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Genotoxicity QSAR (Geno-QSAR) models for the safety prioritization of specialty chemicals

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Toxicity profiling of specialty chemicals is essential, since several studies have reported their role in acute/chronic health effects. It is voluminous to perform a battery of toxicity experiments on available specialty chemicals. In this study, we employed robust QSAR approaches to predict the carcinogenicity and mutagenicity potential for a dataset of 131 specialty chemicals utilizing machine learning tools. Four predictive approaches were selected to benchmark the reliability and applicability of the suitable genotoxicity QSAR (Geno-QSAR) models each for carcinogenicity (CAESAR, ISS, ANTARES, and ISSCAN) and mutagenicity (CAESAR, SARpy, ISS, and KNN). Five-fold statistical evaluation was performed using an external dataset of more than 2000 compounds with their known genotoxicity potential. KNN/Read across and IRFMN/ANTARES resulted as the best model for mutagenicity and carcinogenicity, respectively. Results obtained from the selected predictive models are narrowed down to the potentially safe compounds and are cross-validated with the experimental details compiled through the literature mining. Geno-QSAR approaches demonstrated in this investigation have widespread applicability for safe compound prioritization and toxicity prediction of a large number of chemicals in a lucid way.

Keywords: QSAR, specialty chemicals, genotoxicity, carcinogenicity, mutagenicity, computational toxicology.

1. Introduction

Specialty chemicals are low volume and high-value compounds, commonly used in various sub-segments on the basis of end-use and applications such as agrochemicals, colorants, construction chemicals, flavors and fragrances, paints and coatings, personal care, polymer additives, surfactants, chemicals, and water treatment chemicals. These chemicals are widely utilized by all the age groups from a newborn to an elder in most of the products available in the market today[1]. A continuously growing number of such products containing specialty chemical has developed a critical need for safety assessment and standardization. With this, generating scientifically validated safety data with an adequate screening workflow is also required to estimate the toxicity of the chemicals which are of concern regarding human health and environmental exposure. Several reports have shown that specialty chemicals are interfering with acute/chronic effects including neurological and systemic pathology, developing skin allergies, and respiratory problems, etc.[2–6]. Specialty chemicals regularly appear as the topmost common skin allergens, endocrine disruptors and also provoke respiratory disorders[7–15]. Comprehensive toxicity profiling of a large number of chemicals using *in vivo* studies on rodents and other species would probably require more than 2–3 years and relatively high cost of toxicity assessment (which might be millions of dollars) per chemical[6]. On the other side, experimental methods are resource intensive and time-consuming to perform toxicity testing of the entire list of specialty chemicals used in the large coverage of the product spectrum. The development of *in silico* models for chemical testing is one of the approaches for the rapid toxicity screening. It has emerged as one of the efficient risk assessment technique that analyzes the correlation between chemical structure and its biological properties by building a model that explains the quantitative structure-toxicity relationship[16]. A guideline by the European Chemicals Agency (ECHA) and a revised framework by European Union (EU) about registration, evaluation, authorization, and restriction

of chemicals (REACH) are formulated for chemicals testing using various alternate models including QSAR methods[17,18]. It is necessary here to point out that, the EU has prohibited animal testing of cosmetic ingredients since March 2013. These regulations necessitate a compelling need for evaluating the toxicity potential of chemicals using *in silico* tools such as QSAR for safety prioritization and formulation. Performing initial *in silico* screening for genotoxicity assessment saves cost, improves productivity and also facilitates chemists to modify compounds to reduce toxicity without losing desirable properties[19–21].

