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3. Human exposure to synthetic endocrine disrupting chemicals ( (2020-8)
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### 1) Toddler behavior, the home environment, and flame retardant exposure

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* Chemosphere
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Toddlers are at increased risk of dust ingestion and subsequently flame retardant (FR) exposure because they often play close to the floor and mouth hands and objects. Exposure to some FRs have been associated to endocrine disruption and neurodevelopmental disorders. Previous research has shown higher FR concentrations in toddlers’ serum and urine, but which toddler-behaviors influence exposure levels remains to be determined. We investigated how toddler-behaviors are associated to FRs in hand wipes (HWs) and saliva. Fifty 8-18 month-old children from the Linking EDCs in maternal Nutrition to Child health study, were visited at home. The child's behavior was observed and assessed using a questionnaire. Hand-to-object behavior frequency was associated with HW tris(chloroethyl) phosphate (TCEP), tris(1,3-dichloroisopropyl) phosphate (TDCIPP), tris(phenyl) phosphate, tris(methylphenyl) phosphate, and resorcinol bis(diphenyl phosphate) levels above the detection limit. Children playing with electronics multiple times per week had higher TDCIPP HW levels compared to children playing with electronics once per month or never (p = 0.032 and p = 0.046). Frequent mouth-to-object and frequent mouthing a pacifier were associated with lower TDCIPP (p = 0.019) and tris(2-chloroisopropyl) phosphate (TCIPP) HW levels, respectively (p = 0.002–0.019). Exposure estimates based on hand-to-mouth behavior did not exceed the available reference doses. This is the first study investigating toddler-behavior in relation to FR hand loadings. Although a range of behaviors was investigated, only a few showed a relation with FR HW levels, suggesting that toddler-behavior might not alone be responsible for the elevated FR levels in children. It is therefore important to explore other pathways including dermal absorption and inhalation.

### 2) Development of a high-throughput bioassay for screening of antibiotics in aquatic environmental samples

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The goal of the present study was to select a Gram-positive (Gram+) and Gram-negative (Gram−) strain to measure antimicrobial activity in environmental samples, allowing high-throughput environmental screening. The sensitivity of eight pre-selected bacterial strains were tested to a training set of ten antibiotics, i.e. three Gram+ Bacillus subtilis strains with different read-outs, and five Gram− strains. The latter group consisted of a bioluminescent Allivibrio fischeri strain and four Escherichia coli strains, i.e. a wild type (WT) and three strains with a modified cell envelope to increase their sensitivity. The WT B. subtilis and an E. coli strain newly developed in this study, were most sensitive to the training set. This E. coli strain carries an open variant of an outer membrane protein combined with an inactivated multidrug efflux transport system. The assay conditions of these two strains were optimized and validated by exposure to a validation set of thirteen antibiotics with clinical and environmental relevance. The assay sensitivity ranged from the ng/mL to μg/mL range. The applicability of the assays for toxicological characterization of aquatic environmental samples was demonstrated for hospital effluent extract. A future application includes effect-directed analysis to identify yet unknown antibiotic contaminants or their transformation products.

### 3) Human exposure to synthetic endocrine disrupting chemicals (S-EDCs) is generally negligible as compared to natural compounds with higher or comparable endocrine activity. How to evaluate the risk of the S-EDCs?

* Autrup, H., Barile, F. A., Berry, S. C., Blaauboer, B. J., Boobis, A., Bolt, H., Borgert, C. J., Dekant, W., Dietrich, D., Domingo, J. L., Gori, G. B., Greim, H., Hengstler, J., Kacew, S., Marquardt, H., Pelkonen, O., Savolainen, K., Heslop-Harrison, P., Vermeulen, N. P.
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Theoretically, both synthetic endocrine disrupting chemicals (S-EDCs) and natural (exogenous and endogenous) endocrine disrupting chemicals (N-EDCs) can interact with endocrine receptors and disturb hormonal balance. However, compared to endogenous hormones, S-EDCs are only weak partial agonists with receptor affinities several orders of magnitude lower than S-EDCs. Thus, to elicit observable effects, S-EDCs require considerably higher concentrations to attain sufficient receptor occupancy or to displace natural hormones and other endogenous ligands. Significant exposures to exogenous N-EDCs may result from ingestion of foods such as soy-based diets, green tea and sweet mustard. While their potencies are lower as compared to natural endogenous hormones, they usually are considerably more potent than S-EDCs. Effects of exogenous N-EDCs on the endocrine system were observed at high dietary intakes. A causal relation between their mechanism of action and these effects is established and biologically plausible. In contrast, the assumption that the much lower human exposures to S-EDCs may induce observable endocrine effects is not plausible. Hence, it is not surprising that epidemiological studies searching for an association between S-EDC exposure and health effects have failed. Regarding testing for potential endocrine effects, a scientifically justified screen should use in vitro tests to compare potencies of S-EDCs with those of reference N-EDCs. When the potency of the S-EDC is similar or smaller than that of the N-EDC, further testing in laboratory animals and regulatory consequences are not warranted.

### 4) Human exposure to synthetic endocrine disrupting chemicals (S-EDCs) is generally negligible as compared to natural compounds with higher or comparable endocrine activity. How to evaluate the risk of the S-EDCs?

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* Chemico-Biological Interactions
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* Corresponding author: Greim, H.
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Theoretically, both synthetic endocrine disrupting chemicals (S-EDCs) and natural (exogenous and endogenous) endocrine disrupting chemicals (N-EDCs) can interact with endocrine receptors and disturb hormonal balance. However, compared to endogenous hormones, S-EDCs are only weak partial agonists with receptor affinities several orders of magnitude lower. Thus, to elicit observable effects, S-EDCs require considerably higher concentrations to attain sufficient receptor occupancy or to displace natural hormones and other endogenous ligands. Significant exposures to exogenous N-EDCs may result from ingestion of foods such as soy-based diets, green tea and sweet mustard. While their potencies are lower as compared to natural endogenous hormones, they usually are considerably more potent than S-EDCs. Effects of exogenous N-EDCs on the endocrine system were observed at high dietary intakes. A causal relation between their mechanism of action and these effects is established and biologically plausible. In contrast, the assumption that the much lower human exposures to S-EDCs may induce observable endocrine effects is not plausible. Hence, it is not surprising that epidemiological studies searching for an association between S-EDC exposure and health effects have failed. Regarding testing for potential endocrine effects, a scientifically justified screen should use in vitro tests to compare potencies of S-EDCs with those of reference N-EDCs. When the potency of the S-EDC is similar or smaller than that of the N-EDC, further testing in laboratory animals and regulatory consequences are not warranted.