Updated Mode of Action Information Informing the Risk Assessment of HFPO-DA (GenX)

L.C. Haws, M.M. Heintz, and C.M. Thompson

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Abstract:
Risk assessments for HFPO-DA, a short-chain polyfluorinated alkyl substance (PFAS) used in the manufacture of some types of fluorinated polymers, have proposed reference dose (RfD) values ranging from 0.000003 to 0.01 mg/kg-day. These differences are due, in part, to mode of action (MOA) determinations influencing the selection of critical effects for risk assessment and the choice of uncertainty factors. Subsequent and concomitant to the development of these HFPO-DA risk assessments, new research on the mechanisms and adverse effects of HFPO-DA have been conducted. Herein, we review new data that inform the risk assessment of HFPO-DA and perhaps other PFAS. These data include newly published *in vivo* liver transcriptomic analyses in mice, unpublished *in vitro* transcriptomic analyses in human and rodent hepatocytes (including knockout mice), development of adverse outcome pathways (AOPs) for developmental effects in rodents, as well as published analyses on the applicability of the threshold of toxicological concern (TTC) to PFAS and metanalyses on how TTC and RfD values might inform the magnitude of RfD values. In the mouse liver, both molecular signatures and histopathological analyses do not support a cytotoxic MOA, but rather provide clear evidence of peroxisome proliferator-activated receptor-alpha (PPARα) activation. *In vitro* comparisons of transcriptomic signatures between HFPO-DA and cytotoxic agents (e.g., acetaminophen), rosiglitazone (PPARγ activator), and GW7647 (PPARα activator) indicate molecular overlap primarily with GW7647. Analyses on the impact of the addition of PFAS to the chemicals comprising Cramer Class III compounds indicate little effect on the Class III TTC value of 0.0015 mg/kg-day. Metanalyses comparing Class III TTC and respective RfD values indicate that TTC values are, on average, ~6-fold lower than RfD values, whereas some RfD values for HFPO-DA are >400-fold lower than the Class III TTC value—perhaps indicating that such RfD values are overly conservative. Overall, these new data support that liver effects in mice are the result of a species-specific MOA with little human relevance, and that RfD values for HFPO-DA should not include liver effects that are the result of PPARα signaling.