Due to the safety requirements of various regulatory agencies, it is necessary to test different toxicity endpoints such as skin irritation, penetration, sensitization, photo-toxicity, carcinogenicity and mutagenicity potential of the specialty chemicals for registration of new substances and product development[22]. Chemical structures based risk assessment of compounds using computational approaches are promising for the development of predictive toxicity model which are constructed using available experimental data for early decision making and risk assessment of chemicals. From the regulatory perspective, machine learning QSARs models have attained some degree of acceptance for genotoxicity prediction[23]. Various open sources and commercial tools which are available for predicting genotoxicity of chemicals, are mostly developed for pesticides and pharmacological impurities[24,25]. Though certain overlap exists with these groups of compound with specialty chemicals, it is essential to develop more suitable predictive models for genotoxic risk assessment. In order to identify the best predictive model for mutagenicity and carcinogenicity for specialty chemicals, we have systematically evaluated Geno-QSAR expert rule-based approaches from the structural alerts and machine learning based statistical models. To evaluate the performance of these predictive tools, we compiled and curated a large training set which comprised 2146 chemicals of known mutagenicity and carcinogenicity potential. Finally, the predictive power of the resulting Geno-QSAR models was assessed for 131 specialty chemicals and cross-validated with available experimental data.

2. Materials and methods

2.1. Data preparation

The training set for the Geno-QSAR model building was collected from two open source databases such as Carcinogenic Potency Database (CPDB)[26] and the Istituto Superiore di Sanità Chemical Carcinogens Database (ISSCAN)[27]. A total of 1229 chemicals with experimental carcinogenicity in rat and mutagenicity in *Salmonella typhimurium* have been taken from Berkeley CPDB. Chemicals with the positive experimental response at least in one sex of species were considered as carcinogenic. From ISSCAN database, 1150 chemicals were extracted along with their experimental carcinogenicity and mutagenicity data. The data extracted from this database provide identification codes for carcinogenicity and mutagenicity (Ames test) data where 3 = carcinogen/mutagen; 2 = equivocal; 1 = non-carcinogen/non-mutagen. Chemicals for the test data set were extracted from the available list of 131 specialty chemicals tested for skin absorption percentage on human/pig skin reported by Shen *et al.*[28]. They have collected 45 chemicals from the RIFM database[29] and remaining from the EDETOX database[30].

For this study, all the canonical simplified molecular input line entry system (SMILES) string of the chemicals were collected from PubChem to develop Geno-QSAR predictive model for specialty chemicals compounds using VEGA platform. These specialty chemicals are categorized into seven segments as personal care active ingredients, agrochemicals, flavours and fragrances, construction chemicals, dyes and pigments, surfactants, food additives and medication (Supporting Table 1)[31]. Many of these chemicals are overlapping in different categories[31] and used for multiple purposes/applications.

2.2. Geno-QSAR models

Benchmarking of QSAR models for toxicity prediction is necessary to fulfill the deep gap of knowledge intended for selecting potentially suitable and applicable methods with high predictive power for the specific chemical category. VEGA predictive platform is an open source environment that offers thirty-three models for various toxicity endpoints such as hepatotoxicity, developmental toxicity, persistence, log P, bioconcentration factor (BCF), carcinogenicity, mutagenicity, and skin sensitization. Several organizations including regulators and public bodies in Europe and the USA have contributed to the development of VEGA platform[32]. We selected eight models in this investigation, including CAESAR (carcinogenicity), CAESAR (mutagenicity), ISS (carcinogenicity), ISS (mutagenicity), ANTARES, IRFMN/ISSCAN, SarPy, KNN for the predictions of both carcinogenicity and

