

# Pred-Skin: A Fast and Reliable Web Application to Assess Skin Sensitization Effect of Chemicals

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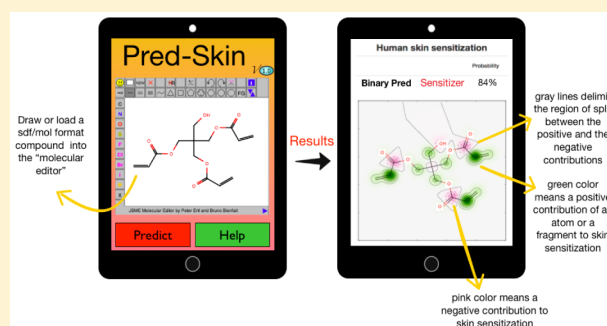
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## Supporting Information

**ABSTRACT:** Chemically induced skin sensitization is a complex immunological disease with a profound impact on quality of life and working ability. Despite some progress in developing alternative methods for assessing the skin sensitization potential of chemical substances, there is no in vitro test that correlates well with human data. Computational QSAR models provide a rapid screening approach and contribute valuable information for the assessment of chemical toxicity. We describe the development of a freely accessible web-based and mobile application for the identification of potential skin sensitizers. The application is based on previously developed binary QSAR models of skin sensitization potential from human (109 compounds) and murine local lymph node assay (LLNA, 515 compounds) data with good external correct classification rate (0.70–0.81 and 0.72–0.84, respectively). We also included a multiclass skin sensitization potency model based on LLNA data (accuracy ranging between 0.73 and 0.76). When a user evaluates a compound in the web app, the outputs are (i) binary predictions of human and murine skin sensitization potential; (ii) multiclass prediction of murine skin sensitization; and (iii) probability maps illustrating the predicted contribution of chemical fragments. The app is the first tool available that incorporates quantitative structure–activity relationship (QSAR) models based on human data as well as multiclass models for LLNA. The Pred-Skin web app version 1.0 is freely available for the web, iOS, and Android (in development) at the LabMol web portal (<http://labmol.com.br/predskin/>), in the Apple Store, and on Google Play, respectively. We will continuously update the app as new skin sensitization data and respective models become available.



## ■ INTRODUCTION

Skin sensitization is a key step in the complex immune-mediated inflammatory skin reaction called allergic contact dermatitis. Although not life threatening, this disease has a profound impact on individual working ability and quality of life.<sup>1</sup> The murine local lymph node assay (LLNA)<sup>2</sup> is regarded as the preferred in vivo test for evaluating skin sensitization hazard and the potency of chemicals regulated not only by REACH,<sup>3</sup> but various other regulatory agencies, such as the UK Health and Safety Executive<sup>4</sup> and the US EPA.<sup>5</sup> Since animal experiments are prohibited for cosmetic ingredients in Europe,<sup>6</sup> there is a strong need for the development of alternative methods to assess the skin sensitization potential of chemicals. Several in vitro tests have been proposed, but a single test will most likely be insufficient to predict human skin sensitization

due to the complex adverse outcome pathway (AOP) of the disease.<sup>7</sup> As an alternative, it has been proposed that multiple key steps of the AOP should be addressed through a combination of in vitro, in chemico, and in silico approaches.<sup>8,9</sup>

Predictive computational modeling is a fast and inexpensive approach that has become widely used within integrated testing strategies for chemical safety assessment.<sup>10</sup> Structural alerts, chemical grouping, and read-across have been incorporated into several computerized expert systems to evaluate skin sensitization (e.g., OECD QSAR Toolbox,<sup>11</sup> OCHEM ToxAlerts,<sup>12</sup> Toxtree (<http://toxtree.sourceforge.net/>), etc.). However, as we have recently shown,<sup>13</sup> using several case

