表5　ゴム製品によるアレルギー事例

原因化学物質	アレルギー症状	用途	報告年
〈ジチオカーバメート系加硫促進剤〉			
ジメチルジチオカルバミン酸亜鉛	ACD	医療用ゴム手袋	1989, 1991
ジエチルジチオカルバミン酸亜鉛	ACD	医療用ゴム手袋	1989
ジブチルジチオカルバミン酸亜鉛	ACD	医療用ゴム手袋	1989
エチルフェニルジチオカルバミン酸亜鉛	ACD	作業用ゴム手袋	1987
〈アミン〉			
ジメチルアミン	ACD	医療用ゴム手袋	1991
ジエチルアミン	ACD	医療用ゴム手袋	1986, 1987
ピペリジン	ACD	医療用ゴム手袋	1986, 1987
〈メルカプトベンゾチアゾール系加硫促進剤〉			
2-メルカプトベンゾチアゾール	ACD	ゴムはきもの	1982, 1983, 1990
	ACD	膝装具（ゴムベルト）	2000
2,2′-ジベンゾチアジルジスルフィド	ACD	ゴムはきもの	1983, 1990
〈チオウレア系加硫促進剤〉			
ジエチルチオウレア	ACD	膝装具（パッド）	1999
〈P-フェニレンジアミン系老化防止剤〉			
N-イソプロピル-N′-フェニル-p-フェニレンジアミン	ACD	作業用ゴム手袋	1980
	ACD	工業用ゴム製品	1990
	ACD	農作業用ゴム長靴	1996
	ACD	イヤホン（ゴムリング）	2001
N-1,3-ジメチルブチル-N′-フェニル-p-フェニレンジアミン	ACD	農作業用ゴム長靴	1996
6-エトキシ-2,2,4-トリメチル-1,2-ジヒドロキノリン	ACD	農作業用ゴム長靴	1996
〈クロロプレンゴム系接着剤，固着剤樹脂〉			
p-tert-ブチルフェノルホルムアルデヒド樹脂	ACD	靴用接着剤	1985
	ACD	テーピングテープ	1987
	ACD	スニーカー	1987
	ACD	膝装具	1990, 1992
	ACD	マーカーペン	1990
	ACD	ウェットスーツ	2000

ACD: アレルギー性接触皮膚炎

沿って，業界団体である繊維評価技術協議会（SEK），抗菌製品技術協議会（SIAA）を中心に，①製品に抗菌剤の種類（無機系，有機系，天然系）を表示する，②安全性評価のために皮膚感作性試験を新たに実施する，③消費者の声を取り入れるために消費者代表を加えた委員会を新たに設置する等が具体的に実施されてきている。

さらに，「改正・消費生活用製品安全法」（2007年5月14日施行）に基づき，重大製品事故（治療に要する期間が30日以上の負傷・疾病，死亡事故，後遺障害事故）の発生事例について，経済産業省による公表・注意喚起とともに，製造メーカーによる対象製品の社告等での公表，製造・出荷の停止，製品の回収等が規定されている。

2006年，TCMSPにより抗菌加工されたデスクマットによるACD事例が数多く発生していたことが確認されたことから，家庭用品における重大製品事故の第一号として認定され，社告等の注意喚起，製品回収・交換が実施された（表4）。

原因化学物質：ゴム添加剤

1980年以降，患者でのパッチテスト，GPMT法等によるアレルゲン検索，原因製品の化学分析，文献情報，メーカー情報等を総合して，天然ゴム・合成ゴムに配合されるゴム添加剤によるACDの原因解明を進めることにより，原因製品と原因化学物質との関連性を明らかにできた（表5）。

手術用・家庭用ゴム手袋ではジチオカーバメート（DTC）系加硫促進剤やアミン化合物，ゴムはきものではメルカプトベンゾチアゾール系加硫促進剤，工業用ゴム製品や農作業用ゴム長靴ではアミン系老化防止剤が主要な原因となっていた。

