$	
174	2-Amino-5-methylbenzenesulfonicacid	Taka88-44-8	C1=C(C)C=CC(=C1[S](=O)(=O)O)N	187.22	$C_7H_9NO_3S$	1
175	2-Amino-5-chloro-4-methyl-benzenesulfonicacid	Taka88-53-9	C1=C([S](O)(=O)=O)C(=CC(=C1Cl)C)N	221.66	$C_7H_8ClNO_3S$	1
176	6-tert-Butyl-m-cresol	Taka88-60-8	C(c1c(cc(C)cc1)O)(C)(C)C	164.25	$C_{11}H_{16}O$	1
177	2,4-Dimethylbenzenesulfonicacid	Taka88-61-9	C1=CC(=CC(=C1[S](O)(=O)=O)C)C	186.23	$C_8H_{10}O_3S$	1
178	2,4,6-Trinitrophenol	Taka88-89-1	C1=C([N+]([O-])=O)C=C([N+]([O-])=O)C(=C1[N+]([O-])=O)O	229.10	$C_6H_3N_3O_7$	
179	1,2,4-Benzenetricarboxylic acid,trioctylester	Taka89-04-3	C1=C(C(=CC=C1C(OCCCCCCCC)=O)C(OCCCCCCCC)=O)C(OCCCCCCCC)=O	546.78	$C_{33}H_{54}O_6$	
180	benzene-1,2,4,5-tetracarboxylic	Taka89-05-4	c1(c(cc(C(O)=O)c(c1)C(O)=O)C(O)=O)C(O)=O	254.15	$C_{10}H_6O_8$	1
181	1,4-Dichloro-2-nitrobenzene	Taka89-61-2	C1=C(Cl)C=CC(=C1[N+](=O)[O-])Cl	192.00	$C_6H_3Cl_2NO_2$	1
182	o-sec-Butylphenol	Taka89-72-5	c1(c(cccc1)O)[C@@H](CC)C	150.22	$C_{10}H_{14}O$	
183	Thymol	Taka89-83-8	C1=C(C(=CC(=C1)C)O)C(C)C	150.22	$C_{10}H_{14}O$	1
184	2-Hydroxybenzaldehyde	Taka90-02-8	C1=CC=CC(=C1C=O)O	122.12	$C_7H_6O_2$	
185	1-Chloronaphthalene	Taka90-13-1	c12c(c(ccc1)Cl)cccc2	162.62	$C_{10}H_7Cl$	1
186	1,2-Dicyanobenzene	Taka91-15-6	C1=CC=CC(=C1C#N)C#N	128.13	$C_8H_4N_2$	1
187	DecahydroNaphthalene	Taka91-17-8	C12C(CCCC1)CCCC2	138.25	$C_{10}H_{18}$	
188	2,4-Diamino-6-phenyl-s-triazine	Taka91-76-9	C1=CC=CC=C1C2=NC(=NC(=N2)N)N	187.20	$C_9H_9N_5$	
189	AzoicCC5	Taka91-96-3	C2=C(C1=CC(=C(NC(CC(C)=O)=O)C=C1)C)C=CC(=C2C)NC(CC(C)=O)=O	380.44	$C_{22}H_{24}N_2O_4$	

190	2-Hydroxypropylmethacrylate	Taka923-26-2	C(OC(C(C)=C)=O)C(C)O	144.17	$C_7H_{12}O_3$	
191	AzoicCC2	Taka92-77-3	O=C(Nc1ccccc1)c1c(O)cc2c(cccc2)c1	263.29	$C_{17}H_{13}NO_2$	1
192	4,4'-Biphenyldiol	Taka92-88-6	C2=C(C1=CC=C(O)C=C1)C=CC(=C2)O	186.21	$C_{12}H_{10}O_2$	
193	o-Acetoacetotoluidide	Taka93-68-5	C1=CC=CC(=C1NC(CC(C)=O)=O)C	191.23	$C_{11}H_{13}NO_2$	
194	2-(4-Morpholinyldithio)benzothiazole	Taka95-32-9	C1=CC=CC3=C1N=C(SSN2CCOCC2)S3	284.43	$C_{11}H_{12}N_2OS_3$	1
195	N-Cyclohexyl-2-benzothiazolesulfenamide	Taka95-33-0	c12c(sc(n1)SNC1CCCCC1)cccc2	264.43	$C_{13}H_{16}N_2S_2$	1
196	o-Dichlorobenzene	Taka95-50-1	C1=C(C(=CC=C1)Cl)Cl	147.00	$C_6H_4Cl_2$	1
197	2-Chlorophenol	Taka95-57-8	C1=C(C(=CC=C1)Cl)O	128.56	C_6H_5ClO	1
198	1,2,4-Trimethylbenzene	Taka95-63-6	C1=C(C)C=CC(=C1C)C	120.20	C_9H_{12}	
199	3,4-Dimethylaniline	Taka95-64-7	c1(c(ccc(c1)N)C)C	121.20	$C_8H_{11}N$	1
200	Ethylmethylketoxime	Taka96-29-7	C(\C(=N\O)C)C	87.12	C_4H_9NO	
201	2-Imidazolidinethione	Taka96-45-7	C1NC(NC1)=S	102.16	$C_3H_6N_2S$	
202	4,4'-Thiobis(6-tert-butyl-m-cresol)	Taka96-69-5	C1=C(C(C)(C)C)C(=CC(=C1SC2=CC(=C(C=C2C)O)C(C)(C)C)C)O	358.54	$C_{22}H_{30}O_2S$	1
203	2,4-Di-tert-butylphenol	Taka96-76-4	C1=C(C=CC(=C1C(C)(C)C)O)C(C)(C)C	206.32	$C_{14}H_{22}O$	1
204	1,3-Bis(2-methylphenyl)guanidine	Taka97-39-2	C2=C(NC(N)=NC1=CC=CC=C1C)C(=CC=C2)C	239.32	$C_{15}H_{17}N_3$	1
205	4-Nitro-o-anisidine	Taka97-52-9	C1=C(C=CC(=C1OC)N)[N+](=O)[O-]	168.17	$C_7H_8N_2O_3$	1
206	Butylmethacrylate	Taka97-88-1	C(OC(C(C)=C)=O)CCC	142.20	$C_8H_{14}O_2$	
207	Tetrahydrofurfurylalcohol	Taka97-99-4	C(C1CCCO1)O	102.13	$C_5H_{10}O_2$	1
208	Trifluoromethylbenzene	Taka98-08-8	C1=C(C=CC=C1)C(F)(F)F	146.11	$C_7H_5F_3$	1
209	Benzenesulfonamide	Taka98-10-2	c1(ccccc1)S(N)(=O)=O	157.19	$C_6H_7NO_2S$	
210	p-tert-Butyltoluene	Taka98-51-1	C1=C(C(C)(C)C)C=CC(=C1)C	148.24	$C_{11}H_{16}$	
211	p-tert-Butylphenol	Taka98-54-4	C1=C(C(C)(C)C)C=CC(=C1)O	150.22	$C_{10}H_{14}O$	1
212	1-Methylethenylbenzene	Taka98-83-9	c1(ccccc1)C(C)=C	118.19	C_9H_{10}	1
213	3-Methylbenzoicacid	Taka99-04-7	C1=C(C=CC=C1C)C(O)=O	136.15	$C_8H_8O_2$	
214	3-Nitrobenzenamine	Taka99-09-2	C1=C(C=CC=C1[N+](=O)[O-])N	138.13	$C_6H_6N_2O_2$	

215	4-(1-Methylpropyl)phenol	Taka99-71-8	c1(ccc(O)cc1)[C@@H](CC)C	150.24	$C_{10}H_{14}O$	1
216	4-(1-Methylethyl)aniline	Taka99-88-7	C1=C(C(C)C)C=CC(=C1)N	135.21	$C_9H_{13}N$	1
217	4-Methylbenzoicacid	Taka99-94-5	c1(C(O)=O)ccc(C)cc1	136.15	$C_8H_8O_2$	
218	4-Hydroxybenzoic	Taka99-96-7	C1=CC(=CC=C1C(O)=O)O	138.13	$C_7H_6O_3$	

