Developmental Toxicity of Perfluorohexane Sulfonate (PFHxS) - Effects on the Immune and Thyroid Hormone Systems

Both the immune and the thyroid hormone systems are integral to human physiology and health. They are also important for normal development from early in fetal life, but simultaneously vulnerable to chemical exposures and disruption during fetal and early postnatal life. If disrupted during development, both systems can become compromised leading to negative consequences later in life. This includes effects on immune function, neurobehavior and cognitive abilities. In fact, since thyroid hormones are crucial for brain development there are correlations between low maternal serum thyroxine (T4) levels and subsequent adverse effects on child neurobehavior and intelligence quotient (IQ). Poly- and perfluorooalkyl substances (PFAS) are compounds linked to immunotoxicity and thyroid hormone disruption. They are ubiquitous and persistent in the environment and human exposure is universal, hence a potential risk to human health. Yet the toxicity potential of several PFASs, including perfluorohexane sulfonate (PFHxS), remains largely unknown. This PhD project therefore aimed at investigating the developmental toxicity of PFHxS, with an emphasis on the reproductive, the thyroid hormone and the immune systems. PFHxS toxicity was further investigated in combination with exposure to a human-relevant mixture of 12 endocrine disrupting chemicals. These studies showed that, for some endpoints, there was increased sensitivity to PFHxS exposure when it was combined with the mixture and that PFHxS and the mixture could potentiate the effect of each other. This indicates that the current European approach for regulating chemicals, relying on risk assessment of one chemical at a time, may underestimate the risk to humans who are exposed to a multitude of chemicals on a daily basis. The main finding in these studies was that PFHxS reduced maternal and offspring thyroid hormone levels. This happened without apparent activation of the compensatory feedback responses. We were not able to correlate the decreased thyroid hormone levels to behavioral effects in the offspring, but the literature suggests that the employed tests are insensitive measures of altered brain development due to developmental thyroid hormone reductions. In humans, however, even smaller reductions in thyroid hormone levels during development, may affect complex functional parameters as language development and IQ, endpoints which are not measurable in rodents. Hence, in order to protect human brain development there is a strong need for development of new test methods for identification of adverse effects on brain development due to disruption of the thyroid hormone system. Preferably, these would include assays that are sensitive to more moderate reductions of thyroid hormone levels (reduction in T4<50%). Such tests are necessary because the legislative framework for regulating the use of chemicals relies on assays showing downstream adverse outcomes. Until a suitable test for adverse effects due to developmental thyroid hormone disruption has been identified, a compromise designed to protect human cognition could be to regard decreased serum T4 as an adverse outcome in itself. PFHxS exposure had limited effects on the immune system in our study; however, a faulty study design impedes conclusions on especially functional immune endpoints, which in theory should be the most sensitive measure of immune competence. At the highest tested dose, PFHxS may reduce immune organ weights, but this could not be replicated in the larger study that investigated lower doses. Hence, further studies of immunotoxicity of PFHxS are warranted.