AGENCE NATIONALE DE LA RECHERCHE

ANR

Presentation of the funded projects in 2010 for the « Contaminants - Ecosystems - Health » Programme

AFAQ ISO 9001

« Contaminants - Ecosystems - Health » programme

YEAR 2010

Project title	**AirDustMito** Effects of chronic exposure of Airways to house Dust mite on bronchial asthmatic smooth muscle Mitochondria
Abstract	This project will evaluate the effect of chronic exposure to house dust mite (HDM) on the bronchial smooth muscle (BSM) remodelling observed in asthma and particularly the number of mitochondria. Indeed, the increased number of mitochondria is a key factor of BSM remodelling. The increased mass of BSM in asthma is still insensitive to current therapeutics, and has been associated with a poor prognosis including decrease in lung function and high morbidity. In addition, chronic exposure to HDM is an important determinant of asthma control but preventing human exposure to HDM allergens is difficult to implement. Thus, a better understanding of the effect of chronic exposure to BSM remodelling and reversing BSM remodelling must be the main objectives for the future treatment of asthma. The general aim of this project is to determine the effect of HDM on BSM mitochondria. The specific aims are (i) to determine the effects of chronic exposure to HDM on BSM mitochondria in vivo, (ii) to explore the effects of chronic exposure to HDM on BSM mitochondria in an in vitro model of BE/BSM interaction, (iii) to identify the role of mitochondria in allergic asthmatic BSM cell apoptosis in vitro, and (iv) to develop pro-apoptotic strategies of allergic asthmatic BSM cells targeted on mitochondria. This is a translational project which associates in vivo approach using a murine model of asthma, and in vitro approaches using BSM cells obtained from allergic asthmatic patients. For this purpose, we will use samples from recent clinical trials such as "Remodel'Asthme" study supported by both PHRC and INSERM-DHOS grants.
Partners	Université Bordeaux 2 - Laboratoire de Physiologie Cellulaire Respiratoire
Coordinator	Patrick Berger patrick.berger@u-bordeaux2.fr
ANR funding	250 000€
Starting date	11/15/2010 - 36 mois

and duration	
Reference	ANR-10-CESA-001
Cluster label	

« Contaminants - Ecosystems - Health » programme

YEAR 2010

Project title	**READ** Effects of radiofrequency exposure in aged and Alzheimer's disease mice: a combined behavioural and neurovascular approach
Abstract	Environmental exposure to radiofrequency (RF) fields is increasing worldwide due to the development of wireless communications. First confined to mobile telephony networks (base station and mobile phones), exposure is nowadays related to the multiplicity of RF emitting sources, such as Bluetooth, Wi-Fi, UWB equipments. Questions about the sensitivity of specific populations to mobile communications RF signals focus almost exclusively on children and adolescents. However, the elderly represent a significant population, which may be more sensitive to environmental exposures than young adults. This raises the question about the possibility that such exposure to the RF environmental agent could impact the development or progression of neurodegenerative diseases, such as Alzheimer disease (AD), the most common type of dementia in the elderly. This 4-year basic-science project aims at investigating the effects of Wi-Fi radiofrequency (RF) exposures during normal and pathological ageing. By using a combined behavioural and neurovascular approach in rodents (use of transgenic mice reproducing symptoms of the AD pathology and aged mice), the current proposal seeks to explore whether deleterious effects of RF exposure on neurovascular functions can be exacerbated in aged and AD rodents as compared to normal adults. This research axis has just been selected as of "high priority" by the expert group of WHO that updated the research agenda for RF bioeffects (WHO, 2010). The three READ partners are physicists and neuroscientists. They are located in adjacent buildings at the Bordeaux University and have very complementary expertises and equipments. They have organized the work into seven tasks including task 0 for coordination and task 6 for dissemination. Task 1 deals with the preparation of the double-mutation transgenic mice, task 2 with the exposure of the animals to the RF fields (Wi-Fi) and task 3, 4, and 5 with behaviour, biomarkers, and cerebro-vascular functions, respectively. If detrimental effects are found in aged or AD mice, it will imply that the sensitivity threshold to RF fields should be reduced during normal or pathological ageing. Accordingly, such findings would question the validity of exposure limits currently

	at use and call for a re-evaluation of these limits to take into account differential thresholds among population subtypes.
Partners	CNRS DR15 Aquitaine Limousin - Centre de Neurosciences Intégratives et Cognitives CNRS DR15 Aquitaine Limousin - Centre de Neurosciences Intégratives et Cognitives Institut Polytechnique de Bordeaux - Laboratoire Intégration du Matériau au Système
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ANR funding	600 000€
Starting date and duration	11/15/2010 - 48 mois
Reference	ANR-10-CESA-002
Cluster label	

« Contaminants - Ecosystems - Health » programme

YEAR 2010

Project title	**MYCODIAG** Integration of selective tools for the determination of Ochratoxin A: diagnostic methods for the assesment of the toxicological risk
Abstract	Ochratoxin A (OTA) is the most common mycotoxin found in our temperate regions that contaminates food commodities prior to harvest or more commonly during storage. OTA inhibits protein synthesis and lipid peroxidation by oxidative processes. These mechanisms may generate nephrotoxic, neurotoxic and immunotoxic effects. After its ingestion or its inhalation, OTA reaches blood streams and is transported to kidney that ensured its biotransformation in metabolites that are responsible of its toxicity and that are present in biological fluids. Therefore, there is an important request for fast, reliable and low-cost analytical methods for the monitoring of OTA in food. Moreover, inhalation in the workplace could be considered as a route of exposure additional to the consumption. The conventional method used for the identification of OTA is based on the use of liquid chromatography and fluorescence detection (LC/Fluo), the native fluorescence of OTA favoring the development of a very sensitive method. An immunoaffinity column (IAC) for the sample treatment is currently associated to LC/Fluo to remove matrix components. The study of the impact of OTA in inhalation studies requires a very sensitive method. It also requires a method of sampling adapted to small-size samples preventing the use of IACs. Moreover, underestimation of OTA contamination in food has been already reported. At last, antibodies involved in IAC are not adapted to the selective extraction of the OTA metabolites and of OTA DNA adducts that have to be studied in biological fluids and tissue to understand the action mode of OTA and then explain its toxicity. So, the lack of powerful methods for these OTA analogues constitutes a real limitation for toxicological studies. The aim of MYCODIAG is to propose more powerful and less expensive extraction devices as an alternative to IAC by developing molecularly imprinted polymers (MIP) and aptamer based sorbents for the selective extraction of OTA and its structural analogs from complex samples. Both approaches will be developed in conventional format to be evaluated and compared with IAC and also in miniaturized formats (pipet tips, strips, microsystems) to circumvent the drawbacks of IAC for small-size samples and to

develop analytical devices that can be directly applied on field. MIPs are obtained by the polymerization of monomers in the presence of a template molecule, i.e OTA or an analogue, in the presence of cross-linking agent. The non-covalent bonds taking place between the monomers and the template allows the removal of the template after the polymerization and thus to obtain a polymer that possesses cavities complementary in term of shape and functionalities to the template. Different templates will be envisaged for obtaining a MIP with the properties to trap OTA but also its structural analogues. The aptamers are composed by a well defined nucleotides sequence that is able to bind selectively the target analyte but also structural analogues. Moreover, the highest capacity already demonstrated for MIPs (developed for other molecules and compared to IAC) and expected for oligosorbents (because of the smaller size of the oligonucleotides compared to the size of antibodies thus allowing higher binding ratio) makes them very attractive for the development of miniaturized devices. Moreover, the retention process on these chemical and biological tools should be different thus rendering them complementary for the trapping of target compounds. These tools will be evaluated for the analysis of OTA in well-defined airborne particles and be used for estimating workers exposure and in the future to inhalation studies. They will be also evaluated for toxicological studies in biological fluids (blood, urine) from animal submitted to OTA ingestion to analyze OTA and also metabolites and DNA adducts. This evaluation in real biological matrices also constitutes an important point before to start inhalation studies.