[a] Compound ID is “Taka” + CAS number. CAS numbers are unique numerical identifiers assigned by the Chemical Abstracts Service (CAS)

[b] Molecular weight

[c] 1 if the compound is contained in the 114Model

II. Experimental Data

No.	Observed Data					Calculated Data	
	Study[a]	Duration (days)	Institu-tion[b]	NOEL (mg/kg/day)	NOEL (mmol/kg/day) (log scale)	Predicted Value	Residual Value
1	A	28	1	20	-0.7207	-0.8985	0.1778
2	A	28	7	5	-1.3186	-1.0270	-0.2916
3	A	28	5	12.5	-0.9249	-0.8985	-0.0264
4	A	28	3	50	-0.3624	-0.6880	0.3256
5	A	28	2	2	-2.1257	-1.3050	-0.8207
6	A	28	3	20	-0.9574	-0.9838	0.0264
7	A	28	5	10	-1.3248	-0.9358	-0.3890
8	B	48	4	1000	0.6611	0.0994	0.5618
9	A	28	3	25	-0.8409	-0.5402	-0.3007
10	B	42	3	300	-0.1385	-0.1548	0.0163
11	A	28	6	8	-1.2908	-0.6992	-0.5916
12	A	28	2	1	-2.0835	-1.3510	-0.7325
13	A	28	5	50	-0.4321	-0.8484	0.4163
14	B	51	5	30	-0.6507	-0.8981	0.2474
15	B	54	6	50	-0.5688	-0.4947	-0.0741
16	B	49	7	1000	0.9351	0.0980	0.8371
17	A	28	4	1000	0.5877	-0.1566	0.7443
18	A	28	2	4	-1.7707	-0.8198	-0.9509
19	A	28	7	20	-0.8081	-0.7730	-0.0351
20	B	47	0	10	-1.1528	-0.4613	-0.6915
21	A	28	1	100	-0.0340	-0.7656	0.7316
22	B	45	2	300	0.3560	0.0014	0.3546
23	A	28	7	10	-1.0835	-0.9283	-0.1552
24	A	28	2	300	0.3764	-0.5628	0.9392
25	B	48	2	600	0.6673	-0.4126	1.0800
26	B	46	8	5	-1.2700	-0.8367	-0.4333
27	A	28	6	10	-1.3051	-0.7803	-0.5248
28	A	28	3	20	-0.8961	-0.7808	-0.1153
29	B	42	3	25	-0.5271	-0.7871	0.2600

30	A	28	5	1000	0.2269	-0.2295	0.4564
31	B	49	7	30	-0.7435	-0.6815	-0.0620
32	A	28	4	200	0.0501	-0.4086	0.4587
33	A	28	6	60	-0.2395	-0.5961	0.3566
34	B	55	5	1000	0.6689	0.0472	0.6217
35	B	35	4	10	-1.1652	-0.7398	-0.4254
36	B	46	1	100	-0.1940	-0.7443	0.5503
37	A	28	5	50	-0.5730	-0.6837	0.1107
38	B	42	3	1000	0.4678	-0.4757	0.9435
39	B	48	6	500	0.6228	-0.2871	0.9099
40	B	46	1	100	-0.1341	-0.1785	0.0444
41	B	42	3	30	-0.7298	-0.9053	0.1755
42	B	48	5	100	-0.5196	-0.7484	0.2288
43	A	28	2	8	-1.7249	-1.1570	-0.5679
44	B	42	3	10	-1.7250	-0.5161	-1.2090
45	D	52	8	12.5	-1.4352	-1.3920	-0.0432
46	B	50	6	175	-0.0938	0.3203	-0.4141
47	A	28	1	300	0.2386	0.1124	0.1262
48	B	48	6	100	-0.2431	-0.6254	0.3823
49	A	28	1	100	-0.0869	-0.7727	0.6858
50	B	42	3	20	-0.8330	-0.7410	-0.0920
51	A	28	4	20	-0.7370	-0.6566	-0.0804
52	B	45	2	30	-0.5880	-0.5307	-0.0573
53	A	28	6	100	-0.1211	-0.6656	0.5445
54	C	98	3	300	0.4124	-0.2560	0.6684
55	B	46	5	100	-0.0177	-0.3467	0.3290
56	A	28	2	60	-0.3016	-0.6424	0.3408
57	A	28	3	300	0.1246	0.1907	-0.0661
58	A	28	3	300	0.0875	0.3518	-0.2643
59	B	53	8	30	-0.6375	-0.8179	0.1804
60	B	42	3	1000	0.3659	0.7002	-0.3343
61	A	28	7	300	-0.0648	0.3523	-0.4171
62	A	28	4	15	-1.1385	-0.7399	-0.3986
63	B	52	2	2	-2.0907	-1.0430	-1.0480
64	D	45	5	50	-0.4352	-0.6876	0.2524

65	A	28	4	120	-0.5394	-0.8681	0.3287
66	A	28	12	10	-1.1373	-0.7357	-0.4016
67	A	28	2	60	-0.3760	-1.0020	0.6260
68	A	28	1	300	0.0224	-0.0945	0.1169
69	B	42	1	40	-1.3590	-0.6269	-0.7321
70	B	46	8	62.5	-0.6041	-1.1340	0.5299
71	A	28	2	40	-0.4480	-0.7925	0.3445
72	B	48	5	6	-1.4730	-1.3350	-0.1380
73	A	28	1	100	-0.1710	-0.8264	0.6554
74	A	28	1	40	-0.6350	-0.8103	0.1753
75	A	28	5	20	-1.0006	-0.7969	-0.2037
76	A	28	8	30	-0.7221	-0.6121	-0.1100
77	A	28	3	100	-0.1341	-1.0560	0.9218
78	B	43	4	4	-1.5539	-0.5558	-0.9981
79	B	49	8	200	0.0171	-0.5349	0.5520
80	A	28	6	15	-1.1670	-0.7979	-0.3691
81	A	28	7	30	-0.7331	-0.9466	0.2135
82	B	42	4	60	-0.3749	-0.6662	0.2913
83	D	46	1	100	-0.1851	-0.6366	0.4515
84	A	28	4	20	-1.1341	-1.1480	0.0139
85	A	28	1	100	-0.3143	-0.1698	-0.1445
86	A	28	6	1000	0.1056	-0.4240	0.5296
87	A	28	2	40	-0.5322	-0.7913	0.2591
88	A	28	3	60	-0.5447	-0.9353	0.3906
89	B	43	4	40	-0.5945	-0.4955	-0.0990
90	A	28	1	10	-1.2311	-1.1390	-0.0921
91	B	53	6	1000	0.3585	-0.9006	1.2590
92	B	44	2	5	-1.5843	-0.9384	-0.6459
93	A	28	5	1000	0.2621	-0.3205	0.5826
94	B	46	1	12	-1.0769	-0.6665	-0.4104
95	A	28	4	20	-0.9644	-1.0530	0.0886
96	A	28	1	62.5	-0.7634	-0.5212	-0.2422
97	B	55	2	20	-1.2701	0.0890	-1.3590
98	A	28	6	15	-1.1938	-1.0770	-0.1168
99	B	49	7	4	-1.4318	-0.5400	-0.8918

