Effects of New Generation Per and Polyfluoroalkyl Substances on Gap Junctional Intercellular Communication. Are They Safer?

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Gap junctional intercellular communication (GJIC) is significant in developing a systems-based *in vitro* model assessing the toxic potential of environmental contaminants. This is crucial for integrating signaling mechanisms among cells in tissues and is an important early-stage event in abnormal cell proliferation. We determined the effects of new generation per- and polyfluoroalkyl substances (PFAS) on GJIC. Specifically, we determined the effects of GenX, perfluorohexane sulfonic acid (PFHxS) and perfluorohexane carboxylic acid (PFHxA) on GJIC and compared these effects with the legacy PFAS, perfluorooctane sulfonic acid (PFOS) and perfluorooctane carboxylic acid (PFOA). We used the "scalpel load – dye transfer" assay to assess GJIC as a function of dose and time using the F344 WB rat liver epithelial cell line. This is an *in vitro* cell model of liver oval cells, a bipotent stem/progenitor cell that give rise to hepatocytes and hepatic biliary duct cells and self-renew. PFHxS inhibited GJIC at higher doses than PFOA and PFOS while PFHxA did not inhibit GJIC. Preliminary results indicated that GenX can close GJIC channels. Results indicate a significant difference in the cutoff points of active vs. inactive carboxylic vs. sulfonic acid PFAS. We determined PFHxS and PFOS did not close channels through a phosphatidylcholine phospholipase-C mechanism whereas the PFOA did. This indicates that the new generation of PFAS could induce adverse health effects by dysregulating GJIC.

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