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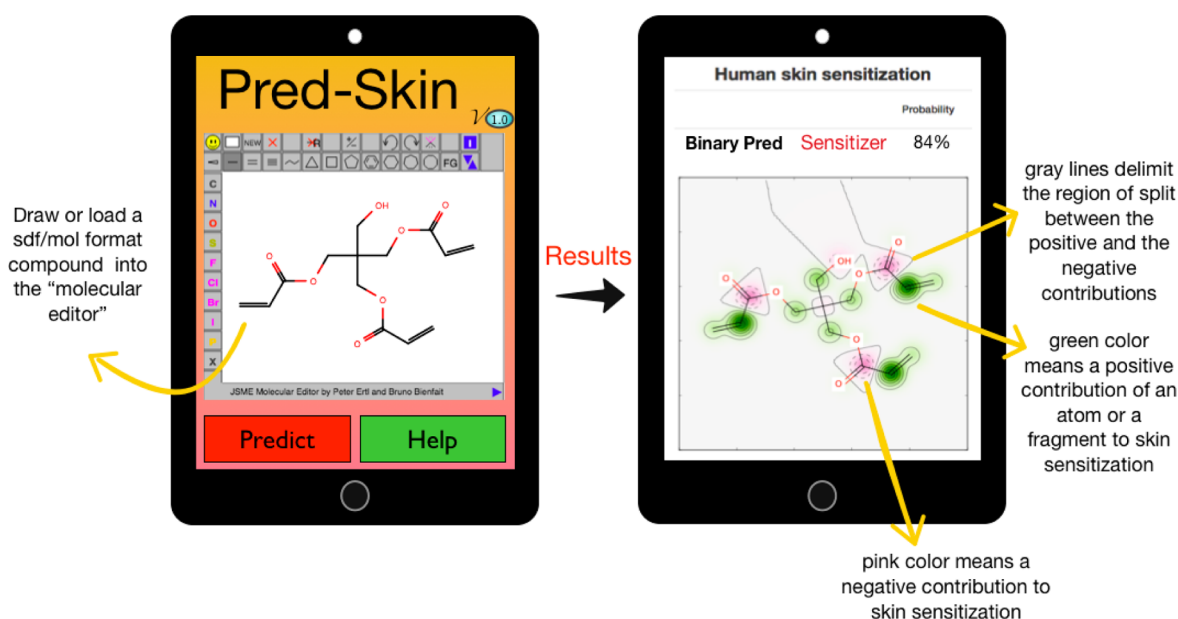


**Figure 1.** General scheme for usage and outcome interpretation of the Pred-Skin web app.

studies, the mere presence of structural alerts in the chemical structure is an unreliable marker of its chemical toxicity.

In our previous studies, we have built a series of QSAR (quantitative structure–activity relationships) models from a LLNA data set consisting of 387 diverse compounds<sup>14</sup> and a human data set consisting of 109 compounds.<sup>15</sup> Here, we report on a web-accessible app to predict skin sensitization potential of chemicals that integrates a novel curated database of 515 compounds with LLNA data and the same set of 109 compounds with human skin sensitization data. The app also incorporates new models for predicting the skin sensitization effect of chemicals generated using only open-source tools. We describe the implementation of the developed models on two platforms: Pred-Skin web version 1.0 for any operating system and a mobile version 1.0 for iOS. It will also be available soon for Android. Our freely available Pred-Skin web app (<http://labmol.com.br/predskin/>) allows users to perform rapid virtual screening of large chemical libraries in order to identify putative skin sensitizers.

## ■ PRED-SKIN

**Data Collection and Curation.** Human skin sensitization data were retrieved from the ICCVAM *Test Method Evaluation Report*.<sup>16</sup> For LLNA, we used the data compiled by the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM).<sup>17</sup> Chemical structures were retrieved from either Chemicalize (<http://www.chemicalize.org/>), ChemSpider (<http://www.chemspider.com/>), or SciFinder (<https://scifinder.cas.org>) databases using Chemical Abstracts Service (CAS) registry numbers and chemical names. Data sets were thoroughly curated according to the workflows proposed by Fourches et al.<sup>18–20</sup> Curated data sets are available in the [Supporting Information](#).

**Human Data Set.** The original human data set consisted of 302 chemical records (every record refers to a chemical compound but because of the presence of multiple tests, several records could describe the same compound) and associated human data. Skin sensitization potency relies on human DSA<sub>05</sub> data (dose per skin area that produces a positive response in 5%

of the tested population). After curation, 135 unique substances remained. Twenty-six inorganic compounds or coformulated mixtures were then removed from the modeling sets to avoid problems with the structural fingerprint representation. The final data set contained 109 compounds (63 sensitizers and 46 nonsensitizers).