100	A	28	5	100	-0.5264	-1.3420	0.8156
101	A	28	1	30	-0.6506	-0.6826	0.0320
102	A	28	3	100	-0.3550	-0.7559	0.4010
103	B	49	6	300	0.4045	-0.5796	0.9841
104	B	47	4	12	-0.7137	-0.6587	-0.0550
105	D	46	4	1000	1.0753	-0.5634	1.6390
106	B	51	2	25	-1.1419	-0.7716	-0.3703
107	A	28	3	500	0.3815	-0.4989	0.8804
108	A	28	3	300	-0.0904	-0.4550	0.3646
109	A	28	2	10	-1.2651	-0.7419	-0.5232
110	A	28	2	20	-0.6485	-0.5033	-0.1452
111	A	28	2	10	-1.3010	-0.3910	-0.9100
112	A	28	4	1000	0.5593	-0.4076	0.9669
113	A	28	4	100	-0.3146	-0.7083	0.3937
114	D	46	1	200	0.1185	-0.6946	0.8131
115	B	42	4	10	-1.0741	-0.8371	-0.2370
116	A	28	8	40	-0.7529	-0.7422	-0.0107
117	A	28	2	1000	0.4669	1.3380	-0.8711
118	B	42	3	0.5	-2.1651	-0.7118	-1.4530
119	A	28	2	60	-0.2944	-0.6196	0.3252
120	A	28	5	30	-0.7917	-0.8518	0.0601
121	A	28	3	20	-0.9597	-0.9051	-0.0546
122	B	45	4	200	0.3462	-0.3852	0.7314
123	A	28	4	20	-0.8519	-0.5176	-0.3343
124	A	28	2	60	-0.3759	-0.8269	0.4510
125	A	28	1	100	-0.3269	-0.9612	0.6343
126	A	28	10	100	-0.3245	-0.1145	-0.2101
127	A	28	3	1000	0.7954	0.5063	0.2891
128	B	52	5	100	-0.4316	-0.3753	-0.0563
129	B	48	4	2	-1.9059	-1.1520	-0.7539
130	A	28	1	300	0.3902	-0.7504	1.1410
131	A	28	3	60	-0.5234	-0.8452	0.3218
132	A	28	1	1.25	-2.0108	-1.2200	-0.7908
133	A	28	5	1000	0.6728	-0.7426	1.4150
134	D	53	3	100	-0.4284	0.4393	-0.8677

135	A	28	1	100	-0.1340	-0.3839	0.2499
136	B	47	4	300	-0.1527	-0.1095	-0.0432
137	A	28	3	1000	0.2072	0.1095	0.0977
138	A	28	5	1000	0.7118	0.0069	0.7049
139	B	42	4	10	-1.4337	-0.4655	-0.9682
140	B	53	5	30	-0.9799	-0.1669	-0.8130
141	B	49	8	30	-0.8203	-0.4723	-0.3480
142	B	42	1	40	-0.3230	-0.8084	0.4853
143	B	54	3	1000	0.1932	-0.0117	0.2049
144	B	42	3	40	-0.1696	-0.7706	0.6010
145	B	47	4	4	-1.4704	-0.6591	-0.8114
146	B	46	2	2	-1.7958	-0.8781	-0.9178
147	A	28	6	12	-1.3661	-1.2070	-0.1591
148	A	28	5	30	-0.7490	-0.7882	0.0392
149	B	42	3	300	0.3974	-0.2626	0.6600
150	B	52	5	200	0.1734	-0.2226	0.3960
151	A	28	2	40	-0.8610	-0.7244	-0.1366
152	B	45	4	6	-1.0736	-0.6448	-0.4288
153	A	28	2	6	-1.7605	-0.9502	-0.8103
154	A	28	3	4	-1.8267	-1.3550	-0.4717
155	A	28	4	1000	0.2645	-0.8891	1.1540
156	D	46	6	10	-1.3984	-0.3999	-0.9985
157	A	28	5	60	-0.6538	-0.8719	0.2181
158	A	28	1	10	-1.5544	-0.3625	-1.1920
159	B	49	8	200	-0.0478	0.4105	-0.4583
160	A	28	1	15	-1.1861	-0.6754	-0.5107
161	A	28	6	160	-0.0029	-0.6711	0.6682
162	A	28	6	12	-1.1090	-0.9341	-0.1749
163	B	49	8	300	0.0601	0.0068	0.0533
164	B	53	8	1000	0.6122	0.1407	0.4715
165	A	28	1	100	-0.5803	0.4899	-1.0700
166	B	46	1	500	0.5313	-0.0930	0.6242
167	A	28	5	25	-0.8721	-0.7576	-0.1145
168	A	28	7	1000	0.6211	0.9887	-0.3675
169	B	55	2	10	-1.0834	-1.0710	-0.0124

170	A	28	4	140	-0.5641	-0.8672	0.3031
171	B	42	3	10	-1.0651	-0.4839	-0.5812
172	A	28	4	20	-0.8757	-0.9778	0.1021
173	A	28	3	20	-0.9325	-0.6086	-0.3239
174	A	28	2	300	0.2048	-0.1006	0.3054
175	A	28	5	1000	0.6543	0.1803	0.4740
176	B	42	3	12.5	-1.1186	-1.1500	0.0314
177	B	46	11	100	-0.2700	-0.0505	-0.2196
178	A	28	4	4	-1.7580	-0.6247	-1.1330
179	B	42	3	30	-1.2607	-0.3163	-0.9444
180	B	46	6	300	0.0720	0.0961	-0.0240
181	D	49	8	20	-0.9823	-0.9093	-0.0730
182	B	42	3	12	-1.0975	-0.8043	-0.2933
183	B	43	4	8	-1.2736	-1.1300	-0.1436
184	B	46	6	10	-1.0868	-0.6614	-0.4254
185	A	28	9	30	-0.7341	-0.8531	0.1191
186	B	46	4	1	-2.1077	-1.2200	-0.8877
187	A	28	1	40	-0.5386	-0.7963	0.2577
188	B	49	7	4	-1.6702	-0.5792	-1.0910
189	A	28	6	8	-1.6772	-0.7243	-0.9529
190	B	49	8	300	0.3182	-0.2376	0.5559
191	A	28	2	1000	0.5796	0.2196	0.3600
192	B	52	3	8	-1.3669	-0.6423	-0.7246
193	B	45	2	25	-0.8836	-0.7584	-0.1252
194	D	52	8	100	-0.4540	-0.6774	0.2234
195	A	28	2	80	-0.5192	-0.7321	0.2129
196	A	28	3	20	-0.8663	-0.8804	0.0141
197	A	28	4	40	-0.5070	-0.7730	0.2660
198	A	28	8	100	-0.0799	-1.0400	0.9601
199	A	28	5	10	-1.0835	-0.9296	-0.1539
200	A	28	1	4	-1.3381	-0.6290	-0.7091
201	A	28	4	1	-2.0093	-0.6680	-1.3410
202	A	28	6	15	-1.3784	-1.0860	-0.2925
203	A	28	7	20	-1.0135	-1.0770	0.0635
204	A	28	7	7.5	-1.5039	-1.0970	-0.4069

205	A	28	5	30	-0.7486	-0.6532	-0.0954
206	B	45	2	30	-0.6758	-0.4727	-0.2031
207	A	28	2	40	-0.4071	-0.5411	0.1340
208	B	49	7	20	-0.8636	-1.0490	0.1854
209	A	28	2	6	-1.4183	-0.5919	-0.8264
210	A	28	8	1.5	-1.9949	-1.1340	-0.8609
211	B	42	3	60	-0.3986	-0.9103	0.5117
212	B	45	4	40	-0.4705	-0.7944	0.3239
213	B	45	2	100	-0.1340	-0.4523	0.3183
214	D	42	3	5	-1.4413	-0.6481	-0.7932
215	A	28	3	100	-0.1768	-0.7368	0.5600
216	B	48	5	6	-1.3529	-1.0310	-0.3219
217	A	28	3	300	0.3431	-0.4523	0.7954
218	B	42	3	1000	0.8597	-0.3239	1.1840

[a] (Study)

A: 28-day repeated oral dose toxicity study

B: Repeated dose and reproductive/developmental toxicity study

C: One-generation reproduction toxicity

D: Simple oral administration reproductive toxicity study

[b] (Institution)

1: Safety Research Institute for Chemical Compounds Co., Ltd.

2: Research Institute for Animal Science in Biochemistry and Toxicology

3: Food and Drug Safety center, Hatano Research Institute, Japan

4: Mitsubishi Chemical Medience Corporation

5: Public Interest Incorporated Foundation BioSafety Research Center

6: Bozo Research Center

7: Panapharm Laboratories Co., Ltd.

8: Nihon Bioresearch Inc.