Partners	CNRS DR02 Paris B - Laboratoire Sciences Analytiques Bioanalytiques et Miniaturisation POLYINTELL SA INRS - Centre de Lorraine - Département Métologie des polluants Institut National polytechnique de Toulouse - Laboratoire de Génie Chimique
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ANR funding	375 000€
Starting date and duration	12/15/2010 - 36 mois
Reference	ANR-10-CESA-003
Cluster label	

Project title	**BISCOT** BIological, Structural and COmputational Tools to study nuclear hormone receptors and endocrine disruptors interactions
Abstract	Human nuclear hormone receptors (NHRs) are a family of 48 transcription factors, many of which have been shown to be activated by ligands. NHRs regulate cognate gene networks involved in key physiological functions such as cell growth and differentiation, development, homeostasis or metabolism. As a consequence, dysfunctions in NHR signaling (i.e. receptor mutation or inappropriate exposure to environmental pollutants) often leads to proliferative, reproductive, and metabolic diseases, including hormonal cancers, infertility, obesity, or diabetes. NHRs are modular proteins composed of several domains, most notably an N-terminal domain which harbors a ligand-independent activation function (AF-1), a central DNA-binding domain (DBD) and a C-terminal ligand-binding domain (LBD) hosting a ligand-dependent transcriptional activation function (AF-2). Ligand binding induces major structural alterations of the receptor LBDs leading to (i) destabilization of corepressor or chaperone interfaces, (ii) exposure of nuclear localization signals which allow nuclear translocation of cytoplasmic receptors (iii) DNA binding and recruitment of coactivators triggering gene transcription through chromatin remodeling and activation of the general transcription machinery. The crystal structures of many NHR LBDs have been determined, revealing a conserved core of 12 alpha-helices (H1 to H12) and a short twostranded antiparallel beta-sheet (s1 and s2), arranged into a three-layered sandwich fold. This arrangement generates a mostly hydrophobic cavity in the lower half of the domain which can accommodate the cognate ligand. In all hormonebound LBD structures, the ligand-binding pocket (LBP) is sealed by helix H12. To date, only a very few EDC-bound human NHRs have been crystallized as compared with the 140,000 synthetic chemicals used in consumer products. Furthermore, not or really very few animal NHRs structures have been described. Thus, it appears that efforts in elucidating the mechanisms of human and animal NHR/EDC interactions by crystallography and other structural methods must be pursued in order to deal with difficult cases and to increase our knowledge of the structural mechanisms and molecular

interactions used by different receptors and a wide range of structurally and chemically diverse compounds. As exemplified by organotin compounds, such studies can also reveal unforeseen binding modes and provide guidelines for the rational design of novel NHR modulators. Together with the improvement of computational methods, this mounting structural data should increase the effectiveness of in silico screening strategies. The first objective of BISCOT is to establish human, zebrafish and xenopus ERs, AR, ERRs and PPARs reporter cell lines. If many reporter cell lines expressing human receptors were established, few cell lines expressing animals receptors were described. Thus, BISCOT will increase the number of available reporter cell lines expressing zebrafish and xenopus NHRs and thus enable to better estimate wild life impact of EDCs. The second objective of BISCOT is to increase the number of NHR/ EDCs structures. This task will allow to precise, at the lolecular level, the intimate interactions of NHRs with different structurally unrelated EDCs. The third objective is to generate and evaluate a complete set of 3D models for human, mouse, zebrafish and xenopus NHRs using as templates either known human and mouse crystal structures or structures obtained through BISCOT. These tools will help the scientific community to evaluate EDC effects on human and wild life. The resulting software and model database for focused search on a given human, mouse, zebrafish, xenopus NHR (virtual screening) or on an additional EDC (reverse-docking) will be provided to the scientific community.

Partners	Inserm ADR Languedoc Rousillon - Institut de Recherche en Cancérologie CNRS DR13 Languedoc Roussillon - Centre de Biochimie Structurale
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ANR funding	350 000€
Starting date and duration	12/1/2010 - 36 mois
Reference	ANR-10-CESA-004
Cluster label	

Project title	**PerinaTox** Early life effects of Bisphenol A on the maturing gut barrier and metabolic programming in the liver and adipose tissue: long term consequences in adulthood

Abstract

In the last decade evidences have accumulated that exposure to low doses of endocrine disruptors during the foetal and neonatal periods may favour the emergence of diseases in adulthood. Regarding the striking example of diethylstilbestrol prescribed to pregnant women from the 1940s to the 80s, recent studies have reported adverse effects in adulthood of perinatal exposure to another non-steroidal xenoestrogen, namely bisphenol A (BPA). Consequently, in 2010, risk evaluation agencies such as the FDA and AFSSA reevaluated their positions concerning this compound and emphasized the need for new investigations. BPA is the monomer of polycarbonate and epoxy resins found in a wide array of plastic goods including food/drinks packaging and baby bottles. Its release from plastic goods leads to significant levels of exposure, mainly via oral route, for a large majority of the population of industrial countries, especially babies and infants. Exposure to BPA is considered as a major concern for human health, since recent animal studies demonstrate deleterious effects at environmentally relevant doses in developing organs including the gut, the liver and the white adipose tissue. However, the precise events disrupted by BPA during the foetal and early life remain unknown. Such data are critically needed to identify the molecular targets of low BPA doses, and to understand how disruption in different target organs may promote diseases in adults. The partners of the PerinaTox project propose to investigate the effects of perinatal exposure to low doses of BPA on the coordinate development of gut, liver and adipose tissue, as well as the resulting impacts in susceptibility to develop inflammatory (Inflammatory Bowel disease and Irritable Bowel Syndrome), neoplastic (colon cancer) or metabolic diseases in adulthood. Recently, we have shown that BPA exposure in adults targets the gut (Braniste et al, PNAS 2010), reducing gut permeability and inflammatory response, but increasing visceral sensitivity, thus evoking the effects of endogenous estrogens. Conversely, perinatal exposure to BPA results in an increased inflammatory response in offspring female rats and reduced expression of estrogen

receptor (ER) beta in the gut of males, demonstrating that exposure during this critical window of development is able to disrupt organ physiology for long term. Other groups have also shown that perinatal BPA exposure results in some level of metabolic disruption, especially in adipose tissue and liver, favouring overweight in adult rodents. To unravel the mechanisms underlying this range of effects, and to further characterize the perinatal BPA imprinting, we propose: 1) to investigate the coordinate chronological development/maturation of the gut, liver and adipose tissue during the perinatal period, and to evaluate the effects of BPA on this coordinate maturation process, 2) to assess whether BPA-mediated ERbeta downregulation in males results in increased susceptibility to colorectal cancer, 3) to evaluate the impacts of perinatal BPA exposure on adult liver and adipose tissue functions related to metabolic pathways and chronic low grade inflammation, both being key factors of the metabolic syndrome, 4) to evaluate the effects of BPA in specific human cell models of each organ studied, 5) to systematically evaluate in each model used the exposure levels of tissues and cells to BPA and its main metabolites. To take up these challenges, we have gathered expertises in toxicology, endocrinology, metabolism, physiology, molecular and cellular biology, biochemistry and analytical chemistry. We expect from the PerinaTox program that it unravels mechanisms that would shed a new light on both the generic and transgenerational effects of perinatal xenoestrogen exposure, and the interplay between targeted organs in the emergence of altered physiology at adulthood. These outputs should contribute to the reevaluation of BPA safety for babies, and young infants.