**LLNA Data Set.** The original data set consisted of 1060 records. After curation, 515 compounds (331 sensitizers and 184 nonsensitizers) were available for this study. This data set is biased toward sensitizers and thus, for the development of binary models, we balanced the number of sensitizers and nonsensitizers by subsampling from the sensitizer group. Briefly, we used the 184 nonsensitizers as probes to search for the most structurally similar sensitizers as the first half of the sensitizer group (93 compounds). This similarity-based selection procedure was performed with the HiT QSAR software.<sup>21</sup> The remaining half (92 compounds) was randomly selected from the remaining sensitizers class to maximize the coverage of chemical space. The multiclass data set for skin sensitization potency consisted of a larger set of 184 nonsensitizers, 235 weak/moderate sensitizers, and 71 strong/extreme sensitizers, totaling 490 compounds. Twenty-five sensitizers present in the data set were not used for multiclass models due to the absence of potency data.

**QSAR Modeling.** Binary and multiclass QSAR models were developed and rigorously validated according to the best practices of QSAR modeling.<sup>22</sup> The QSAR models were developed using open-source chemical descriptors based on ECFP4-like circular fingerprints with 2048 bits and an atom radius of 2 (Morgan2) calculated in RDKit (<http://www.rdkit.org>), along with the random forest (RF) algorithm<sup>23</sup> using Python 2.7. We followed a 5-fold external cross-validation procedure to estimate the predictive power of the models.<sup>24</sup> The full set of compounds with known experimental activities was divided into five subsets of similar size (external folds) using a modified Kennard–Stone algorithm.<sup>25</sup> For each fold, we selected five models with the highest correct classification rate (CCR, computed as the average of the model's sensitivity

and specificity). Also, 20 rounds of Y-randomization<sup>26</sup> were performed to ensure the absence of chance correlations.

**Model Implementation and Usage.** The Pred-Skin web app version 1.0 is implemented on an Ubuntu Server. The app is encoded using Flask (<http://flask.pocoo.org>), uWSGI (<https://uwsgi-docs.readthedocs.org>), Nginx (<http://nginx.org>), Python (<https://www.python.org>), RDKit (<http://www.rdkit.org>), scikit-learn (<http://scikit-learn.org>), and JavaScript (<http://www.ecma-international.org>). Pred-Skin also includes the JSME molecule editor written in JavaScript,<sup>27</sup> which is supported by the most popular web browsers. Java or Flash plugins are not required to use the app. Moreover, a mobile app for iOS is available via the Apple App Store and will soon be available for Android via Google Play.

The Pred-Skin app has a new architecture that extends our previous work with the Pred-HERG web app.<sup>25,28</sup> Pred-Skin has an intuitive user interface, in which the user may draw a molecule of interest or load .sdf or .mol files in the *molecular editor* box (Figure 1). Alternatively, the user can directly paste the SMILES string of the queried chemical structure in the appropriate area. After hitting the “Predict” button, the user will receive the predicted skin sensitization potential based on the models built with human data and LLNA data, as well as the predicted probability maps for the structure (see Figure 1). Batch processing is also possible by clicking on the “Bulk Predictions” section. In this case, it is necessary to fill out the form containing user’s name and e-mail. Then, the user may upload an sdf file containing up to 10 000 compounds. The job will be submitted to the server; the results will be available for download and a copy will be sent by e-mail. Processing time is less than few seconds for one molecule.

**Outcome Interpretation.** The user will receive the final predictions of the QSAR models based on human and LLNA skin sensitization data. For each model, we also provide a graphical means to help the interpretation of the outcome. Binary models classify new compounds as sensitizer or nonsensitizer. These predictions are followed by the probability of the prediction, which is estimated by the ratio of predictions made by internal models (trees in the RF model).<sup>23</sup> Multiclass potency models have a similar outcome, but they provide the probability that the compound is a nonsensitizer, weak/moderate sensitizer, or strong sensitizer, respectively.

The predicted probability maps provide a graphical visualization of the contribution of structural fragments to the activity derived from developed QSAR models.<sup>29</sup> The atoms are highlighted according to their predicted activity contribution. Atoms and molecular fragments highlighted in green represent an increase in skin sensitization potential; whereas, pink fragments represent a decrease in skin sensitization potential, and gray fragments do not contribute to skin sensitization potential. Gray isolines define the frontier between the positive (green) and the negative (pink) contributions. Additional information can be found in the help guideline available at <http://labmol.com.br/predskin/>.