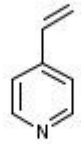
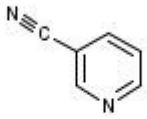
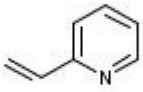
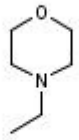
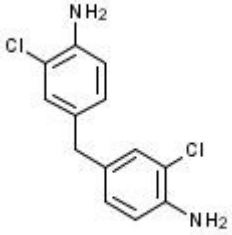
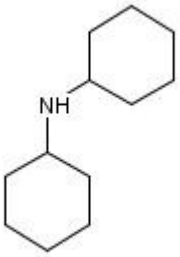
9: Drug Safety Testing Center Co., Ltd.

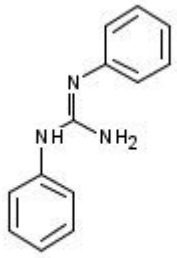
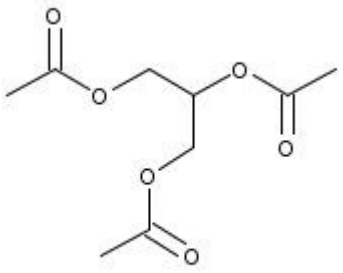
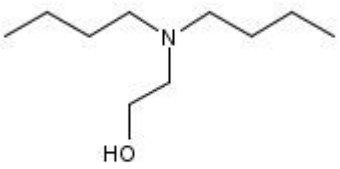
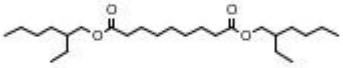
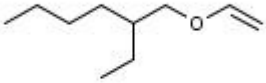
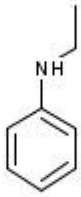
10: NOTOS B.V. 5231 DD' sHertogenbosch

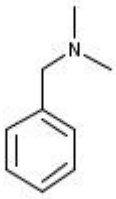
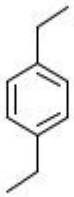
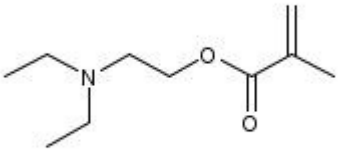
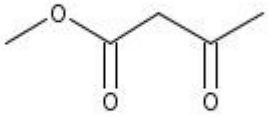
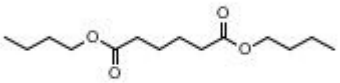
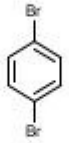
11: Japan Bioassay Research Center

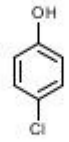
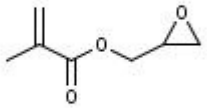
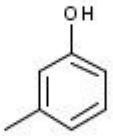
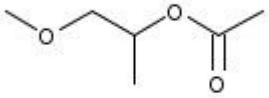
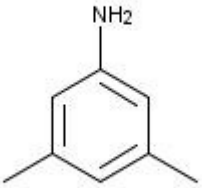
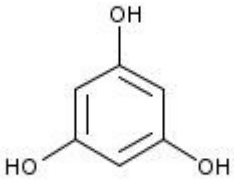
12: National Institute of Health Science

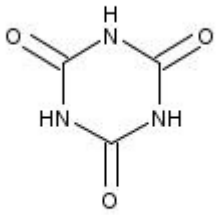
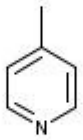
III. Chemical Structures of the 218 Chemical Compounds

No.	Structure	No.	Structure
1	 Taka100-43-6	2	 Taka100-54-9
3	 Taka100-69-6	4	 Taka100-74-3
5	 Taka101-14-4	6	 Taka101-83-7

7	 Taka102-06-7	8	 Taka102-76-1
9	 Taka102-81-8	10	 Taka103-24-2
11	 Taka103-44-6	12	 Taka103-69-5

13	 Taka103-83-3	14	 Taka105-05-5
15	 Taka105-16-8	16	 Taka105-45-3
17	 Taka105-99-7	18	 Taka106-37-6

19	 Taka106-48-9	20	 Taka106-91-2
21	 Taka108-39-4	22	 Taka108-65-6
23	 Taka108-69-0	24	 Taka108-73-6

25	 Taka108-80-5	26	 Taka108-89-4
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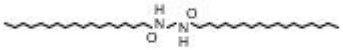
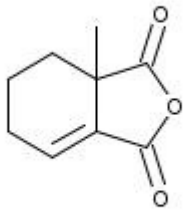
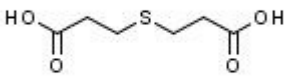
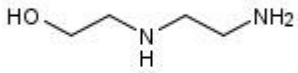
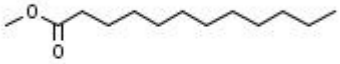
29	 Taka110-02-1	30	 Taka110-30-5

31	 Taka11070-44-3	32	 Taka111-17-1
33	 Taka111-41-1	34	 Taka111-82-0
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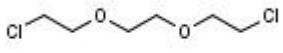
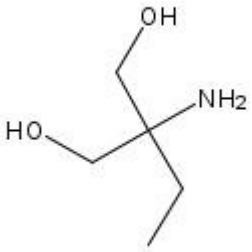
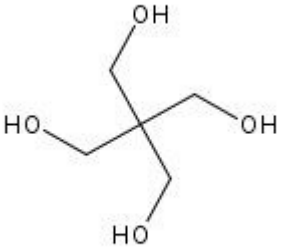
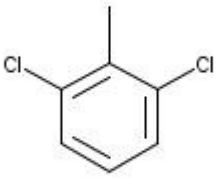
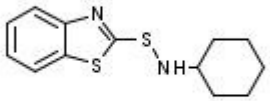
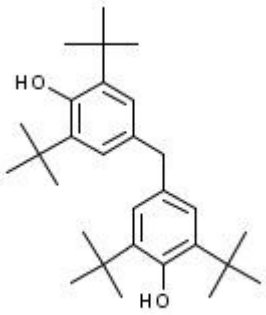
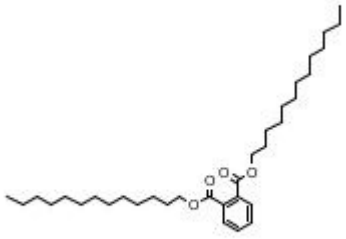
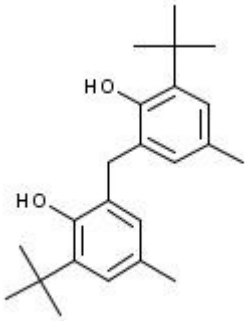
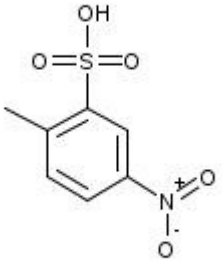
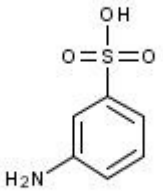
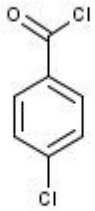
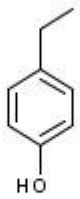
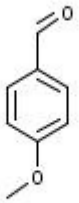
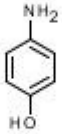
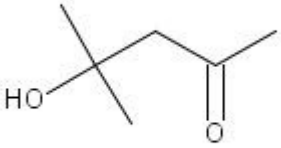
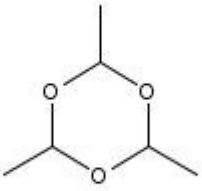
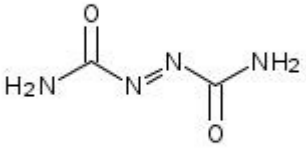
37	 Taka112-26-5	38	 Taka112-85-6
39	 Taka115-70-8	40	 Taka115-77-5
41	 Taka118-69-4	42	 Taka118-79-6

