PERITOX

The PeriTox unit's prime scientific challenge is to study **the impact of perinatal exposure to environmental factors on the health of the newborn and the child**, and**particularly the physiological functions involved in the maintenance of the energy balance required for survival and development**. This challenges fits into the **D OHaD concept** and **the exposome** concept of disease.

The newborn is fragile; after birth, it has to confront an environment that is very different from that experienced in utero. The newborn has to respond and adapt rapidly to this environment, despite having limited and immature resources. Furthermore, an inappropriate and/or costly response is likely to be particularly harmful. Homeostasis is thus essential for limiting mortality and morbidity in the infant and the consequences in adulthood; this is a true challenge, and one that should not be under-estimated.
The energy balance is zero when energy production and/or gains compensate for energy losses. In the newborn, energy expenditure is dedicated to (i) the operation of vital organs, (ii) thermoregulation and (iii) growth, in that order. Many physiological functions are involved in the energy balance:
• **Thermoregulation** and the maintenance of homeothermy have key roles in energy homeostasis. This is particularly true in the newborn; although it has limited energy reserves, it has to deal with very large, rapid heat exchanges with its environment. Although the newborn is a homeotherm, its thermoregulatory responses are weak and cannot be maintained if the thermal stress persists. This is why caring for a newborn in a thermoneutral incubator (in which there is no need to activate thermoregulatory responses to warm or cold, i.e. with a zero energy balance) guarantees the best chances of survival, good health and optimal growth. The difficulty lies in determining the thermoneutral zone, which is particularly narrow in the newborn and depends on many intrinsic parameters (clinical status, morphology, age, health, sleep, nutrition, medication, etc.) and extrinsic parameters (the physical characteristics of the environment). This is why even slight thermal stress (variations of 1.5-2°C or less relative to thermoneutrality – the magnitude typically measured in an incubator and during care procedures) can trigger costly thermoregulatory responses.
• **Respiration**: an increase in oxygen consumption (VO2) is observed when a newborn is exposed to cold; this reflects the oxygen required for non-shivering thermogenesis and increased body movements (including during sleep). VO2 also increases when the newborn is exposed to warm (increased body movements).
• **Sleep**, which enables the replenishment of energy reserves and limits energy expenditure.
• **Food intake and digestion**, to provide energy. However, this requires an adequate level of gastrointestinal maturation for the digestion and absorption of nutrients and for other functions of the digestive tract (endocrine, nervous and immunological functions).
Our objective is thus to determine **how toxic or physical factors in the environment can disrupt one or more of these functions and induce a functional impairment and/or an inappropriate physiological response in the infant or later in childhood/adulthood.**

These effects are exacerbated in premature infants and/or those having experienced in utero growth restriction (IUGR), which emphasizes the importance of the foetal development phase and **the neonatal period**. **The whole perinatal development phase therefore constitutes a time of significant vulnerability.**

Our activities are focused on two environmental toxics: pesticides and physical agents. This organization generates synergy between researchers working on common themes and joint projects, by combining their skills, models and resources. **It provides a true cross-sector approach within and between themes; this constitutes a key feature of our work and forms the basis for our novel research themes and approaches.**

For each of the two themes, t**hese studies are performed in a coherent, complementary manner by working on the human newborn, in vitro systems and in silico models and by analyzing the effects of exposure on the major physiological functions involved in the energy balance.** This encompasses a mutually beneficial "from bench to bed and back" approach.
This complementarity is also reflected by our tools, scientific expertise, techniques and approaches. Our studies are part of an integrated approach that ranges from exposure assessment, molecular biology and cell biology to integrated physiology. In vivo approaches in the child, in vitro studies and modelling are brought to bear on the same scientific questions.

When relevant, **we favour models that avoid the need for experiments on animals or humans (such as the SHIME artificial intestine, the thermal mannequin, etc.).**Conversely, if animal or human experiments are necessary, we use stress-free and/or contact-free methods (wireless EEGs, infrared cameras, etc.). Most of these methods have been designed, developed and validated in-house.