Partners	INRA Centre Midi Pyrénées – Toxalim Inserm ADR Toulouse - Institut de Médecine Moléculaire de Rangueil Inserm ADR Grand Ouest - Foie, Métabolismes et Cancer
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ANR funding	750 000€
Starting date and duration	11/15/2010 - 48 mois
Reference	ANR-10-CESA-005
Cluster label	

« Contaminants - Ecosystems - Health » programme

YEAR 2010

Project title	**SyMetal** Rhizostabilisation of highly heavy metal contaminated mine spoils by using METALlicolous plants associated with microbial SYMbionts
Abstract	Numerous degraded land areas resulting from industrial or mining activity are still remaining in France and in Europe. Most of those areas were not restored before being abandoned and constitute "hot spots" of metal pollution. Moreover, under the action of water and wind erosion, the metal pollution is being dispersed and contaminate in a diffuse and continuous way soils, cultures and river sediments. Restoration of such surfaces by physical or chemical methods would be very delicate and extremely expensive. Therefore treatments such as phytoremediation, a technology that uses selected tolerant plants to immobilize metals in contaminated soils, appears the most economic and effective solution for a long-lasting restoration. However, ecological engineering for phytoremediation of mining areas remains inefficient due to the very low level of fertility and the strong toxicity linked to high metal contents in those soils, limiting the development of a plant cover. The success of the phytostablisation of the mining clearings cannot be thus envisaged without the consideration of these constraints. Therefore, the study of the biological resources including native plants and bacteria of mine areas and the elaboration of a rational approach in order to improve both the development of plants and associated microorganisms to increase vegetation cover and soil rhizostabilisation, are thus indispensable to develop effective strategies of ecological engineering adapted to the management of former mining sites. The area selected for this study proposed within the framework of the project SyMetal is the old mine of Les Avinières. The site is located in the mining district of the Malines within the region of Saint-Laurent-le-Minier (Gard) which constituted the most important zone of lead and zinc exploitation in France in the XIX-XXth centuries. The contaminated area covers a surface of about fifteen ha and it is an example of strong metallic pollution in Mediterranean region. Mine soils are very unfertile with a low organic matter content and a shortage of major plant nutrients. Total metal concentrations in mine tailings located in the tailing ponds located just near the river, La Vis, are extremely high (total Zn: 161 000 mg kg-1, Pb: 92 700 mg kg-1 and Cd: 1382

mg kg-1) and is to a large extent, one of the most polluted sites in Europe. High concentrations in Zn and Pb than 1000 mg kg-1 were also observed in an area of 4,5 km downstream the mine. The aim of the SyMetal project is to utilize heavy metal tolerant plants and associated microorganisms growing in these ecosystems for the development of innovative environmental engineering with the aims to immobilize in situ soil metallic pollutants of highly polluted areas. The SyMetal Project is based on: (i) the identification and selection of symbiotic microorganisms such as mycorrhizal fungi adapted to highly metal polluted soils and increasing the diversity of available plants (ii) the selection of metal tolerant plant species, especially Fabaceae, associated with their symbiotic legume bacteria in order to improve ecosystem development by naturally increasing the nitrogen content in the soil and thus raising soil fertility (iii) a specific study of the influence of rhizostabilisation on the metal immobilisation and speciation in the soil under plant cover. In this context we propose an integrated and multidisciplinary approach to promote innovative environmental engineering with the aims to phytostabilize metal contaminated soils and minimize the dispersion of contaminants in the environment.

Partners	IRD Marseille - Laboratoire des Symbioses Tropicales et Méditerrannéennes CNRS DR13 Languedoc Roussillon - Centre d'Ecologie Fonctionnelle Evolutive Université de Pau - Laboratoire Chimie Analytique, Bio-inorganique et Environnement CNRS DR11 Alpes - Laboratoire d'étude des Transferts en Hydrologie et Environnement INRA Dijon - Plante Microbe Environnement
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ANR funding	600 000€
Starting date and duration	11/15/2010 - 48 mois
Reference	ANR-10-CESA-006
Cluster label	

« Contaminants - Ecosystems - Health » programme

YEAR 2010

Project title	**Neuropest** Xenobiotics, endocrine disruption and neurotoxicity: impact of chronic exposure to pesticides on reproduction, development and function of the central nervous system of a mammalian model.
Abstract	Pesticides are a real problem of public health not only for users who are the most exposed, but also for general population. Epidemiological studies of populations exposed to these toxics suggest an increased of cancer risk, birth defects, infertility, neurodegenerative diseases and immune deficiencies. In our days, it seems well established that the highly exposed populations have an increased risk of developing neurodegenerative diseases. Because neurons are the common target of these toxins, and because they are also involved in certain neurodevelopmental genetic disease such as autism and mental retardation, we must raise the question about the potential existence of "toxic" cases of autism or mental retardation. Furthermore, studies establish the link between pesticide exposure, infertility, increased risk of abnormal child development, abnormal neuro-developmental and reproductive. Evaluation of pesticides toxicities is complex task because many parameters should be considered. Chronic damages, in which pesticides are suspected, were denounced by many scientists. However, risks studies provided to test pesticides effect are insufficient 1/ to raise their real potential hazards, 2/ to understand the mechanisms of toxicity and, 3/ to develop policies to protect these dangers. Our project falls within the context of xenobiotics risk analysis by taking account of the vulnerability of early development and long-term implications of an altered function of the nervous system and the reproduction. It fits in the pursuit of studies already conducted by our partners in the framework of a project (ANR 2006-2009 - "herbitox") which showed that chronic treatment with glufosinate ammonium in adult mice induces behavioral changes correlated with modified brain tissue. One purpose is to extend this work by conducting a chronic administration during early development in the closest human exposure condition and, associating them with an approach on the toxicological analysis of reproductive system disturbances. We chose to study the neurotoxic effects

	of glufosinate ammonium, herbicide active compound, and cypermethrin, insecticide active compound. Both molecules have the particularity to target proteins involved in neurotransmission. The atrazine, another herbicide molecule, will also be studied because of its well known effect on the reproductive system as well as on the neurotransmitters recapture. These neurotoxic compound effects should take place in the induction of neurodevelopmental disorders such as autism and/or mental retardation. Our objective is to conduct a full neurotoxicological study taking account of anatomical, biochemical, cellular and behavioral considerations. This neurotoxicoloxic study is associated with an expertise in the reproductive system. Indeed studies have shown that exposure to certain pesticides, could not only lead to neurochemical changes associated with cognitive deficits and a general decline in memory performance, but also have deleterious effects on reproductive function. This work program should: allow the assessment of risks to strength the security of people, contribute to public debate, highlight societal choices and provide scientific support to public decision.
Partners	CNRS DR08 Poitou-Charentes - Immunologie et Embryologie Moléculaires Université d'Orléans - Laboratoire de neurobiologie Inserm DR Nantes - GERHM U625
Coordinator	Stephane Mortaud stephane.mortaud@univ-orleans.fr
ANR funding	350 000€
Starting date and duration	11/15/2010 - 36 mois
Reference	ANR-10-CESA-007
Cluster label	

