

The K-Env Programme

*Research Projects in the Field of the Effects of the Exposure to
Environmental Risk Factors on Cancer*

Ex Post Analysis
2012-2017

(June 2020)

Introduction

The Multi-Organization Thematic Institute (ITMO) Cancer of the Alliance for Life Sciences and Health (AVIESAN) is since 2011 responsible for the programming of thematic calls for projects to support emerging research domains. These funding instruments, which operational management falls to the French National Institute for Medical Research (INSERM), were until 2019 launched in the frame of the research part of the 2nd and 3rd French Cancer Plans coordinated by the National Cancer Institute (INCa).

In 2017, ITMO Cancer-Aviesan started the assessment of programmes for which a sufficient hindsight is possible. A generic analysis grid that can be used for all programmes has been implemented to achieve this. The analysis methodology can be slightly adapted to the specificities of the different calls for projects.

The ex post analyses of ITMO Cancer-Aviesan are fulfilling the following objectives:

- To determine if a funding programme has reached its objectives and to which Cancer Plan objectives it contributed to;
- To gain insights on the impacts of the funding in terms of generation of tools developed and scientific advances in oncology;
- To provide data and information allowing ITMO Cancer-Aviesan to implement evidence-based strategic steering of cancer research.

Elements Taken into Account in the Analyses

- Key figures of the number of projects submitted, success rate, average budget over time
- Analysis of the projects (*using the submitted information and the selection committee reports*):
 - ✓ PI profile: scientific domain*, experience on cancer, demographic data, affiliation;
 - ✓ Project types: domain (CSO categories), cancer type, duration of funding;
 - ✓ consortiums: partner number, domains*, type (industrial or academic, international);
 - ✓ main reasons of the rejection of non-selected project.
- Impact of the project (*based in the final reports and discussions with PI during the restitution seminars*):
 - ✓ Tools developed: diagnostics, therapeutics, follow up, uses by others;
 - ✓ Advances in knowledge: oncogenesis mechanisms, resistance pathways, potential therapeutic target identifications;
 - ✓ Socio-economical outcomes: manpower hired, patents, collaborations, PI career evolutions, leverage effects;
 - ✓ Communication: publications, oral or poster presentations in congresses, lay public reaching.

**Medicine/Clinical Research, Biology, Physics, Mathematics/Informatics/Engineering, Chemistry*

This document recapitulates the main elements of the ex post analysis of the programme “Research projects in the field of the effects of the exposure to environmental risk factors on cancer” (K-Env) over the 2012-2017 period. Since 2011, ITMO Cancer-Aviesan also funds projects in the frame of the Programme national de recherche Environnement-Santé-Travail (PNR-EST) led by ANSES (Agence nationale de sécurité sanitaire de l’alimentation, de l’environnement et du travail). These funded projects were also analysed over the 2012-2017 period to provide insights on the complementarity of the two programmes.

Context and Objectives of the Programme

The K-Env programme led by ITMO Cancer-Aviesan have been launched in 2012 in the frame of the 2nd (2009-2013) and 3rd (2014-2019) Cancer Plans:

- 2nd Cancer Plan: action 3.4 “Mobilise public health, animal health and environment players to launch calls for projects and fund research teams [...]”, in order to assess the impact of the environment on some animal pathologies modelling human cancers, to model the effects linked to multiple exposure to environmental factors (interactions, prolonged and multichannel exposures), and to identify biomarkers of early prediction of oncological transformation or susceptibility;
- 3rd Cancer Plan: action 12.5 “Develop the observation and surveillance, and improve the knowledge about cancers linked to environmental exposures in the general population.”

The K-Env programme had two main ambitions:

- to develop new tools to assess the impact of environmental factors on the onset of cancer;
- to improve the understanding of the mechanisms underlying the apparition of cancer in the aftermath of environmental factor exposure.

“Environmental factors” were including chemical, biological and physical agents, produced by the habitat, society, or the urban way of life as well as factors related to the climate. Their degradation by-products, and their possible interactions were also considered. The eligible fields were defined by an expert committee set by ITMO Cancer-Aviesan.

In addition to the K-Env programme, ITMO Cancer-Aviesan holds since 2011 a partnership with the ANSES Agency to fund research projects on cancer within its PNR-EST programme.

