Mixtures of endocrine disrupting contaminants modelled on human high end exposures

Mixtures of endocrine disrupting contaminants modelled on human high end exposures: an exploratory study in rats

By diminishing the action of androgens during gestation, certain chemicals can induce irreversible demasculinization and malformations of sex organs in the male rat after gestational exposure. Studies with mixtures of such anti-androgener have shown that substantial combined effects occur even though each individual chemical is present at low, ineffective doses, but the effects of mixtures modelled based on human intakes have not previously been investigated. To address this issue for the first time, we selected 13 chemicals for a developmental mixture toxicity study in rats where data about in vivo endocrine disrupting effects and information about human exposures was available, including phthalates, pesticides, UV-filters, bisphenol A, parabens and the drug paracetamol. The mixture ratio was chosen to reflect high end human intakes.

To make decisions about the dose levels for studies in the rat, we employed the point of departure index (PODI) approach, which sums up ratios between estimated exposure levels and no-observed-adverse-effect-level (NOAEL) values of individual substances. For high end human exposures to the 13 selected chemicals, we calculated a PODI of 0.016. As only a PODI exceeding 1 is expected to lead to effects in the rat, a total dose more than 62 times higher than human exposures should lead to responses. Considering the high uncertainty of this estimate, experience on lowest-observed-adverse-effect-level (LOAEL)/NOAEL ratios and statistical power of rat studies, we expected that combined doses 150 times higher than high end human intake estimates should give no, or only borderline effects, whereas doses 450 times higher should produce significant responses. Experiments indeed showed clear developmental toxicity of the 450-fold dose in terms of increased nipple retention (NR) and reduced ventral prostate weight. The 150-fold dose group exhibited significantly increased NR. These observations suggest that highly exposed population groups, especially women of reproductive age, may not be protected sufficiently against the combined effects of chemicals that affect the hormonal milieu required for normal male sexual differentiation.

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