The "human approach" subtheme

Meconium: a new tool for estimating chronic exposure to pesticides.
The MecoExpo cohort (993 pairs of mothers and newborns) was created so that we could analyze the pesticides to which newborns in the Picardie region are exposed in utero. We measure pesticide levels in the meconium (the first faeces produced by the newborn); this reflects exposures to xenobiotics via the blood and the placenta during the 2nd and 3rd trimesters of pregnancy). In contrast to conventional biological matrices (blood, urine, etc.), meconium is a marker of chronic in utero exposure. It can also be used to screen for heavy metals, drugs of abuse, alcohol, tobacco, medications, etc. Nevertheless, few studies have used meconium to indicate the accumulation of pesticides. An American study showed that meconium is a more sensitive biological matrix than cord blood and the hair for reliably estimating chronic foetal exposure to pesticides. In Europe, only a few studies have been performed. As of 2009, no-one in France had studied meconium as a marker of pesticide exposure.

The first step consisted in optimizing and validating the pesticide assay technique in meconium. We screened for a total of 21 compounds (9 pesticides and 12 metabolites) in 462 samples. The sources of this in utero exposure (according to a self-questionnaire) were studied with regard to the clinical parameters at birth.

Dialkylphosphates (organophosphorus metabolites) were most frequently found (with DMTP and DEP in 59% and 38% of samples, respectively). Non-specific metabolites of mancozebe (EU and ETU) were the next most frequently detected compounds (in 27% and 26% of samples, respectively). Only 15% of the samples did not contain any of the pesticides in the test panel. This unique assay method was transferred from the INERIS' NOVA unit to the University of Picardie's ICAP analytical facility in 2014. The ICAP facility is continuing to assay the cohort's latest samples.
The study emphasized the chronic in utero exposure to pesticides in newborns in the Picardie region.

Endocrine disruptor effects
We are currently comparing 57 hypospadic newborn boys with 162 unaffected newborn boys. We have already evidenced a link between the mother's workplace exposure to endocrine disruptors (evaluated by a job-exposure matrix) and the occurrence of hypospadias. Our results also revealed (for the first time, as far as we know) a link between the use of cosmetic hair products and the occurrence of hypospadias.

Functions involved in the energy balance: sleep, respiration and the digestive system
Organophosphates (found in more than half of meconium samples analyzed) inhibit acetylcholinesterase and induce the accumulation of acetylcholine. Given the latter's major role in ventilatory control and sleep, this accumulation during development might disrupt these functions at birth..

The PhysioMeco project addresses this hypothesis in the newborn. Our laboratory's experimental facilities for investigating newborns (with the simultaneous recording of sleep, thermoregulation and respiration) now also include a method for studying the ventilatory control exerted by peripheral chemoreceptors. Specific equipment (a pneumotachograph, a gas analyzer, etc.) that complies with the morphological constraints in the premature newborn (small ventilatory volumes) now also enables us to assess the activity of peripheral chemoreceptors in an hypoxic test.

The "experimental approach" subtheme

Functions involved in the energy balance: sleep, respiration and the digestive system
In parallel, we are using in vitro and in vivo approaches to study the mechanisms that operate during controlled, limited exposure to the pesticide chlorpyrifos (CPF). We have shown that CPF exposure and the reduction in AChE activity has an effect on birth weight, respiratory function (with a decrease in ventilatory frequency and an increase in the number of apnoea episodes) and contractile function of the diaphragm (increased fatigability).

In the digestive tract (the first system to come into contact with the pesticide), our work has evidenced intestinal dysbiosis (with a decrease in beneficial bacteria and an increase in potentially pathogenic bacteria), increased bacterial translocation to sterile organs, morphological and functional alterations, and a delay in digestive maturation. These morphological and functional alterations of the digestive system persist over time.
On the endocrine level, CPF induces metabolic dysregulation that can lead to a higher risk of metabolic disease (type 2 diabetes, changes in lipid metabolism, etc.). These changes may corroborate Slotkin's hypothesis, in which exposure to pesticides contributes to obesity and prediabetes.

In light of these observations (and in the current absence of a sharp reduction in the agricultural use of phytosanitary products), it is important to limit these compounds' physiological impact on the future generations as much as possible. This is why one of the solutions envisaged for reducing the impact of CPF is the use of food fibres (prebiotics) that have widely acknowledged benefits for human health.

A number of experiments performed in collaboration with the Institute LaSalle Beauvais have shown that the ingestion of prebiotics (notably inulin) strengthens the intestine's barrier function by modulating (i) bacterial composition and metabolism and (ii) the immune system. Moreover, other work has shown that prebiotic supplements are involved in the regulation of energy metabolism. In this context, we have tried to determine whether an oral supplementation with a prebiotic (inulin) during the perinatal period limits the harmful effects of CPF on the development, maturation and function of the digestive system and on the regulation of food intake. We found that the decrease in the numbers of beneficial bacteria and the rise in numbers of potentially pathogenic bacteria observed with CPF alone were not seen after concomitant exposure to prebiotic + CPF. These results suggest that inulin is able to counterbalance (in part) the harmful effects of CPF.