43	 Taka118-82-1	44	 Taka119-06-2
45	 Taka119-47-1	46	 Taka121-03-9
47	 Taka121-47-1	48	 Taka122-01-0

49	 Taka123-07-9	50	 Taka123-11-5
51	 Taka123-30-8	52	 Taka123-42-2
53	 Taka123-63-7	54	 Taka123-77-3

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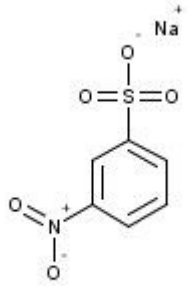
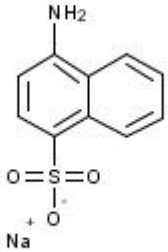
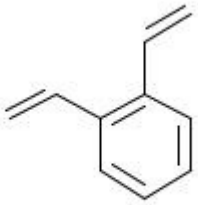
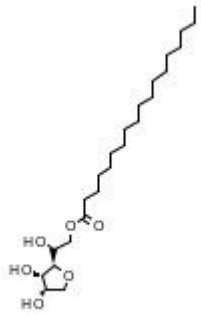
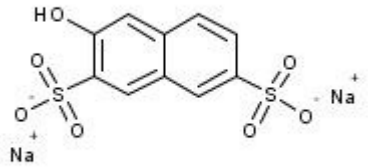
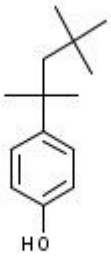
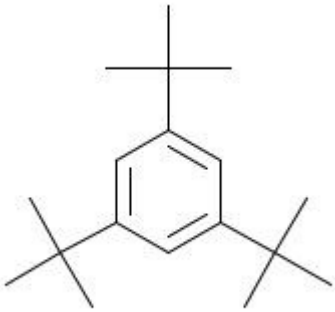
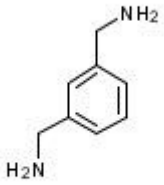
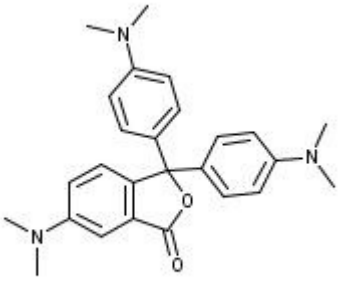
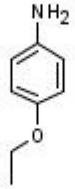
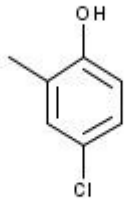
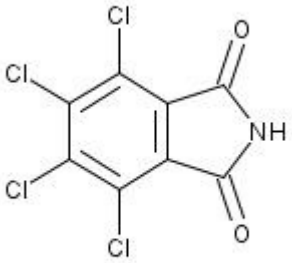
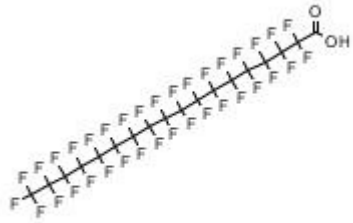
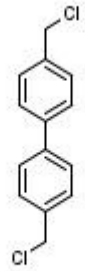
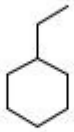
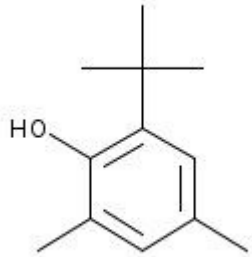
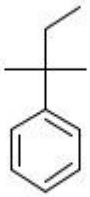
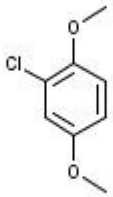
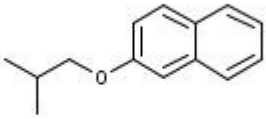
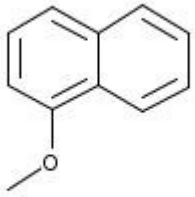
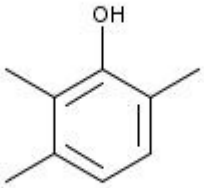
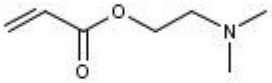
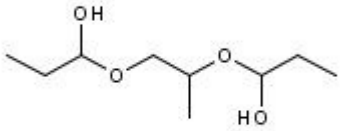
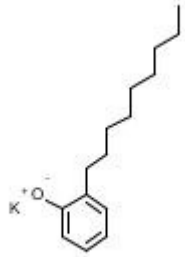
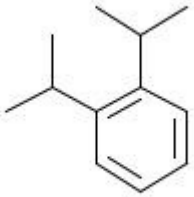
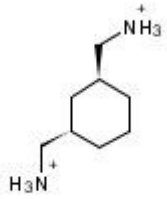
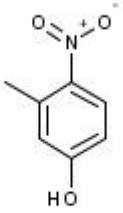
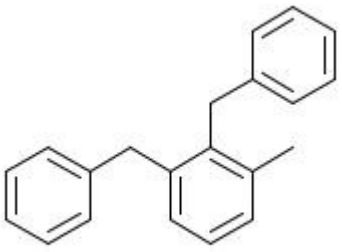
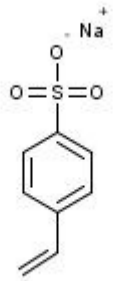
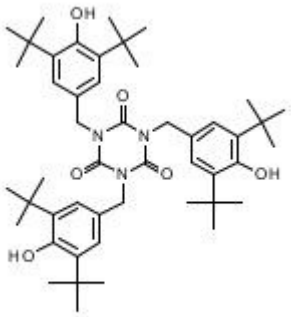
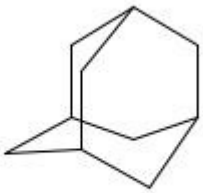
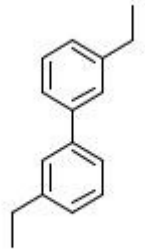
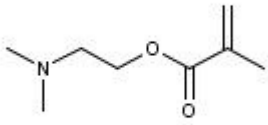
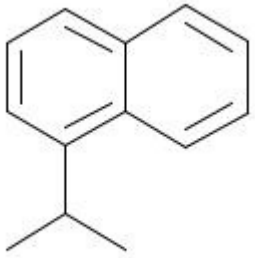
57	 Taka127-68-4	58	 Taka130-13-2
59	 Taka1321-74-0	60	 Taka1338-41-6

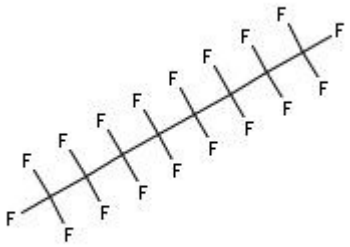
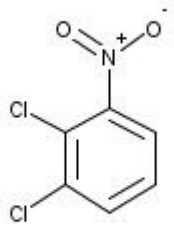
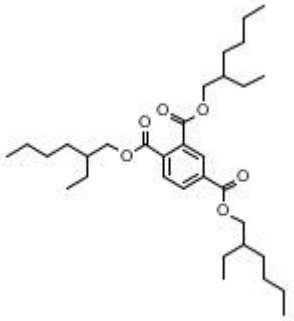
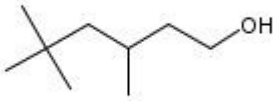
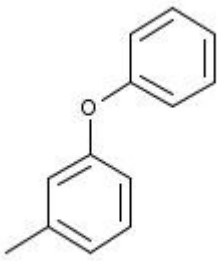
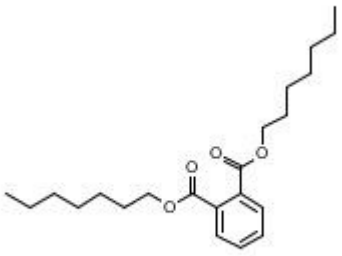
61	 Taka135-51-3	62	 Taka140-66-9
63	 Taka1460-02-2	64	 Taka1477-55-0
65	 Taka1552-42-7	66	 Taka156-43-4