mutagenicity of chemicals. CAESAR[33] is a European Commission funded project which is dedicated to developing QSAR models for the REACH legislation. VEGA-CAESAR mutagenicity model was built on a large dataset of 4202 compounds with their Ames test results while VEGA-CAESAR carcinogenicity model was built on a dataset of 805 chemicals. CAESAR automatically calculates chemical descriptors and contains a subset of Toxtree rules. CAESAR utilizes two complementary techniques to refine its predictions: support vector machine (SVM) algorithm to build an early model with the best statistical accuracy, along with two sets of rules for the removal of false negatives based on known structural alerts from Toxtree. VEGA-SARpy (SAR in python) automatically generate SAR models by finding the relevant rules from data, without any prior knowledge[34]. The training set of SarPy is the same used for VEGA-CAESAR. The algorithm of VEGA-SARpy generates substructure fragments. Structural alerts from these fragmented candidates were selected on the basis of their prediction performance for a training set. This model classifies the chemicals either as a mutagen or non-mutagen from the presence or absence of structural alerts, respectively. KNN/Read-Across model performs a read-across on a dataset of 5770 chemicals from the Hansen dataset and also from the data produced within the Ames QSAR project carried out by the National Institute of Health Sciences of Japan[35]. The read-across model was built using the KNN approach[36]. VEGA-ISS Toxtree is based on a series of rules defined by Benigni and Bossa that detects mutagenic chemicals[37]. Toxtree includes alerts for genotoxic carcinogenicity and non-genotoxic carcinogenicity. This model compiles thirty-three structural alerts that mainly refer genotoxic carcinogens so they hold importance for their mutagenic activity as well. Hence, it is considered an important tool for the detection of compounds that yield positive results in the Ames test. This tool also flagging mutagenic or non-mutagenic potentials based on structural alerts. ISSCAN[38] is not only a repository of chemical compounds tested with the carcinogenicity bioassay on rodents but also an expert decision support tool. This database contains only the experimental results from the carcinogenicity bioassay. The structure of this database was established on the basis of Distributed Structure-Searchable Toxicity (DSSTox) Network developed by the US Environmental Protection Agency (EPA). ANTARES[39] is a useful tool to reduce the gap in assessing Non-Testing Methods (NTM) as an alternative approach for the REACH legislation. This method includes QSAR models and read-across.

2.3. Geno-QSAR predictive performance evaluation

In this study, the performance of these predictive models was assessed according to the guidelines of the Organization for Economic Co-operation and Development (OECD)[40]. All models were validated by five-fold cross-validation method which included accuracy, sensitivity, specificity, positive predictivity and negative predictivity[41]. The sensitivity (SE) which means the rate of true positive compounds, the specificity (SP) means the rate of true negative, and the whole predictive accuracy (Q) which represents the total correct predictive accuracy of the condition under study. In statistics, the proportions of positive and negative results are represented by the positive and negative predictive values (PPV and NPV respectively). These were calculated using the following equations.

$$\text{Accuracy} = (\text{True Positives} + \text{True Negatives})/\text{Total} \quad (1)$$

$$\text{Sensitivity} = \text{True Positives}/(\text{True Positives} + \text{False Negatives}) \quad (2)$$

$$\text{Specificity} = \text{True Negatives}/(\text{True Negatives} + \text{False Positives}) \quad (3)$$

$$\text{Positive Predictivity} = \text{True Positives}/(\text{True Positives} + \text{False Positives}) \quad (4)$$

$$\text{Negative Predictivity} = \text{True Negatives}/(\text{True Negatives} + \text{False Negatives}) \quad (5)$$

In addition, the receiver operating characteristic (ROC) curve analysis was performed to identify the best predictive method for Geno-QSAR. This analysis was carried out by considering True Positive rate (Sensitivity) on the Y-axis and False Positive rate on the X-axis (1-specificity), and the result of the curve offers a clearer understanding of the accuracy of prediction.

3. Results and discussion

3.1. Data analysis

A dataset of 2379 chemicals was compiled from CPDB and ISSCAN database for testing carcinogenicity and mutagenicity endpoints. This dataset contains compound details as SMILES string, CAS number together with the corresponding experimental toxicity values. Before evaluating the performance of the models, a number of false SMILES strings,

duplicates, salts, mixtures, and ambiguous compounds were refined and removed from the selected dataset. The final number of chemicals under examination for carcinogenicity was 1336 which include 790 known carcinogens and 546 known non-carcinogens. Similarly, there were 810 mutagenicity compounds selected include 387 known mutagens and 423 known non-mutagens. Consequently, the experimental data in the total set are quite balanced between carcinogenic/non-carcinogenic and mutagenic/non-mutagenic compounds. For these selected datasets of mutagenic/non-mutagenic and carcinogen/non-carcinogen chemicals, all the genotoxicity QSAR models in the Vega platform were assessed by the nicity (Fig. 2) and mutagenicity (Fig. 3) using eqs. (1)-(5). For the compounds in the carcinogenicity prediction set, sensitivity ranged between 69% and 81% wherein ISS and ANTARES provided the highest value. However, specificity was higher for CAESAR. The specificities obtained by ISS, ANTARES, ISSCAN were also incomparable range. Accuracy varied from 64% for ISSCAN to 71% for ISS (Supporting Table 3). The positive predictive value was highest for CAESAR with 75% while the negative predictive value for all the models ranged between 57% and 67% (Fig. 2). Similarly, for the compounds in the mutagenicity prediction set, accuracy is high for all the four QSAR models, varying from 76% for

