

## Mixture assessment of Endocrine Disrupting Compounds (EDC) with emphasis on thyroidogenicity - using cats as model for human indoor exposure

Short Title: Mixture aSSessments of EDCs

Acronym: *MISSE*

Several studies have demonstrated pet cats to be good sentinels for human indoor exposure to chemicals. Particularly for toddlers, due to the elevated intake of dust particles. In 2007 it was suggested that cats' increasing incidence of hyperthyroidism could be due to exposure to chemicals via dust. To follow-up on that, we collected a larger number of cat serum in 2010 to be analyzed for a range of persistent organic pollutants (POPs). We could report that cats diagnosed with feline hyperthyroidism were indeed having higher serum levels of certain POPs [1-2]. That study was the starting point of the MiSSE project. It was decided that it should be focusing on the thyroid hormone (TH) system. THs play an important role in the maintenance of a normal physiological state and are essential for metabolism and growth. Especially TH alterations during early life stages are critical, as it can effect the health throughout the whole life, such as puberty, reproduction, diabetes and menopause onset. Many of the chemicals leaking out from household products, indoor materials and goods have been shown to be reflected in household dust, and to be endocrine disrupting compounds. In MiSSE we wanted to establish dust as a relevant chemical exposure pathway, and consequently estimate the indoor exposure to cats and small children. We aimed to map the dust chemical composition and characteristics, by chemical analysis, reviews and *in silico* modelling. Secondly, we wanted to examine whether the exposure of the mixture of chemicals associated to dust, could pose a risk for the health of the cat by testing dust related chemicals in a series of *in vivo* and *in vitro* assays.

A strength of the project was that we used so-called paired samples, i.e. blood serum samples from cats and dust samples from the household were taken at the same time. By using paired sampling we had a statistically more powerful sample set for the evaluation of dust as the exposure route to these compounds. In total, 17 families participated in the study, having pet cat(s) and a household representing a typical child-living environment. The cat's health was checked by a simple clinical examination and their thyroid status was evaluated by measuring the levels of THs. All cats (n=29) were clinically healthy. Dust samples were sampled from 3-4 rooms (n=52) using a dust collector containing a disposable filter attached to a household vacuum cleaner tube. The dust and serum samples were analyzed for a range of POPs [1-7].

Initially, a database was compiled containing; chemicals tested for their thyroid hormone disrupting potency; dust related chemicals; their *in silico* modelled metabolites; and *in silico* modelled TH disrupting compounds [8-14]. Together with the information from the chemical analysis realistic mixtures corresponding to dust, human and cat's serum chemical profiles were created. Both individual chemicals and the mixtures were tested *in vitro* (binding to transport protein and cell based bio reporter assays) and *in vivo* (zebrafish and amphibian) for their toxicity [15-18].

Major findings of MiSSE project were:

- The importance of metabolic activation in TH disruption was highlighted, and a range of new chemicals of concern were identified in the *in silico* studies.
- Phthalates are the major dust contaminants, followed by the organophosphorus flame retardants.

- Higher POP concentrations were found on fine particles compared to larger size fractions due to the increasing surface-to-volume ratio for smaller particles. Despite that, ingestion of dust is higher compared to inhalation of the respirable fraction (<5 µm).
- PFASs are the major blood contaminants, both in cats and humans.
- Dust could be confirmed as a relevant exposure pathway by statistical significant correlations between serum and dust samples for PBDEs, PCB and PFOA.
- The *in vitro* tested mixtures indicated that human and cat serum levels are close to relevant levels to be TH disrupting by inhibition of 1-6% of the T4-TTR binding *in vivo*.
- We have clearly showed that using cats as sentinel for human exposure is advantageous, and two state-of-the-art reviews in the topic has been submitted, one targeting veterinarians [19-20].

We recommend expanding the study design to include other endocrine related health outcomes, such as diabetes and obesity, relevant for both humans and cats.

## References

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In addition:

- 5 manuscripts in the pipe-line
- 5 diploma theses
- 27 conference proceedings
- Several articles and interviews in the public media ([www.aces.su.se/misse/](http://www.aces.su.se/misse/))