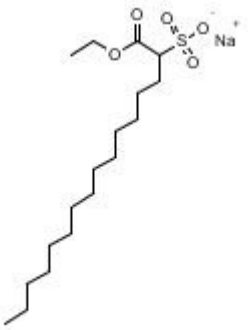
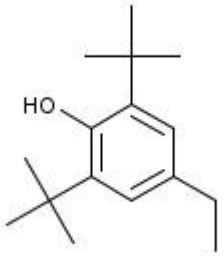
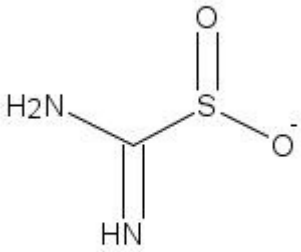
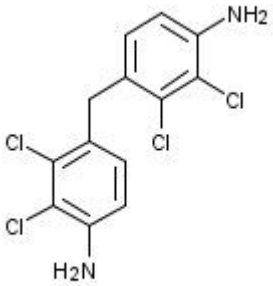
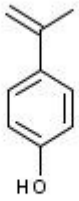
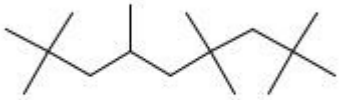
67	 Taka1570-64-5	68	 Taka1571-13-7
69	 Taka16517-11-6	70	 Taka1667-10-3
71	 Taka1678-91-7	72	 Taka1879-09-0

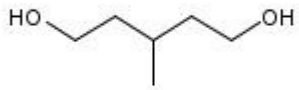
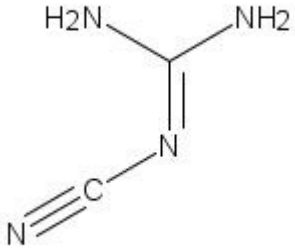
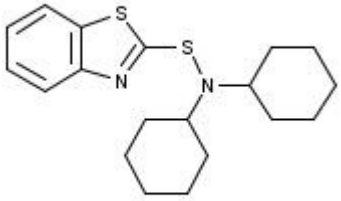
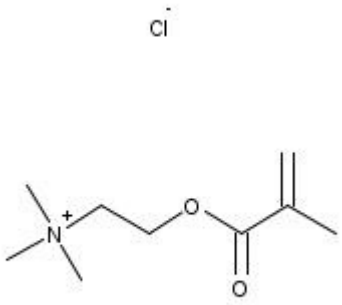
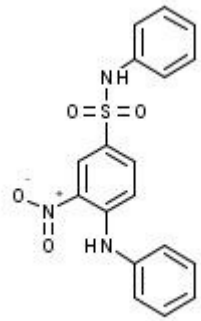
73	 Taka2049-95-8	74	 Taka2100-42-7
75	 Taka2173-57-1	76	 Taka2216-69-5
77	 Taka2416-94-6	78	 Taka2439-35-2

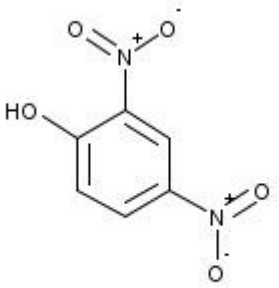
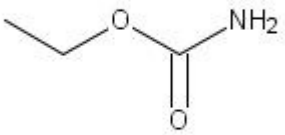
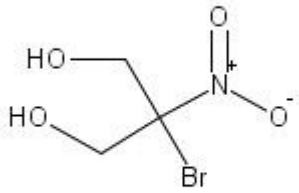
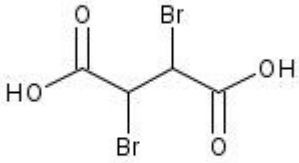
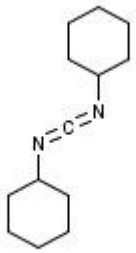
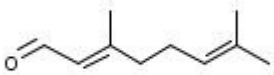
79	 Taka24800-44-0	80	 Taka25154-52-3
81	 Taka25321-09-9	82	 Taka2579-20-6
83	 Taka2581-34-2	84	 Taka26898-17-9

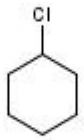
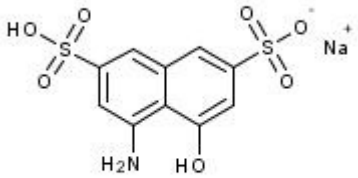
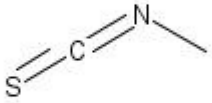
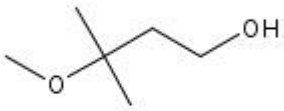
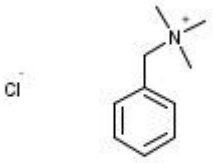
85	 Taka2695-37-6	86	 Taka27676-62-6
87	 Taka281-23-2	88	 Taka28575-17-9
89	 Taka2867-47-2	90	 Taka29253-36-9

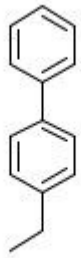
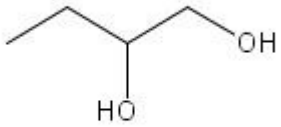
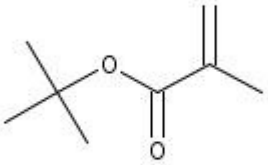
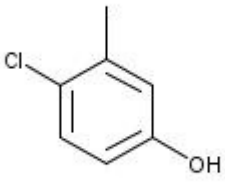
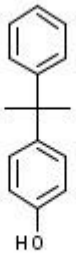
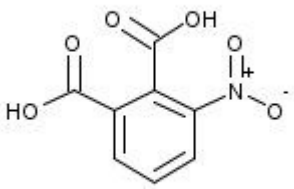
91	 Taka307-34-6	92	 Taka3209-22-1
93	 Taka3319-31-1	94	 Taka3452-97-9
95	 Taka3586-14-9	96	 Taka3648-21-3

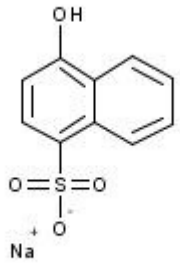
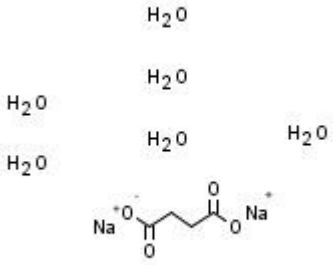
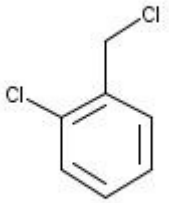
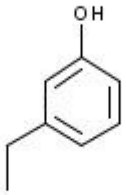
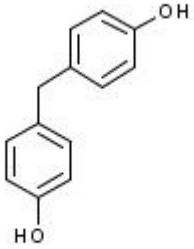
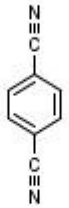
97	 Taka4016-24-4	98	 Taka4130-42-1
99	 Taka4189-44-0	100	 Taka42240-73-3
101	 Taka4286-23-1	102	 Taka4390-04-9

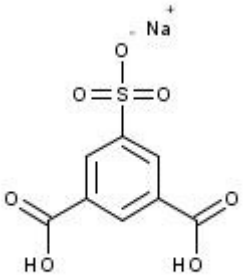
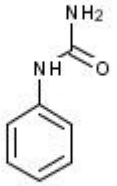
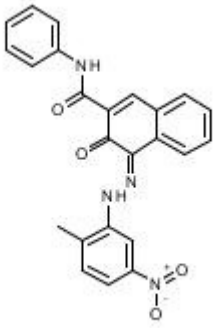
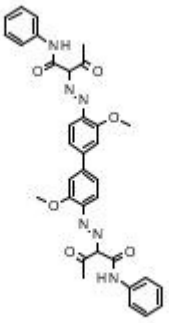
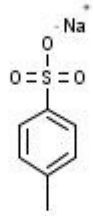
103	 Taka4457-71-0	104	 Taka4461-52-3
105	 Taka461-58-5	106	 Taka4979-32-2
107	 Taka5039-78-1	108	 Taka5124-25-4