## RESULTS AND DISCUSSION

The statistical characteristics of binary QSAR models are summarized in Table 1. The CCR of binary models was 0.72–0.80 for the human data set and 0.72–0.84 for the LLNA data set. We calculated both positive and negative predictive values (PPV and NPV) of the binary models to estimate the probability of an accurate annotation of a new compound as a sensitizer or nonsensitizer, respectively. The PPVs were 0.72–

**Table 1. Statistical Characteristics of Binary QSAR Models Assessed by 5-fold External Cross-Validation**

| model        | CCR  | sensitivity | PPV  | specificity | NPV  | coverage |
|--------------|------|-------------|------|-------------|------|----------|
| human        | 0.72 | 0.72        | 0.74 | 0.71        | 0.69 | 1.00     |
| human AD     | 0.80 | 0.75        | 0.75 | 0.85        | 0.85 | 0.65     |
| LLNA         | 0.72 | 0.75        | 0.71 | 0.70        | 0.73 | 1.00     |
| LLNA AD      | 0.84 | 0.82        | 0.80 | 0.87        | 0.88 | 0.66     |
| Consensus    | 0.75 | 0.75        | 0.76 | 0.75        | 0.74 | 1.00     |
| Consensus AD | 0.85 | 0.84        | 0.82 | 0.87        | 0.88 | 0.60     |

0.75 for the human data set and 0.75–0.82 for the LLNA data set, with NPVs of 0.71–0.85 and 0.70–0.87, respectively. The use of an applicability domain (AD) estimation increased the CCR by 8–12%, at the expense of coverage (decreased by 22–35%). We rebuilt the previously published LLNA models<sup>14</sup> using only open-access chemical descriptors and a bigger data set to implement the models on the freely accessible web app. A consensus model was generated by integrating and averaging independent predictions made by QSAR models based on human and LLNA skin sensitization data. The consensus model produced a CCR of 75%. The estimation of AD for the consensus model afforded a higher CCR of 85%, but reduced the coverage to 60%. Nevertheless, consensus between the QSAR models based on human and LLNA data afforded higher accuracy than individual models alone. Although recent studies<sup>15,30</sup> have shown that usually LLNA does not correlate well with human potency, it certainly contributes valuable information toward skin sensitization hazard categorization.<sup>16</sup> While we failed to build multiclass models based on human data due to the relatively small number of compounds (109), we succeeded to build multiclass potency models based on LLNA data. The performance of the multiclass models is shown in Table 2. The accuracy of LLNA multiclass models was 0.73–

**Table 2. Statistical Characteristics of Multiclass QSAR Model Assessed by 5-fold External Cross-Validation**

| model              | accuracy | precision | recall | F <sub>1</sub> score | coverage |
|--------------------|----------|-----------|--------|----------------------|----------|
| LLNA multiclass    | 0.73     | 0.73      | 0.73   | 0.72                 | 1.00     |
| LLNA multiclass AD | 0.76     | 0.75      | 0.76   | 0.75                 | 0.78     |

0.76. These models provide an innovative tool to classify skin sensitizers into the following potency categories: nonsensitizers, weak/moderate sensitizers, and strong/extreme sensitizers. These multiclass models represent an advance in the computational prediction of skin sensitization, as no prior study had succeeded in developing models of this type.

## CONCLUSIONS

The Pred-Skin web app is a fast, reliable, and user-friendly tool for the early assessment of chemically induced skin sensitization potential. The app provides a straightforward method for end users to make predictions using externally validated QSAR models for skin sensitization based on murine and human data. The predictions for a single compound are produced in a few seconds. The web app does not require computational or programming skills from the user. The following outcomes are provided: (i) binary predictions of human and murine skin sensitization potential; (ii) multiclass predictions of murine skin sensitization potency; and (iii) probability maps illustrating the predicted contribution of chemical fragments. The app represents a benchmark in prediction of skin sensitization,

since it is the first tool to provide predictions from models based on human data as well as multiclass models for LLNA. The Pred-Skin app will be continuously updated and upgraded as new data become available. This service is freely available to the public at <http://labmol.com.br/predskin/> and the Apple Store.

## ■ ASSOCIATED CONTENT

### ■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jcim.7b00194.

Curated data sets (XLSX)

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### Notes

The authors declare no competing financial interest.

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