« Contaminants - Ecosystems - Health » programme

YEAR 2010

Project title	**CONTREPERF** Emerging perfluorinated contaminants: contribution to the human exposure assessment, to the study of their metabolism and to the characterisation of their toxicological impact.
Abstract	Perfluorinated compounds (PFCs) are synthetic chemical substances produced and used to exploit their hydrophilic-lipophilic balance through anti-sticking material or surfactant related products. Consequently, consumers from industrialised countries are today in contact with these chemicals in their daily life, through a high number of manufactured products. In parallel, as many other chemicals of entropic origin, PFCs may be released into the environment at each step of their living cycle, and retrieved in various components of the food chain. Food exposure, especially through particular vectors of chemical exposure such as fish, represents a main route of exposure to PFCs for consumers. In parallel, PFCs have been considered as endocrine disruptor chemicals (EDCs). In this case, the problem is not related to acute or sub-acute toxicity issues, but rather to low doses and long term exposure. In this context, the question of potential transfer of PFCs from the mother to the foetus (through the cord blood) and/or newborn (through breastfeeding) is clearly posed. Contreperf is first expected contributing significantly to improve the knowledge related to the human exposure to PFCs, and answer to a clear and current need expressed at the national and international levels. Clearly not designed and positioned as an epidemiological study, the project will not be focused on the general population; otherwise the envisaged collection of a relatively limited volume of data (n=100) would not be adapted for relevant interpretation of tendencies. Conversely, our choice is to focus the study on two main different population sub-groups, one with a supposed high risk of exposure (high fish consumers), and one with a high vulnerability (foetus/newborn). Contreperf is secondly expected contributing significantly to improve the knowledge related to the possible impact of PFCs on human health using four distinct but complementary approaches focused on human liver as a central biological target. Thus, the simultaneous investigation of (1) the biotransformation products of PFOA and PFOS, (2) their

global impact in terms of metabolic disruption, (3) their genotoxicity potency, and (4) their transactivation and/or binding capabilities on nuclear receptors, clearly represents another particularly innovative and integrated proposal and positioning in terms of hazard characterisation. In the national context, a first specificity of the present project is to combine several aspects which are in direct relation with the thematic axes pointed out as a priority for the present call. This includes thematic axes 1, 2 & 3. Contreperf clearly deals with several keys words of this call, among them "toxic agents", "biomarkers", "endocrine disruptors", "persistent organic pollutants", "emerging risks", "human health", or "toxicology". Next, this project is to our knowledge the first and unique one proposing such biomonitoring research work for PFCs, mainly due to the absence of other existing analytical methodologies on the French territory. The present project is unambiguously expected to reinforce the leader position of the partners on these aspects, while the generated knowledge is promised to a significant and high impact level academic valorisation and to be of valuable usefulness for national agencies in charge of risk assessment, public authorities, and finally consumers. In the international context, one may consider this emerging problematic as a really "hot" and current issue, for which a French significant contribution would be more than beneficial to maintain its competitive position in Europe in the field of chemical food safety.

Partners	Ecole nationale vétérinaire - Agroalimentaire et de l'alimentation Nantes Atlantique (ONIRIS) INRA Toulouse - UMR Xenobiotiques Inserm ADR Languedoc Roussillon - Institut de recherche en cancérologie de Montpellier CHU Toulouse - Hôpital Paule de Viguier ANSES - Direction Santé Alimentation, Maisons Alfort
Coordinator	Jean-Philippe Antignac jean-philippe.antignac@oniris-nantes.fr
ANR funding	400 000€
Starting date and duration	11/15/2010 - 36 mois
Reference	ANR-10-CESA-008
Cluster label	

Project title	**TITANIUMS** Toxicity and Internalisation mechanisms of titanium oxide Nanoparticles In eukaryotic and Multicellular Specimens
Abstract	The explosive growth in nanotechnology, which refers to the study and design of systems at the atomic or nano- scale, and in bioengineering fields has led to a large number of new nanomaterials in order to create unique devices with novel targeted physical and chemical functional properties. Most of theses manufactured nanoparticles have been produced for several decades on an industrial scale. Certain metal oxide nanoparticles possess photo-catalytic ability, electrical conductivity, ultraviolet absorption, and photooxidizing capacity against chemical and biological species. As nanotechnologies move into large-scale production in many industries, it is just a matter of time before gradual as well as accidental releases of manufactured nanoparticles into the environment occur. Some applications like cosmetic products ingredients will be diffused source of nanoparticles. In addition, some applications such as environmental remediation with the help of nanoparticles could lead to the deliberate introduction of nanoparticles into the environment. This is an area, which will probably lead to the most significant release in terms of quantity of nanoparticles in the coming years. Deciphering the molecular and cellular basis of nanotoxicology mechanism remains an essential challenge. In particular, the behavior of nanoparticles inside the cells is still an enigma, and no metabolic responses induced by these particles are understood so far. Titanium dioxide (TiO2) is widely used in cosmetics, water treatment, and pigment industries. TiO2 nanoparticles were previously classified as biologically inert, but after such widespread use, their potential to penetrate human body suggests that TiO2 nanoparticles could induce an exposure risk to humans. Up to now, it has been very difficult to detect, track, and precisely quantify TiO2 nanoparticles (with high resolution microscopy), in cell cultures, in a concomitant way with proteins localization, specific sub-cellular compartments as well as metabolic pathways. The goal of the interdisciplinary project, involving 3 teams CENBG/ICMCB/IECB (from physics, chemistry to biology-) is to define precisely the molecular and cellular mechanisms involved in the nanotoxicity of TiO2 nanoparticles in eukaryotic cells and in multi-cellular organisms

such as C. elegans. In the present research program, we propose to apply an original imaging methodology (Ion nanobeam Analysis, Transmission Electron and Confocal microscopies) that allows in vitro studies and combining technologies for on the one hand, the detection, tracking, and quantification of TiO2 nanoparticles and on the other hand, the use of indicators for ion homeostasis, cell metabolism, or cell fate. The research program will try to answer the following questions: (i) What are the parameters influencing the TiO2 nanoparticles bio-availiability and interaction? (ii) How do TiO2 nanoparticles enter the cells ? and what are the molecular and cellular mechanisms involved? (iii) What are the TiO2 nanoparticles physicochemichal properties that determine their bio-distribution, bio-accumulation and bio-persistence? What are the relations between bio-distribution and nanotoxicity? (iv) What is the fate of non-biodegradable TiO2 nanoparticles in cells? How do cells eliminate internalized TiO2 nanoparticles? This project is devoted to a better understanding of the interaction between naonparticles, human cells and C. elegans, as a test organism in nanoecotoxicology research. It will reinforce a teamwork already on course and structure a fruitful interaction already engaged between chemistry, biology, and physics (ICMCB, IECB, CENBG).The different partners of the project are involved in all the concern fields of research and expertise: (i) nanoparticles synthesis and characterisation, (ii) high resolution imaging analysis and methods, (iii) biological models developement and characterization, (iv) toxicological studies.

Partners	CNRS DR15 Aquitaine Limousin - Centre Etudes Nucléaires Bordeaux Gradignan CNRS DR15 Aquitaine Limousin - Institut de Chimie de la Matiere Condensée Inserm ADR Bordeaux - Institut Européen de Chimie et Biologie
Coordinator	Hervé Seznec seznech@cenbg.in2p3.fr
ANR funding	500 000€
Starting date and duration	11/15/2010 - 48 mois
Reference	ANR-10-CESA-009
Cluster label	