すなわち，アミン系老化防止剤のN-イソプロピル-N′-フェニル-p-フェニレンジアミン（IPPD），MBT系加硫促進剤の2-メルカプトベンゾチアゾール（MBT），2,2′-ジベンゾチアジル ジスルフィド（MBTS），接着剤成分のp-tert-ブチルフェノール ホルムアルデヒド樹脂（PTBP-FR）等のような既知ゴムアレルゲンだけでなく，これまで注目されてこなかったDTC系化合物のジメチルジチオカーバメート亜鉛（ZDMC），ジエチルジチオカーバメート亜鉛（ZDEC），ジブチルジチオカーバメート亜鉛

(ZDBC)，エチルフェニルジチオカーバメート亜鉛(ZEPC)，アミンのジメチルアミン（DMA)，ジエチルアミン（DEA)，ピペリジン（PIP)，アミン系老化防止剤のN-1,3-ジメチルブチル-N'-フェニル-p-フェニレンジアミン（DMBPPD)，6-エトキシ-2,2,4-トリメチル-1,2-ジヒドロキノリン（ETMDQ）のような新規ゴムアレルゲンについても注目する必要があることを明らかにできた。

また，チオウレア系加硫促進剤については，日本では，輸入・膝装具によるACD事例において，ジエチルチオウレア（DETU）が原因化学物質であったことを明らかにできた1例のみであった。しかし，欧米ではかなりの数のACD事例が報告されており，しかも，DETUだけでなく，ジブチルチオウレア（DBTU)，ジラウリルチオウレア（DLTU)，ジフェニルチオウレア（DPTU）等も，GPMTにより強いアレルギー性物質であることが確認されたことから，日本においても，チオウレア系加硫促進剤の今後の用途展開に注目していく必要がある。

これらのゴムアレルゲン情報は，日本皮膚アレルギー・接触皮膚炎学会刊行の学会誌，「アレルゲン解説書」等に掲載されるとともに，これらのゴムアレルゲンを除去したアレルギー患者用の代替製品の開発にも活用されてきた。

ACD患者用代替品としては，既知のゴムアレルゲンを配合していない製品が有効である。すなわち，手袋ではポリクロロプレン（ネオプレン）ゴム，ウレタンゴム，シリコーンゴム等のゴム製品，熱可塑性樹脂，ポリ塩化ビニル，ポリエチレン等のプラスチック製品が，靴ではウレタン製品（テニスシューズ等）が使用できる。また，消費者がすぐにできるACD予防策としては，ゴム手袋の下に綿手袋を着けたり，靴をはくとき必ず靴下を着けるようにする等，製品が直接皮膚に触れないようにすることが，簡単で，しかも効果的な方法として推奨できる。

2.4　安全対策

今後，消費者，特に有害性情報を必要とするアレルギー患者等のために，①健康被害の原因解明を進め，原因製品と原因化学物質の関連性を明らかにすること，②MSDSの充実をはかり，労働衛生上の健康被害の発生防止のために，ゴム添加剤メーカーから中間・最終製品メーカーへ，用途，曝露ルート・曝露レベルを考慮したリスク評価も含めた有害性情報等の製品情報を伝達できること，③消費者にも具体的でわかりやすい製品表示を通じて，製品情報の伝達機能を質量ともに高めていくとともに，製品表示，業界・メーカーのホームページ等を通じて，幅広く製品情報を公開して，消費者の理解度を高めていくことが重要である。

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本稿のもとになった，家庭用品に関する調査研究は，当該機関の研究倫理委員会等の承認を得るとともに，実験動物等の管理・使用に関するガイドライン等に従って，調査研究は実施されました。その際，多くの関係諸氏に御指導・御協力をいただきました。当所の療品部を始め関係部の皆さん，都道府県市・衛生研究所等公的試験研究機関の関係諸氏に，心より深謝いたします。また，家庭用品による健康被害の原因解明に際して御協力いただいた，学会，病院皮膚科医，家庭用品関連業界・メーカー等の関係諸氏に感謝申し上げます。

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ORIGINAL ARTICLE

Skin Sensitization Study by Quantitative Structure-Activity Relationships (QSAR)

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Abstract

In silico assessment of skin sensitization is increasingly needed owing to the problems concerning animal welfare, as well as excessive time consumed and cost involved in the development and testing of new chemicals. Skin sensitization positive/negative prediction models with discriminant function were generated and parameter analysis was discussed on the basis of QSAR technology.