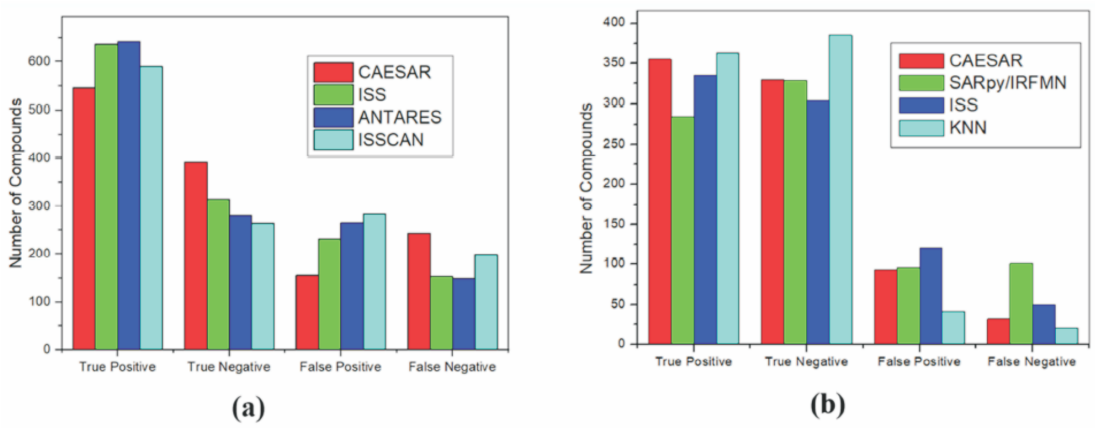

Fig. 1. Benchmarking of genotoxicity QSAR models by predicting the counts of True Positive (TP), True Negative (TN), False Positive (FP) and False Negative (FN) in the dataset of (a) carcinogenicity and (b) mutagenicity models, respectively.

counts (Fig. 1) of True Positives (TP), True Negatives (TN), False Positives (FP), and False Negatives (FN). True positive refers to the positives and True negative refers to the negative output that was correctly labeled by the classifier (Supporting Table 2). False positives are the negatives that were incorrectly labeled as positive whereas false negatives are the positives that were incorrectly labeled as negative by the classifier. For carcinogenicity, the best model for TP is ANTARES, TN is CAESAR, FP is ISSCAN and FN is CAESAR. For mutagenicity, the best model is TP is KNN, TN is KNN, FP is ISS and FN is SARpy.

3.2. Performances of five-fold cross-validation

To evaluate the performance of each QSAR method, the five-fold statistical parameter analysis was performed using calculated specificity, sensitivity, accuracy, positive predictive value, and the negative predictive value for carcinoge-

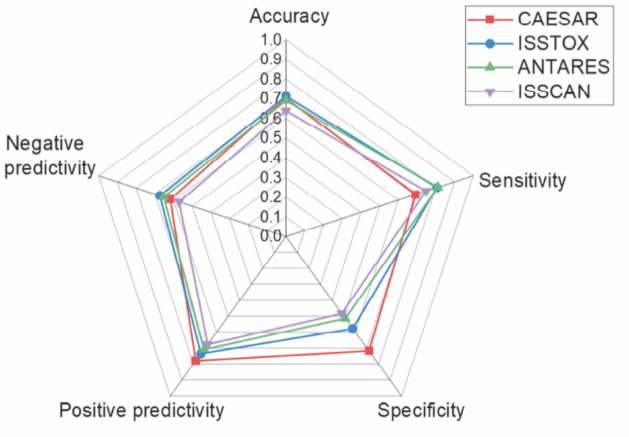

Fig. 2. Radar plot summary for carcinogenicity dataset. Sensitivity was best predicted by ISS and ANTARES. CAESAR gave the highest positive predictive values while negative predictive values were best described by ISS.