Project title	**HEVECODYN** Hepatitis E dynamics in related ecosystems: from pig farms and wastewaters to shellfish
Abstract	Hepatitis E virus is responsible for an acute Hepatitis similar to Hepatitis A but usually more severe with anorexia, jaundice and liver enlargement. Although HEV infection is associated with a low mortality rate, fulminate hepatitis requires liver transplantation which is a very demanding and expensive procedure. In France, hepatitis E is a disease for which declaration is not compulsory. Surveillance of Hepatitis E in humans is carried out by the National Reference Centre for enteric Hepatitis (A and E) set up in 2002 and located in Paris (Hôpital du Val de Grace). Hepatitis E infection was responsible for almost 150 locally-acquired cases in France in 2008 and has significantly increased since 2002. The perception of Hepatitis E epidemiology has clearly changed over the years. From an initial view of a disease contracted after travelling in hyperendemic regions, there has been accumulating evidence of zoonotic transmission from various animal reservoirs (pigs, wild boar, deer) through consumption of contaminated products (meat, offal). These potential sources are not enough to explain all the locally acquired cases and several outbreaks suggest that the shellfish with their particularity of filtrating and concentrating HEV particles originating from human and animal sewage pollution, are potential additional sources. A major goal of this project is to propose a transversal view of HEV epidemiology from pigs farms, wild animals and environmental waters from various sources to contamination of shellfish. The first aim of the proposed project will be to investigate the relationships between the different ecosystems shared by the Hepatitis E virus by assessing the presence of HEV in the various ecosystems: (i) pig farm and exports from this ecosystem (manure sewage, pig products, immediate environment of the farm), (ii) wild boar, (iii) waste waters, (iv) coastal waters and shellfish. HEV strains isolated from the different ecosystems will be compared by phylogenetic analysis. The second aim will be to examine the dynamics of the pig farm system and its consequences on HEV export from the different sources.The third aim will be to assess HEV adaptation to different hosts in the various ecosystems (swine, wild boar, rodents, humans and shellfish tissues) and

relate this adaptation to the observed dynamics in the corresponding ecosystems. Different complementary approaches will be associated to attain each objective. Observational studies will be carried out in the different ecosystems to investigate the presence of HEV. These studies will be carried out in real conditions and supplemented by rather experimental approaches to investigate the survival of HEV in the different matrices (pig manure, waste waters, saline waters) and the effect of different slurry treatments on virus survival. Experimental studies under controlled conditions will also be carried out in pigs to quantitatively estimate key parameters for the epidemiological model of within-farm HEV dynamics. More fundamental knowledge will also be produced regarding the ability of shellfish to selectively concentrate HEV through cross-recognition of glycans. The project will therefore bring together the efforts of different specialists in epidemiology, ecology, virology, biochemistry and mathematical modelling to produce the complementary information required to determine the relationships between the different ecosystems and the impact of their respective dynamics on HEV spread in various environments. Hence, an assessment of the probability and level of HEV contamination in shellfish should provide reliable data and a basis for prevention and recommendations regarding the level of risk associated with different species of molluscs, season, and geographical location in relation to the exposure to waste water and manure sewage pollution.

Partners	ANSES Maisons Alfort - ANSES site de Ploufragan/Plouzané ANSES Maisons Alfort - Laboratoire Santé Animale UMR 1161 Ifremer - Unité de Virologie Centre Européen d'expertise et de recherche sur les agents microbiens SAS Inserm ADR Nantes - Centre de recherche sur le cancer Centre National de Référence des hépatites entérotransmissibles
Coordinator	Nicolas Rose nicolas.rose@anses.fr
ANR funding	600 000€
Starting date and duration	11/15/2010 - 36 mois
Reference	ANR-10-CESA-010
Cluster label	

Project title	**GENOTOXTRACK** Genotoxicity biomarkers ex vivo et in vivo.

Abstract

Genotoxic substances induce DNA damage. DNA double-dtrand breaks (DSBs) are considered the most lethal form of DNA damage as they can result in cell death and, if misrepaired, they have the potential to result in chromosomal translocations and genomic instability. The H2AX protein phosphorylation at its C-terminal part, gH2AX, is a sensitive and a quantitative way to study DSB and to measure the DNA repair. However, the detection of gH2AX depends on antibodies used on fixed cells. Here, we propose to develop biomarkers to detect and follow DNA damage and their repair mechanisms ex vivo, within living cells, and in alternative animal models. As a proof-of concept, nanobodies directed against gH2AX will be developed but we will also develop other DSBs and/or repair biomarkers. In addition to the conventional antibodies, llamas produce antibodies only composed of heavy chains and their antigen-binding site is formed by a single domain (VHH or nanobody). After immunization, a llama VHH library will be made and screened by phage display. Nanobodies binding to the gH2AX target will be isolated and their sequence subcloned in fusion with a fluorescent tag in a mammalian vector. Each fluobody will be tested in human cells and different parameters will be assayed (foci formation, signal amplification/disappearance, fluorescent background) to validate the biomarkers. At this step of the program, we will develop the FRET technology to enhance the signal and follow, at the same time, two markers. Particularly, new markers of repair or apoptosis, on H2AX histone, have been recently described in human cells. We will test different markers association to differenciate specifically among these processes and to follow the cell output of a genotoxic exposure. Biomarkers allowing to follow, real-time, the occurrence of DSB and to determine genotoxicity in vivo, will be patented. A direct application of our tools will be to study genotoxins, produced by E. coli bacteria -pathogenic or not. Genotoxins induce cell cycle defect and DSBs in host cells. We will study the mechanisms leading to DSBs in order to define new targets for biomarkers and we will use our tools to screen bacteria strains and assay their potential genotoxicity. We will particularly focus on intra-S checkpoint as it bridges together replication, repair and cell

	cycle in a coordinated network. We will also particularly study which repair mechanism is set up in different context (toxic dose, time exposure, mutations/knocked-down) as a deregulation of these processes may lead to genomic instability. Finally, we plan to transfert our tools in alternative animal models -zebrafish or nematod- to track genotoxic pollutants in rivers and/or soils. Overall, this project will help to develop exclusive tools to determine the toxicity of known or new substances, and to follow genotoxic stress ex vivo or in vivo. It will help to analyse the cell output after a genotoxic exposure and o predict processes leading to genetic instability. In conclusion, our tools will help to gain insights on these mechanisms and be used in the prevention and/or diagnosis of exposure to genotoxic, improving environmental protection and human health.
Partners	INRA Centre Toulouse - Phamacologie/Toxicologie Toxalim CNRS DR14 Midi-Pyrénées - CRT-RIV-ITAV Recherche INRA Centre Toulouse - Interaction hôte - agents pathogènes
Coordinator	Gladys Mirey gladys.mirey@ipbs.fr
ANR funding	400 000€
Starting date and duration	11/15/2010 - 48 mois
Reference	ANR-10-CESA-011
Cluster label	

Project title	**DON&Co** Production of mycotoxins in wheat: from the diversity of the Fusarium community to the toxicological impact of mycotoxins.
Abstract	Food safety is a major issue in France and in the world. In this respect, much attention requires to be paid to the possible contamination of food and feed by fungi and the risk of mycotoxin production. Mycotoxins are frequent contaminants of cereal. According to survey data published by ONU, 25 % of the world crops are contaminated. Most mycotoxins are not degraded by the common technological treatments and thus remain present in finished products. Thus, mycotoxins contamination is a significant problem of food safety throughout the food chain. The control of the mycotoxins contamination represents a major challenge for the wheat sector (soft wheat and hard wheat). These are the fungi of the Fusarium genus and the associated production of trichothecenes (with deoxynivalenol or DON as the main contaminant) that are, due to their potential toxicity and their occurrence, the most worrying contaminants. The wheat contamination by mycotoxins is particular complex for at least two reasons i) different fungal species contaminate simultaneously wheat grains and ii) these fungi produce concurrently several trichothecenes. The aim of the DON&Co project is to answer the question "how the composition of the Fusarium community influences the concentration and the type of trichothecenes accumulated in the grain and, as a consequence, its toxicity?" The DON & Co project will lead to the definition of agronomic tools allowing the respect of current European regulations/recommendation (EC N 1881/2006 and 2006/L229) but also to the acquisition of reference data concerning the toxicity of DON and its acetylated derivates. These references will lead to a better appreciation of the "mycotoxin risk" in wheat and could contribute to the evolution of regulations. Only an integrated approach, such as the one proposed in the project DON & Co, combining descriptive studies, epidemiological analysis (from the flora to the toxins) with mechanistic approaches, will allow answering the proposed question.
Partners	INRA Centre de Bordeaux - Mycologie et Sécurité des Aliments ARVALIS - Institut du végétal

