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In vitro screening for population variability in toxicity of pesticide-containing mixtures

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Abstract: Population-based human in vitro models offer exceptional opportunities for evaluating the potential hazard and mode of action of chemicals, as well as variability in responses to toxic insults among individuals. This study was designed to test the hypothesis that comparative population genomics with efficient in vitro experimental design can be used for evaluation of the potential for hazard, mode of action, and the extent of population variability in responses to chemical mixtures. We selected 146 lymphoblast cell lines from 4 ancestrally and geographically diverse human populations based on the availability of genome sequence and basal RNA-seq data. Cells were exposed to two pesticide mixtures - an environmental surface water sample comprised primarily of organochlorine pesticides and a laboratory-prepared mixture of 36 currently used pesticides - in concentration response and evaluated for cytotoxicity. On average, the two mixtures exhibited a similar range of in vitro cytotoxicity and showed considerable inter-individual variability across screened cell lines. However, when in vitro-to-in vivo extrapolation (IVIVE) coupled with reverse dosimetry was employed to convert the in vitro cytotoxic concentrations to oral equivalent doses and compared to the upper bound of predicted human exposure, we found that a nominally more cytotoxic chlorinated pesticide mixture is expected to have greater margin of safety (more than 5 orders of magnitude) as compared to the current use pesticide mixture (less than 2 orders of magnitude) due primarily to differences in exposure predictions. Multivariate genome-wide association mapping revealed an association between the toxicity of current use pesticide mixture and a polymorphism in rs1947825 in C17orf54. We conclude that a combination of in vitro human population-based cytotoxicity screening followed by dosimetric adjustment and comparative population genomics analyses enables quantitative evaluation of human health hazard from c