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In Vitro Transcriptomic Analyses Informing the Mode of Action of HFPO-DA (GenX) in the Liver

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Abstract:

Like many polyfluorinated alkyl substances (PFAS), toxicity studies with HFPO-DA, a short-chain PFAS used in the manufacture of some types of fluorinated polymers, indicate that the liver is the primary target of toxicity in rodents following oral exposure. To further evaluate the MOA underlying the non-neoplastic liver changes in rodents associated with HFPO-DA exposure, whole-transcriptome templated oligomer sequencing (TempO-Seq) was conducted on primary human, rat, and mouse (including wild-type and PPARα-knockout mouse strain) hepatocytes treated for 12, 24 or 72 hours with various concentrations of HFPO-DA, as well as with known agonists of PPARα (i.e., GW7647), PPARγ (i.e., rosiglitazone), and known cytotoxic agents (i.e., acetaminophen or D-galactosamine). Differentially expressed genes and enriched gene sets, as well as dose-responsive genes and functional classification (i.e., pathway enrichment) of dose-responsive genes were determined for each chemical, timepoint and species/strain. Concordance analyses of differentially expressed genes across chemicals within a species/strain demonstrate more similarity between HFPO-DA and PPARα agonist, GW7647, compared to the other chemicals evaluated. These findings are supported by benchmark dose modeling and pathway enrichment results. Further, similarity analyses across species indicates greater mechanistic commonalities between rodent species, i.e., rats and mice, and minimal mechanistic similarities between humans and rats or mice. In addition, the overall response of human hepatocytes to chemical exposure at the pathway signaling level was generally lower, indicating that rodent hepatocytes may be more sensitive to the chemicals examined. Consistent with previously published transcriptomic analyses, these results further support that the liver effects associated with HFPO-DA are mediated through rodent-specific PPARα signaling mechanisms. Therefore, the liver effects observed in mice are not appropriate endpoints for use in the development of toxicity values for HFPO-DA in human health risk assessment.