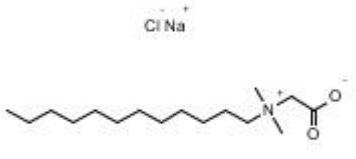
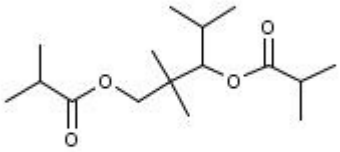
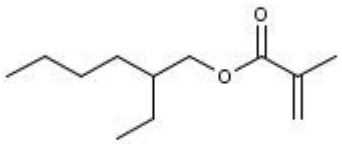
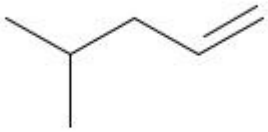
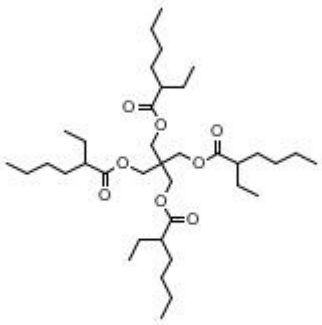
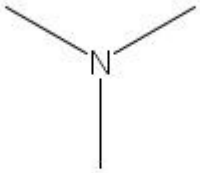
109	 Taka51-28-5	110	 Taka51-79-6
111	 Taka52-51-7	112	 Taka526-78-3
113	 Taka538-75-0	114	 Taka5392-40-5

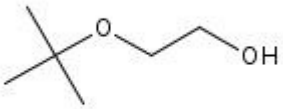
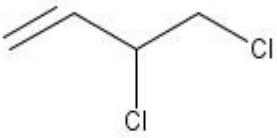
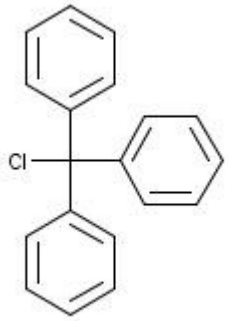
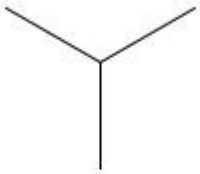
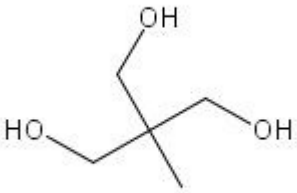
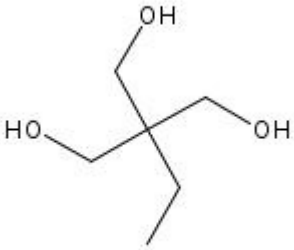
115	 Taka542-18-7	116	 Taka544-76-3
117	 Taka5460-09-3	118	 Taka556-61-6
119	 Taka56539-66-3	120	 Taka56-93-9

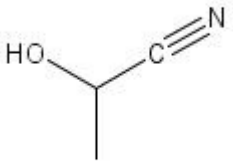
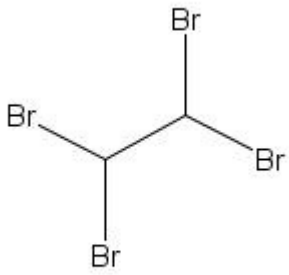
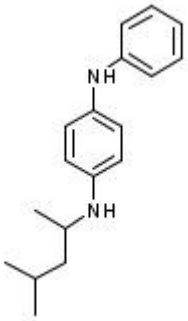
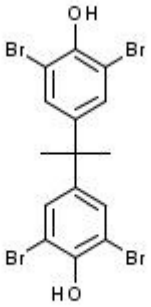
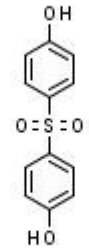
121	 Taka5707-44-8	122	 Taka584-03-2
123	 Taka585-07-9	124	 Taka59-50-7
125	 Taka599-64-4	126	 Taka603-11-2

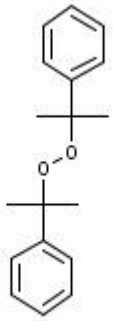
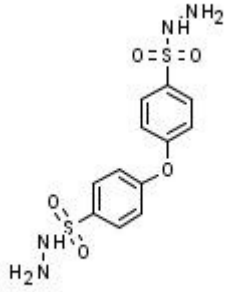
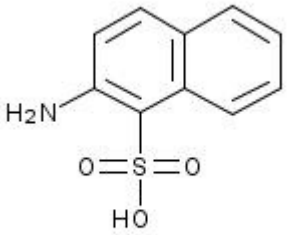
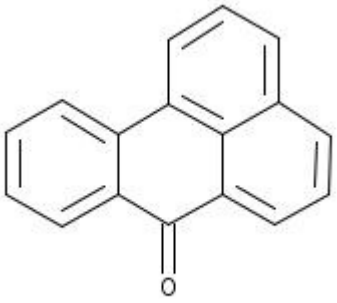
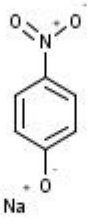
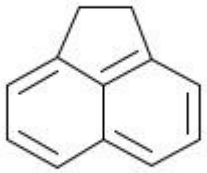
127	 Taka6099-57-6	128	 Taka6106-21-4
129	 Taka611-19-8	130	 Taka620-17-7
131	 Taka620-92-8	132	 Taka623-26-7

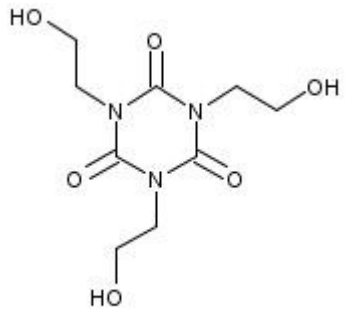
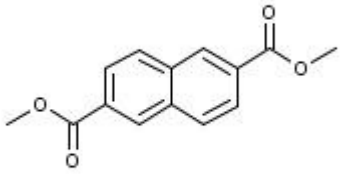
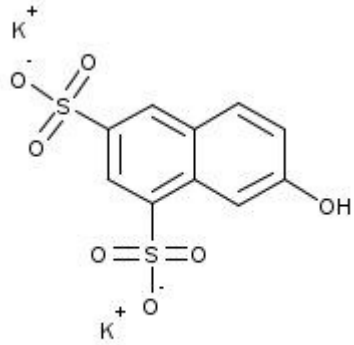
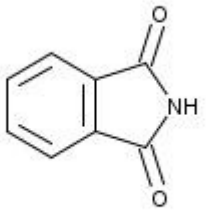
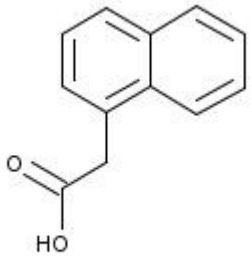
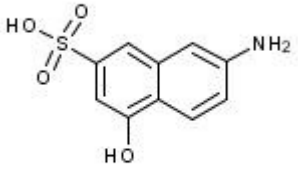
133	 Taka629-62-9	134	 Taka6362-79-4
135	 Taka64-10-8	136	 Taka6448-95-9
137	 Taka6505-28-8	138	 Taka657-84-1

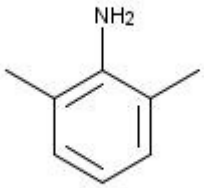
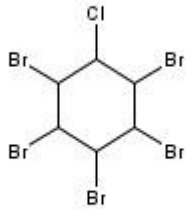
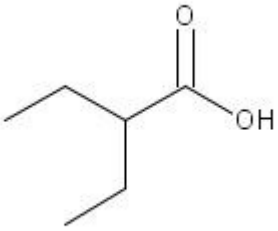
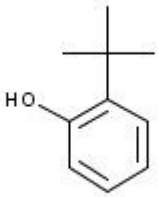
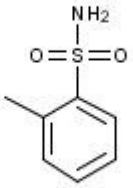
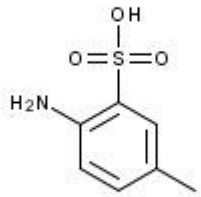
139	 Taka683-10-3	140	 Taka6846-50-0
141	 Taka688-84-6	142	 Taka691-37-2
143	 Taka7299-99-2	144	 Taka75-50-3

