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Mechanism-based QSAR modeling of skin sensitization

Byline: QSAR study of skin sensitization

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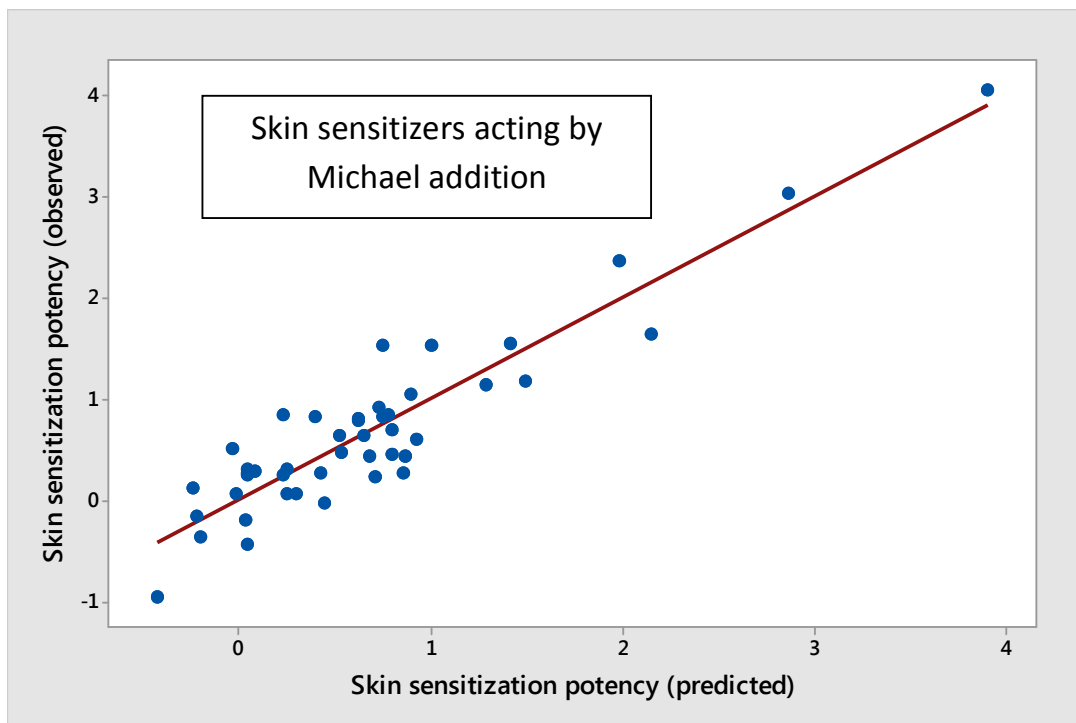
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Professor Alan Katritzky passed away on 10 February 2014. We dedicate this paper to his memory.

Many chemicals can induce skin sensitization, and there is a pressing need for non-animal methods to give a quantitative indication of potency. Using two large published data-sets of skin sensitizers, we have allocated each sensitizing chemical to one of ten mechanistic categories, and then developed good QSAR models for the seven categories with a sufficient number of chemicals to allow modeling. Both internal and external validation checks showed that each model had good predictivity.

1

2 Introduction

3 Skin sensitization (allergic contact dermatitis) is a common problem arising from the contact
4 of certain chemicals with the skin. Once sensitized, an individual remains so for life, and it is
5 therefore important to know whether or not a chemical possesses skin sensitization potential
6 before skin contact is made.

7 In order for skin sensitization to be induced, a chemical must first penetrate into the viable
8 epidermis and bind to skin proteins/peptides to form an immunogenic complex.¹ The binding
9 is almost always covalent, with the chemical (hapten) acting as an electrophile and the
10 protein as nucleophile; a few haptens operate *via* a free radical mechanism.² The
11 immunogenic complex is taken up by dendritic cells, which convert the complex into a form
12 that can be recognized by T-cells, causing their stimulation and proliferation, and the
13 formation of so-called memory T-cells; this is the induction process.³ Upon re-exposure, the
14 memory T-cells release cytotoxic mediators that cause local tissue inflammation.

15 A number of methods are available for the determination of skin sensitization potential; the
16 current method of choice, and the one initially required for regulatory purposes⁴ is the
17 LLNA,^{5,6} which yields a quantitative endpoint. Much work has also been done on *in silico*
18 prediction of skin sensitization potential, in order to reduce animal usage and save time; this
19 has become more important with the advent of the recent REACH legislation,^{7,8} which
20 requires assessment of toxicity for all chemicals produced in or imported into the European
21 Union at levels above 1 tonne per annum, but which also requires animal testing to be carried
22 out only as a last resort.⁹

23 Despite the LLNA's having a quantitative endpoint, most *in silico* prediction studies of skin
24 sensitization to date have been categorical (i.e. sensitizer/non-sensitizer),¹⁰ as have most other

1 attempts to use biological assays. A small number have used classical QSAR regression to
2 model the LLNA endpoints of, for example, Schiff base electrophiles (aldehydes and
3 ketones),¹¹ Michael acceptors,¹² S_NAr electrophiles,¹³ and diverse organic chemicals.¹⁴
4 Roberts and Patlewicz¹⁵ have reviewed the subject.

5 In order to develop good QSAR models, all chemicals used in the training set should exert
6 their effect by the same mechanism. Since it is often difficult to determine mechanisms of
7 action, the default position has been to use chemicals of the same class (e.g. benzoic acids,¹⁶
8 nitrobenzenes¹⁷) in the expectation that they have a common mechanism. However, with the
9 emphasis in recent years on mechanistically based QSAR modeling, and with current
10 knowledge of mechanisms involved in skin sensitization,¹⁸ we decided to try to use this
11 approach to model the relatively large data-sets of Gerberick et al.¹⁹ and Kern et al.,²⁰
12 comprising 211 chemicals and 108 chemicals respectively.

13 **Methods**

14 *Skin sensitization data*

15 The Gerberick et al.¹⁹ and Kern et al.²⁰ data-sets contain a total of 85 non-sensitizers, which
16 of course cannot be included in MLR modeling. In addition, two chemicals (cinnamic
17 aldehyde and 2-amino-6-chloro-4-nitrophenol) were duplicated in the data-sets. In the case of
18 cinnamic aldehyde, for one duplicate there was some difference between the EC₃ value of 1.4
19 reported by Gerberick et al.¹⁹ and the value of 2.05 reported in the original publication;²¹ in
20 addition, the original publication²¹ reported that the value of 2.05 was an average, indicating
21 that a range of values had been obtained. Because of the doubt about the true EC₃ value, we
22 selected the other duplicate, with an EC₃ value of 3.0. In the case of 2-amino-6-chloro-4-
23 nitrophenol we rejected one EC₃ value (2.2), as it was obtained from an erratic dose-response
24 curve. One chemical (*bis*-3,4-epoxycyclohexyl-ethyl-phenyl-methylsilane) contained

1 silicon and several were ionic chemicals, which could not be handled by our software.
2 Isopropyl myristate was removed because it was listed as a false positive,¹⁹ and methyl
3 hexadecene sulfonate was deleted because the molecular structure and CAS numbers given in
4 Gerberick et al.¹⁹ are incorrect. These deletions left a total of 204 skin sensitizers for
5 modeling.

6 The LLNA involves the topical exposure of the ear dorsum of CBA female mice to 25 μL of
7 at least three different concentrations of test chemical, daily for three days. After a further
8 two days an injection is given of 250 μL of phosphate-buffered saline containing 20 μCi of
9 tritiated thymidine. Five hours later the animals are sacrificed, the draining auricular lymph
10 nodes are excised, and the incorporation of tritiated thymidine measured. From these results,
11 the EC3 value is calculated.

12 It should be noted that EC3 values are reported as g/100 ml. Four potency ranges are used, as
13 follows: $\text{EC3} \geq 10$ to ≤ 100 , weak; $\text{EC3} \geq 1$ to < 10 , moderate; $\text{EC3} \geq 0.1$ to < 1 , strong; EC3
14 < 0.1 , extreme.¹⁹ Use of weight concentrations can give rise to a classification problem.
15 Strictly, concentrations and dosages should be given in molar units (e.g. mmol.L^{-1} , $\mu\text{mol.kg}^{-1}$),
16 for comparison, because effects are initiated by the number of molecules present, and not by
17 how much they weigh.²² Hence we have used SSP, defined as $\text{SSP} = \log (\text{MW}/10\text{EC3})$, in
18 our modeling. The importance of this is demonstrated by two chemicals from our data-set,
19 formaldehyde (MW 30.03) and 3-methylisoeugenol (MW 178.23). They have almost
20 identical skin sensitization potencies (1.692 and 1.695) based on their molar concentrations,
21 yet their EC3 values are quite different (0.61% and 3.6%), meaning that formaldehyde is
22 classified as a strong sensitizer, whilst 3-methylisoeugenol is classified as a moderate
23 sensitizer.

