# Compilation and Characterization of a Human Skin Sensitization Data Set

J Strickland[1], D Allen[1], AM Api[2], J Gordon[3], N Kleinstreuer[4], H-S Ko[5], J Matheson[3], H-J Thierse[6], J Truax[1], and M Herzler[6]

[1]ILS, RTP, NC, USA; [2]RIFM, Woodcliff Lake, NJ, USA; [3]US CPSC, Rockville, MD, USA; [4]NIH/NIEHS/DNTP/NICEATM, RTP, NC, USA; [5]US FDA, Silver Spring, MD, USA; [6]BfR, Berlin, Germany

## Introduction

- New approach methodologies are usually evaluated with animal reference data, which are typically standardized and available.
- While humans are generally the most relevant species for regulatory purposes, availability of human data is usually limited because of ethical concerns about testing on human subjects.
- Allergic contact dermatitis is an adverse outcome produced by skin contact with chemical substances that induce hypersensitivity.
- Skin sensitization tests conducted in humans with a wide range of chemical substances can be obtained from the scientific literature.

## Database Development

- We collected data from over 1700 publications for 2277 human predictive patch tests: the human repeated insult patch test and the human maximization test.
- A Relative Reliability Score (RRS) was developed and applied to each test based on reported protocol elements and outcomes (see Figure 1).
- Scores of 1 to 4 were deemed acceptable because:
  — Dose metrics were reported or calculable.
  — The primary report, test substance, and test type were identified.
  — The number of positive responses and the total number of subjects tested were reported.
- The 2255 tests with Relative Reliability Scores of 1 to 4 (Figure 3) included data on 1366 unique substances; 1149 had CASRNs. We characterized these substances using physicochemical properties, chemical structure categories, protein binding mechanisms, and consumer product categories using CASRN as the primary identifier.

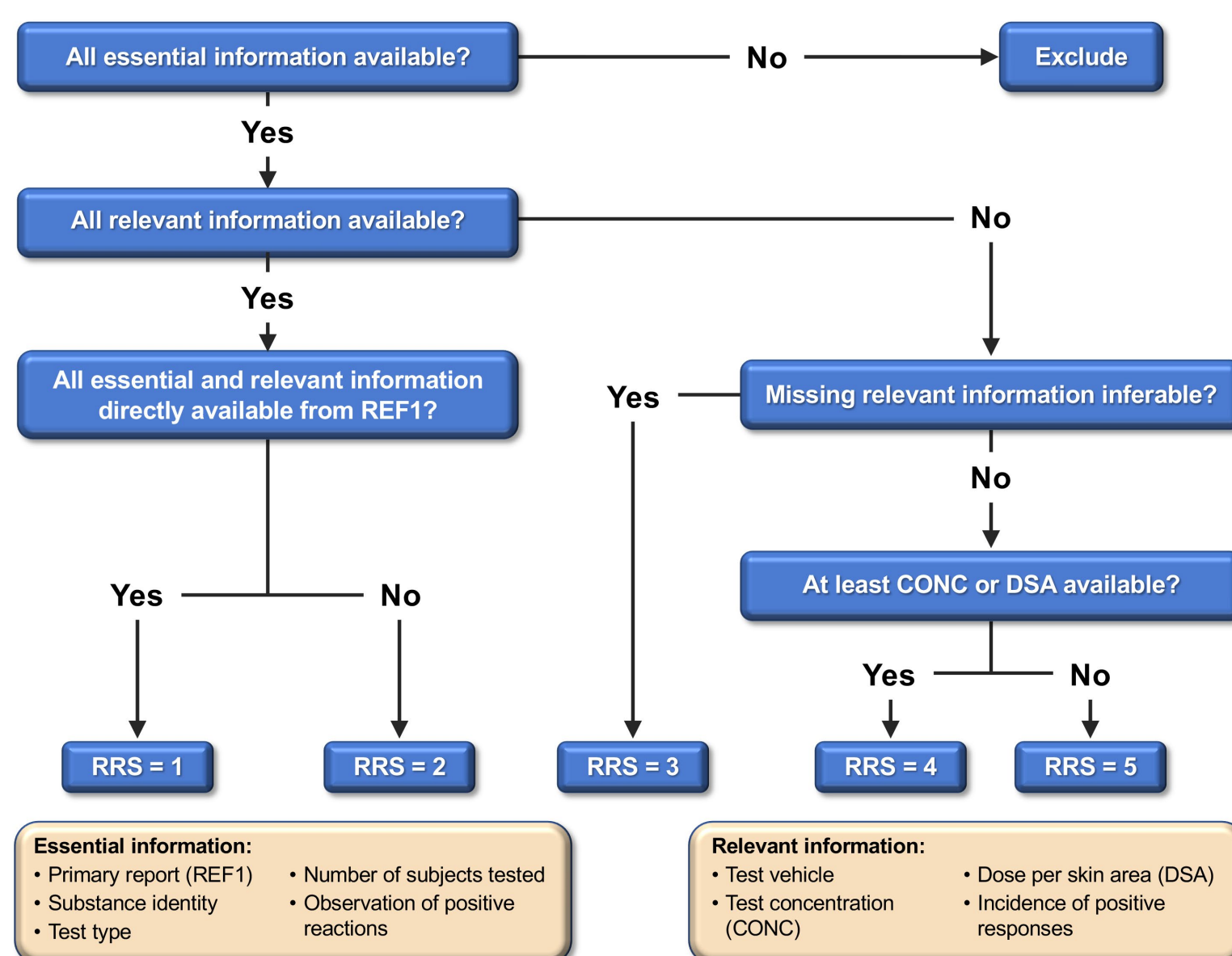## Figure 1. Relative Reliability Score Decision Tree



