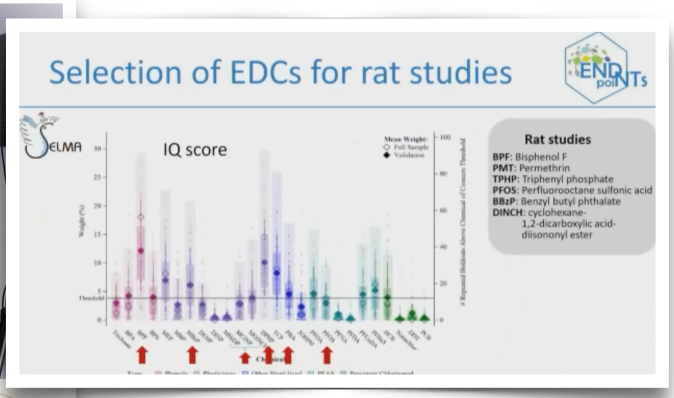
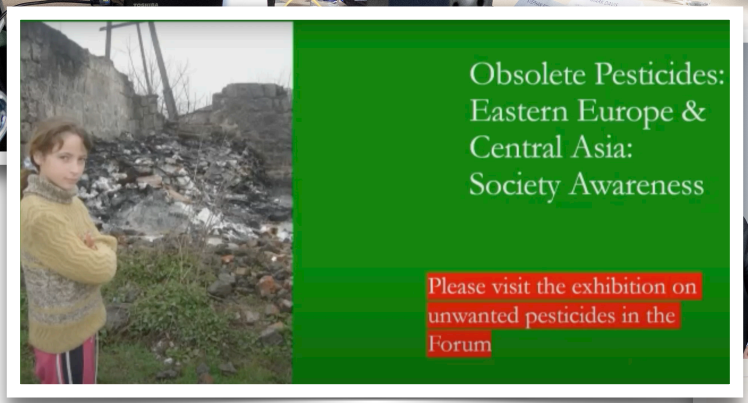
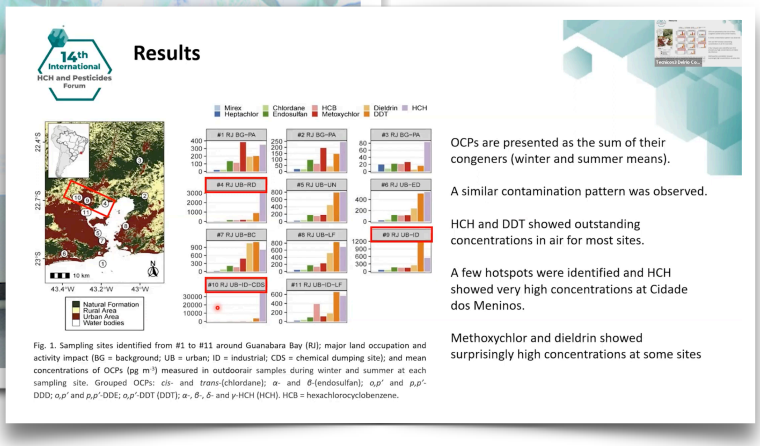
Block 11

NEW APPROACHES TO TESTING OF CHEMICALS BASED ON OMICS AND EPIDEMIOLOGY: EXAMPLE DEVELOPMENTAL NEUROTOXICITY







PART I.
EXPOSURE OF WILDLIFE AND HUMANS TO CHEMICALS

DEVELOPMENT OF APPROACHES TO REMOVE TOXIC SUBSTANCES FROM THE ENVIRONMENT

Vijgen, J.

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Abstract

Photographical journey starting from the situation in the 1980s onwards on the problems of HCH in the Netherlands from scratch confronting huge regional problems with people living in houses in HCH landfills and a famous farmer with dying cows and being accused from not feeding their cows and being brought to court. But nobody wanted to know that these cows were grazing for years on highly contaminated fields and farmers lost their property all leading finally to huge clean-up for more than 15 years.
Another pictorial travel to Central and Eastern Europe and Central Asia, where in Western Europe unknown obsolete pesticide stockpiles were all over the countries as a consequence of the collapse of the Former Soviet Union. Inventories were organized mainly by FAO, where the experiences made in Africa were used to start to get first impression of the huge number of stockpiles in the region. The many pictures show old sheds and stores with cows running around right through the obsolete pesticides and children playing in villages in contaminated DDT. The process of solutions, starting with inventories, take years and slowly with mainly help of The GEF and UN agencies part by part slowly move forward but still can take decades as project often deal with hundred of tons or sometimes a couple of thousand tons in areas where are still tens and hundreds of thousands of tons present.