1 Using our in-house expertise,¹⁸ now incorporated into the Toxtree software,²³ together with
2 additional expert knowledge (DWR and SJE), we classified the chemicals into their
3 mechanistic categories. The chemicals are listed in Table 1. We have retained the chemical
4 names used by Gerberick et al.¹⁹ and Kern et al.²⁰ for ease of cross-reference, and have
5 included CAS numbers for all of the 204 chemicals save for four chemicals whose CAS
6 numbers we were unable to find.

7 Table 1 here

8 *QSAR modeling*

9 It is widely acknowledged that for a QSAR model to be predictive, external test chemicals
10 should be similar to one or more chemicals in the training set used to build the model.²⁴⁻²⁶
11 There are a number of methods used to achieve this,²⁷ although the topic is still open and has
12 not been completely solved.²⁸ Perhaps the most widely practised approach is that using a
13 clustering technique on the whole data set in order to select test set chemicals that are similar
14 to one or more chemicals in the remaining chemicals (i.e. the training set).

15
16 It has also been pointed out^{24,29} that external test set chemicals should, strictly speaking, be
17 completely independent of the training set. However, the clustering technique does not
18 comply with that requirement,^{22,29} since the selection of test chemicals that are very similar to
19 chemicals in the training set means that they carry the same structural information.³⁰

20
21 In addition, for relatively small data sets such as ours, removal of even a small number of test
22 set chemicals results in loss of a significant amount of information.³¹ This is of even more
23 concern when the data set comprises chemicals of a range of chemical classes, as is the case

with our skin sensitizers (see Table 1). It is thus likely that the use of leave-many-out and bootstrap techniques²⁴ would also be inappropriate.

Using the clustering technique for selection of test chemicals, Gramatica et al.³² found that the four descriptors used to develop a good 93-chemical training set QSAR for K_{oc} prediction ($R^2 = 0.82$, $s = 0.539$) also yielded a good QSAR on the whole 643-chemical data set ($R^2 = 0.79$, $s = 0.547$). However, this was not the case with our small data sets. For example, for the Michael acceptor chemicals, a 6-descriptor QSAR developed using the 36-chemical training set had $R^2 = 0.866$, $s = 0.344$. When the same 6 descriptors were used to develop a QSAR for all 45 Michael acceptor chemicals, the result was poor ($R^2 = 0.636$, $s = 0.570$). This confirms the view of Roy et al.³¹ that removal of test set chemicals from a small data set results in loss of information, and thus changes the applicability domain of the model. Partly for this reason, Hawkins³³ recommended that external validation should not be carried out on data sets much below 50 chemicals, whilst Tropsha²⁷ recommended a minimum of 30-40 chemicals and Gramatica³⁴ recommended a minimum of 25 chemicals. From Table 1 it can be seen that our data sets range in size from 11 to 45 chemicals, and thus are at least verging on the size where external validation may be expected not to perform well. It may be noted also that because of the diversity of our data sets, a greater number of descriptors are required to give good models.²⁶

The above paragraph indicates that because of the smallness and chemical diversity of our data sets, we could not expect to obtain good predictive models based on descriptors selected during development of the training sets. We therefore decided to use for the training sets the descriptors selected for the corresponding QSARs developed for the full data sets. We recognise that this means that the training set QSARs are not fully independent of the test set

1 chemicals, but we believe that this is no less valid than the widely used clustering approach
2 for the selection of test set chemicals, which also involves some loss of independence of test
3 set chemicals. Our approach also means that the applicability domains of the full data sets are
4 preserved to some extent at least, and thus overcomes the concerns of Hawkins³³ and
5 Gramatica³⁴ in that respect. We stress, however, that this approach should be used only for
6 small, very diverse data sets, but in such cases we believe that it fits with the dictum of Albert
7 Einstein: *Everything should be made as simple as possible, but not simpler.*

8
9 There were too few chemicals acting by S_N1, pro-S_N2 and S_NAr mechanisms (2, 2, and 4
10 chemicals respectively) to allow us to develop QSARs in these categories. Hence 196
11 chemicals constituted our pool of chemicals used for modeling.

12
13 Various methods can be employed for the splitting of a data-set into training and test sets,
14 from random selection to activity sampling, clustering techniques, self-organising maps and
15 formal statistical experimental design.²⁴ Random selection is intuitively unappealing, and
16 “could result in a subsequent application of the model out of its applicability domain,
17 resulting in erroneous conclusions on the model’s performance”.³⁴ In addition it does not
18 provide any rationale for selection.³⁵ However, it was found to yield similar predictive
19 power to methods based on clustering.³⁵ Activity sampling (e.g. ordering the chemicals
20 according to their activity, then taking every *n*-th chemical for the test set) ensures a good
21 coverage of activity, but does not necessarily take account of chemical diversity, and thus
22 again risks subsequent application outside the applicability domain. The other techniques can
23 be complex,²⁷ and can give conflicting results.³⁵ Tropsha et al.²⁴ have stated that “the
24 underlying goal...is to ensure that both the training and test sets separately span the whole
25 descriptor space occupied by the entire data set and the chemical domains in the two sets are

1 not too dissimilar”. Chirico and Gramatica²⁸ have commented that “the topic (of external
2 validation) is still open, and the problem in QSAR modelling has not yet been completely
3 solved, though many techniques have been proposed to validate models”. The above
4 approaches have been designed for large or relatively large data sets, and we did not have that
5 luxury. In fact, the external validation of small heterogeneous data sets has not been
6 addressed before. Martin et al.³⁵ have pointed out that rational design of test sets should
7 ensure that “the compounds in the training and test sets should be close to each other”.
8 However, as stated earlier, selection of test chemicals that are very similar to chemicals in a
9 training set means that they carry the same structural information,³⁰ which would lead to
10 over-estimation of the predictivity of the model. We therefore used a manual sampling
11 approach that ensured a good range of activities and chemical domains in the test sets, whilst
12 never selecting the chemicals with the highest and lowest activities in the whole data sets³⁶ to
13 avoid the risk of extrapolation of the training set models. Care was taken that the test set
14 chemicals covered approximately the same chemical and biological space as the training set
15 chemicals in each category, and were not too close to or too far from the line of best fit in the
16 relevant whole data set model.

17
18
19 It is likely that with small, heterogeneous data sets there is no entirely satisfactory way to
20 demonstrate true prediction capability using QSAR modeling. We believe that the simple
21 method that we have adopted, whilst not perfect, is acceptable, and that the alternatives are
22 open to at least as much criticism as the one that we have used. We recognize that our
23 approach could be controversial, but we believe that it is a useful and pragmatic method for
24 QSAR prediction using small, diverse data sets. We do not recommend it for use with large
25 and/or homogeneous data sets. A reviewer has commented that the Q^2 (leave-one-out) value

1 of each training set could be more valuable than the test set values. In fact, as can be seen
2 from Table 2, all of our training set Q^2 values are above the recommended lower limit of
3 0.5,³⁷ and are no more than the recommended³⁸ 0.3 below the corresponding R^2 value, with
4 the exception of the Schiff base model, instead of which we recommend the combined Schiff
5 base and pro-Schiff base model, which has good statistics ($R^2 = 0.836$, $Q^2 = 0.736$).

6
7 A total of about 1600 descriptors were generated from CODESSA,³⁹ MOE⁴⁰ and
8 winMolconn⁴¹ software. These were pruned, by removal of descriptors with the same values
9 for all chemicals and by removal of descriptors with high pair-wise collinearity, to about 880
10 descriptors. Statistical analysis was carried out using the simple wrapper method of step-wise
11 MLR⁴² in Minitab v17 software⁴³ on the chemicals in each mechanistic category. Modeling
12 was first performed on the total number of chemicals in each category. Then approximately
13 20% of the chemicals in each category were removed to serve as a test set, and each model
14 was re-developed on the remaining (training set) chemicals, using the same descriptors as
15 were obtained for the model developed with the total number of chemicals in the category.
16 The predicted skin sensitization potencies of test set chemicals were calculated from the
17 QSARs developed for the corresponding training set chemicals.

