Read-Across for 90-Day Rat Oral Repeated-Dose Toxicity for Selected Perfluoroalkyl Acids: A Case Study

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A previously published strategy is followed to structure and report this case study which builds a read-across line of reasoning for selected perfluoroalkyl acids (PFAAs). This case study represents a scenario of chemicals with no or very slow metabolism. Based on similarities in chemistry, toxicokinetics, especially clearance, and toxicodynamics, especially peroxisome proliferator-activated receptor (PPARα and/or PPARγ) activation, a small congeneric series (i.e., C7-C10) of straight-chain PFAAs is proposed as a read-across category.

Perfluoronated octanoic acid (PFOA) is identified as the source substance. It was demonstrated that i*n vivo* oral repeated-dose exposure of rats to PFAAs gives rise to a standard set of symptoms, including liver toxicity. Specifically, hepatocellular injury is accompanied by oxidative stress and inflammatory response, as well as alteration in lipid transport and metabolism. While there is evidence that PFAAs activate a multiplicity of nuclear receptors, peroxisome proliferator-activated receptors (PPARα and/or PPARγ) activation are the most likely initiating events leading to rat oral repeated-dose, liver toxicity.

Following the "traditional" group formation for read-across basis on *in vivo*, *in vitro* and structure-activity data, similarity and uncertainty for the category were assessed. Chemical uncertainty is deemed low. Uncertainty associated with the fundamentals of toxicokinetic similarity is deemed low-to-moderate. Because of sex and analogue differences half-life or clearance in the rat is identified as the weakest issue in toxicokinetic similarity.

Uncertainty associated with the fundamentals of toxicodynamic similarity is also deemed to be low-to-moderate. Because of multiple receptor interactions, the premise that PPARα and/or PPARγ) activation are the most likely initiating events leading to rat oral repeated-dose, liver toxicity in rats is identified as the weakest issue in toxicodynamic similarity. Lastly, uncertainty associated with mechanistic relevance and completeness of the read-across is judged to be low-to-moderate.

Following the consideration of information derived from NAM approaches, including results of the US EPA ToxCast programme, uncertainty and strength-of-evidence associated with toxicokinetic were unchanged; however, uncertainty and strength-of-evidence associated with toxicodynamic similarity were reduced and increased, respectively.

It is concluded that the rat oral 90-day NOAEL for PFOA, 0.06 mg/kg body weight (bw)/day (d) (based on hepatocyte necrosis and hepatocellular hypertrophy and increased liver weight), may be read across to the untested C9 and C10 analogues with acceptable uncertainty and used to inform regulatory decisions. Importantly, this conclusion is supported by the *in vivo* data (i.e., NOAELs of 0.1 mg/kg bw/d) for the C11 and C12 derivatives. Further, it is concluded that the oral 90-day NOAEL for PFOA can be read across to the C7 derivative as the most conservative argument.