Samples used in this research were selected from the list of "Maximale Arbeitsplatz-Konzentration" (MAK) and "Biologischer Arbeitsstoff-Toleranz-Wert" (BAT) values 2008, Deutschen Forschungsgemeinschaft (DFG) for positive samples (skin sensitizers) and from the classification results of the Japanese Globally Harmonized System of Classification and Labeling of Chemicals (GHS) Inter-ministerial Committee of the National Institute for Technology and Evaluation for negative skin sensitizers (controls). A total of 291 compounds (122 positive sensitizers and 169 negative sensitizers) were used in this study.

Parameters were generated from 2-D and 3-D structures of compounds. All of the approximately 800 parameters generated were reduced to 47 parameter sets and 32 parameter sets by feature selection. Various linear and non-linear discriminant analysis methods were applied using 2 parameter sets. All data analyses were performed using ADMEWORKS/ModelBuilder software.

Perfect classification ratios (100%) were achieved using Support Vector Machine and AdaBoost for 32 parameters. The highest prediction ratio of 81.44% by Leave-Ten-Out Cross-Validation was achieved with Neutral Network for 47 parameter sets. Log P was not found to be important.

This is the first QSAR model for skin sensitization from Japan. Future studies of this QSAR model are needed to improve its efficacy.

Key words: *skin sensitization, QSAR, animal study, occupational exposure limit*

Introduction

Occupational skin disorders are the most common non-traumatic occupational condition. They include contact dermatitis, contact urticaria, eczema, skin cancer and other conditions (Fedorowicz *et al.*, 2005). Among them, contact dermatitis is by far the most common form of occupational skin illness. In the United Kingdom, approximately 22% of all occupational diseases are skin diseases and 80% of them are contact dermatitis (Cherry *et al.*, 2000). Contact dermatitis was found to be the most prevalent occupational allergic disease treated by medical doctors in Japan (Sato *et al.*, 2004).

In July 2003, the United Nations published the Globally Harmonized System of Classification and Labelling of Chemicals (GHS). GHS became available in 2008 all over the world (United Nations, 3rd rev. 2009). The classification criteria for skin sensitizers in GHS include evidence from animal studies, for example, OECD Guideline 406 (the guinea pig maximization test and the Buhler guinea pig test) and Guideline 429 (local lymph node assay). According to DFG, 2009, in Germany and the European Chemical Bureau (ECB), European Union (EU), the criteria for skin sensitizers also include evidence from validated animal studies. In Japan, the criteria from the Japan Society for Occupational Health (JSOH) for skin sensitizers do not include evidence from animal studies (Japan Society for Occupational Health, 2008), an issue that may warrant revision.

Under the new European Union (EU) Registration, Evaluation and Authorization of Chemicals (REACH) rules, all chemicals in the EU that are produced or imported in quantities of more than 1 ton per annum will need to be assessed as potential human and environmental hazards, for example, in terms of their carcinogenicity; human sensitivity to such chemicals will also need to be determined. REACH calls for increased use of hazard assessment alternatives such as *in vitro* methods and QSARs. Since no *in vitro* replacement is currently available for skin sensitization, nor is expected to be ready in the near future, the use of QSAR approaches presents an attractive alternative (Patlewicz *et al.*, 2008). Furthermore, the legislative trend towards the abolition of the animal testing of cosmetic products in the seventh Amending Directive 2003/15/EC to Cosmetics Directive 76/768/EEC includes a demand for alternative evaluation procedures (Carrera *et al.*, 2009). Although reliable procedures for skin sensitization (OECD guideline) exist, their application is limited by time and cost constraints for the development of new chemicals (Golla *et al.*, 2009). Owing to this legislation and animal welfare concerns, computational techniques, such as QSARs, have recently been advanced for assessing various human toxicities (e.g., carcinogenicity, skin sensitivity).