18 The number in brackets after each coefficient in a QSAR is the standard error on the
19 coefficient. For a descriptor to be valid, the standard error on its coefficient should be
20 significantly lower than the value of the coefficient itself. This is also reflected in the p value
21 for each descriptor, a measure of the probability that the descriptor is there by chance; for a
22 descriptor to be valid in a QSAR, its p value should generally be < 0.05 (that is, less than a
23 5% risk that it is present by chance).

24

1 The statistics given with each QSAR are: R^2 (indicating the proportion of the variation of
2 skin sensitization potency (SSP) modeled by the QSAR); R^2_{adj} , which allows comparison
3 between QSARs with different numbers of descriptors; Q^2 , an internal measure of
4 predictivity, obtained using the leave-one-out procedure in Minitab; s ; and F (the Fisher
5 statistic, an indication of the fit of the regression equation to the training set data).

6
7 We also carried out 20 Y-randomizations of the SSP values within each mechanism in order
8 to check the robustness of the QSARs generated. For each mechanism, all R^2 values obtained
9 using randomized SSP values were significantly lower than the values obtained with non-
10 randomized SSP values.

11
12 For the test set results, the correlation between observed and predicted SSP values should
13 have an intercept close to zero and a slope close to unity. However, it has been pointed out
14 that correlation alone is not an adequate criterion for agreement between predicted and
15 observed values of biological endpoints.²⁴ To establish agreement it is necessary to exclude
16 three potential problems: (i) random disagreement, (ii) biased disagreement with one set of
17 values being systematically greater than (or less than) the other, and (iii) gradient problems
18 (the points on a graph of predicted versus observed values adhering to a line with a gradient
19 other than +1.0). Tropsha et al.²⁴ have recommended a multi-step procedure for assessing
20 how well those criteria are met.

21
22 However, there is a simpler alternative, the ICC, that serves just as well and has been
23 available for many years.⁴⁴ There are various ways in which the ICC can be calculated but in
24 some of its forms it will produce a value close to +1.0 only if the data adhere tightly to all
25 three of the criteria set out above. It can therefore act as a single unified indicator of

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1 agreement between predicted and observed values. In the event that the ICC value was low,
2 the exact nature of the problem could be diagnosed by plotting the discrepancies between the
3 values against the average of the two (Bland-Altman plot) as advised by Machin, Campbell
4 and Walters.⁴⁵ We have used the ICC to assess how well our test set data meet the above
5 criteria. Weir⁴⁶ has pointed out that the ICC is conceptually akin to R^2 from regression, so it
6 is reasonable to assume that a value that is considered good for R^2 (say, 0.9), can also be
7 considered good for the ICC.

8
9 ICC values were calculated using the Reliability Analysis procedure in SPSS v20.⁴⁷ The
10 statistical model was set to Two-Way Mixed and the ICC type was set to Absolute
11 Agreement. The ICC values reported are for those for Single Measures.

12
13 It is also important that there should be no high pair-wise correlations between the various
14 descriptors incorporated into a QSAR, otherwise the statistics could be flawed.²³ Using a cut-
15 off point of $r = 0.9$,⁴⁸ we found no such high correlations between any of the descriptors used
16 in each QSAR.

17
18 **Results and discussion**

19
20 The QSARs that we developed for each mechanistic category, as well as that for all 204
21 chemicals together, are given in Table 2.

22
23 Table 2 here
24

1 Explanations of the descriptors are given in Table 3. We recognize that in some cases the
2 explanations are sparse, but descriptor software is frequently short on detail. Table 3 also
3 includes the ranges of SSPs and descriptor values in each mechanistic category, as an
4 indication of the applicability domains of each category. The SSPs cover a very wide range of
5 potency ranging from weak to strong or extreme, save for the oxidation potential category, in
6 which the range is from weak to moderate (EC3 values from 89% to 5%).

7
8 Table 3 here
9

10 For each category with adequate numbers of chemicals, with two exceptions, we were able to
11 formulate good QSARs with good internal and external validation. The first exception is the
12 Schiff base category, for which we could obtain a QSAR that, whilst acceptable, was not
13 good enough for our purposes, namely to provide QSAR models that can offer good
14 prediction. However, by combining the Schiff base chemicals with the five in the pro-Schiff
15 base category we were able to develop a QSAR with good internal and external predictive
16 ability. The second exception is the acyl transfer category, for which a good model could not
17 be developed using all 23 acyl transfer chemicals, owing to one chemical, C11 azlactone,
18 being a pronounced outlier. Several azlactones, with alkyl chains ranging from C4 to C19,
19 have been tested in the LLNA (see Table 1), and they appear to fall into two groups,
20 separated by an activity cliff.⁴⁹ Shorter chain-length azlactones (C4 to C9) are quite potent,
21 with EC3 values between 1% and 3%, whereas longer-chain homologs (C15 to C19) are
22 much weaker, with EC3 values of about 20%. This presumably reflects a change in the rate-
23 determining step (possibly mass transfer) becoming rate-limiting for azlactones with high
24 hydrophobicity.⁵⁰ Our model is able to make this distinction, but it appears that the C11
25 homolog, structurally between these two sub-sets, and which should belong to the low-

potency sub-set, is treated by our model as belonging to the high-potency sub-set. When the C11 azlactone was removed, a good QSAR model was obtained (Table 2, equations 17 and 18). The statistical quality of all the models can be seen from Table 4.

Table 4 here

It would, of course, have been possible to increase R^2 and s values for most of the models by increasing the number of descriptors incorporated. However, as we have pointed out elsewhere,²² “the principle of Occam’s razor (principle of parsimony) applies here: ‘One should not increase beyond what is necessary the number of entities required to explain anything’. We suggest that five or six descriptors are generally the maximum that one should generally use in a QSAR/QSPR, partly because it is difficult to comprehend the mechanistic significance of large numbers of descriptors”. We were surprised but very pleased that the two categories with the smallest number of chemicals (acyl transfer and oxidation potential) could nevertheless allow the development of good QSARs. In fact the latter category yielded the best QSAR of all.

The observed SSPs for all 195 skin sensitizers used in our modeling were correlated with the cumulative SSP values calculated from each appropriate local mechanistic domain QSAR, and as expected a very good correlation was found:

$$\text{SSP (observed)} = 0.000 + 1.000 \text{ SSP (predicted)} \quad (22)$$

$$n = 195 \quad R^2 = 0.884 \quad Q^2 = 0.882 \quad \text{ICC} = 0.939 \quad s = 0.296 \quad F = 1471$$

A graphical representation of these results is shown in Figure 1.

Figure 1 here

All test sets yielded very good predictions, fortuitously with all R^2 values higher than those of the full and training set QSARs.

The correlation between observed and predicted SSP values for all 37 test set chemicals was found to be:

$$\text{SSP (obsd)} = -0.070 + 1.002 \text{ SSP (pred)} \quad (23)$$

$$n = 37 \quad R^2 = 0.947 \quad Q^2 = 0.940 \quad \text{ICC} = 0.971 \quad s = 0.209 \quad F = 627.3$$

The overall ICC of 0.971 for all test set results indicates that the test set results for all mechanisms were valid. This can also be seen from Figure 2.

Figure 2 here

The QSAR derived for the complete dataset of 204 active chemicals, covering all the reaction mechanistic categories, is very much inferior to any of the QSARs for the individual mechanistic categories (Table 2), and the descriptors found to model the potency best are different for each mechanistic category, as can be seen from Table 3. These findings reinforce the argument that for skin sensitization, modeling reaction mechanistic domains/categories has more realistic prospects of success than attempting a global model.

The model obtained for Schiff base chemicals was not very good ($n = 35$, $R^2 = 0.837$, $Q^2 = 0.644$, $s = 0.259$, $F = 19.9$). However, inclusion of the five pro-Schiff base chemicals improved the model considerably ($n = 40$, $R^2 = 0.850$, $Q^2 = 0.781$, $s = 0.233$, $F = 25.9$).

