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Predicting chemically-induced skin reactions. Part I: QSAR models of skin sensitization and their application to identify potentially hazardous compounds

Vinicius M. Alves [a,b], Eugene Muratov [b,c], Denis Fourches [b], Judy Strickland [d], Nicole Kleinstreuer [d], Carolina H. Andrade [a], Alexander Tropsha [b,*]

[a] Laboratory of Molecular Modeling and Design, Faculty of Pharmacy, Federal University of Goiás, Goiânia, GO 74605-220, Brazil
[b] Laboratory for Molecular Modeling, Division of Chemical Biology and Medicinal Chemistry, Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, NC 27599, USA
[c] Laboratory of Theoretical Chemistry, A.V. Bogatsky Physical-Chemical Institute NAS of Ukraine, Odessa 65080, Ukraine
[d] ILS/Contractor Supporting the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), P.O. Box 13501, Research Triangle Park, NC 27709, USA

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ABSTRACT

Repetitive exposure to a chemical agent can induce an immune reaction in inherently susceptible individuals that leads to skin sensitization. Although many chemicals have been reported as skin sensitizers, there have been very few rigorously validated QSAR models with defined applicability domains (AD) that were developed using a large group of chemically diverse compounds. In this study, we have aimed to compile, curate, and integrate the largest publicly available dataset related to chemically-induced skin sensitization, use this data to generate rigorously validated and QSAR models for skin sensitization, and employ these models as a virtual screening tool for identifying putative sensitizers among environmental chemicals. We followed best practices for model building and validation implemented with our predictive QSAR workflow using Random Forest modeling technique in combination with SiRMS and Dragon descriptors. The Correct Classification Rate (CCR) for QSAR models discriminating sensitizers from non-sensitizers was 71–88% when evaluated on several external validation sets, within a broad AD, with positive (for sensitizers) and negative (for non-sensitizers) predicted rates of 85% and 79% respectively. When compared to the skin sensitization module included in the OECD QSAR Toolbox as well as to the skin sensitization model in publicly available VEGA software, our models showed a significantly higher prediction accuracy for the same sets of external compounds as evaluated by Positive Predicted Rate, Negative Predicted Rate, and CCR. These models were applied to identify putative chemical hazards in the Scorecard database of possible skin or sense organ toxicants as primary candidates for experimental validation.

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Introduction

Humans are exposed to a variety of natural and synthetic substances that have never been tested in any toxicity assay. Information regarding the risks posed to human health and the environment for all these chemicals is limited and often inadequate, even among high production volume chemicals (Chuprina et al., 2010; Egeghy et al., 2012; Muir and Howard, 2006). Many chemical hazards cause their adverse effects through skin contact; the associated phenomena include skin sensitization, skin penetration, and skin irritation (Dickel et al., 2002; Grandjean et al., 1988; Kimber et al., 2011). Each of these phenomena has been studied largely independently even though there may be functional links between them (Lepoittevin, 2011; Magnusson et al., 2004; Strid and Strobel, 2005).

The sequence of biological responses starting from the molecular initiating events and leading to *in vivo* adverse outcome(s) is represented by an adverse outcome pathway (AOP) (Ankley et al., 2010; Knudsen and Kleinstreuer, 2011; OECD, 2012; Watanabe et al., 2011). Protein haptenation, the molecular initiating event for skin sensitization, results in a delayed-type hypersensitivity called allergic contact dermatitis (ACD) (Aeby et al., 2010; Hennino et al., 2005). ACD is a common occupational and environmental health issue (Keegel et al., 2009; Kimber et al., 2002), and its AOP consists of two phases, *i.e.*, skin sensitization and elicitation of the immune response. The first phase, skin sensitization, is initiated by the contact and penetration of the chemical through the skin (Karlberg et al., 2008). During their passage through the skin layers, chemicals can be subjected to different bio-transformations that may change their allergenic potential (OECD, 2012). Several haptens (*i.e.*, small molecules that can elicit an immune response only when attached to a large carrier such as a protein) are known to bear lipophilic moieties and have low molecular weight (usually <500 Da), allowing them to easily cross the *stratum corneum* barrier (Bos and Meinardi,

* Corresponding author at: 100K Beard Hall, Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, NC 27599, USA. Fax: +1 919 966 0204.
E-mail address: alex_tropsha@unc.edu (A. Tropsha).

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2000). They can also possess electrophilic moieties that can covalently bind the nucleophilic residues of cutaneous proteins to form stable conjugates, characterizing the molecular initiating event, which seems to be the major structure-dependent determinant of skin sensitization potential (Roberts and Aptula, 2008). These conjugates, also called hapten–protein complexes, are processed by dendritic (Langerhans) cells that subsequently mature and migrate to lymph nodes (OECD, 2012; Saint-Mezard et al., 2004). Those processed complexes are presented to naive T-cells resulting in the proliferation of hapten-specific T-cells that emigrate from the lymph nodes and enter the blood through the thoracic duct (Hennino et al., 2005). The second phase, elicitation, occurs after a subsequent contact with the same hapten. Haptens diffuse into the skin and form the hapten–protein complexes, which are taken up by skin cells. The circulating hapten-specific T-cells are activated by the keratinocytes, fibroblasts, and dendritic cells in the dermis and the epidermis, ultimately triggering the inflammatory process responsible for lesions (Hennino et al., 2005; OECD, 2012; Saint-Mezard et al., 2004).

