Biotransformation is an important physiological process whereby a fish can convert a chemical to a more polar form so that it may be eliminated from the whole body. An understanding of the potential for a chemical to be biotransformed provides important information for a bioaccumulation assessment. Octamethylcyclotetrasiloxane (D4) and decamethylcyclopentasiloxane (D5) are widely used in consumer products and industrial applications. These two siloxanes have a high octanol-water partition coefficient ($\log K_{ow} > 6$), which is suggestive of a high aqueous bioconcentration factor (BCF). Several studies employing high performance liquid chromatography demonstrate that D4 and D5 siloxanes are biotransformed into more polar metabolites. A third in vivo study employed whole body autoradiography (WBA) and found that a bulk of the $^{14}$C-D4 and $^{14}$C-D5 radioactivity was associated with the liver, gall bladder and digestive tract during and after exposure. In vitro microsomal studies suggest that $^{14}$C-D5 was biotransformed by rainbow trout, while minimal biotransformation was observed with common carp and channel catfish. Using these data-sets, an estimated $K_{bw}$ for D4 and D5 siloxane is > 0.01 day$^{-1}$. Based on the available data, there is conclusive evidence that D5 siloxane is biotransformed to more polar metabolites in fish. This biotransformation is important and provides rationale for D4 and D5 biodilution behavior generally observed in aquatic food webs (i.e. a TMF < 1).

**State of The Science**

- **D4**
  - Juvenile rainbow trout (1.38 ± 0.29 g wet weight) were fed $^{14}$C-D4 siloxane for 35 days and then allowed to depurate for 42d (Woodburn et al. 2013; Drottar 2007). The dietary route of exposure represents the most likely exposure route for fish to D4. Whole body measurements from the last three sampling points of the uptake period revealed that the fish achieved steady-state as the residue concentrations did not significantly differ over time. An empirical BMF value for D4 siloxane was 0.28. More importantly, whole body autoradiography (WBA) was conducted on Days 1 and 10 of the uptake period and Days 12, 14, 21, 41, and 42 of depuration (Drottar 2006 a and b). The concentration of $^{14}$C radioactivity in the liver and digestive tract was high throughout the entire study, which is suggestive of metabolism and elimination. After 42 d of depuration, most of the radioactivity was found in the liver and digestive tract (Drottar 2006 a and b).

- **D5**
  - Juvenile rainbow trout (1.38 ± 0.29 g wet weight) were fed $^{14}$C-D5 siloxane for 35 days and then allowed to depurate for 42 d (Woodburn et al., 2013, Drottar 2007). The dietary route of exposure represents the most likely exposure route for fish to D5. Whole body measurements from the last three sampling points of the uptake period revealed that the fish achieved steady-state as the residue concentrations did not significantly differ over time. An empirical BMF value for D5 was 0.32. Whole body autoradiography (WBA) was conducted on Days 1 and 10 of the uptake period and Days 1, 4, 42 and 84 of depuration (Drottar 2006 a and b). The concentration of $^{14}$C radioactivity in the liver and digestive tract was high throughout the entire study, which is suggestive of metabolism and elimination. After 42 d of depuration, most of the radioactivity in the fish homogenates was D5 siloxane metabolites.

- **In vivo S9 and microbial bioactivation** of $^{14}$C-D5 was studied in a trout, carp and catfish (Cantu et al. 2015). Biotransformation was observed in fish, though was typically < 5% of the starting concentration.