GLOBAL EFFECTS OF POLLUTANTS AND OTHER RISK FACTORS ON INVERTEBRATE FAUNA

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Abstract

Biodiversity is eroding at an increasing pace, with current species extinction rates being up to 1000x higher than background rates. The causes for these are multiple, from habitat loss, degradation, and fragmentation, use of polluting and harmful substances, the spread of invasive species, global climate change, direct overexploitation, and co-extinction of species dependent on other species. The relative importance of each is however taxon- and context-dependent.
Insects and other invertebrates constitute the vast majority of species at any spatial scale, from small habitat patches to the global level. In agricultural areas they provide fundamental ecosystem services, including pollination, soil formation, nutrient cycling, and pest control. There has been a recent interest in their fate, as recent research suggested alarming rates of species extinctions and population reductions across the world. The causes for such are however less clear. Some authors suggest that pollution, including pesticides, herbicides and others, are causing most of these effects on invertebrates.
In this talk I will review what is known at a global scale, how pollutants are affecting communities in multiple settings, and how much still must be done to cover our knowledge gaps. I will finally cover the importance of dialogue between interested parties, which are often in conflict but whose cooperation is essential for averting future species extinctions and population declines, with consequences on our own well-being.

BRAZILIAN PEOPLE STILL UNDER INCREASED RISK OF CANCER DEVELOPMENT DUE TO HEXACHLOROCYCLOHEXANE INHALATION EXPOSURE

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Abstract

Organochlorine pesticides (OCPs) have been restricted in most countries worldwide for being toxic, persistent, bioaccumulative and prone to long-range transport. In Brazil, OCPs were produced and used in industrial scales for both agricultural and public health purposes for several years, but most of them were restricted in the late 1980's and 1990's. Nevertheless, their environmental occurrence due to secondary sources still plays a key role on the environmental contamination and human health in the country. Therefore, we aimed to investigate the occurrence of some OCPs in outdoor air of urban sites from two major regions of southeast Brazil known to be impacted by industrial irregular dumpings of hazardous chemicals, such as OCPs. Inhalation cancer risk (ICR) assessments were performed following measurements of OCP concentrations in ambient air during winter and summer seasons. Ambient air was mainly affected by Σ-HCH (median = 340 pg m−3) and Σ-DDT (median = 233 pg m−3), the only two OCPs registered for public health purposes (fight insect-borne diseases) in Brazil. OCP concentrations were higher in summer than in winter and were associated with known secondary sources, such as industrial dumping sites. Both deterministic and probabilistic assessments indicated an increased risk of hepatic cancer for people living in the studied regions. Infants and toddlers (0 < 2 y) were exposed to the highest ICRs compared to other age groups. More studies covering other exposure pathways, such as ingestion and dermic uptake, are needed for a more comprehensive risk assessment. Moreover, those people are exposed to several OCPs and other hazardous chemicals that may have synergistic effects on human health. Finally, we reinforce a need to review the human inhalation exposure to OCPs and their associated risk in other impacted areas worldwide, especially where high levels of OCPs are still found.

PART II.
NEW APPROACHES TO TESTING OF CHEMICALS BASED ON OMICS AND EPIDEMIOLOGY: EXAMPLE DEVELOPMENTAL NEUROTOXICITY

CONCEPT: EPIDEMIOLOGY- AND OMICS-BASED DEVELOPMENT OF A TEST BATTERY FOR DEVELOPMENTAL NEUROTOXICITY INDUCED BY ENDOCRINE DISRUPTION

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Abstract

Clear evidence supports associations between exposure to endocrine disrupting chemical (EDC) and impaired neurodevelopment. Yet, current hazard assessment of EDCs does not address developmental neurotoxicity. This is due to lack of scientific knowledge on how endocrine disruption is linked to developmental neurotoxicity (DNT). Thus, there is an urgent need for novel testing and screening tools to address endocrine disruption (ED-)induced DNT, based on new scientific knowledge.

The ENDpoiNTs project is designed to address the scientific and regulatory gaps with regards to ED-induced DNT. ENDpoiNTs is a H2020 research and innovation action involving 16 participants in Europe, USA and Australia. It integrates expertise in ED and DNT and combines state-of-the-art *in silico* and *in vitro* tools, innovative experimental designs and technologies, and advanced biostatistics on human epidemiological and biomonitoring data. This enables the ENDpoiNTs consortium to generate the necessary scientific insights on the correlative and causal links between ED and DNT, and to develop *in silico* and *in vitro* tools for chemical screening as well as novel OMICs endpoints for existing animal-based test guidelines.

In this first part, I will present the concept on which ENDpoiNTs is built on, namely the interaction between epidemiology and experimental toxicology to link changes in OMICs signatures and cellular key events to human relevant exposures and health outcomes.