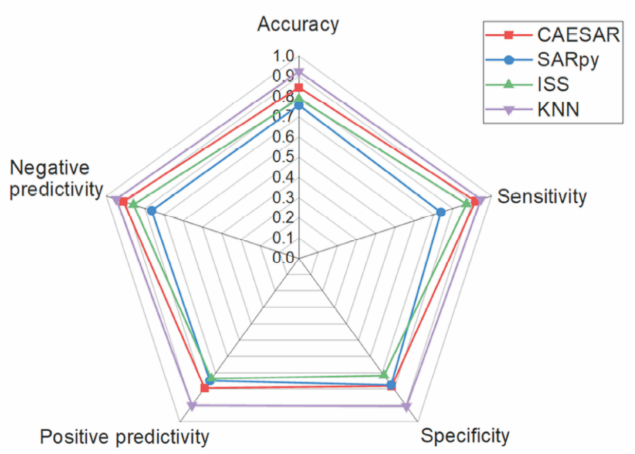

Fig. 3. Radar plot summary for mutagenicity dataset. The most sensitive (0.95), specificity (0.90), and accuracy (0.92) model is KNN. KNN also gave the highest positive (0.90) and negative predictive values (0.95).

SARpy up to 92% for KNN/Read across. This can be attributed to the high sensitivity (between 74% and 95%) and high positive predictivity (between 73% and 90%) reported for all the QSAR models (Fig. 3) (Supporting Table 4). A model with high sensitivity provides a better prediction on regulatory perspective than specificity which is justified in our data as well. To draw a clear inference from a five-fold statistical parameter, ROC was plotted (Fig. 4). ROC analysis reveals the true positive rate (or sensitivity) against the false positive rate (1-specificity). The closer is the model to the point (0, 1) the better it is. Hence, the ANTARES QSAR model for carcinogenicity and the KNN/Read across model for mutagenicity performed better compared to the other QSAR genotoxicity predictive approaches.

3.3. Performance of Geno-QSAR on test dataset

The main objective of the study is to develop the best predictive Geno-QSAR models for the carcinogenicity and mutagenicity and risk assessment of 131 compounds enlisted in the dataset (Supporting Table 1). Firstly, a larger dataset of genotoxicity endpoints was evaluated using the models available in the VEGA platform. The results showed a clear predictive trend for mutagenicity with some close range of selected predictive models and some variations found for carcinogenicity prediction using those models. To get an overall best predictive models of genotoxicity without performing *in vitro* tests, OECD based five-fold performance evaluation method and ROC analysis were carried out. These analyses revealed that the most suitable QSAR model for mutagenicity is KNN/ Read across and for carcinogenicity is ANTARES for the selected dataset from CPDB and ISSCAN database. Using the best-performed models, we finally predicted the