**Expert Opinion**

- **D4**
  - D4 siloxane is biotransformed by fish. The HPLC metabolite profiling in two in vivo studies clearly shows the presence of multiple biotransformation products (Springer 2007; Durham et al. 2009; Domoradzki et al. 2007 and 2009). All of these biotransformation products are more polar than D4 parent siloxane. The presence of these polar metabolites indicates that these metabolites will likely be eliminated quickly from the fish. Further chromatographic data can be found on Domoradzki et al. 2015 (Poster WE224).
  - The metabolic rate constant ($K_{bw}$) for D4 siloxane is 0.01 day$^{-1}$. $K_{bw}$ of 0.14 day$^{-1}$ has been suggested for D4 siloxane and is based on the blood time course data from the D4 rainbow trout gavage study (Domoradzki et al. 2009 a and b). This analysis assumes that the partitioning of D4 between the blood and whole body is identical. While this assumption may not be incorrect based on review of the blood/tissue partitioning data from that study, there is uncertainty around deriving a $K_{bw}$ based on blood time course data versus whole body data. Applying an uncertainty factor of 10 brings the experimentally-derived D4 $K_{bw}$ value to 0.01 day$^{-1}$. A value of this magnitude would be consistent with a majority of TMF aquatic food web data on D4, showing biodilution (i.e., TMF < 1).
  - The empirical BMF (wet weight basis) for D4 siloxane is < 1, with hepatic biotransformation playing a minor role. Woodburn et al. (2013) reported an empirical BMF for D4 siloxane of 0.28. In addition, based on the $^{14}$C dosed and $^{14}$C recovered in the carcass and tissues from adult rainbow trout at 96 hr in the oral gavage study, a comparable empirical D4 BMF of 0.63 may be calculated (Springer 2007; Domoradzki et al. 2006). We know from multiple studies that D4 siloxane biotransformation products were present in fish after a single oral dose (Durham et al. 2009; Domoradzki et al. 2008 and 2009).
  - During D4 siloxane dosing and depuration periods, a majority of the D4 residues are located in the liver, gall bladder and GI tract. The residues being located in the liver and GI tract indicates that the residues are in the process of being cleared from the body.

- **D5**
  - D5 siloxane is biotransformed by fish. The HPLC metabolite profiling utilized in the two in vivo studies clearly show the presence of multiple biotransformation products (Durham et al. 2009; Springer 2007; Domoradzki et al. 2007). All of these biotransformation products are more polar than D5 parent siloxane. The presence of these polar metabolites indicates that these metabolites will likely be eliminated quickly from the fish.
  - The metabolic rate constant ($K_{bw}$) for D5 siloxane is 0.01 day$^{-1}$. In the oral gavage study, approximately 14% of the original D5 siloxane dose was converted to metabolites. Given the trout were dosed orally, the blood was sampled over 96 hr (time points of 0, 2, 4, 8, 12, 24, 48, 72, 96 hr), and both parent and metabolites were measured, a metabolic rate constant ($K_{bw}$) was estimated from the blood temporal data to be 0.17 day$^{-1}$ (Woodburn et al. 2008; Domoradzki et al. 2009). This analysis assumes that the partitioning of D5 between the blood and whole body is identical. While this assumption may not be incorrect based on review of the blood/tissue partitioning data from that study, there is uncertainty around deriving a $K_{bw}$ based on blood time course data as opposed to whole body data. Applying an uncertainty factor of 10, brings the experimentally-derived D5 $K_{bw}$ value to 0.017 day$^{-1}$. A value of this magnitude would be consistent with a majority of TMF aquatic food web data on D5, showing biodilution (i.e., TMF < 1).
  - The empirical BMF for D5 siloxane is < 1, with hepatic biotransformation seemingly playing a pivotal role. Woodburn et al. (2013) reported an empirical BMF for D5 siloxane of 0.32. In addition, based on the $^{14}$C dosed and $^{14}$C recovered in the carcass and tissues of adult rainbow trout at 96 hr in the oral gavage study, an average empirical D5 BMF of 0.19 may be calculated. We know from multiple studies that D5 siloxane biotransformation products are present in fish after only 4-5 days of oral exposure (Durham et al. 2009; Springer 2007; Domoradzki et al. 2007 and 2009).
  - During D5 siloxane dosing and depuration periods, a majority of the D5 residues are located in the liver and GI tract. The residues being located in the liver and GI tract indicates that the residues are in the process of being cleared from the body.
  - In vivo biodistribution data in rainbow trout demonstrate that D5 is converted to more polar metabolites (Cantu et al. 2015).

**Conclusion**

Based on the available data, there is unequivocal evidence that D4 and D5 siloxane are biotransformed to more polar metabolites in fish. The biotransformation of D4 and D5 siloxanes provide one rationale for biodilution behavior in most natural aquatic food webs (i.e. a TMF < 1). Redman et al. (2012) reported a dietary uptake efficiency of ~10% for D4 and D5 based on measured fish data from Lake Poinin. Goss et al. (2013) suggested that at a 10% dietary uptake efficiency, a threshold for $K_{res}$value of 0.001 day$^{-1}$ was needed for a BMF/TMF < 1. Empirical data support that both D4 and D5 $K_{res}$values are > 0.01 day$^{-1}$, which provides underlying rationale for the BMF/TMF for both D4 and D5 being < 1.

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