Common *in vivo* tests for skin sensitization include the occluded patch test (Buehler, 1965), the guinea pig maximization test (Magnusson and Kligman, 1969), and the murine local lymph node assay (LLNA) (Basketter et al., 2002); the latter is regarded as the preferred test for evaluating skin sensitization (OECD, 2010). A modification of the LLNA, the reduced LLNA (rLLNA), which decreases the number of animals used for testing by 40%, was recently validated (ICCVAM, 2009). Despite some successful reductions in animal usage, these tests are still costly and have low throughput. In 2013, the European Union banned *in vivo* testing of cosmetic and toiletry ingredients, which leads for an urgent development of alternative methods to evaluate safety and efficacy of new chemicals (Adler et al., 2011). So far, there is no *in vitro* method for evaluating skin sensitization (Johansson and Lindstedt, 2014).

Meanwhile, *in silico* computational methods are emerging as a practical solution for the evaluation of substances lacking experimental data (Raunio, 2011). However, modeling chemical toxicity is very challenging due to the high complexity of the underlying biological mechanisms and experimental variability (Gleeson et al., 2012). Although many previous skin sensitization models described in the literature (Table S1) appear to be well-fitted and robust, critical analysis of these studies reveals important problems. In our observation, most of the published QSAR models do not comply with the statistical procedures, statistical criteria, and recommendations for external validation that constitute common best practices (Golbraikh and Tropsha, 2002; Tropsha, 2010) and thus these models are not compliant with the OECD guidance on QSAR model development and validation (OECD, 2004). More specifically, the main drawbacks of the majority of published models are: *(i)* models' predictivity was not properly assessed and/or tested on external compounds; *(ii)* models did not have applicability domain (AD) estimations; *(iii)* no proof of passing the Y-randomization test (almost all the models from Table S1) was presented; and *(iv)* the use of unbalanced datasets has resulted in the generation of models biased towards the most populated class of compounds. As a consequence, despite the large number of previous QSAR studies, only one model (Nandy et al., 2014) can actually be employed to reliably predict skin sensitization potential of new chemicals. However it is not publicly available and only 67 compounds were used in the modeling set.

The major drawbacks of previous QSAR studies of skin sensitization compromise the practical use of prior methods and models for reliably assessing chemical-induced skin sensitization. For instance, the dataset studied by (Cronin and Basketter, 1994) contained many activity cliffs (Maggiora, 2006), *i.e.*, structurally similar compounds with the same scaffolds (phenols and acetates in this case) that had drastically different properties; this explains why phenols and acetates were predicted so poorly.

The feasibility of building models for fragrance allergens using classification and ranking approaches was investigated in several studies (Hostýnek and Magee, 1997; Magee et al., 1994). In these papers, the authors also tried to relate the permeability of fragrances with their skin sensitization potency. In another study (Devillers, 2000), the author attempted to compare the prediction power of artificial neural networks and linear discriminant analysis but selected a test set that contained only 7% of the overall number of compounds, which is not large enough for proper validation. The TOPS-MODE (Topological Substructural Molecular Descriptors) approach used by (Estrada et al., 2003) demonstrated relatively good predictive performance but the reported accuracy is likely to be overly optimistic because of the very small size of the two external validation sets (15 and 6 compounds, respectively). Similarly, a model developed in another study (Miller et al., 2005) appeared to be highly accurate; however, a detailed analysis revealed that 20 compounds were designated as outliers and removed from the modeling set because of their poor fit between experimental and predicted values, most likely resulting in an artificially overestimated predictive performance of the model.

One study described an external validation procedure that was carried out on Tissue Metabolism Simulator for Skin Sensitization (TIMES-SS) (Roberts et al., 2007b). The authors experimentally tested 40 chemicals in the LLNA assay and then compared the results with computationally-derived predictions made by TIMES-SS. Despite the high specificity (*ca.* 87.5%), the sensitivity of the model was poor (*ca.* 56%). Another study (Golla et al., 2009) presented a QSAR model developed using a dataset compiled by the Federal Institute for Health Protection of Consumers and Veterinary Medicine (Schlede et al., 2003). The dataset was collected from clinical and experimental data on humans as well as animal tests. The authors divided the investigated compounds into three groups: *(i)* significant contact allergen; *(ii)* solid-based indication for contact allergenic effect; and *(iii)* insignificant contact allergen. This classification system was unclear and ambiguous, making the modeling efforts described by the authors (Golla et al., 2009) less practical for future use and more difficult to compare with those from other studies.

Given the frequency of dermal exposure to diverse chemicals and the lack of reliable *in silico* models to predict skin sensitization potential for new chemicals, the main objectives of this study were to: *(i)* compile, curate, and integrate skin sensitization data from various literature sources; *(ii)* develop and rigorously validate predictive and robust QSAR models for skin sensitization; *(iii)* compare these models with the Skin Sensitization modules in OECD QSAR Toolbox and VEGA as a benchmarking; and *(iv)* apply developed models to the Scorecard chemical library for identifying potential skin or sense organ toxicants. In a companion study (Part II), we have developed similar QSAR models of skin permeability and elucidated the relationship between skin permeability and skin sensitization (Alves et al., 2015).

Materials and methods

The workflow developed in this work is illustrated in Fig. 1.

Datasets

Skin sensitization dataset (dataset A). The dataset used in this study was retrieved from the ICCVAM (Interagency Coordinating Committee on the Validation of Alternative Methods) report on the rLLNA (ICCVAM, 2009). The binary skin sensitization potential (sensitizer *vs.* non-sensitizer) based on the LLNA data obtained by ICCVAM from the literature was reported for 471 records (every record refers to a chemical compound but because of the presence of duplicates, several records could describe the same compound). Before merging these data from different studies made by independent laboratories in one single dataset, we have checked the literature and found that the inter-laboratory variance of LLNA test was low, in agreement with an earlier analysis (ICCVAM and NICEATM, 1999; Scholes et al., 1992). Data discrepancy could have been introduced also by different vehicles used in LLNA assay to achieve optimal solubility and skin penetration of

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