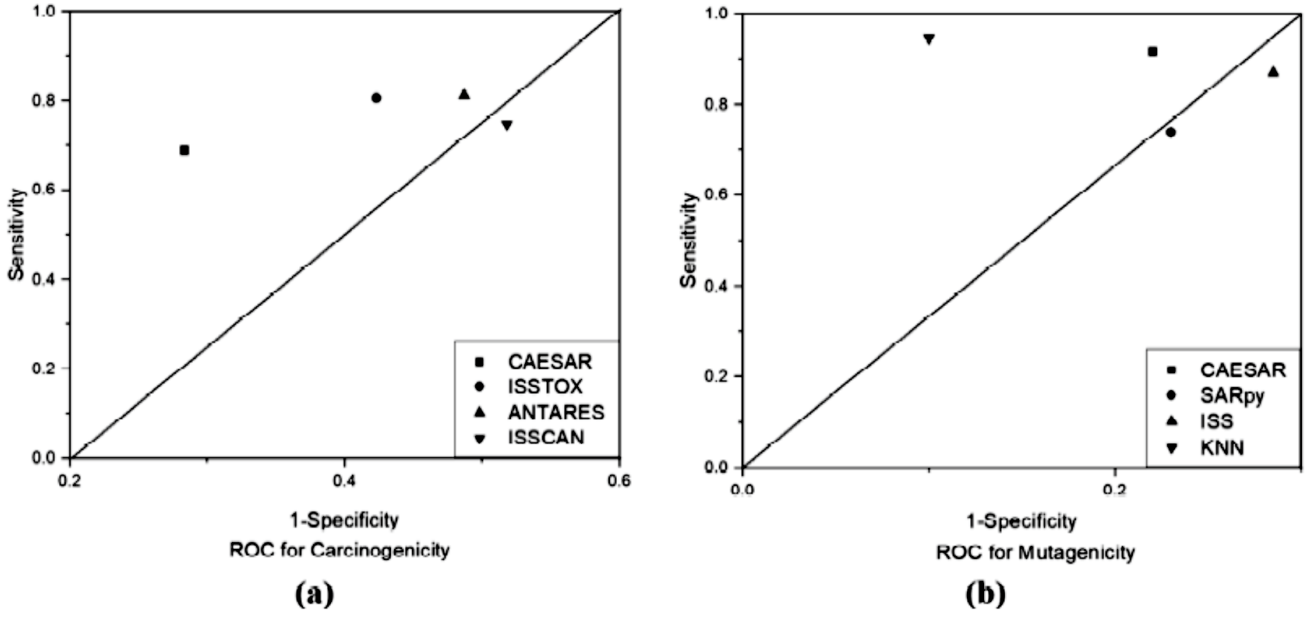

Fig. 4. Performance evaluation using ROC analysis of genotoxicity prediction (a) carcinogenicity and (b) mutagenicity. ANTARES is the best model for the predictions of carcinogenicity and KNN is the best for mutagenicity.

Table 1. List of selected specialty chemicals with predicted genotoxicity risk characterization*

Non-Mutagen + Carcinogen	Non-Mutagen + Non-Carcinogen	Mutagen + Carcinogen	Mutagen + Non-Carcinogen
Musk ketone	**Farnesol**	**Dimethylnitrosamine**	**Coumarin**
Nitrobenzene	**α-Hexycinnamaldehyde**	**Dinitrochlorobenzene**	**Methyl salicylate**
Benzyl benzoate	**P-t-butyl-α-methyl-hydrocinnamicaldehyde**		**3 and 4-(4-hydroxy-4-methyl-pentyl)-3-cyclohexene-1-carboxaldehyde**
Benzyl salicylate	**d-Limonene**	4-Amino-2-nitrophenol	**2-Methoxyethyl acetate**
Safrole	**Butyl salicylate**	4-Dimethylaminobenzene	Hippuric acid
Eugenyl methyl ether	**Methyl dihydrojasmonate**	4-Nitroaniline	
Estragole	**dl-Citronellol**	Azodrin	Acetylcysteine
Diethyl phthalate	**Benzyl acetate**	Butachlor	Dimethoate
	Eugenol	DFP	4-Heptyloxyphenol
Acetyl cedrene	**Cinnamic acid**	MbOCA	Methiocarb
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	**Diethyl malonate**	MDA	Phosmet
6-Acetyl-1,1,2,4,4,7-hexamethyltetraline	**Benzoic acid**	Methyl-parathion	Propoxur
Trichloromethyl phenyl carbinyl acetate	**Geraniol**	*o*-Cresyl glycidyl ether	4-Pentyloxyphenol
Methyl 2-nonynoate	**Linalool**	*o*-Toluidine	
4-Aminobenzoic acid	**Cinnamyl alcohol**	Paraoxon	
4-Nitrophenol	**Phenethyl alcohol**	1,6-Hexanedioldiglycidyl ether	
Benzocaine	**Benzyl alcohol**	2-Naphthylamine	
Beta-estradiol	**Phenol**	2-Nitro-4-phenylenediamine	
Chloramphenicol	**Ethyl alcohol**	Carbaryl	
Cinnamyl anthranilate	**Geranyl nitrile**		
Dhea	**Methyl trarate**		
Diazinon	**Lactic acid**		
Flutamide	**Triethanolamine**		
Lindane	**2-Ethyl-1-hexanol**		
Nicotinamide	**2-Butoxyethanol**		
Nicotinic acid	**2-Ethoxyethanol**		
N-Phenyl-2-naphthylamine	**2-Phenylphenol**		
Pentachlorophenol	**Caffeine**		
Phoxim	**Catechol**		
Pirimicarb	**Propylene glycol**		
Trichloromethane	**Trimethylamine**		
	Boric acid		
	1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-γ-2-benzopyran		
	Triclopyr		
	Trichlorocarbanilide		
	Thiourea		
	Theophylline		
	Testosterone		

Table-1 (contd.)