	INRA Centre de Versailles - UMR 1290 BIOGER INRA Centre de Dijon - UMR 1229 Microbiologie du Sol et de l'Environnement INRA Centre de Toulouse - UR66 Pharmacologie-Toxicologie Ecole Nationale Vétérinaire de Toulouse INRA Centre de Bordeaux - UMR1202 Biodiversité, gène et communauté
Coordinator	Florence Forget-Richard fforget@bordeaux.inra.fr
ANR funding	560 000€
Starting date and duration	3/1/2011 - 36 mois
Reference	ANR-10-CESA-012
Cluster label	12:00:00 AM

Project title	**Pharm@ecotox** Pharmaceutical residues and ecotoxicology in seawater

Abstract

The pharmaceutical substances represent a diverse collection of over 1000 biologically active molecules used in human and veterinary medicine. Increased consumption of drugs and the development of more powerful analytical techniques in environmental resulted in the identification of these emerging contaminants in all aquatic compartments, ranging from the effluent of wastewater treatment plants, surface water, groundwater in the marine environment . Unlike conventional pollutants (pesticides, detergents, hydrocarbons ....), pharmaceutical residues are released continuously and at low doses in the environment, leading to potential chronic poisoning. From a regulatory standpoint, the dangers posed by the release of pharmaceutical substances towards aquatic organisms are taken into account in recent years and only when the predicted concentrations in the environment exceed a threshold value of 0.01 ?g/l. Thus the data on the ecotoxicity of these substances are relatively sparse. The studies conducted so far on the topic mainly concern the identification and determination of residues in surface waters with a strong interest in terms of human health towards the consumption of drinking water. The available ecotoxicological data mainly concern hazard assessment related to acute toxicity. They focused on fifteen of molecules while their metabolites and certain drug classes such as anti-cancer agents and neuroleptics are poorly informed. Finally, data on the impact of these residues in sea level and especially on invertebrates is extremely low. Our project aims to assess the impact of these substances from a global ecotoxicology point of view towards the aquatic organisms but also in marine organisms and especially in those with a significant economic impact for Normandy: abalone, oysters, cuttlefish. An integrated approach will link the observed effects on marine organisms to measure environmental contamination carried out into 3 separate zones: a densely anthropized area, a moderately anthropized area and a breeding area. Beside theses measures, the level of contamination for individuals will be done. To determine the potentially toxic residues in silico, in vitro and in vivo methods will be used. The use of in silico approaches coupled with experimental validation will predict the toxicity of

	many residues and their metabolites belonging to different drug classes. This approach can be used within a regulatory framework. It will also highlight some particular modes of action contributing to a better understanding of mechanisms in relation to toxic action in invertebrates. Pharmaceutical substances are inherently biologically active substances. In silico approach will be combined with an in vitro approach to highlight potential effects on specific physiological functions of invertebrates: immune system, digestive system, nervous system, endocrine system and DNA. However, if in vitro assays allow sensitive detection and early effects of exposure to a contaminant, in vivo assays are essential for the study of long-term effects. Therefore, according to the analytical results, impacts on the same physiological functions with environmental concentrations will be assessed.
Partners	Université de Caen - EA4258 Centre d'Etudes et de Recherche sur le Médicament Université de Bordeaux 1 - UMR5255 Institut des Sciences Moléculaires - UMR5255 Laboratoire de Physico- et Toxico-Chimie de l'environnement Université de Caen - EA4259 Groupe Mémoire et Plasticité comportementale Université de Caen - UMR_M 100 Laboratoire de Physiologie et Ecophysiologie des Mollusques Marins CNRS DR Centre Est - UMR7146 Laboratoire des interactions écotoxicologie, biodiversité, écosystèmes
Coordinator	Marie-Pierre Halm marie-pierre.halm@unicaen.fr
ANR funding	550 000€
Starting date and duration	1/3/2011 - 48 mois
Reference	ANR-10-CESA-013
Cluster label	

Project title	**MACHLOMA** Mechanisms of accumulation, elimination and disturbances of the nervous and endocrine systems induced by chlordecone in Macrobrachium rosenbergii in the French West Indies.
Abstract	In the French West Indies, chlordecone was used on bananas till the beginning of the '90s. This resulted in a highly persistent contamination of soils, water and living organisms. In freshwater environments, crustaceans present high concentrations of chlordecone in their organs. Therefore, more severe controls have been made on farms that produce the giant river prawn (Macrobrachium rosenbergii). As the result, the analysis showed that, in several aquaculture farms of Guadeloupe and Martinique, chlordecone levels in the shrimps was over the maximal limit of residues established at 20 µg/kg. Up to now, the studies designed to tackle this problem only addressed the level of contamination of freshwaters and crustaceans, and empirically observed changes in populations of aquatic animals (crustaceans and fish) in contaminated rivers. Many questions remained unsolved regarding the route of entry of chlordecone in the shrimps, on the bioavailability of the compound in freshwater ecosystems, and the capabilities of the shrimps to biotransform and eliminate residues. In addition, intoxication mechanisms which could results in chlordecone-induced alterations of the nervous and endocrine systems remain poorly understood in these invertebrates, so that specific biomarkers of exposure and toxic effects are not available yet. In the MACHLOMA project, which will benefit of interactions with aquaculture farms in Guadeloupe, we propose to use Macrobrachium rosenbergii as a model species to increase the knowledge on (i) the mechanisms of bioconcentration/bioaccumulation of chlordecone, by comparison with the concentrations measured in environmental matrices (water, sediments, particulate materials), (ii) the enzymatic mechanisms of detoxication and depuration of chlordecone, and (iii) the mechanisms of neurotoxicity and endocrine disruption, which are known to occur in mammals. Experiments will be performed (i) in control and contaminated ponds used for shrimp production in local aquaculture farms and (ii) in the

	laboratory, in order to build concentration-response relations based on environmental realistic exposure concentrations (which can reach 0.5 to 10 µg/L in some locations). Integration of the information acquired on these mechanisms will be facilitate by the use of the same individuals for both residue measurements, detoxication/depuration studies, and effects analysis. Acquisition of a sound knowledge on the fate and effects of chlordecone in M. rosenbergii will be of primary importance (i) to contribute to solve the problem the aquaculture is currently facing in the French West Indies and to propose solutions to maintain this activity which is important in the local economy, and (ii) to identify relevant biomarkers that could be transferred to species naturally present in rivers (e.g., Macrobrachium faustinum) and used for risk assessment and remediation in natural freshwater ecosystems.
Partners	Université des Antilles et de la Guyane - EA926 DYNECAR INRA Centre de Rennes - UMR985 Equipe Ecotoxicologie et qualité des milieux aquatique Université du Havre - EA3222 Laboratoire d'Ecotoxicologie - Milieux aquatiques
Coordinator	Soazig Lemoine slemoine@univ-ag.fr
ANR funding	290 000€
Starting date and duration	12/15/2010 - 36 mois
Reference	ANR-10-CESA-014
Cluster label	

Project title	**PlasticAhR** Structural Adaptive Response of the Aryl hydrocarbon Receptor (AhR) to Xenobiotics: Implication in predicting the toxicity of pollutants in both humans and ecosystems

