## Proceedings of the International Conference on Occupational & Environmental Exposures of Skin to Chemicals: Science & Policy

Hilton Crystal City September 8-11, 2002

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# Development of New QSAR Approaches in Occupational Contact Dermatitis

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The Bureau of Labor Statistics estimates that occupational skin diseases constitute the second largest group of occupational injuries in the U.S. [1 Among them, occupational contact dermatitis (OCD) is the most commor cause of work-related skin illness comprising up to 95% of registered cas Allergic contact dermatitis (ACD) may lead to severe recurrent forms of OCD because of long-lasting memory of the immune system. ACD usual develops as a result of repetitive skin exposures to a sensitizing chemica agent. Usually at least a single excessive exposure is essential in the development of the immune response.

A variety of experimental tests have been suggested to assess the skin sensitization potential of a chemical [2]. Providing information that leads t the development of recommended skin exposure limits that would prever workers from sensitizing overexposures may be an important factor in predictive testing. Unfortunately, many experimental protocols result in a dichotomous conclusion, more appropriate for denial/acceptance decisio making in chemical manufacturing rather than for protection of workers occupationally involved with sensitizing chemical agents. Essentially only one of them, the murine Local Lymph Node Assay (LLNA), has the capa to provide a reliable continuous scale in the quantitative assessment of s sensitization.

A combination of methods in statistics and computational chemistry, commonly referred to as Quantitative Structure-Activity Relationship (QSAR) modeling, complements the experimental approach. A method o QSAR is based on the examination of measured and calculated physical chemical properties, called molecular descriptors, of many chemical compounds with known biological activity, in this work the sensitization potential, and then relating a few of the informative descriptors to the tarç bioactivity. The structure-activity relationships constructed this way provi a means of investigating and predicting the toxicological effect of a chem with yet unknown sensitization potential.

We rely on LLNA data to quantify the skin sensitization potential [3]. At present the LLNA data are (1) outnumbered by the long history of guinea pig assays, and (2) often reported as a dichotomous scale congruous to guinea pig data. Therefore, the work has been started using the dichotomous LLNA data to identify molecular descriptors that may be effective in the continuous-scale LLNA QSAR. The work began from building a database of chemical names, structures, properties and bioactivities, along with design of appropriate software. Our immediate g is to identify a pool of potentially informative molecular descriptors and chemical classes that are most appropriate for QSAR modeling to predic LLNA results.

In the present work a QSAR based on a generalized linear model of logis regression is proposed. The logistic regression permits construction of standard QSAR equations, in which the activity data are represented onl terms of activity (1) or non-activity (0) values. In order to evaluate molecu properties, which are significantly associated with LLNA data on skin sensitization, 1203 molecular descriptors were calculated and tested for their significance in predicting the skin sensitization potential. Only a sma number of molecular descriptors were found to be statistically significantl associated with skin sensitization.

At this stage we were able to define a statistically significant QSAR on 5 selected compounds, which includes three molecular descriptors. These specialized descriptors from computational chemistry are (1) the number double bonds, nDB, (2) mass-weighted Geary graph autocorrelation coefficient of the sixth lag, GATS6m, and (3) the spatial first component accessibility directional unweighted holistic invariant molecular descripto index, E1u [4]. A QSAR model built on only these three descriptors using logistic regression is successful as shown by the chi-square goodness of test, indicating the suitability of these descriptors to predict the sensitizati potential. We are in the process of refining these results by: (1) the investigation of the probability of correct classification of a compound usi the fitted logistic regression based on these three descriptors and (2) the study of interrelationships between various descriptors and their effect or the fitting of the logistic regression.

These results suggest that a comprehensive QSAR model of ACD may b built by using only few appropriate parameters, although the relevance o

identified descriptors to the continuous-scale ACD QSAR has yet to be shown. Further work will be focused on populating the QSAR database w continuous-scale ACD data and molecular descriptors that are obtained i the present study. New predictive QSARs are expected to be useful in screening large sets of compounds for their potential impact on skin sensitization, and thus may suggest a useful order of priorities in experimental testing.

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The National Institute for Occupational Safety and Health (NIOSH) co-sponsored this inaugural conference to bring together dermatologists, occupational hygienists, laboratory researchers, policy makers and other to focus on the science, knowledge gaps and policy opportunities related occupational and environmental exposures of the skin to chemicals.

The site was the Hilton Crystal City at Ronald Reagan National Airport hotel. The main conference was followed by a one-day workshop focusin on specific research and public health opportunities for decreasing the burden of skin exposures to chemicals in both workplaces and the gener environment.

Approximately 135 individuals attended. A second conference is expecte in 2004.

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