Progesterone
Deoxycorticosterone
Diethylene glycol monobutyl ether acetate
Dipropylene glycol methyl ether
Malathion
N,N-Diethyl-m-toluamide
N-Propoxyethanol
Atrazine
4-Acetamidophenol
4-Aminophenol
4-Cyanophenol
4-Iodophenol
Acetylsalicylic acid
Androstenedione
Aniline
2-Isopropoxyethanol
1-Decanol
Octanoic acid
Lauric acid
17*a*-Hydroxyprogesterone
1-Methoxypropan-2-ol
2,4-dichlorophenoxyacetic acid
Diethyl maleate
2-Methyl-2-propanol
2-Phenoxyethanol
2-Hydroxybenzoic acid
Dihydro-α-terpineol
Dihydromyrcenol
2-Methoxy-4-vinylphenol
α-Methyl-1,3-benzodioxole-5-propionaldehyde
Amyl salicylate
Isoeugenol
2-Methoxy-4-propylphenol

*Validation of predicted genotoxicity was carried out from the data available in the literature for 46 speciality chemicals compounds in each category (in Bold).

carcinogenicity and mutagenicity of specialty chemicals chosen in this investigation. Furthermore, these 131 specialty chemicals were characterized to find the safest chemicals that can be used in consumable products. By performing computation on the best predictive Geno-QSAR models on 131 specialty chemicals are categorized into four groups such as mutagen and carcinogen, non-mutagen and carcinogen, non-carcinogen and mutagen and non-mutagen and non-carcinogen (Fig. 5, Table 1). Further to enhance the risk assessment and safety prioritization specialty chemicals, results are refined into three different groups such as (1) potentially most harmful, (2) potentially harmful, and (3) potentially safe (Fig. 6). "Potentially most harmful" category includes 18 chemicals which are both mutagenic and carcinogenic. "Potentially harmful" category included 42 compounds which are predicted as either non-mutagenic and carcino-

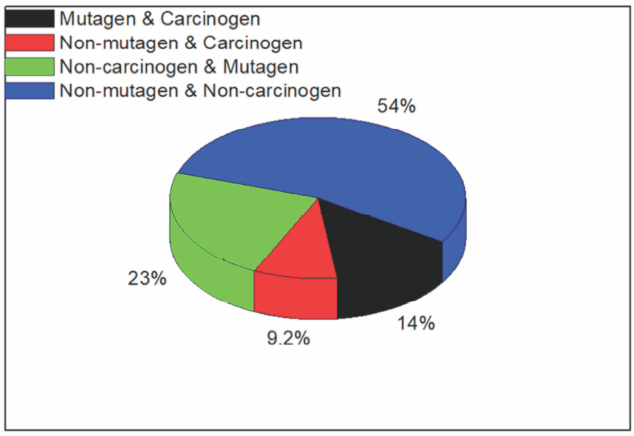

Fig. 5. Grouping of 131 specialty chemicals into 4 classes: Class 1 has 18 chemicals which are both mutagenic and carcinogen. Class 2 has 12 chemicals which are both mutagenic and non-carcinogen. Class 3 has 30 chemicals which are both non-mutagen and carcinogen. Class 4 contains 71 chemicals which are both non-mutagenic and non-carcinogenic.