We performed discriminant analyses for skin sensitizers and control chemicals and identified classification rates and prediction rates using ADMEWORKS/ModelBuilder (Fujitsu Kyusyu Systems Limited, Japan) (Hayashi, 2005). This is the first QSAR model for skin sensitization from Japan. Log P is an octanol/water partition coefficient. When it is large, the substance is hydrophobic and can permeate through a membrane. A substance with small Log P is hydrophilic and has difficulty permeating through a membrane. We postulated that Log P is important and therefore assigned it a high weight of the discriminant function. However, the weight of Log P was small at -0.05034 among 47 sets (Table 1). There was Log P, not remaining in 32 parameters (Table 2). Therefore, on the basis of the sample set used, these indicated that Log P is not important in skin sensitization.

Materials and Methods

Data sources for chemicals assessed

Positive data are for skin sensitizers from a list of 190 compounds as allergens, that is, Sh and Sah (Deutschen Forschungsgemeinschaft, DFG, 2008). The criteria are based on human epidemiological studies, case reports or validated animal studies (guinea pig maximization test, Buhler guinea pig test or mouse local lymph node assay). On the other hand, negative data are for 218 control compounds belonging to the group defined as 'not applicable' for skin sensitization in the results of the classification by the Japanese GHS Inter-ministerial Committee in NITE. Information concerns the status of the implementation of GHS in Japan, which means that these are reported as non-skin sensitizers. However, inorganic chemicals, organic metal chemicals and polymers are special compounds, and are not analyzed with general organic compounds in computational chemistry. Therefore, we deleted these compounds (117) and finally assessed 122 positive sensitizing compounds and 169 negative sensitizing compounds.

Parameters and discriminant function

A total of 291 compounds (122 positive sensitizing

chemicals and 169 negative sensitizing chemicals) were used. Parameters were generated from 2-D and 3-D structures of the compounds. All of the approximately 800 generated parameters were reduced to 47 parameter sets (Table 1) and further reduced to 32 parameter sets (Table 2) by feature selection (e.g. removing low incidence parameter, multicolinearity or noise parameter). Various linear and non-linear discriminant analyses including Neural Network (NN), Support Vector Machine (SVM), AdaBoost and the Iterative Least Squares linear discriminant (TILSQ) methods were applied using these 2 parameter sets. Negative coefficients in discriminant function indicate negative informa-

Table 1 47 parameter sets used in discriminant analysis

Parameter name	Weight	Average	SD
Superpendentivity index Halogen only	0.429203	32.604599	334.51001
All-path calc for substructure (-C-)	-0.32713	20.749599	31.982901
6th order cluster MC Simple	0.271849	0.031052	0.149152
Secondary sp3 carbon count	0.252074	0.405498	2.11412
Environment molecular connectivity of substructure (-O-C)	0.244973	0.235354	0.822589
Molecular distance edge between all sec quat C	-0.240368	0.478886	1.30622
Environment molecular connectivity of substructure (-C-)	0.218623	1.02915	0.970193
All-path calc for substructure (-C-C)	0.206777	6.86598	18.7416
Balabans topological index J	-0.19464	2.76624	0.6826
Environment molecular connectivity of substructure (-C(O)-)	0.178496	0.674613	0.839489
Molecular distance edge between all tert tert C	0.171595	0.189843	0.909471
Number of double bonds	-0.169725	1.43986	1.47356
7th order chain MC Simple	-0.161363	0.177073	0.30573
Environment molecular connectivity of substructure (-O-)	0.147864	0.877878	1.20036
Fractional mass of rotatable atoms	-0.143224	0.325496	0.295169
Distance weighted flexibility	-0.127034	10.1204	16.4505
Count of substructure (DMPATH) (-ester-)	-0.123993	0.309278	0.643709
Number of Chlorine atoms	0.114879	0.426117	1.03917
4th order cluster MC Valence	-0.102821	0.051807	0.144251
Shadow area 5 (normalized SHDW2)	0.102563	0.509005	0.091085
Superpendentivity index Carbons only	0.097147	69.290604	427.22699
Count of substructure (DMPATH) (-N)	-0.083129	0.171821	0.503125
All-path calc for substructure (=C=)	0.081448	16.8459	49.176701
Count of donors	0.080329	0.261168	0.765982
Environment molecular connectivity of substructure (-C)	0.079397	0.738309	0.633582
Shadow area 6 (normalized SHDW3)	-0.063777	0.509172	0.086962
Shadow area 3 (YZ plane)	0.05985	52.3074	29.987499
Non-bonded strain energy of molecule	0.056804	9.79443	12.5073
All-path calc for substructure (-O)	-0.055832	3.31443	10.7888
Mass weighted Width/Thickness	0.054246	318.558014	460.709015
Fractional mass of rigid atoms	0.053567	0.502532	0.257671
Angle strain energy of molecule	0.051041	17.335699	56.981201
FQlogP	-0.05034	2.04563	2.01295
Average E-State value over all hetero-atoms	-0.049819	6.93422	2.51043
Molecular distance edge between all primary quat C	0.048143	0.238553	0.629589
First/second moment of inertia with H	0.041074	1.2189	0.207198
Count of substructure (DMPATH) (-O-C)	-0.036965	0.178694	0.577473
4th order cluster MC Simple	0.036219	0.078392	0.166832
Number of Sulfur atoms	0.029465	0.278351	0.66554
All-path calc for substructure (-C)	0.027272	15.5115	21.1327
Intermolecular distance between Emin and Emax	-0.026139	2.69278	1.9522
Combined symmetry	-0.025709	0.831032	0.211908
Environment molecular connectivity of substructure (-N=)	0.025219	0.309299	0.812074
Count of substructure (DMPATH) (-N-)	-0.01344	0.199313	0.499793
Shadow area 4 (normalized SHDW1)	-0.012423	0.486792	0.076058
Third moment of inertia with H	0.01242	525.281006	598.361023
All-path calc for substructure (-N=)	0.009968	9.52062	28.847401
CONSTANT	0.163538		