It has been found that depending on the reaction mechanism of the protein-binding step, there are different relationships between model reactivity parameters and potency.⁵⁰⁻⁵² This is

1 argued to be because, depending on the reaction mechanism, relative reactivities towards the
2 several nucleophilic protein sites will differ. Thus, for example, the Schiff category chemicals
3 probably sensitize via reaction with amino groups of proteins, whereas the Michael acceptor
4 category chemicals probably sensitize via reaction with protein thiol groups. Even where
5 compounds from two different mechanistic categories sensitize via reaction with the same
6 type of protein nucleophile, the proportionality between the *in cutaneo* reactivity and
7 reactivity determined in a model cannot be assumed to be the same. This should apply
8 irrespective of whether the model reactivity is based on experimental data with model
9 nucleophiles, on classical linear free energy relationship indices based on Hammett and Taft
10 substituent constants, on quantum mechanical indices such as activation energy,⁵³ or on
11 combinations of less transparent descriptors such as those used here. Furthermore, for some
12 reaction mechanistic categories (Schiff base,^{11,50} S_N2 and acyl transfer⁵⁰), potency has been
13 found to be dependent not only on reactivity but also on hydrophobicity, whilst for others
14 (Michael acceptors,¹² S_NAr electrophiles¹³) reactivity parameters alone can give good models
15 for potency. as been argued that depending on the reaction mechanism of the protein-
16 binding step, there are different relationships between model reactivity parameters and
17 potency.⁵⁰⁻⁵² This is argued to be because, depending on the reaction mechanism, relative
18 reactivities towards the several nucleophilic protein sites will differ. Thus for example, the
19 Schiff base category chemicals probably sensitize via reaction with amino groups of proteins,
20 whereas the Michael acceptor category chemicals probably sensitize via reaction with protein
21 thiol groups. Even where compounds from two different mechanistic categories sensitize via
22 reaction with the same type of protein nucleophile, the proportionality between the *in cutaneo*
23 reactivity and reactivity determined in a model cannot be assumed to be the same. This
24 should apply irrespective of whether the model reactivity is based on experimental data with
25 model nucleophiles, on classical linear free energy relationship indices based on Hammett

1 and Taft substituent constants, on quantum mechanical indices such as activation energy,⁵³ or
2 on combinations of less transparent descriptors such as those used here. Furthermore, for
3 some reaction mechanistic categories (Schiff base,^{11,50} S_N2 and acyl transfer⁵⁰), potency has
4 been found to be dependent not only on reactivity but also on hydrophobicity, while for
5 others (Michael acceptors,¹² S_NAr electrophiles¹³) reactivity parameters alone give good
6 models for potency. It has already been mentioned that many descriptors are difficult to
7 interpret. Those selected for the Michael addition category suggest that reactivity and surface
8 area, and perhaps especially hydrophobic surface area, enhance skin sensitization potency.
9 For pro-Michael addition several descriptors represent hydrogen bonding, although there
10 does not appear to be a consistent pattern; for example, SssNH has a positive coefficient,
11 whereas that for vsurf_HB7 is negative.

12
13 From equation 8 it can be seen that for Schiff base chemicals, polarity and molecular
14 flexibility increase potency. There are also some specific atom effects (S7 and S10), although,
15 as the nature of those atoms is not known, no interpretation of those effects can be made. The
16 situation is somewhat clearer for the combined Schiff base and pro-Schiff base model
17 (equation 11), with hydrogen bonding (represented by HS6, E_{sol} and possibly DPSA1)
18 being important for potency, together with molecular shape (dx2 and Kier FI).

19
20 S_N2 chemicals appear to require hydrophobicity (SsCH₃, eaC2C3a) for potency, although
21 descriptors representing both negative and positive surface area also have positive
22 coefficients. Electron-donating ability (MNDO_HOMO) decreases potency, which is to be
23 expected since Michael reactivity is dependent on the electron deficiency of the double or
24 triple bond.

1 Acyl transfer appears to be highly dependent on hydrogen bonding, as all four descriptors are
2 E-state values for different hydrogen atoms. Finally, oxidation potential appears possibly to
3 be dependent on molecular shape as well as the location of interacting atoms or groups, as
4 contact distances are important (vsurf_DD12, vsurf_DD23).

5 It should be noted that whilst hydrophobicity (represented in many QSAR studies as log P,
6 the logarithm of the octanol-water partition coefficient) is not specifically selected as a
7 descriptor in any of our models, it is a composite descriptor with components of polarity,
8 polarizability, hydrogen bonding and molecular size,⁵⁴ so our models are not incompatible
9 with previous studies^{11, 50} that found hydrophobicity to be important.

11 Based on the above perspective, we have shown that quantitative predictive models for
12 sensitization potency can be derived by: (i) assigning chemicals to reaction mechanistic
13 domains; (ii) determining appropriate reactivity parameters and (if necessary) hydrophobicity
14 within a mechanistic domain; (iii) deriving regression-based quantitative mechanistic models
15 and using these to estimate the potency for untested chemicals. This chemistry-based
16 approach can already enable potency to be predicted for many chemicals.⁵¹ The findings
17 presented here strongly reinforce the argument that assignment of chemicals to their reaction
18 mechanistic domains (categories) is an essential step before attempting to predict potency by
19 *in chemico* or *in silico* approaches.

21 All the QSARs reported here satisfy all or almost all of the OECD Principles for the
22 Validation of (Q)SARs.⁵⁵ The work described here offers one solution to the vital need,
23 emphasized by Basketter et al.,⁵⁶ for information on the potency of identified skin sensitizers
24 in order to permit risk assessment.

Conclusions

Using in-house expertise, we have allocated 204 skin-sensitizing chemicals to their respective mechanistic categories, and then developed good QSAR models, with good predictive ability, for chemicals in seven out of ten categories. Only one chemical had to be omitted as an outlier, and an explanation is provided for that omission. Data on too few chemicals were available to allow QSAR modeling for three categories, namely S_N1 , pro- S_N2 and S_NAr . The QSARs reported here can be used, either on their own or as part of a weight-of-evidence approach, in risk assessments of skin sensitization.

Notes

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Abbreviations

Ac, acyl transfer; CAS, Chemical Abstracts Service; EC₃, the concentration (g/100 ml) that induces a threefold increase in local lymph node proliferative activity relative to controls; F , coefficient of variance (Fisher statistic); ICC, intraclass correlation coefficient; LLNA, murine local lymph node assay; MA, Michael addition; MLR, multiple linear regression; MW, molecular weight (relative molecular mass); OxPot, oxidation potential; p-MA, pro-Michael addition; OECD, Organisation for Economic Cooperation and Development; p value,

1 probability that a descriptor is there by chance; p-SB, pro-Schiff base; p-S_N2, pro-bimolecular
2 aliphatic nucleophilic substitution; Q², cross-validated coefficient of variation (leave-one-out
3 procedure); QSAR, quantitative structure-activity relationship; r, correlation coefficient; R²,
4 coefficient of variation; R²_{adj}, coefficient of variation adjusted for degrees of freedom;
5 REACH, Registration, Evaluation, Authorisation and restriction of Chemicals; s, standard
6 error of estimate; SB, Schiff base; S_N1, unimolecular aliphatic nucleophilic substitution; S_N2,
7 bimolecular aliphatic nucleophilic substitution; S_NAr, bimolecular aromatic nucleophilic
8 substitution; SSP, skin sensitization potency.