Our research themes fit with the priorities defined in SCALE (reduce environmental stress on health); four high-priority child diseases: respiration, neurological development, endocrine perturbations ; **the French National Environment Healthcare Plan**: developing new markers, methodologies and measurement tools, augmenting research, training and information dissemination, targeting populations at risk (children, pregnant women, etc.) , and reducing inequalities in environmental healthcar e; the exposome concept ; and **REACH**: "improve the protection of human health and the environment", analyzing functional impacts, etc.).

The objective of our **"thermal" studies** is **to assess the failure of neurovegetative regulatory mechanisms during moderate thermal stress**.**We are seeking to improve the clinical management of premature newborns by combining integrated neurophysiology experiments in the child with indirect approaches using mathematical models and physical models (the thermal mannequin) for the analysis of heat exchanges between the newborn and its environment.**
Faced with strong societal concerns over the effects of EMFs on health, epidemiological studies have provided few answers. Uncertainty and controversy surround the physiological and clinical effects of EMFs and the mechanisms of action in the organism. It is nevertheless important to study the effects of EMFs: it has been estimated that between 1% to 3% of the world's population suffering from symptoms that they attribute to prolonged exposure to EMFs. In France, about a thousand people are currently registered as suffering from idiopathic environmental intolerance attributed to EMFs (IMI-EMF).
The studies performed to date were based on poorly developed physiological hypotheses because the level of knowledge (notably about EMFs' mechanism(s) of action) was limited. Unusually, this research is based on looking for effects in the absence of a prior scientific hypothesis. A large number of the studies performed to date in our laboratory were therefore based on an approach that combined fundamental biology and biomedical research to identify effects, check whether they constituted risks, find biomarkers or physiological indicators, and understand their mechanisms. The effects being screened for are related to the symptoms reported by EMF-hypersensitive people and deal mainly with the organs that are most exposed during mobile phone use (the skin and the brain). Hence, we particularly study the functions involved in homeostasis (cardiovascular and thermoregulatory functions, the nervous system, and sleep).
We hypothesize that the current low level of proof is related to failure to take account of possible environmental co-exposures (thermal stress, in particular). These are likely to increase an individual's susceptibility and/or potentiate the effects of EMFs. We have therefore decided to analyse co-exposures by studying sensitive populations, particularly during development in humans and in animal models (to take account of higher level of vulnerability of children, even though it is sometimes necessary to have reference data for adults, such as those affected by IMI-EMF).

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With over 70% of its land area used for agriculture, the Picardie region (now part of the Hauts de France region) uses large amounts of pesticides. Furthermore, the birth rate in the Hauts de France region is the 2nd highest in France, which emphasizes the importance of working on these substances' impacts on sensitive populations such as newborns.

We therefore decided to analyse the impact of perinatal exposures to pesticides on the physiological functions involved in the energy balance. All our studies comply with the Unit's strategy for choosing exposure windows, durations and levels: exposure during the perinatal period, chronic exposure, "low"-level exposure, etc. We mainly study the effects of chlorpyrifos (CPF). The compound was chosen on the basis of our initial measurements of the in utero exposure of newborns in Picardie. This organophosphorus pesticide inhibits acetylcholinesterase, an enzyme that degrades a neurotransmitter involved in many regulatory pathways (and notably those regulating sleep, respiration and thermoregulation). This is why studying CPF's impacts on functions involved in the energy balance is particularly relevant.
Pesticides' possible impacts on physiological functions (such as respiration) in the newborn following in utero exposure have rarely been studied. We are the only group in the world studying these functions in the human newborn; most of the other studies in this field are epidemiological assessments.

However, studying physiological impacts in the human newborn requires being able to quantify in utero exposure to pesticides. This is why one part of the “pesticide” studies consists in the development of a pesticide assay technique that reflects chronic in utero exposure (a meconium assay). We adapted a previously published technique and validated it with meconium samples from the “MecoExpo” cohort that we had founded. This work also enabled us to perform (i) epidemiological studies on the clinical impact at birth of pesticide exposure during pregnancy (as reported in a questionnaire) and (ii) exposure assessment. Now that the assay method has been set up, we are studying the physiological functions involved in energy balance (sleep, respiration, the digestive system, etc.) and that are likely to be disrupted by the presence of acetylcholinesterase inhibitors.

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