Abstract

Contamination of ecosystems and organisms by environmental pollutants are among the major health concerns of the twenty first century. Over the last decades, toxicities of some xenobiotics have been characterized. However, despite intensive research, our ability to predict the toxicity of persistent organic pollutants (POP) or of other toxic compounds (coming from food derivatives, other combustion products, etc…) is still limited. Cellular receptors for xenobiotics are critical components of the cellular adaptative pathway as well as being intimately related to the toxicity of these compounds. The AhR (Aryl hydrocarbon Receptor) which is the focus of this application is one of the three major xenobiotic receptors. It is unique in that it is a member of the bHLH-PAS (basic Helix Loop Helix – Per Arnt Sim) protein family. Following ligand binding, the cytoplasmic Ah receptor translocates into the nucleus and associates with the ARNT protein (AhR Nuclear Translocator), another bHLH-PAS family member. The N-terminal halves of the AhR/ARNT complex are essential and sufficient for xenobiotic and DNA binding. They contain a PAS-A domain sandwiched by a DNA binding domain (DBD, bHLH) and a ligand binding domain (LBD, PAS-B). The PAS-B domain of the AhR can bind a wide spectrum of xenobiotics including a variety of pollutants (like dioxins, cigarette smoke compounds, etc…) as well as food components such as polyphenols. Remarkably, depending upon the type of ligand, AhR activation triggers adaptive, detrimental or protective transcription responses (cytotoxicity, apoptosis or cardio protecting effects). We hypothesize that different ligands elicit different structural conformations of the receptor thus leading to selective binding to one of the three xenobiotic responsive elements families, called XRE (initially identified in the CYP1A1, PON1 and BAX promoters). However, despite years of study, the molecular mechanisms leading to the triggering of a particular transcriptional pathway by a ligand remain elusive. To date, there is no structural information available on the AhR and many issues remain to be addressed: for example, what are the xenobiotic chemical determinants that lead to a specific

AhR-bound conformation? What are the amino acids responsible for species-dependent AhR responses? How is the signal transmitted towards the bHLH domain upon ligand binding to the AhR PAS-B domain? How can AhR and cytochrome P450s share the same wide ligand binding spectrum without any sequence similarities? Can we anticipate the effects of xenobiotics on a whole organism from the unique knowledge of their chemical structures? We present here an ambitious but realistic project in which we will address all of these questions in three specific tasks. Several ligand or DNA-bound structures will be determined by X-ray crystallography, namely cytochrome P450s and LBD, DBD, LBD-DBD domains from the Ah Receptor and ARNT. We will attempt to solve those complex structures using proteins from different organisms. We will then use molecular modeling and a cellular assay to identify differences between species. By combining these data, we will define precise species-dependent AhR xenobiotic binding determinants in order to predict in silico, which chemicals will bind to the AhR and activate one or several characteristic AhR XRE. This information will be essential for industrial and/or governmental organizations to estimate the toxicity of new developing or existing compounds (REACH regulation). Patenting this in silico model will be the end product of this project.

Partners	Université Paris Descartes - UMR_S 747 Equipe de Pharmacotoxicologie et Biologie Structurale Inserm DR Paris 12 - U829 Structure Activité des Biomolécules Normales et Pathologiques Université Paris Descartes - UMR_S 747 Equipe de Signalisation en Toxicologie de l'Environnement et du Médicament
Coordinator	Pierre Nioche pierre.nioche@gmail.com
ANR funding	450 000€
Starting date and duration	3/1/2011 - 48 mois
Reference	ANR-10-CESA-015
Cluster label	

Project title	**POLARTOP** Contaminants in POLAR TOP Predators : Levels and effects of persistent organic pollutants and Heavy metals on stress physiology and fitness in Antarctic seabirds
Abstract	Biodiversity in Antarctica is characterized by spectacular colonies of seabirds and sea mammals. Despite their remote location, Polar Regions are subject to anthropogenic (metals and organic pollutants) inputs due to global transport of elements in the atmosphere and through oceanic circulation. Antarctica has been considered being pristine until the contamination by anthropogenic compounds, such as Persistent Organic Pollutants (POPs), was documented in the 1960s. In Antarctica, the presence of contaminants may threaten wildlife since several POPs accumulate in the tissues of top predators. In the Arctic, very high contaminant levels and serious physiological, behavioural and fitness effects have been well documented in several top predators. On the other hand, little information is available about contaminants and their effects in Antarctica: Levels of some semi-volatile compounds, such as HCBs and some PCBs congeners, appear to be relatively high and environmental concern has also arisen as previously undetected brominated and fluorinated chemicals have been recently identified in tissues of Antarctic wildlife. However, most research on POPs and heavy metals levels has focused on a limited number of species and in high-Antarctica. On the other hand, data on contaminant levels are critically lacking further north, in the subantarctic area (and adjacent subtropical zone), where huge populations of seabird (penguins, albatrosses, petrels) are major consumers of the Austral Ocean. This is especially true for the Indian Ocean subantarctic and subtropical areas of the French Southern Territories, which holds large seabird populations including endemic and endangered species. France is therefore responsible for a significant part of the biodiversity in the Southern Ocean and there is an urgent need to increase our knowledge of contaminants levels in top predators from this area. The Centre d'Etudes Biologiques de Chizé is running a long-term capture-mark-recapture program of several seabird species in the French Southern Territories, which allows precise recording of the age and reproductive success of several hundred individuals. We want to take advantage of this unique situation to bring together ecologists, physiologist and eco-

toxicologists for a multi-disciplinary project (POLARTOP) to: 1) Establish baseline levels of persistent organic pollutants (POPs) and heavy metals in the main species of seabirds breeding along a sub-tropical, subantarctic and Antarctic gradient in the French Southern Territories. We will use non destructive sampling (blood and feathers) and search for organo-chlorine compounds (DDT, DDD, DDE, HCB, PCBs, and (PBDEs), which are known to be highly toxic and to accumulate in tissues; and for heavy metals which are known to be highly toxic for Vertebrates (As, Cd, Hg, Pb) and essential ones (Cu, Se and Zn) which may interact with the previous ones in their detoxification; 2) Compare and discuss differences in contaminant burdens between species and between individuals in the context of trophic ecology and individual features. One of the main goals of this program is to use seabirds as sentinels of exposure to contaminants in the Southern Ocean. To do so, we will analyse stable isotopes (?15N & ?13C) in seabird tissues to elucidate broad-scale, inter-and intra-specific dietary patterns, and so determine whether differences in foraging strategy explained variation in contaminant uptake; 3) Assess the effects of POPs and heavy metals on the stress axis and fitness. To do so, we will measure baseline levels of stress hormones and test the stress susceptibility by way of temporary capture/restraint acute stress protocols. To investigate the impact of contaminant burdens on the fitness of seabirds, we will use the capture-mark-recapture approach which explicitly allows taking into account capture probability and temporary absence from the study area, and thus provides unbiased estimators of adult survival.

Partners	CNRS DR Centre Poitou-Charentes - UPR1934 Centre d'Etudes Biologiques de Chizé Université de Bordeaux 1 - Institut des Sciences Moléculaires - UMR5255 Laboratoire de Physico- et Toxico-Chimie de l'environnement CNRS DR Centre Poitou-Charentes - UMR6250 Littoral Environnement et Sociétés
Coordinator	Olivier Chastel chastel@cebc.cnrs.fr
ANR funding	500 000€
Starting date and duration	12/15/2010 - 48 mois
Reference	ANR-10-CESA-016
Cluster label	

Project title	**BioREF** Biomarkers for electromagnetic exposures to future wireless systems