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2 Table 1. Chemicals used in this study, their potencies and mechanisms of action

Name	CAS No.	MW	EC3	Class	SSP	Mechanism
4'-Hydroxychalcone	2657-25-2	224.26	0.002	Extreme	4.050	MA
<i>p</i> -Benzoquinone ^a	106-51-4	108.10	0.0099	Extreme	3.038	MA
2',3',4'-Trihydroxychalcone	1482-74-2	256.25	0.11	Strong	2.367	MA
Methyl 2-octynoate	111-12-6	154.21	0.45	Strong	1.535	MA
2',4'-Dihydroxychalcone	1776-30-3	240.26	0.56	Strong	1.632	MA
Isopropyl isoeugenol	2953-00-7	206.29	0.6	Strong	1.536	MA
β -Phenylcinnamaldehyde	1210-39-5	208.26	0.6	Strong	1.540	MA
Isoeugenol ^a	97-54-1	164.20	1.2	Moderate	1.136	MA
2-Hydroxyethyl acrylate ^a	818-61-1	116.12	1.4	Moderate	0.919	MA
3-Methyl-4-phenyl-1,2,5-thiadiazole-1,1-dioxide (MPT)	3775-21-1	208.24	1.4	Moderate	1.172	MA
6-Methylisoeugenol	13041-12-8	178.23	1.6	Moderate	1.047	MA
Vinyl pyridine	100-43-6	105.14	1.6	Moderate	0.818	MA
5,5-Dimethyl-3-methylene-dihydro-2(3H)-furanone	29043-97-8	126.16	1.8	Moderate	0.846	MA
<i>trans</i> -Anethol ^a	104-46-1	148.21	2.3	Moderate	0.809	MA
<i>trans</i> -2-Decenal	3913-71-1	154.25	2.5	Moderate	0.790	MA
Methyl 2-nonynoate	111-80-8	168.24	2.5	Moderate	0.828	MA
3,4-Dinitrophenol	577-71-9	184.10	2.6	Moderate	0.850	MA
Cinnamic aldehyde	104-55-2	132.16	3	Moderate	0.644	MA
2,4-Hexadienal	142-83-6	96.13	3.5	Moderate	0.439	MA
3-Methylisoeugenol ^a	186743-29-3	178.23	3.6	Moderate	0.695	MA
Benzylidene acetone (4-phenyl-3-buten-2-one)	122-57-6	146.19	3.7	Moderate	0.597	MA
2,4-Heptadienal ^a	5910-85-0	110.16	4	Moderate	0.440	MA
Tropolone	533-75-5	122.12	4.3	Moderate	0.453	MA
5-Methyl-2-phenyl-2-hexenal	21834-92-4	188.27	4.4	Moderate	0.631	MA

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5	α -Methylcinnamaldehyde	101-39-3	146.19	4.5	Moderate	0.512	MA
6	<i>trans</i> -2-Hexenal	6728-26-3	98.15	5.5	Moderate	0.252	MA
7	Diethyl maleate	141-05-9	172.18	5.8	Moderate	0.473	MA
8	1,1,3-Trimethyl-2-formylcyclohexa-2,1-diene (safranal)	116-26-7	150.22	7.5	Moderate	0.302	MA
9	Perillaldehyde	2111-75-3	150.22	8.1	Moderate	0.268	MA
10	1-(<i>p</i> -Methoxyphenol)-1-penten-3-one ^a	104-27-8	190.24	9.3	Moderate	0.311	MA
11	Linalool aldehyde	Not known ^b	168.24	9.5	Moderate	0.248	MA
12	2-Ethylhexyl acrylate	103-11-7	184.28	10	Weak	0.265	MA
13	α -Amylcinnamaldehyde	122-40-7	202.30	11	Weak	0.265	MA
14	α -Butylcinnamaldehyde	7492-44-6	188.27	11	Weak	0.233	MA
15	Hexyl cinnamaldehyde	101-86-0	216.32	11	Weak	0.294	MA
16	Butyl acrylate	141-32-2	128.17	11	Weak	0.066	MA
17	R-Carvone ^a	6485-40-1	150.22	12.9	Weak	0.066	MA
18	Benzyl cinnamate	103-41-3	238.29	18.4	Weak	0.112	MA
19	Methyl acrylate ^a	96-33-3	86.09	20	Weak	-0.366	MA
20	Cinnamic alcohol	104-54-1	134.18	21	Weak	-0.195	MA
21	α -iso-Methylionone	127-51-5	206.33	21.8	Weak	-0.024	MA
22	Ethyl acrylate	140-88-5	100.12	28	Weak	-0.447	MA
23	Ethylene glycol dimethacrylate	97-90-5	198.22	28	Weak	-0.150	MA
24	2,2-bis-[4-(2-Hydroxy-3-methacryloxypropoxy)phenyl]-propane	1565-94-2	512.65	45	Weak	0.057	MA
25	Methyl methacrylate	80-62-6	100.12	90	Weak	-0.954	MA
26	Bandrowski's base	20048-27-5	318.38	0.04	Extreme	2.901	p-MA
27	3,4-Diaminonitrobenzene	99-56-9	153.14	0.05	Extreme	2.486	p-MA
28	4-((2-Hydroxyethyl)amino)-3-nitrophenol	65235-31-6	198.18	0.07	Extreme	2.452	p-MA
29	1,4-Dihydroquinone	123-31-9	110.11	0.11	Strong	2.000	p-MA
30	1,4-Phenylenediamine	106-50-3	108.14	0.16	Strong	1.830	p-MA
31	2,5-Diaminotoluene	95-70-5	122.08	0.2	Strong	1.786	p-MA
32	4-Amino-3-nitrophenol	610-81-1	154.12	0.2	Strong	1.887	p-MA
33	Lauryl gallate (dodecyl gallate) ^a	1166-52-5	338.44	0.3	Strong	2.052	p-MA
34	2-Aminophenol	95-55-6	109.13	0.4	Strong	1.436	p-MA

2-Methyl-5-hydroxyethylaminophenol	55302-96-0	167.21	0.4	Strong	1.621	p-MA
2-Nitro- <i>p</i> -phenylenediamine ^a	5307-14-2	153.14	0.4	Strong	1.583	p-MA
1,3-Phenylenediamine ^a	108-45-2	108.14	0.49	Strong	1.344	p-MA
R-Carvoxime	55658-55-4	165.23	0.6	Strong	1.440	p-MA
Hydroxytyrosol	10897-60-1	154.16	0.6	Strong	1.410	p-MA
1,2-Dibromo-2,4-dicyanobutane	35691-65-7	265.94	0.9	Strong	1.471	p-MA
1-Naphthol	90-15-3	144.17	1.3	Moderate	1.045	p-MA
4-Amino-3-methylphenol	2835-99-6	123.15	1.45	Moderate	0.929	p-MA
2-(4-Amino-2-nitrophenylamino)-ethanol	2871-01-4	197.19	2.2	Moderate	0.952	p-MA
3-Aminophenol	591-27-5	109.13	3.2	Moderate	0.533	p-MA
5-Amino-2-methylphenol ^a	2835-95-2	123.15	3.4	Moderate	0.559	p-MA
3-Bromomethyl-5,5-dimethyl-dihydro-2(3H)-furanone	154750-20-6	207.07	3.6	Moderate	0.760	p-MA
2-Methoxy-4-methyl-phenol	93-51-6	138.17	5.8	Moderate	0.377	p-MA
Anisyl alcohol	105-13-5	138.17	5.9	Moderate	0.370	p-MA
Dihydroeugenol	2785-87-7	166.22	6.8	Moderate	0.388	p-MA
2-Amino-6-chloro-4-nitrophenol ^a	6358-09-4	188.57	6.85	Moderate	0.440	p-MA
1-Amino-2-nitro-4-bis(2-hydroxyethyl)-amino-benzene	29705-39-3	241.24	8.2	Moderate	0.469	p-MA
Eugenol	97-53-0	164.20	13	Weak	0.101	p-MA
5-Methyleugenol	186743-25-9	178.23	13	Weak	0.137	p-MA
6-Methyleugenol	186743-24-8	178.23	17	Weak	0.021	p-MA
4-Allylanisole	140-67-0	148.21	18	Weak	-0.084	p-MA
2,2'-Azobisphenol ^a	2050-14-8	214.20	27.9	Weak	-0.115	p-MA
3-Methyleugenol	186743-26-0	178.23	32	Weak	-0.254	p-MA
Glutaraldehyde	111-30-8	100.12	0.1	Strong	2.001	SB
Chloroatranol	57074-21-2	186.59	0.4	Strong	1.669	SB
Atranol ^a	526-37-4	152.15	0.6	Strong	1.404	SB
Formaldehyde	50-00-0	30.03	0.61	Strong	0.692	SB
1-Phenyl-1,2-propanedione	579-07-7	148.16	1.3	Moderate	1.057	SB
Glyoxal	107-22-2	58.04	1.4	Moderate	0.618	SB
Methyl pyruvate ^a	600-22-6	102.09	2.4	Moderate	0.629	SB

