Perfluorinated compounds (PFCs) have been recognized as an important class of environmental contaminants commonly detected in blood samples of both wildlife and humans. These compounds have been in use for more than 60 years as surface treatment chemicals, polymerization aids, and surfactants. They possess a strong carbon–fluorine bond, which leads to their environmental persistence. There is evidence from both epidemiology and laboratory studies that PFCs may be immunotoxic, affecting both cell-mediated and humoral immunity. Reported effects of PFCs include decreased spleen and thymus weights and cellularity, reduced specific antibody production, reduced survival after influenza infection, and altered cytokine production. Immunosuppression is a critical effect associated with exposure to PFCs, as it has been reported to reduce antibody responses to vaccination in children. Mounting evidence suggests that immunotoxicity in experimental animals can occur at serum concentrations below, within, or just above the reported range for highly exposed humans and wildlife. Considering bioaccumulation and exposure to multiple PFCs, the risk of immunotoxicity for humans and wildlife cannot be discounted. This review will discuss current and recently published work exploring the immunomodulatory effects of PFCs in experimental animals and humans.