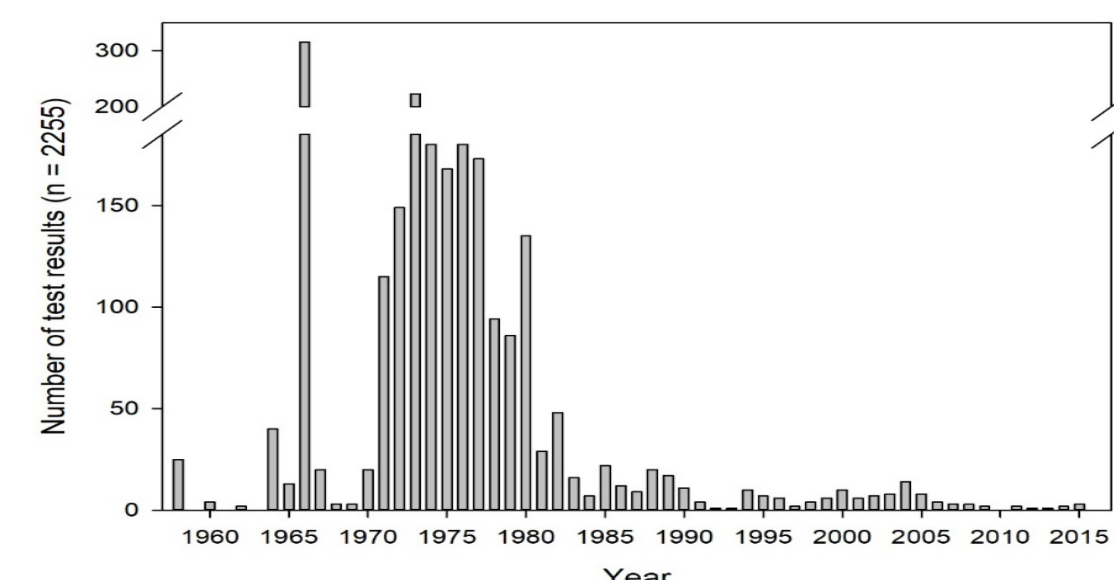## Figure 2. Distribution of Primary References from 1958-2015