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5	Phenylacetaldehyde	122-78-1	120.15	3.0	Moderate	0.603	SB
6	α -Methylphenylacetaldehyde	93-53-8	134.18	6.3	Moderate	0.328	SB
7	Undec-10-enal	112-45-8	168.28	6.8	Moderate	0.394	SB
8	1-(2',3',4',5'-Tetramethylphenyl)butane-1,3-dione	167998-73-4	218.30	8.3	Moderate	0.420	SB
9	1-(2',5'-Diethylphenyl)butane-1,3-dione	167998-76-7	218.30	9.6	Moderate	0.357	SB
10	Camphorquinone	465-29-2	166.22	10	Weak	0.221	SB
11	2-Methylundecanal	110-41-8	184.32	10	Weak	0.266	SB
12	2,3-Butanedione ^a	431-03-8	86.09	11	Weak	-0.106	SB
13	1-Phenyloctane-1,3-dione	55846-68-1	218.30	11	Weak	0.298	SB
14	Farnesal	502-67-0	220.36	12	Weak	0.264	SB
15	Citral	5392-40-5	152.44	13	Weak	0.069	SB
16	1-(2',5'-Dimethylphenyl)butane-1,3-dione	56290-55-2	190.24	13	Weak	0.165	SB
17	4-Methylhydrocinnamic aldehyde	5406-12-2	148.21	14	Weak	0.025	SB
18	α -Methyl-1,3-benzodioxole-5-propionaldehyde ^a	1205-17-0	192.21	16.4	Weak	0.069	SB
19	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-						
20	carboxaldehyde	31906-04-4	210.32	17	Weak	0.092	SB
21	4- <i>tert</i> -Butyl- α -ethylhydrocinnamal	80-54-6	204.31	19	Weak	0.032	SB
22	N,N-Dibutylaniline ^{ac}	613-29-6	205.30	19.6	Weak	0.020	SB
23	4,4,4-Trifluoro-1-phenylbutane-1,3-dione	326-06-7	216.16	20	Weak	0.034	SB
24	4,4'-Dibromobenzil ^{ac}	35578-47-3	368.02	20.5	Weak	0.254	SB
25	Cyclamen aldehyde ^{ad}	103-95-7	190.29	22	Weak	-0.063	SB
26	<i>cis</i> -6-Nonenal	2277-19-2	140.23	23	Weak	-0.215	SB
27	5-Methyl-2,3-hexanedione	13706-86-0	128.17	26	Weak	-0.307	SB
28	2,2,6,6-Tetramethyl-heptane-3,5-dione	1118-71-4	184.28	27	Weak	-0.166	SB
29	1-Phenyl-2-methylbutane-1,3-dione	6668-24-2	176.22	29	Weak	-0.216	SB
30	3-Ethoxy-1-(2',3',4',5'-tetramethylphenyl)propane-1,3-dione	170928-69-5	248.32	33	Weak	-0.124	SB
31	Hydroxycitronellal	107-75-5	172.27	33	Weak	-0.282	SB
32	2-(4- <i>tert</i> -Amylcyclohexyl)acetaldehyde ^a	620159-84-4	196.33	37	Weak	-0.275	SB
33	Diethyl acetaldehyde	97-96-1	100.16	76	Weak	-0.880	SB
34	3-Dimethylaminopropylamine	109-55-7	102.18	2.2	Moderate	0.667	p-SB

Ethylenediamine	107-15-3	60.10	2.2	Moderate	0.436	p-SB
Diethylenetriamine ^{ad}	111-40-0	103.17	5.8	Moderate	0.250	p-SB
3-Methyl-1-phenylpyrazolone	89-25-8	174.20	8.5	Moderate	0.312	p-SB
Geraniol	106-24-1	154.25	26	Weak	-0.227	p-SB
1-Chloromethylpyrene	1086-00-6	250.73	0.005	Extreme	3.700	S _N 2
5-Chloro 2 methyl 4 isothiazolin-3-one	26172-55-4	149.60	0.009	Extreme	3.221	S _N 2
1-Methyl-3-nitro-1-nitrosoguanidine	70-25-7	147.09	0.03	Extreme	2.690	S _N 2
<i>N</i> -Methyl- <i>N</i> -nitrosourea	684-93-5	103.08	0.05	Extreme	2.314	S _N 2
4-Nitrobenzyl bromide ^a	100-11-8	216.03	0.05	Extreme	2.636	S _N 2
β-Propiolactone	57-57-8	72.06	0.15	Strong	1.682	S _N 2
Dimethyl sulfate ^a	77-78-1	126.13	0.19	Strong	1.822	S _N 2
Benzyl bromide	100-39-0	171.04	0.2	Strong	1.932	S _N 2
Methyl dodecane sulfonate	2374-65-4	264.42	0.39	Strong	1.831	S _N 2
Iodopropynyl butylcarbamate	55406-53-6	281.09	0.9	Strong	1.495	S _N 2
<i>N</i> -ethyl- <i>N</i> -nitrosourea	759-73-9	117.11	1.1	Moderate	1.027	S _N 2
Bisphenol A-diglycidyl ether	1675-54-3	340.42	1.5	Moderate	1.356	S _N 2
2-Methyl-2H-isothiazol-3-one ^a	2682-20-4	115.15	1.9	Moderate	0.783	S _N 2
1,2-Benzisothiazolin-3-one	2634-33-5	151.18	2.3	Moderate	0.818	S _N 2
1-Bromohexadecane	112-82-3	305.34	2.3	Moderate	1.123	S _N 2
Benzyl salicylate	118-58-1	228.25	2.9	Moderate	0.896	S _N 2
Diethyl sulfate	64-67-5	154.18	3.3	Moderate	0.670	S _N 2
2-Bromotetradecanoic acid ^a	10520-81-7	307.27	3.4	Moderate	0.956	S _N 2
1-Bromoheptadecane	3508-00-7	319.37	4.8	Moderate	0.823	S _N 2
1-Bromopentadecane	629-72-1	291.32	5.1	Moderate	0.757	S _N 2
Tetramethylthiuram disulfide	137-26-8	240.42	5.2	Moderate	0.665	S _N 2
1-Bromoeicosane	4276-49-7	361.45	6.1	Moderate	0.773	S _N 2
2-Bromoethylbenzene	103-63-9	185.10	6.2	Moderate	0.475	S _N 2
12-Bromo-1-dodecanol ^a	3344-77-2	265.24	6.9	Moderate	0.585	S _N 2
Methyl methanesulfonate	66-27-3	110.13	8.1	Moderate	0.133	S _N 2
1-Bromodocosane	6938-66-5	389.51	8.3	Moderate	0.671	S _N 2

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Dodecyl methane sulfonate	51323-71-8	264.42	8.8	Moderate	0.478	S _N 2
1-Chlorohexadecane	4860-03-1	260.89	9.1	Moderate	0.457	S _N 2
1-Bromotetradecane	112-71-0	277.29	9.2	Moderate	0.479	S _N 2
1-Bromohexane	111-25-1	165.07	10	Weak	0.218	S _N 2
1-Bromotridecane	765-09-3	263.26	10	Weak	0.420	S _N 2
1-Iodododecane	4292-19-7	296.24	13	Weak	0.358	S _N 2
1-Iodotetradecane ^a	19218-94-1	324.29	14	Weak	0.365	S _N 2
1-Bromooctadecane ^a	112-89-0	333.40	15	Weak	0.347	S _N 2
1-Chlorooctadecane	3386-33-2	288.95	16	Weak	0.257	S _N 2
Benzyl benzoate	120-51-4	212.25	17	Weak	0.096	S _N 2
1-Bromododecane ^a	143-15-7	249.24	18	Weak	0.141	S _N 2
12-Bromododecanoic acid	73367-80-3	279.22	18	Weak	0.191	S _N 2
1-Iodoheptadecane	544-77-4	352.35	19	Weak	0.268	S _N 2
1-Bromoundecane	693-67-4	235.21	20	Weak	0.070	S _N 2
1-Chlorotetradecane	2425-54-9	232.84	20	Weak	0.066	S _N 2
7-Bromotetradecane	74036-97-8	277.29	21	Weak	0.121	S _N 2
1-Iodononane ^a	4282-42-2	254.16	24	Weak	0.025	S _N 2
Oleyl methane sulfonate	35709-09-2	346.57	25	Weak	0.142	S _N 2
Butyl glycidyl ether	2426-08-6	130.19	31	Weak	-0.377	S _N 2
Benzo[a]pyrene	50-32-8	252.32	0.0009	Extreme	4.448	p-S _N 2
7,12-Dimethylbenz[α]anthracene	57-97-6	256.35	0.006	Extreme	3.631	p-S _N 2
4-Ethoxymethylene-2-phenyl-2-oxazolin-5-one	15646-46-5	217.22	0.003	Extreme	3.860	Ac
Tetrachlorosalicylanilide ^a	1154-59-2	351.02	0.04	Extreme	2.943	Ac
Fluorescein-5-isothiocyanate	3326-32-7	389.38	0.14	Strong	2.444	Ac
2-Methyl -4H,3,1-benzoxazin-4-one	525-76-8	161.16	0.7	Strong	1.362	Ac
C6 Azlactone	176665-02-4	197.28	1.3	Moderate	1.181	Ac
2-Mercaptobenzothiazole	149-30-4	167.24	1.7	Moderate	0.993	Ac
C4 Azlactone	176664-99-6	169.22	1.8	Moderate	0.973	Ac
Nonanoyl chloride	764-85-2	176.69	1.8	Moderate	0.992	Ac
Methyl 2-sulfophenyl octadecanoate	Not known ^b	454.67	2	Moderate	1.357	Ac