Abstract

Possible health hazards due to utilization of electromagnetic field in telecommunication technologies represent nowadays a major public worry. Due to the saturation of the lower part of the electromagnetic spectrum and the need of very high data rate transmissions, the operating frequencies of emerging civil and professional wireless communication systems have recently shifted towards new frequencies such as millimeter waves (MMW). Following significant research efforts undertaken in the field of MMW technologies, some general public applications have already been introduced on the market. These near-future wireless technologies increase the number of electromagnetic sources and will modify the characteristic of exposure. Some of them will be directly on contact with human being (body area networks and on-body communications), and/or increase the chronic long-term exposures of workers. All this raised the question about potential health risks related to their utilization. As some of these artificially induced radiations are absent in our natural environment and might interfere with biological systems, the possible relationship between the exposure and diseases has been amplified by mass media. In this framework, the knowledge of the influence of electromagnetic waves on the biological systems and particularly on the human body is of uppermost importance and necessitates preventive rather than reactive research. French authorities including AFSSET are currently investigating this question; however relevant scientific data at these frequencies are extremely poor. The present project is proposed by two collaborating teams which have strong experiences in the fields of i) transcriptional regulation and biological response to cellular stresses ; ii) telecommunication and electromagnetic field, respectively. The major objective of this interdisciplinary project is to investigate in depth the potential direct and/or synergistic biologic effects of various low-power MMW radiations, and to assess the risks related to the exposures of emerging wireless MMW applications using human cell models. This project perfectly fits to the first research axes of the "Contaminants, Ecosystèmes, Santé (CES, 2010)" topic of the call for proposals. Moreover, this project extends our previous research activities in the framework of the

	ANR project entitled « Health impacts of millimeter wave radiations (Himwr) - Programme Santé-environnement et Santé-travail -SEST 2006 ». In the first part, we will continue further explore the most promising results of our previous ANR project. Few genes involved in immunity and inflammation were found to be down-regulated at 60.4 GHz in a power-density dose manner. Secondly, we will perform DNA microarray screening, to identify new potential MMW-exposure impacts upon cellular processes. These genes will serve as biomarkers to asses the impact of physical parameters of MMW (power, frequency, exposure duration and modulation) at cellular levels. This study will be completed by an original approach based on the study of individual cells. Using the Cellomics technology, we will analyse the heterogeneity degree of the sensitivity to MMW in cellular population. All together, this work will contribute to the knowledge of mechanisms involved in bioelectromagnetic interactions. It responds to a strong public concern because there is a scientific gap and high social need in the understanding of potential biological and health impacts. Moreover, this work will provide relevant and extensive scientific data for future definition of international safety standards and recommendations regarding to the near-future wide deployment of new wireless MMW communication system for domestic, office, and professional uses.
Partners	Université de Rennes 1 - UMR 6026 - Interactions Cellulaires & Moléculaires Université de Rennes 1 - UMR 6164 Institut d'Électronique et de Télécommunications de Rennes
Coordinator	Yves Le Drean yves.le-drean@univ-rennes1.fr
ANR funding	350 000€
Starting date and duration	1/1/2011 - 36 mois
Reference	ANR-10-CESA-017
Cluster label	

Project title	**ALTERNATIVES** What alternatives to the chemical control of Chagas disease vectors?

Abstract

Chagas disease or American Trypanosomiasis is an essentially rural disease which affects 20 million people in South America. Transmission to man is mainly the fact of hematophagous bugs of the Reduvidae family of which Triatoma, infestans, a main vector in the Southern Cone countries (Argentina, Bolivia, Paraguay, Peru…). The life cycle of this insect, takes place in human habitations, and because there is no mass prophylactic treatment (vaccine, drugs…) the efforts to control transmission are based on vector control. It consists of peri- and intra-domicile chemical treatments carried out by the services of the health ministries of the countries concerned. After several decades of chemical fight, Chagas disease remains poorly controlled and even seems to spread into new territories so far preserved such as big cities. Recently, high insecticide resistances have appeared jeopardizing the chemical control of these insects. Unfortunately, because of the early success of chemical control, alternative strategies have been neglected and never been developed. To face the recrudescence of Chagas disease and the operational failures of the chemical treatments, new control strategies are urgently needed. They might be developed if the dynamics of the vector population would be fully understood, which is not yet the case. It is thus the main objective of the ALTERNATIVES project which proposes an in-depth analysis of the significant population parameters in the framework of an operational control of such a vectored disease. These are in particular (1) the spatial structures and (2) the analysis of the vectorial capacity of the insect. Then these data will be integrated in a relevant and biologically interpretable mathematical model aimed at simulating various control strategies. The project will take place in Bolivia where field population data will be collected. Spatial structures will be analyzed at various scales: human dwelling, village, amongst villages. They will enable to plan further operational control actions at large scale and identify the control units to treat. Population dynamics, through the analysis of the parameters of the vectorial capacity, will enable to identify the most relevant eco-bio phases to control, and will enable the simulation of control action and their impact on the development of the vector

	population. It will be carried out by the follow-up of a vector population in a village and completed by vector life traits studies in controlled climatic chambers in the laboratory. A mathematical model will be built and calibrated with these field and laboratory data. This model will enable the optimization of the present control strategy and better, will enable to propose new control strategies in which the role pesticides is minimum. The framework of the ALTERNATIVES project may serve as a baseline for the study of other transmitted diseases which vectors are described as "anthropic" such as dengue or chikungunya. Indeed they share numerous concepts and Chagas disease even appears as a sort of model of this type of "anthropic"endemic disease.
Partners	IRD - UMR 224 Unité Stratégies de lutte et prévention du contact homme-vecteurs IRD - UMR 224 Dynamique des Systèmes - Maladies Infectieuses
Coordinator	Frédéric Lardeux frederic.lardeux@ird.fr
ANR funding	260 000€
Starting date and duration	2/1/2011 - 36 mois
Reference	ANR-10-CESA-018
Cluster label	

Project title	**AquaPOL** Degradation and transfer of polyacrylamide based floculents in sludges and industrial and natural waters - Potential impact on aquatic ecosystem
Abstract	Flocculants are widely used in several industrial fields (mineral extracting, chemical industry, food processing industry, treatment of drinking water) to enhance solid/liquid separation in water containing suspended matter. In France, mineral extracting industry is one of the major users of flocculants. The use of flocculants enables to increase the recycling rate of process water and to decrease sludge volumes, and thus the surface of settling impoundments. Those impoundments are open systems with possible exchanges into the near environment (water percolation towards the aquifers, water seepages in natural stream or rivers…), which can lead to the dissemination of flocculants into surface water and groundwater. The question of flocculants innocuousness is now arising as a new environmental issue. The flocculants which are calling into question are composed of polyacrylamide, a polymer synthetised from acrylamide and acrylic acid. The final product contains residual amount of acrylamide which is classified as a carcinogenic (level 2), mutagenic (level 2) and reprotoxic (level 3) compound. The environmental issue does not concern the polyacrylamide, which is not known as a toxic compound, but the acrylamide and the products of polyacrylamide degradation. Although industrialists and administrative authorities in charge of environment protection regard the use of flocculants as an important environmental matter, there is no scientific and multidisciplinary study which can help them to take appropriate measures to prevent potential impact on the ecosystems. In this context, the global objective of "AquaPol" project is to study the behaviour of acrylamide, polyacrylamide and products of polyacrylamide degradation in process and natural waters and their impacts on the balance of aquatic ecosystems. The effort will be put on the particular case study of the mineral extracting industry. It is an applied research project which associates various scientific fields: metrology, process engineering, geochemistry, microbiology, eco-toxicology, and hydrogeology. The heart of this project will be based upon in situ characterisation of the dissemination of polyacrylamide,

	acrylamide and products of polyacrylamide degradation in connexion with the physical, chemical, microbiological and hydrogeological properties of the studied environments. This study will be surrounded by a global environmental evaluation of flocculants use in the mineral extracting industry, analytical developments, an eco-toxicological study, a laboratory characterisation of transfer and degradation mechanisms and the development of bio-hydrogeochemical model. One of the main purposes is to bring to flocculants users and administrative authorities the scientific basis which can enable them to implement the appropriate measures to prevent potential environmental damages linked to the use of flocculants.
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