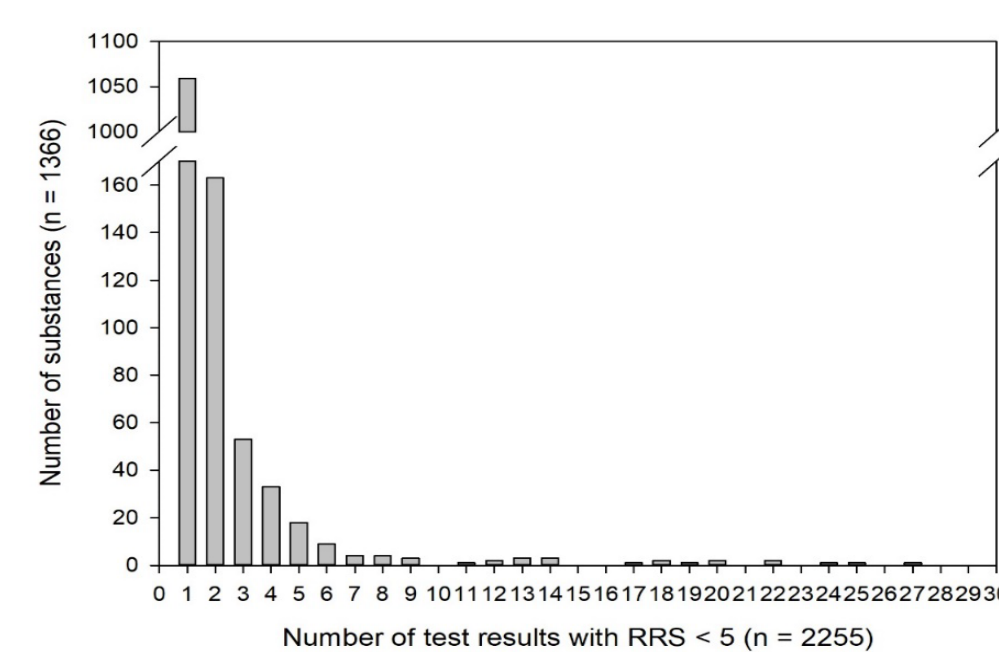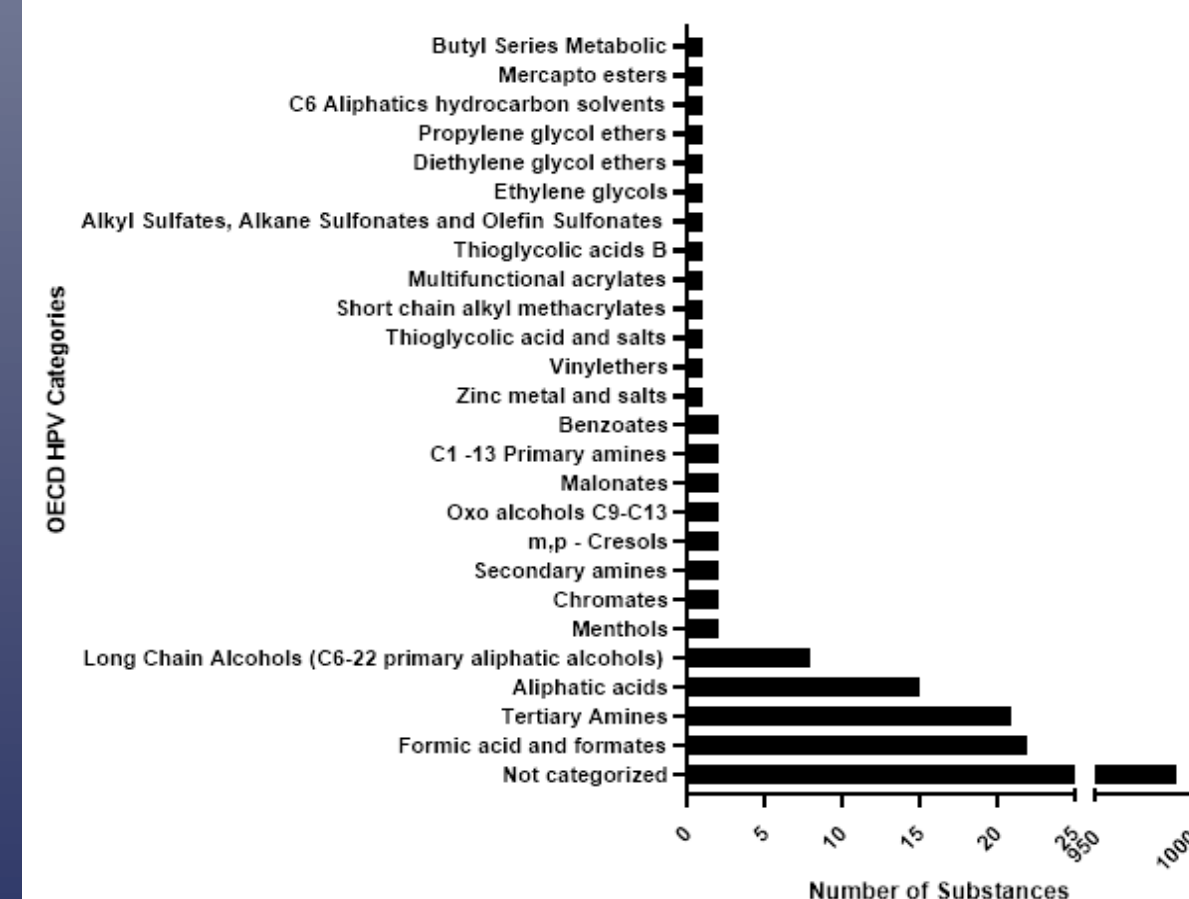
## Figure 3. Number of Tests Per Substance