Isononanoyl chloride ^a	57077-36-8	176.69	2.7	Moderate	0.816	Ac
3,5,5-Trimethylhexanoyl chloride	36727-29-4	176.69	2.7	Moderate	0.816	Ac
C9 Azlactone	176665-04-6	239.36	2.8	Moderate	0.932	Ac
3-Propylidenephthalide	17369-59-4	174.20	3.7	Moderate	0.673	Ac
3,4-Dihydrocoumarin	119-84-6	148.16	5.6	Moderate	0.423	Ac
Palmitoyl chloride ^a	112-67-4	274.88	8.8	Moderate	0.495	Ac
1,2,4-Benzenetricarboxylic anhydride	552-30-7	192.13	9.2	Moderate	0.320	Ac
C11 Azlactone	176665-06-8	267.41	16	Weak	0.223	Ac
C15 Azlactone	176665-09-1	323.52	18	Weak	0.255	Ac
C17 Azlactone	176665-11-5	351.58	19	Weak	0.267	Ac
Phenyl benzoate	93-99-2	198.22	20	Weak	-0.004	Ac
Imidazolidinylurea	39236-46-9	388.30	24	Weak	0.209	Ac
C19 Azlactone ^a	Not known ^b	379.63	26	Weak	0.164	Ac
Penicillin G	61-33-6	334.39	30	Weak	0.047	Ac
5-Chlorosalicylanilide	4638-48-6	247.68	5	Moderate	0.695	OxPot
α -Phellandrene	99-83-2	136.23	5.4	Moderate	0.402	OxPot
β -Phellandrene ^a	555-10-2	136.23	5.6	Moderate	0.386	OxPot
(5R)-5-Isopropenyl-2-methyl-1-methylene-2-cyclohexene	Not known ^b	148.25	7.3	Moderate	0.308	OxPot
2-(Hexadecyloxy)ethanol	2136-71-2	286.50	8.8	Moderate	0.513	OxPot
α -Terpinene	99-86-5	136.24	8.9	Moderate	0.185	OxPot
Acetyl cedrene	32388-55-9	246.39	13.9	Weak	0.249	OxPot
Abietic acid	514-10-3	302.46	15	Weak	0.305	OxPot
Linalool	78-70-6	154.25	30	Weak	-0.289	OxPot
R(+) Limonene	5989-27-5	136.24	69	Weak	-0.705	OxPot
Aniline ^a	62-53-3	93.13	89	Weak	-0.980	OxPot
Chlorothalonil	1897-45-6	265.91	0.004	Extreme	3.823	S _N Ar
1-Chloro-2,4-dinitrobenzene	97-00-7	202.55	0.05	Extreme	2.608	S _N Ar
2,4,6-Trichloro-1,3,5-triazine	108-77-0	184.41	0.09	Extreme	2.312	S _N Ar
Pentachlorophenol	87-86-5	266.34	20	Weak	0.124	S _N Ar
Clotrimazole	23593-75-1	344.85	4.8	Moderate	0.856	S _N 1

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d,l-Citronellol 106-22-9 156.27 43.5 Weak -0.445 S_N1

^aThese chemicals were used as test set chemicals. Those marked ^{ac} were used only in the SB test set, and those marked ^{ad} were used only in the SB + p-SB test set.

^bFor compounds with unknown CAS numbers, the SMILES strings are: linalool aldehyde, C=CC(C)(O)CCC=C(C)C=O ; methyl 2-sulfophenyl octadecanoate, CCCCCCCCCCCCCCCC(C)C(=O)Oc1ccccc1S(=O)(=O)=O ; C19 azlactone, CCCCCCCCCCCCCCCCCCCC1=NC(C)(C)C(=O)O1 ; (5R)-5-isopropenyl-2-methyl-1-methylene-2-cyclohexene, CC(=C)[C@@H]1CC=C(C)C(=C)C1

Table 2. Models developed in this work for skin sensitization

Mech.	Model	Eqn.	No. of chemicals	Equation	R ² (R ² _{adj})	Q ²	s	F	p values
All	Full	1	204	SSP = - 1.164(0.282) + 1.759(0.450) FASA- + 0.174(0.028) eaC2C3a + 0.807(0.155) vsurf_CW2 + 0.012(0.0026) vsurf_D8 - 0.767 (0.202) Hmin - 0.190(0.057) SHCsatu	0.496 (0.480)	0.459	0.689	32.4	<0.001
MA	Full	2	45	SSP = 16.7(2.52) - 0.101(0.020) S4 - 0.760(0.174) HS17 + 0.112(0.015) SlogP_VSA4 + 0.775(0.195) vsurf_CW2 - 8.39(1.14) Max. BC1 - 43.4(7.37) Rel. PMI	0.856 (0.834)	0.793	0.358	37.8	<0.001
MA	Train	3	36	SSP = 16.6(3.77) - 0.094(0.029) S4 - 0.743(0.201) HS17 + 0.113(0.017) SlogP_VSA4 + 0.673(0.257) vsurf_CW2 - 8.26(1.78) Max. BC1 - 42.2(9.9) Rel. PMI	0.825 (0.789)	0.692	0.398	22.9	≤0.015
MA	Test	4	9	SSP (obsd) = - 0.113 + 1.12 SSP (pred) (ICC = 0.977)	0.965	0.937	0.191	195.9	
p-MA	Full	5	32	SSP = - 0.360(0.369) + 1.400(0.194) S24 - 0.319(0.046) e1C3O2a + 0.279(0.085) SssNH - 0.337(0.051) vsurf_HB7 + 0.467(0.108) Av. IC2	0.858 (0.831)	0.790	0.349	31.4	≤0.003
p-MA	Train	6	26	SSP = - 0.139(0.454) + 1.348(0.249) S24 + 0.254(0.097) SssNH - 0.318(0.057) e1C3O2a - 0.359(0.098) vsurf_HB7 + 0.401(0.131) Av. IC2	0.848 (0.810)	0.768	0.380	22.3	≤0.01
p-MA	Test	7	6	SSP (obsd) = 0.039 + 0.958 SSP (pred) (ICC = 0.951)	0.887	0.758	0.305	31.5	

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Table 3. Descriptors and SSPs used in the QSAR models, and their ranges**All 204 active sensitizers**

SSP (-0.980 to 4.050)

FASA-: MOE; Fractional accessible surface area of all atoms with negative partial charge (0.067 to 0.703)

eaC2C3a: winMolconn; Bond-type electrotopological state index for single bond between unsubstituted carbon and carbon with three aromatic neighbours (0 to 18.723)

vsurf_CW2: MOE; Capacity factor (Shape, volume, surface area descriptor) (1.160 to 3.211)

vsurf_D8: MOE; Hydrophobic volume (0 to 112.88)

Hmin: CODESSA; Minimum number of hydrogen bond donors and acceptors (0 to 1.514)

SHCsatu: winMolconn; Number of hydrogen atoms on sp³ carbons bonded to sp² carbons (0 to 4.407)**Michael addition**

SSP (-0.954 to 4.050)

S4: winMolconn; Atom level E-State for atom 4 (-3.617 to 10.190)

