

Identification, Curation, and Prioritization of Food-Use Chemicals in ToxCast

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Evaluating the thousands of chemicals that are directly added to or come in contact with food poses a great challenge due to the time, cost, and sheer volume of data necessary to thoroughly conduct comprehensive toxicological testing. This study compiled a list of food-use chemicals in the United States (U.S.) and demonstrates approaches amenable to the evaluation of this large and diverse chemical inventory. 8,659 unique food-use chemicals were compiled from 8 public sources and mined against the ToxCast *in vitro* high-throughput screening inventory to identify 1,530 food-use chemicals with *in vitro* assay data. Each of these chemicals was then manually evaluated for current registration status and categorized based on exposure likelihood from food in the U.S. into four categories: direct food additive, indirect additive, pesticide/residue, or non-food. Ultimately, 319 chemicals were categorized as non-food and removed from the list, leaving 556 direct additives, 339 indirect additives, and 406 pesticides/residues. The cytotoxicity elicited by the curated list of food-use chemicals in ToxCast revealed that only 10% of direct additives elicited cytotoxicity, while 24% of indirect additives and 41% of pesticides/residues were cytotoxic. To address the need to prioritize chemical mixtures, we used frequent itemset mining (FIM) to identify which individual chemicals or combination of chemicals appear with the greatest frequency in the U.S. Food and Drug Administration's Effective Food Contact Substances (EFCS) database. The EFCS database comprises 978 registrations, containing 715 unique chemicals; in total, 189 of the registrations contain mixtures of ≥ 2 chemicals and 110 registrations contain ≥ 3 chemicals, up to a maximum of one registration containing 9 chemicals. The FIM approach identified acetic acid, hydrogen peroxide, and peracetic acid as the most abundant co-occurring chemicals in EFCS registrations, each occurring in 42 (or 4.3%) of 978 registrations. The combination of peracetic acid and hydrogen peroxide occurred most frequently, appearing in 40 (or 21%) of the 189 registered mixtures. The current inventory and analysis of ToxCast cytotoxicity and EFCS mixture prioritization represent the first evaluation of food-use chemicals on this scale, providing insight into this overlooked but critical chemical inventory. *This work does not reflect EPA policy.*

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