tion of the activity. Positive coefficients indicate positive information (Fig. 1). Classification rates and prediction rates (Cross-Validation, CV) of discriminant function were also calculated. All data analyses were performed using ADMEWORKS / ModelBuilder software (Fujitsu Kyusyu Systems Limited, Japan) (Hayashi, 2005).

Results

Weight of parameter

The weight of 'secondary sp3 carbon count', that is, the number of methylene groups (-CH2-), was 0.290789 and that of 'environment molecular connectivity of substructure' (-O-C) was 0.288673, which were both highly positive values as shown in Table 2. These are considered to induce skin sensitization. On the other hand, the weights of 'all-path calc for substructure' (-C-) of -0.265617 and 'count of substructure (DMPATH)' (-ester-) of -0.233505 were highly negative values and considered to induce no sensitization (Table 2).

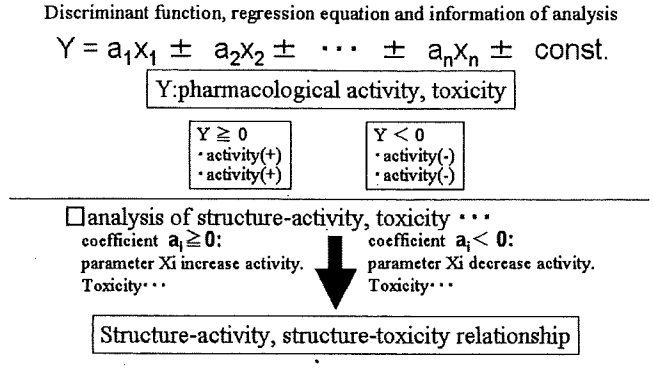

Figure 1 Format of regression equation with feedback of sign and coefficient information

