# Predicting Skin Sensitization Using 21st Century Toxicology

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Allergic contact dermatitis (ACD) is an adverse health effect that develops after repeated exposure to skin-sensitizing chemicals and products. To minimize the occurrence of ACD, regulatory authorities require testing using assays such as the murine local lymph node assay (LLNA) to identify potential skin sensitizers. The Organisation for Economic Co-operation and Development (OECD) established an Adverse Outcome Pathway (AOP) for skin sensitization initiated by covalent binding to proteins. In an effort to reduce or replace animal use, OECD is also pursuing the development of integrated testing strategies using novel *in vitro* and *in silico* approaches. The U.S. Tox21 and ToxCast projects include high-throughput screening (HTS) assays that map to key events in the skin sensitization AOP (e.g., oxidative stress, cytokine expression) from which data on hundreds of potential skin sensitizers have been generated. We built a cross-validated random forest model using ToxCast Phase II data and a balanced training set of 60 chemicals. The model predicted LLNA results with 80% accuracy. The assays with highest variable importance in the random forest model included known AOP targets (e.g., Nrf2, T-cell proliferation) as well as targets outside of the current AOP (e.g., Coll III, PPAR, PXR, ER). Well-characterized AOPs like skin sensitization provide opportunities to use HTS data to develop efficient testing strategies that minimize the use of animals in regulatory testing.

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