## Figure 4. Distribution Among Chemical Structure Categories



- Of the 1149 unique substances, QSAR Toolbox v4.4.1 assigned 1079 substances with defined structures to 24 of the 112 categories of the "OECD HPV Chemical Categories" profiler.
- Of those 1079, seven were assigned to more than one category.
- No substances were assigned to 88 of the 112 available categories.

## Figure 5. Distribution Among Protein Binding Mechanisms
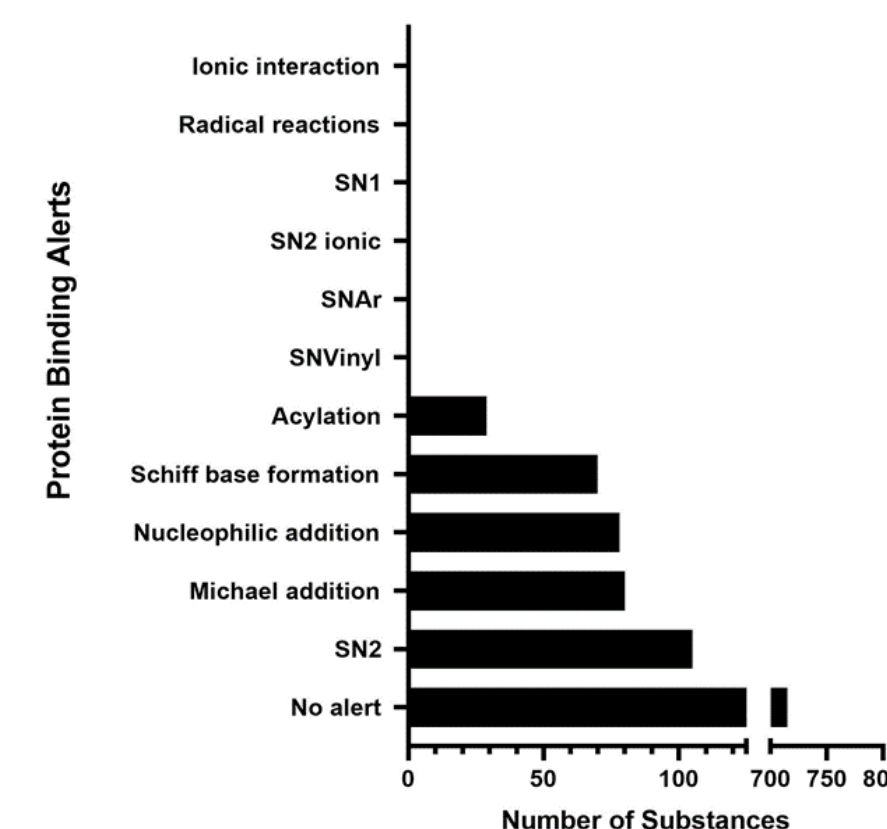


- Bar plot shows the distribution of the 1079 substances with defined structures among the 11 mechanistic domains of the *Protein binding alerts for skin sensitization by OASIS* profiler in QSAR Toolbox v4.4.1.
- The largest group of substances had no protein binding alerts.
- Remaining substances were classified into five mechanistic domains, and five other domains had no substances.

