Web Application to Classify and Subcategorize Skin Sensitizers Using Human Data

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Background and Purpose

Human-relevant reference data is essential for establishing confidence in the use of non-animal test methods for generating data for human risk assessments. To support the evaluation of non-animal approaches for assessing skin sensitization hazard, the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods and the German Federal Institute for Risk Assessment curated data from two types of human predictive patch tests (HPPT). The HPPT data were used to develop a modified approach for assigning skin sensitization potency subcategorizations based on the United Nations Globally Harmonized System of Classification and Labelling of Chemicals (GHS). The modified classification approach improves upon previous methods by considering the number of sensitized human test subjects and addressing uncertainty in assay results. Additionally, the approach includes a weight-of-evidence (WoE) method to consolidate multiple HPPT results into a single GHS classification for each chemical.

To allow users to apply this modified approach to their own HPPT data, we have developed an open-source web application, HPPT App. The app provides an interactive platform for users to input data, visualize results, and understand classification outputs.

Methods

Using the R Shiny platform, which enables interactive web applications powered by R, we built an application that imports user-submitted HPPT data and applies the modified GHS classification approach to classify and subcategorize skin sensitizers. Users input data including the test concentration (%), dose per skin area (DSA, $\mu g/cm^2$), and number of sensitized test subjects. Data manipulation libraries are used to preprocess and analyze the data efficiently. The user interface is designed to provide an intuitive layout for data input and results display. Custom styles and themes were also applied allowing for a user-friendly interface that enhances the overall experience. Upon submission of the HPPT data, the app processes the input using custom algorithms that implement the modified GHS classification criteria, allowing for real-time classification and subcategorization of skin sensitizers. To classify a substance for skin sensitization hazard, the HPPT App first derives the two response values defined within the modified approach: DSA1+, which indicates the dose that sensitizes one test subject, and DSA5%, which indicates the dose that sensitizes 5% of test subjects. The app then assigns classifications for each test result. If at least one test subject was sensitized, classification is based on DSA1+ or DSA5%. If no test subjects were sensitized, classification is based on test concentration. The HPPT App employs a user-friendly interface for data input and visualizing the

output tables generated using the modified classification approach. Users can upload data according to a specified template and choose either DSA1+ or DSA5% for analysis.

Results

A user-friendly R Shiny based web application was developed to streamline the use of the HPPT classification approach allowing users to easily classify HPPT results in a way that reflects human potency. Under standard GHS classification rules, a substance can be classified as a strong sensitizer (1A), a weak sensitizer (1B), or not classified (NC). The HPPT App enables the modified classification approach, addressing uncertainty by defining borderline ranges to assign ambiguous classifications in cases where the data show no evidence of strong sensitization (NC/1B) or provide no information for classifying skin sensitization (NC/1). When possible, the app derives reproducibility metrics using the individual classifications. The HPPT App returns the results of this workflow in a downloadable format.

The HPPT App provides classifications for each substance based on three different classification modes and depending on the input data, the app may provide a binary classification (Category 1 [sensitizer] vs. NC [nonsensitizer]) or may be able to classify sensitizers as Category 1A or Category 1B sensitizers. Derived response values (DSA1+ and DSA5%) and measures of classification reproducibility are also provided. The output section generates interactive tables that can be sorted, filtered, and downloaded.

Additionally, the app provides information on the classification methodology, navigation guidance, and contact details.

Conclusions

Approaches currently used to assign skin sensitizers to GHS potency subcategories overlook the number of sensitized test subjects, potentially leading to an underestimation of potency. The modified approach that incorporates frequency metrics offers more relevant potency classifications to enhance the evaluation of non-animal skin sensitization tests. However, the approach involves complex decision tree logic that may be challenging for non-computational users. The HPPT app demonstrates functionality with various types of data, such as test results from ingredients in consumer goods and cleaning products, highlighting its robust classification performance, applicability and impact. This project was funded in whole or in part with federal funds from the NIEHS, NIH under Contract No. HHSN273201500010C.