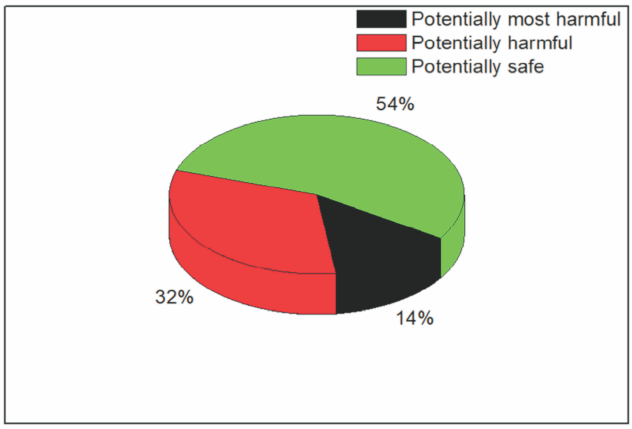

Fig. 6. Risk characterization of specialty chemicals into three categories: "Potentially most harmful" category includes 18 chemicals. "Potentially harmful" category included 42 while remaining 71 compounds fall into "potentially safe" category.

genic or mutagenic and non-carcinogenic. Remaining 71 compounds which are both non-mutagenic and non-carcinogenic are placed in the third category i.e. "potentially safe" and may not impose adverse health effects related to genotoxicity. Further validation of the predictions was verified by exploring the available literature on reported experimental toxicity data of the specialty chemicals (Supporting Table 5). Out of the 131 specialty chemicals, 46 compounds were available in the literature and had known experimental values of genotoxicity[32,42–57]. The categories such as mutagen and carcinogen, non-mutagen and carcinogen and non-carcinogen and mutagen accurately matched with the results obtained by the best QSAR model demonstrated in this study. For the case of non-mutagen and non-carcinogen, we found five compounds were listed as a carcinogen in the literature. This may be due to the comparatively lower % of accuracy in terms of sensitivity and specificity relevant to a true negative prediction by the selected QSAR model for carcinogenicity. The minor deviation of results found for the QSAR models reinforces the importance of improving dataset for model development with a range of more chemical compounds. Additionally, results of skin sensitization[28] and predicted genotoxicity in this work were overlaid to find the relationship among potentially safer chemicals. This comparison revealed that among the compounds listed as non-sensitizers[28] were overlapping as either carcinogen or mutagen. These compounds were also omitted to derive a final safer list of specialty chemicals. Results from these chemical compounds guide a handful of safe chemicals and may be further verified experimentally for its usage in the specific applications. An integrated comparison made in this work on experimental skin sensitization results with the observed toxicity predicted by Geno-QSAR approaches may aid in comprehensible decision making on the regulatory safety assessment.

4. Conclusions

The utilization of experimental data for structure-activity relationship studies strengthens their descriptive assessment and contributes to the reduction, refining, and replacement of animal experimentations. Various QSAR models are developed using different approaches and are available for different chemical species. In our study, we took one hundred thirty-one specialty chemicals to predict the two most important genotoxicity endpoints such as carcinogenicity and mutagenicity using eight QSAR predictive models. The discrepancies in the results provided by each model were quite apparent and contribute to increased levels of complexity at the regulatory purpose. It was difficult to choose the reliable genotoxicity predictive performance of the individual models or to improve the quality of prediction. To overcome the challenges, we built a dataset of 2146 compounds with their known carcinogenicity and mutagenicity values. The best predictive Geno-QSAR models were obtained using ranges

of parameters applying five-fold performance evaluation and ROC analysis. Resulting Geno-QSAR models, ANTARES for carcinogenicity and KNN/Read across model for mutagenicity, we predicted the carcinogenicity and mutagenicity for the selected dataset of specialty chemicals. We also predicted the list of different category for critical risk assessment and safe prioritization of specialty chemicals. Finally, Geno-QSAR models demonstrated in this study were also cross-validated by the experimental genotoxicity data available in the literature. Resulting Geno-QSAR model predictions were more consistent for mutagen and carcinogen, non-mutagen and carcinogen and non-carcinogen and mutagen categories and 90 % prediction were matched for the group of non-mutagen and non-carcinogen experimental results. In this context, the present results suggest that improved Geno-QSAR models are useful to support risk assessment of specialty chemicals. However, a robust QSAR system with accurate genotoxicity prediction of specialty chemicals can aid in decision making support for the regulatory framework.

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