Assessment of the Mode of Action Underlying Development of Liver Lesions in Mice Following Oral Exposure to HFPO-DA (GenX) and Relevance to Humans

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Abstract:

HFPO-DA is a short-chain polyfluorinated alkyl substance (PFAS) used in the manufacture of some types of fluorinated polymers. Like many PFAS, toxicity studies with HFPO-DA indicate the liver is the primary target of toxicity in rodents following oral exposure. Due to the structural diversity of PFAS, the mode of action (MOA) can differ between PFAS for the same target tissue. There is significant evidence for involvement of peroxisome proliferator-activated receptor alpha (PPARα) activation based on molecular and histopathological responses in the liver following HFPO-DA exposure in both rats and mice, but other MOAs have also been hypothesized based on limited evidence. To address this, toxicity data for HFPO-DA from the primary peer-reviewed literature and USEPA's Health and Environmental Research Online (HERO) database were assessed in the context of the Key Events (KEs) outlined in a published MOA framework for PPARα activator-induced rodent hepatocarcinogenesis. Non-neoplastic liver changes observed in mice occur early in the PPARα MOA, therefore this assessment focused on the first three KEs (i.e., PPARα activation, alteration of cell growth pathways, and perturbation of cell growth and survival). Although chronic bioassays with HFPO-DA are not currently available in mice to provide empirical support of the latter KEs (i.e., clonal expansion of preneoplastic foci cells and liver tumors) in the PPARα MOA, chronic exposures in mice are expected to yield similar results as to what has been observed in rats. The concordance of timing and dose-response of observed liver effects for HFPO-DA, biological plausibility, and human relevance were evaluated within the PPARα MOA framework. In addition, the evidence base for alternate MOAs was considered. The first three KEs were found to be supported by several lines of evidence from both *in vitro* and *in vivo* data available for HFPO-DA. Increased peroxisomal and mitochondrial fatty acid β-oxidation were evident at lower HFPO-DA concentrations, whereas changes in cell cycle pathways via altered gene expression and increases in apoptosis, mitosis, hypertrophy and liver weight were observed at higher HFPO-DA concentrations. In contrast, alternate MOAs, including cytotoxicity, participation of other PPAR subtypes (e.g., PPARγ), and mitochondrial dysfunction were determined to not be supported by the scientific literature. The overall weight of the evidence for HFPO-DA demonstrates that liver effects in mice occur via a PPARα MOA and not by alternative MOAs. HFPO-DA-mediated liver effects in mice are not expected in humans as only KE 1, PPARα activation, is shared across species. PPARα-mediated gene expression in humans produces only a subset (i.e., lipid modulating effects) of the responses observed in rodents. As such, the adverse effects observed in rodent livers should not be used as the basis of toxicity values for HFPO-DA for purposes of human health risk assessment.