Table 2 32 parameter sets used in discriminant analysis

Parameter name	Weight	Average	StdDev
Molecular distance edge between all sec quat C	-0.398936	0.478886	1.30622
Secondary sp3 carbon count	0.290789	0.405498	2.11412
Environment molecular connectivity of substructure (-O-C)	0.288673	0.235354	0.822589
All-path calc for substructure (-C-)	-0.265617	20.749599	31.982901
4th order cluster MC Simple	0.251247	0.078392	0.166832
Count of substructure (DMPATH) (-ester-)	-0.233505	0.309278	0.643709
All-path calc for substructure (=C=)	0.226793	16.8459	49.176701
4th order cluster MC Valence	-0.214339	0.051807	0.144251
Environment molecular connectivity of substructure (-C-)	0.208057	1.02915	0.970193
Count of substructure (DMPATH) (-N)	-0.2064	0.171821	0.503125
Count of donors	0.173459	0.261168	0.765982
Environment molecular connectivity of substructure (-O-)	0.173022	0.877878	1.20036
7th order chain MC Simple	-0.159527	0.177073	0.30573
All-path calc for substructure (-C-C)	0.154986	6.86598	18.7416
Average E-State value over all hetero-atoms	-0.153089	6.93422	2.51043
Molecular distance edge between all tert tert C	0.148523	0.189843	0.909471
Environment molecular connectivity of substructure (-C(O)-)	0.147898	0.674613	0.839489
Intermolecular distance between Emin and Emax	-0.136821	2.69278	1.9522
Fractional mass of rotatable atoms	-0.1306	0.325496	0.295169
Number of Chlorine atoms	0.105433	0.426117	1.03917
Third moment of inertia with H	0.10009	525.281006	598.361023
Number of double bonds	-0.096271	1.43986	1.47356
Non-bonded strain energy of molecule	0.095734	9.79443	12.5073
Shadow area 3 (YZ plane)	-0.094677	52.3074	29.987499
Distance weighted flexibility	-0.081716	10.1204	16.4505
Mass weighted Width/Thickness	0.079719	318.558014	460.709015
Shadow area 6 (normalized SHDW3)	-0.058598	0.509172	0.086962
Angle strain energy of molecule	-0.052234	17.335699	56.981201
Count of substructure (DMPATH) (-N-)	-0.028803	0.199313	0.499793
Environment molecular connectivity of substructure (-C)	0.020012	0.738309	0.633582
Count of substructure (DMPATH) (-O-C)	-0.014755	0.178694	0.577473
First/second moment of inertia with H	0.011451	1.2189	0.207198
CONSTANT	0.139817		

Discriminant analysis

We performed discriminant analysis and Leave-Ten-Out Cross-Validation (CV) of 291 (122 positive, 169 negative) chemicals assessed by Neural Network (NN), the Iterative Least Squares linear discriminant (TILSQ), Support Vector machine (SVM) and AdaBoost with 32 or 47 parameter sets (Table 3-10).

Classification rates were 90.38% to 100%. Complete classification (100%) was achieved in SVM and AdaBoost for 32 parameter sets (Table 9 and 10). The prediction rate was assessed by Leave-Ten-Out Cross-Validation (CV). CV results were 73.88% to 81.44%. The highest CV of 81.44% was achieved in NN with 47 parameter sets (Table 3). CV in SVM and AdaBoost with 32 parameter sets were 76.63% and 79.04%, respectively (Table 9 and 10), whose classification rates were 100% in both cases.

Table 3 Neural Network (NN) with 47 parameters

Class	Members	Wrong	Correct (%)
0	169	9	94.67
1	122	7	94.26
Total	291	16	94.50

Class 0: negative (control),
Class 1: positive skin sensitizer
Cross-Validation (CV): 81.44%

Table 4 The Iterative Least Squares linear discriminant (TILSQ) with 47 parameters

Class	Members	Wrong	Correct (%)
0	169	6	96.45
1	122	12	90.16
Total	291	18	93.81

Class 0: negative (control),
Class 1: positive skin sensitizer
CV: 73.88%

Table 5 Support Vector Machine (SVM) with 47 parameters

Class	Members	Wrong	Correct (%)
0	169	0	100.00
1	122	1	99.18
Total	291	1	99.66

Class 0: negative (control),
Class 1: positive skin sensitizer
Cross-Validation (CV): 78.01%

Table 6 AdaBoost with 47 parameters

Class	Members	Wrong	Correct (%)
0	169	0	100.00
1	122	2	98.36
Total	291	2	99.31

Class 0: negative (control),
Class 1: positive skin sensitizer
Cross-Validation (CV): 76.98%

Table 7 Neural Network (NN) with 32 parameters

Class	Members	Wrong	Correct (%)
0	169	9	94.67
1	122	13	89.34
Total	291	22	92.44

Class 0: negative (control),
Class 1: positive skin sensitizer
Cross-Validation(CV): 79.04%