HS17: winMolconn; Hydrogen atom level HE-state for hydrogen atom 17 (0 to 2.690)

SlogP_VSA4: MOE; Sum of van der Waals surface areas such that contribution to log P is in range 0.1-0.15 (0 to 30.233)

vsurf_CW2: MOE; Capacity factor (Shape, volume, surface area descriptor) (1.352 to 2.836)

Max. BC1: CODESSA; Maximum bonding contribution of one (1.84 to 2.14)

Rel. PMI: CODESSA; Relative principal moment of inertia (0 to 0.05)

Pro-Michael addition

SSP (-0.115 to 2.901)

S24: winMolconn; Atom level E-state index for atom 24 (0 to 1.817)

e1C3O2a: winMolconn; Bond-type E-state for single bond between ether oxygen and substituted aromatic carbon (0 to 3.311)

SssNH: winMolconn; Atom type E-state index for >NH nitrogen (0 to 2.952)

vsurf_HB7: MOE; H-bond donor capacity (-3.125 to 3.375)

Av. IC2 : CODESSA; Average information content (₂), a structural descriptor (1.02 to 2.19)**Schiff base**

SSP (-0.880 to 2.001)

S7: winMolconn; Atom level E-state for atom 7 (-0.526 to 11.481)

S10: winMolconn; Atom level E-state for atom 10 (-2.017 to 10.595)

GCUT_PEOE_1: MOE; The GCUT descriptors are calculated from the eigenvalues of a modified graph distance adjacency matrix. Each ij entry of the adjacency matrix takes the value $1/\sqrt{d_{ij}}$ where d_{ij} is the (modified) graph distance between atoms i and j . The diagonal takes the value of the PEOE partial charges. The resulting eigenvalues are sorted and the smallest, 1/3-ile, 2/3-ile and largest eigenvalues are reported (-0.468 to -0.187)

vsurf_Wp7: MOE; Polar volume (Shape, volume, surface area descriptors) (0 to 0.50)

Av. SI2: CODESSA; Average structural information₂, a structural descriptor (0.35 to 0.92)

Av. BO: CODESSA; Average bond order (0.96 to 1.13)

Kier FI: CODESSA; Kier flexibility index (1.25 to 13.94)

Schiff base + pro-Schiff base

SSP (-0.880 to 2.001)

HS6: winMolconn; Hydrogen atom level HE-state for hydrogen atom 6 (0 to 1.391)

dx2: winMolconn; 2nd Order connectivity index difference between a molecule and its unbranched isomer (0 to 2.588)

E_sol: MOE; Solvation energy (-20.623 to -4.438)

Kier FI : CODESSA ; Kier flexibility index (1.25 to 16.57)

DPSA1 : CODESSA; Difference in positive and negative partial surface areas (-100.41 to 563.06)

Av. valency: CODESSA; Average valency (3.63 to 4.47)

Rel. no. O atoms: CODESSA; Relative number of oxygen atoms (0 to 0.50)

S_N2

SSP (-0.377 to 3.700)

S14: winMolconn; Atom level E-state for atom 14 (-3.234 to 11.013)

SsCH₃: winMolconn; E-state for -CH₃ carbon atoms (0 to 7.701)

xvp9: winMolconn; 9th order valence path molecular connectivity (0 to 0.506)

eaC2C3a: winMolconn; Bond-type E-state for single bond between unsubstituted carbon and carbon with three aromatic neighbours (0 to 12.937)

FASA-: MOE; Fractional accessible surface area of all atoms with negative partial charge (0.103 to 0.673)

PEOE_VSA_FPOS: MOE; Fractional positive van der Waals surface area (0.265 to 0.775)

MNDO_HOMO: MOE; Energy of the highest occupied molecular orbital calculated using the MNDO Hamiltonian [MOPAC] (-12.102 to -8.237)

Acyl transfer

SSP (0.075 to 3.860)

S14: Winmolconn; Hydrogen atom level HE-state for hydrogen atom 14 (0 to 2.749)

HS16: Winmolconn; Hydrogen atom level HE-state for hydrogen atom 16 (0 to 2.711)

HS17: Winmolconn; Hydrogen atom level HE-state for hydrogen atom 17 (0 to 1.514)

HS29: Winmolconn; Hydrogen atom level HE-state for hydrogen atom 29 (0 to 2.898)

Oxidation potential

SSP (-0.980 to 0.695)

vsurf_DD12 : MOE; Contact distances of vsurf_DDmin (3 descriptors) (0.500 to 7.697)

vsurf_DD23 : MOE; Contact distances of vsurf_DDmin (3 descriptors) (0.500 to 6.819)

1

Table 4. Comparison of statistical quality of full data-set QSARs

.

Category	All	MA	pMA	SB	SB+pSB	S _N 2	Acyl	OxPot
Equation	1	2	5	8	11	14	17	20
n	204	45	32	35	40	45	22	11
Descriptors	6	6	5	7	7	7	4	2
R ²	0.496	0.856	0.858	0.837	0.850	0.852	0.921	0.930
R ² _{adj}	0.480	0.834	0.831	0.795	0.817	0.823	0.902	0.912
Q ²	0.459	0.793	0.790	0.644	0.781	0.796	0.886	0.856
s	0.689	0.358	0.349	0.259	0.233	0.381	0.304	0.156
F	32.4	37.8	31.3	19.9	25.9	30.3	49.5	52.8

3

4

Figure 1. Observed vs. predicted SSP values for all 196 chemicals. Black diamond = Michael addition; black square = pro-Michael addition; black triangle = Schiff base + pro-Schiff base; cross = S_N2 ; asterisk = acyl transfer; black circle = oxidation potential

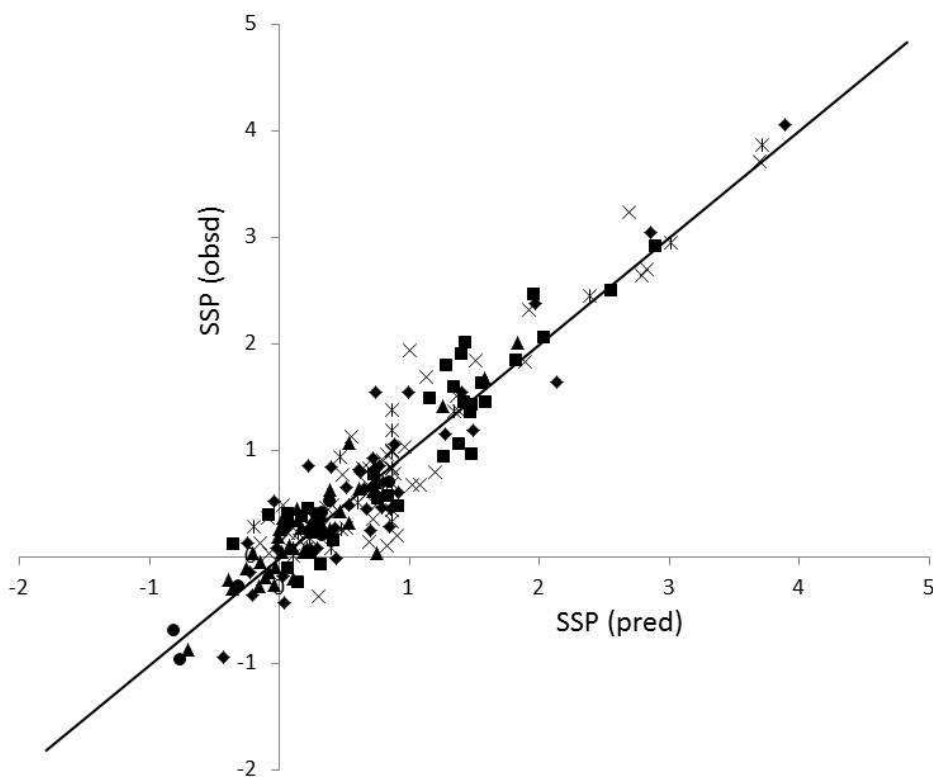


Figure 2. Observed vs. predicted SSP values for all 37 test set chemicals. The 45° line on the graph is virtually indistinguishable from that of equation 22. Black diamond = Michael addition; black square = pro-Michael addition; black triangle = Schiff base + pro-Schiff base; cross = S_N2; asterisk = acyl transfer; black circle = oxidation potential