## Figure 6. Range of Physicochemical Properties
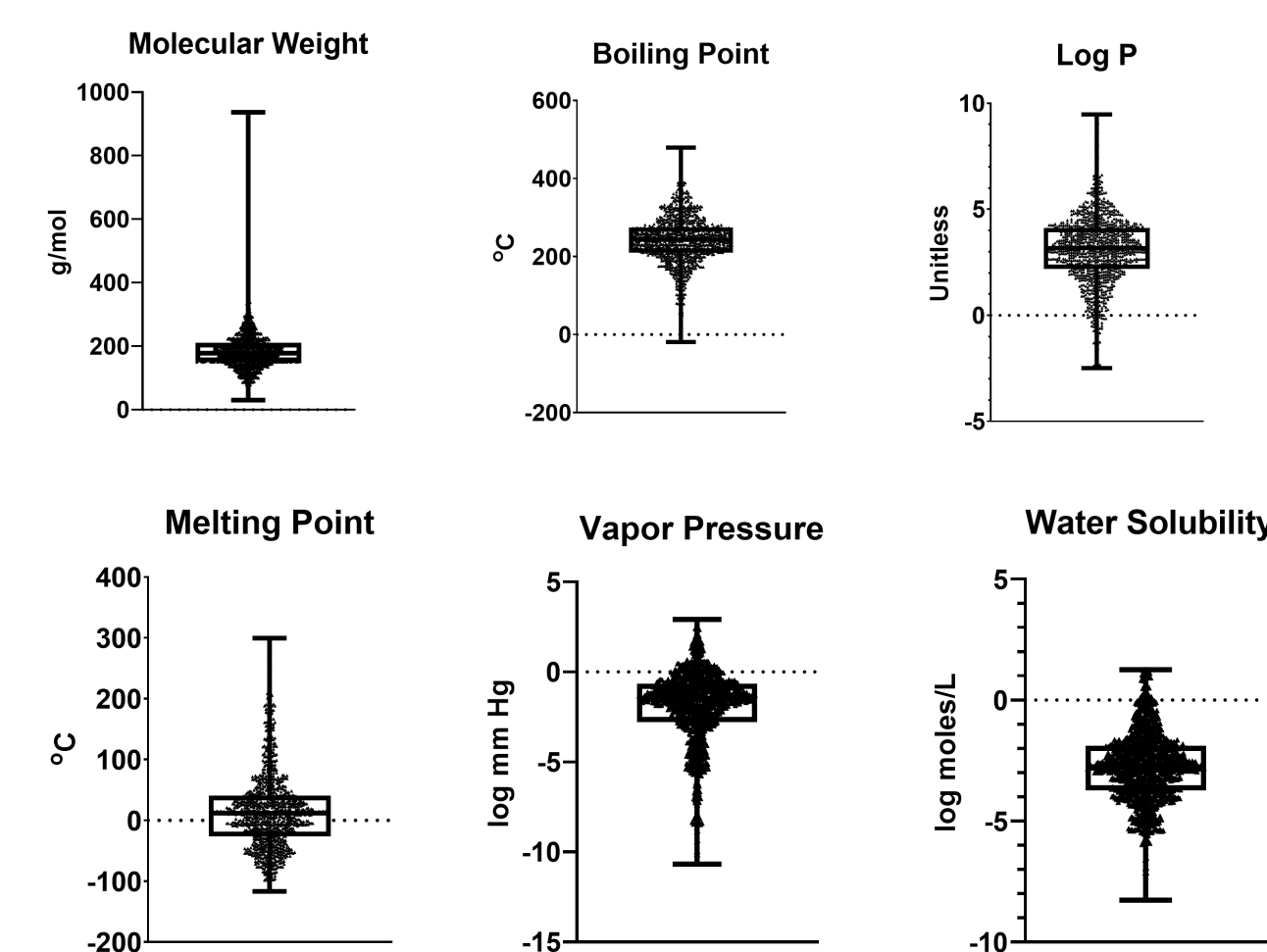


- Of the 1149 unique substances, physicochemical properties were predicted for 1063 substances by the Integrated Chemical Environment v3.4.
- Boxes extend from the 25th to 75th percentiles. Lines in the middle of the boxes show the median values; whiskers show the ranges.
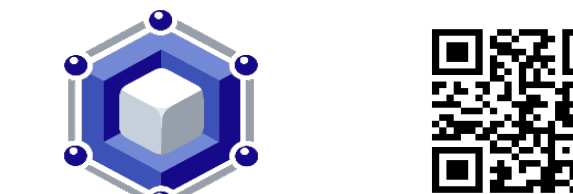
## Figure 7. Consumer Use Category Representation
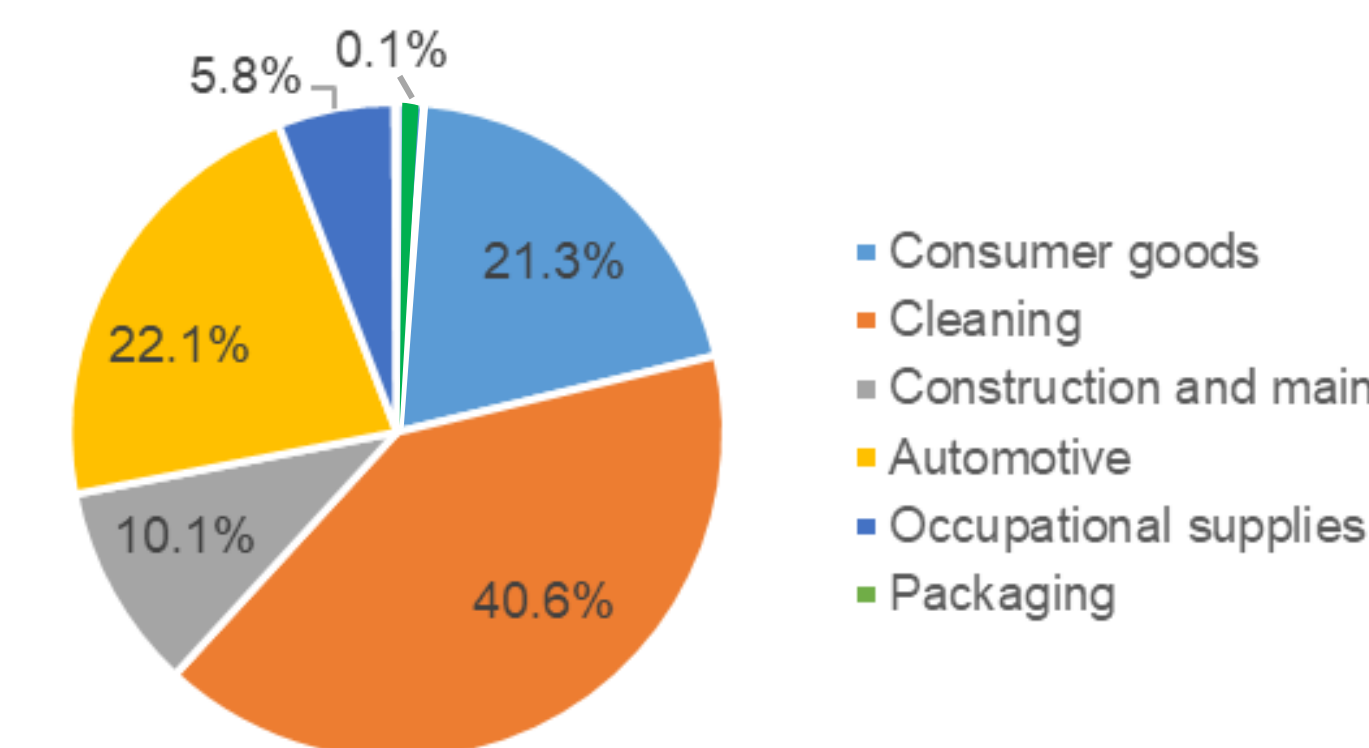


- Pie chart shows the distribution of 433 substances in the human predictive patch test database that could be assigned consumer use categories as defined by the U.S. Environmental Protection Agency's Chemical and Products Database.
- Data obtained from the Integrated Chemical Environment v3.4.

## Summary and Conclusions

- We compiled a database of 2277 human predictive patch tests.
- A decision tree was developed to assess the relative reliability of each test where a Relative Reliability Score of 1 to 4 was determined to be reliable and 5 was considered unreliable.
- Reliable data were evaluated for chemical diversity, protein binding alerts, and physicochemical properties.
- These studies and further characterization of the database will provide context for defining benchmarks for the evaluation of new approach methodologies for skin sensitization assessments.
- The database is publicly available on the NTP Integrated Chemical Environment (ICE) website to serve as a resource for the development and evaluation of new approach methodologies for skin sensitization assessments.

**ICE:** https://ice.ntp.niehs.nih.gov/

## Acknowledgements