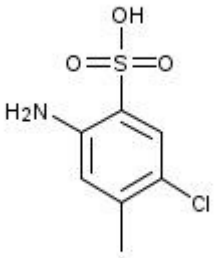
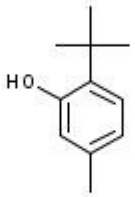
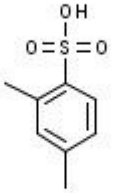
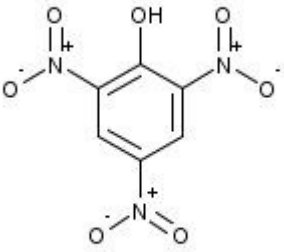
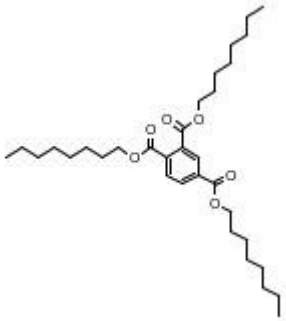
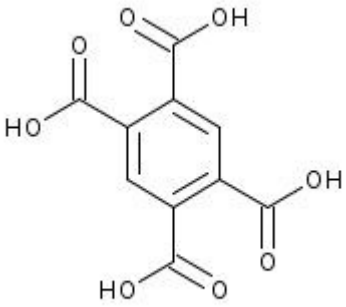
145	 Taka7580-85-0	146	 Taka760-23-6
147	 Taka76-83-5	148	 Taka7756-94-7
149	 Taka77-85-0	150	 Taka77-99-6

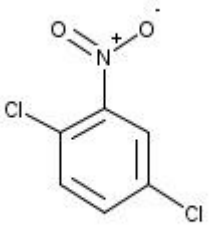
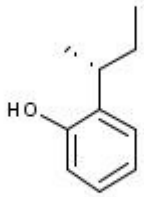
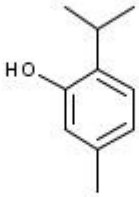
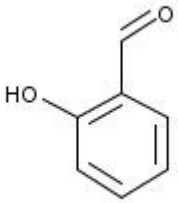
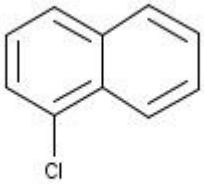
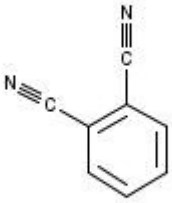
151	 Taka78-63-7	152	 Taka78-97-7
153	 Taka79-27-6	154	 Taka793-24-8
155	 Taka79-94-7	156	 Taka80-09-1

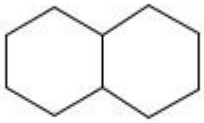
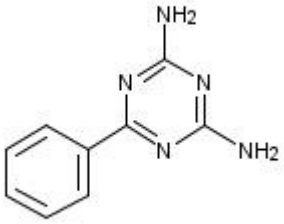
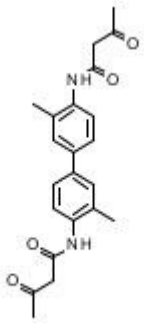
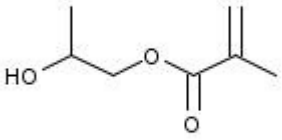
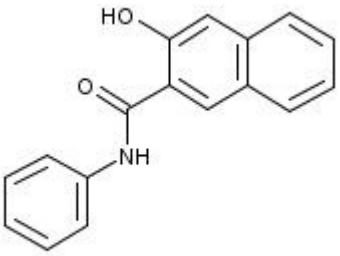
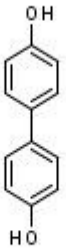
157	 Taka80-43-3	158	 Taka80-51-3
159	 Taka81-16-3	160	 Taka82-05-3
161	 Taka824-78-2	162	 Taka83-32-9

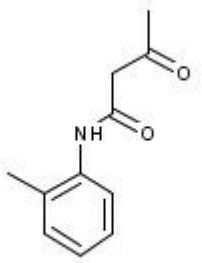
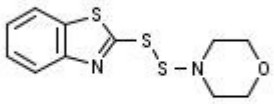
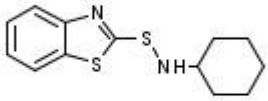
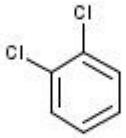
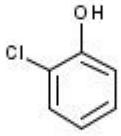
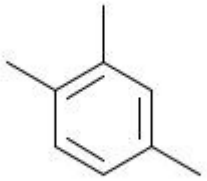
163	 Taka839-90-7	164	 Taka840-65-3
165	 Taka842-18-2	166	 Taka85-41-6
167	 Taka86-87-3	168	 Taka87-02-5

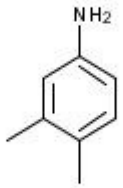
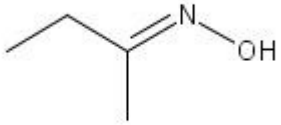
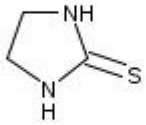
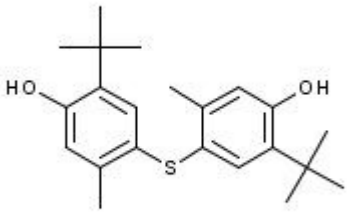
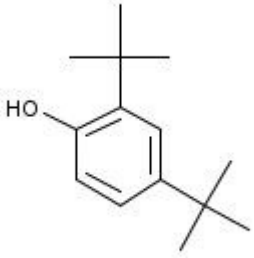
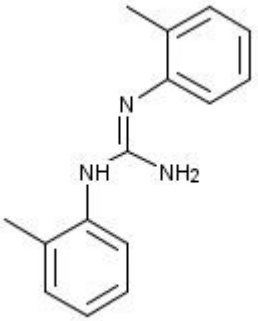
169	 Taka87-62-7	170	 Taka87-84-3
171	 Taka88-09-5	172	 Taka88-18-6
173	 Taka88-19-7	174	 Taka88-44-8

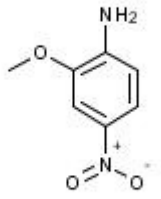
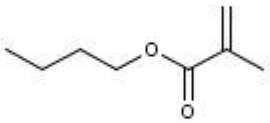
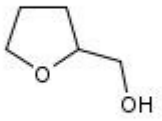
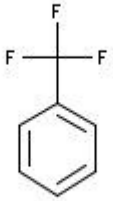
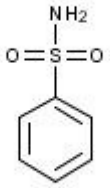
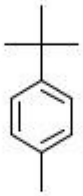
175	 Taka88-53-9	176	 Taka88-60-8
177	 Taka88-61-9	178	 Taka88-89-1
179	 Taka89-04-3	180	 Taka89-05-4

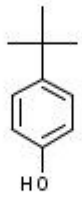
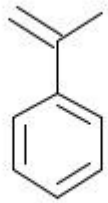
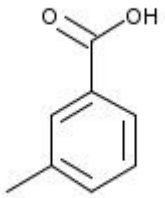
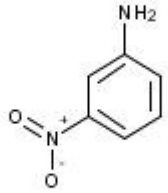
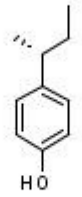
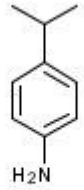
181	 Taka89-61-2	182	 Taka89-72-5
183	 Taka89-83-8	184	 Taka90-02-8
185	 Taka90-13-1	186	 Taka91-15-6

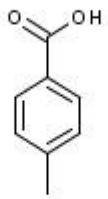
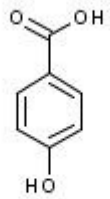
187	 Taka91-17-8	188	 Taka91-76-9
189	 Taka91-96-3	190	 Taka923-26-2
191	 Taka92-77-3	192	 Taka92-88-6

193	 Taka93-68-5	194	 Taka95-32-9
195	 Taka95-33-0	196	 Taka95-50-1
197	 Taka95-57-8	198	 Taka95-63-6

199	 Taka95-64-7	200	 Taka96-29-7
201	 Taka96-45-7	202	 Taka96-69-5
203	 Taka96-76-4	204	 Taka97-39-2

205	 Taka97-52-9	206	 Taka97-88-1
207	 Taka97-99-4	208	 Taka98-08-8
209	 Taka98-10-2	210	 Taka98-51-1

211	 Taka98-54-4	212	 Taka98-83-9
213	 Taka99-04-7	214	 Taka99-09-2
215	 Taka99-71-8	216	 Taka99-88-7

217	 Taka99-94-5	218	 Taka99-96-7