EPIDEMIOLOGY IN CHILDREN AS A BASIS FOR TEST DEVELOPMENT

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Abstract

Humans are constantly exposed to complicated mixtures of chemicals with suspected or proven endocrine-disrupting properties. Prior epidemiology literature also demonstrates that prenatal exposure to numerous of such EDCs may adversely influence neurodevelopment in children such as cognition and behavioral outcomes. In order to identify EDCs to be used in the ENDpoiNTs project, we used the SELMA study, a Swedish pregnancy cohort following around 2,000 families from early pregnancy over birth and up in puberty age. A mixture of 26 EDCs was analyzed in maternal urine and serum during the first trimester, neurodevelopmental outcomes were measured in children at 2.5 and 7 years of age, and data for co-factors were collected by the use of questionnaires and national registers. To assess the association of the EDC mixture on neurodevelopmental outcomes in children and identify the chemicals of concern in that mixture, we used Weighted Quantile Sum (WQS) regression. Briefly, WQS index is regressed on the outcome in a multivariable linear model providing an overall mixture effect estimate. Weights are expressed as percentages that sum to one and indicate the relative strength of each compound within the mixture. In this part, we will present epidemiological results from the SELMA study, i.e., chemicals of concern for neurodevelopmental outcomes in children, to be used in the ENDpoiNTs project.

USE OF COMPARATIVE TRANSCRIPTOMICS FOR TEST DEVELOPMENT

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Abstract

Interactions of endocrine disrupting chemicals with brain development can impair cognitive, emotional, and social behaviors, as shown by human epidemiology and experiments in animal models. Genome-wide analysis of effects of chemicals on gene expression in developing brain of rodents (rats) allows to identify genes with particular roles in developing processes and signaling pathways that are targeted by chemicals. In animal models, the effect of chemicals on molecular processes in developing brain can further be related to behavior of adult offspring and molecular deficits in their brains, as evidence of adversity. The information can be used in the development of new in vitro models for the assessment of chemical risks for brain development, and to better link test systems with adverse effects in humans as well as wildlife.

In the context of the ENDpoiNTs project, we are investigating effects of 6 chemicals out of the chemical mixture identified in children of the SELMA study, on brain development in a rat model. Bisphenol F (plastic monomer), butylbenzylphthalate (plasticizer), 1,2-Cyclohexane dicarboxylic acid diisononyl ester (DINCH, phthalate replacement), perfluorooctanesulfonic acid (fluorosurfactant), permethrin (pesticide), and triphenylphosphate (flame retardant) have been administered to parent (F0) female rats in the feed from premating through mating and pregnancy until end of lactation. Transcriptomic, epigenomic, and metabolomic analyses are performed in developing hippocampus of their offspring (postnatal day 6). Adult offspring are studied for hippocampus-dependent (memory) and other behaviors and transcriptomics in hippocampus. Examples of chemical-specific gene expression patterns in developing hippocampus with possible links to adverse behavioral outcome will be discussed in relation to their use in test development.

CONTRIBUTION OF EPIGENETICS TO TEST DEVELOPMENT

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Abstract

Experimental studies have shown that early life (pre- and early postnatal) exposure to EDCs can induce epigenetic changes that might underlie long-lasting adverse effects of these chemicals in one or over several generations. Epigenetic marks are molecular modifications that regulate temporal and spatial patterns of gene activity and are propagated across generations of cells or organisms, independent of changes in the underlying DNA. They play a critical role in cell differentiation and tissue organisation during development, not least of the brain. Due to its heritable nature, the epigenome is less transient and less tissue specific than other OMICs layers. Thus, epigenetic changes could be highly valuable markers to predict chemical-induced disease risk. However, there is still a lack of conclusive links between exposure, epigenetic changes, and adversity in humans.

In this part, I will present first results on epigenomic patterns indicative for ED-induced DNT, and illustrate how we can link such findings back to human data in order to establish epigenomic markers for exposure-induced adverse outcomes of human relevance.

ROLE OF METABOLOMICS IN TEST DEVELOPMENT

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Abstract

Exposure to endocrine-disrupting chemicals (EDCs) in humans during pregnancy and early stages of life can impair normal brain development and reproductive function patterns, leading to severe pathologies later in life. We study the molecular mechanism of endocrine disruption linked to developmental neurotoxicity (ED-linked DNT) using a metabolomics approach. Metabolomics studies endogenous small molecules, such as steroid hormones or neurotransmitters, in tissues or cells. We study which molecular pathways are affected by EDCs in in vitro and in vivo models. This information is of great significance for deeper understanding the relationship between affected endocrine systems and developmental neurotoxicity of EDCs. We, therefore, applied targeted steroid and thyroid hormones analysis to map the hormonal endpoints mostly influenced by the exposure to six EDCs, namely bisphenol F (BPF), permethrin (PMT), butyl benzyl phthalate (BBzP), triphenyl phosphate (TPHP), perfluorooctane sulfonic acid (PFOS), and 1,2-cyclohexane dicarboxylic acid diisononyl ester (DINCH) in neonatal rats. Hormone levels measurements will be primarily useful for in vivo mechanistic evaluation of EDCs' mechanism of action and for assessing neuro-endocrine toxicity EDCs mediated at early stages of life, but also at which exposure levels effects occur.