Table 8 The Iterative Least Squares (TILSQ) with 32 parameters

Class	Members	Wrong	Correct (%)
0	169	9	94.67
1	122	19	84.43
Total	291	28	90.38

Class 0: negative (control),
Class 1: positive skin sensitizer
Cross-Validation (CV): 75.26%

Table 9 Support Vector Machine (SVM) with 32 parameters

Class	Members	Wrong	Correct (%)
0	169	0	100.00
1	122	0	100.00
Total	291	0	100.00

Class 0: negative (control),
Class 1: positive skin sensitizer
Cross-Validation (CV): 76.63%

Table 10 AdaBoost with 32 parameters

Class	Members	Wrong	Correct (%)
0	169	0	100.00
1	122	0	100.00
Total	291	0	100.00

Class 0: negative (control),
Class 1: positive skin sensitizer
Cross-Validation (CV): 79.04%

Discussion

Since the implementation of Animal Welfare Guideline 86/609/EC in 1986, it is the declared policy of EU institutions to support the development and use of alternative methods of testing chemicals, that is, of "any method that can be used to replace, reduce or refine the use of animal experiments in biomedical research, testing or education" (Lillenblum *et al.*, 2008). However, no *in vitro* replacement is currently available for testing skin sensitization in compliance with the REACH system (Grindon *et al.*, 2007, Patlewicz *et al.*, 2008).

Therefore, several QSAR-related systems have been developed for skin sensitization. These are Toxicity Prediction Komputer-Assisted Technology, (Accelrys Inc., San Diego, CA, USA; TOPKAT) and Multi Computer-Automated Structure Evolution (MultiCASE Inc., Cleveland, Ohio, USA; M-CASE), which are both statistically based, Deductive Estimation of Risk from Existing Knowledge (Derek) for Windows (DfW. LHASA Ltd., Leeds, UK), which is knowledge-based, and Times Metabolism Simulator for Skin Sensitization (LMC, University of Bourgas, Bulgaria; TIMES-SS), which is a hybrid (Patlewicz *et al.*, 2007a, Patlewicz *et al.*, 2007b). In this study, all data analyses were performed with ADMEWORKS/ModelBuilder software (Fujitsu Kyusyu Systems Limited, Japan). ADMEWORKS/ModelBuilder is statistically based software. Of these QSAR-related systems, Derek is the most widely used expert system for predicting skin sensitizing potential (Grindon *et al.*, 2007). Fedrowicz *et al.* (2005) reported that the correct classification of QSAR predictions for guinea pig data achieves values of 73.3% and 82.9% for TOPKAT and Derek, respectively, and that the correct classification using LLNA data equals 73% for Derek. Our results of prediction rates (CV) were 73.88% to 81.44%, almost the same as those in the previous report. Although QSAR systems are still being developed and have yet to become sufficiently powerful, the use of *in silico* methods has been proposed to make predictions of skin sensitization in the first stage of a decision-tree testing strategy for skin sensitization (Grindon *et al.*, 2007). This QSAR system is thought to be at practical use level.

We postulated that skin permeability is an important factor for skin sensitivity of chemicals and that Log P could become an important factor in modeling skin sensitization. Barratt (1994) reported that the molecular volume and the octanol/water partition coefficient (Log P) were important determinants of skin permeability. In this study, solubility was highly correlated with Log P (multicolinearity). We analyzed without solubility. The weight of log P was found to be small and the weight of molecular weight was not extracted in 32 parameters (Table 1 and 2). The limited amount of experimental data available on skin permeability presumably has prevented the development of robust QSAR models for permeability (Golla *et al.*, 2009). Alternatively, in this QSAR study, the octanol/water partition coefficient could be replaced by other more important parameters, or cooperative relationships of several parameters. Many chemicals are dissolved in solvents and exposed to human skin. The skin permeability of these solvents might have larger effects on skin sensitization than Log P. Clearly, more discussions and additional tests must be carried out. Our classification rates and prediction rates were 90.83% to 100% and 73.88% to 81.44%, respectively. To improve these rates, further studies of large amounts of experimental data, revisions of feature selection according to certain hypotheses of parameters, the addition of new parameters and selecting suitable discriminant function for skin sensitization are needed.

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