Research Fields Covered by the K-Env Programme (2017 call)

- Action mechanisms of environmental factors on the normal or pathological biological processes, and their evolution with the duration of the exposure, the type of exposure (multiple exposures), the physiological state (age), or individual characteristics
- Complex interactions resulting from exposure to multiple environmental factors
- Metabolic biomarkers of the effects of various thresholds, notably low doses, of contaminants
- Susceptibility to oncogenic effects of environmental factors (identification of genes, and genetic or epigenetic modifications underlying individual or population susceptibility)
- Potential biological effects of exposure to non-ionising electromagnetic fields, ionising irradiations, and radionuclides in function of the exposure conditions.

The programme funded among others:

- Clinical or epidemiological studies (including work on previously-existing large cohorts recognised by the national programmes « Très grandes infrastructures de recherche » or « Investissement d’avenir »)
- Development of experimental models (animal, cell, tools allowing in vitro-human or animal-human transposition) or mathematical tools (biomathematics, statistics, modelling of environmental data).

Ex Post Analysis of the Programme

KEY FIGURES

The analysis focused on the 43 projects funded by the K-Env programme over the 2012-2017 period, except for the outcomes which only relied on the 31 projects funded over the 2012-2015. These projects were completed at the date of the analysis and were discussed with their PI during a restitution seminar held in March 2020.

Main Figures of the K-Env Programme

Projects 2012-2017

- 152 eligible projects
- 43 funded projects
- Average selection rate: 28%
- 38 laureates (45% women)
- 82 partners
- €18,2M
- laureates median age: 49 y.o.

Outcomes Analysis (2012-2015)*

- 31 projects
- 102 recruitments (3,4 per project)
- 30 international collaborations
- 1 new research team
- 5 patents
- 1 start-up
- 37 original articles
- 37 % of the projects with an additional funding (lever effect)

* At the date of the analysis (June 2020)

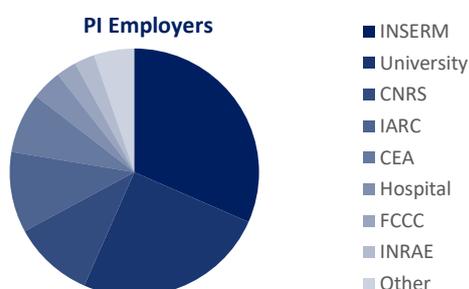
Each year, an average of 25 proposals were evaluated, among which an average of 7 were selected, leading to an average selection rate of 28%.

Eligible and Funded Projects, Success Rate



The average budget was around €400K, except for 2017, where it increased to €630K. This increase was associated with an increase of the average number of partners that year compared to previous years (4,5 vs 3).

The average age of the laureates was higher than for other ITMO Cancer Aviesan calls for projects (49 years old vs 44 years old). Senior researchers (45 y.o. or more) were thus representing the majority of the candidates (64% of the eligible submissions) and had furthermore a higher success rate than younger scientists (42% vs 30%).



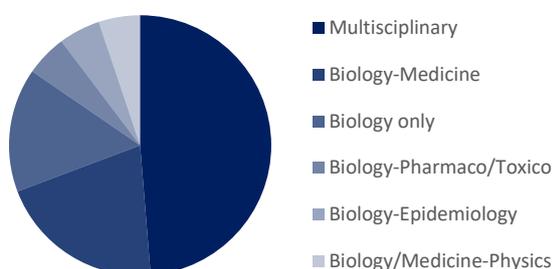
The laureates were mostly employed by the French National Institute for Medical Research (INSERM) (32% of the laureates) and universities (25%). The French National Centre for Scientific Research (CNRS) and the WHO's International Agency for Research on Cancer (IARC) employed each 11% of the laureates. The French Alternative Energies and Atomic Energy Commission (CEA) and Hospitals (University Hospitals or French Comprehensive Cancer Centers, FCCC) were accounting for 8% and 7% of the employers, respectively, whereas the French National Research Institute for Agriculture, Food and Environment (INRAE) employed 3% of the laureates.

PROJECTS BREAKING DISCIPLINARY BORDERS

The great majority of the laureates had a biomedical background with 60% of biologists, 13% of pharmacologists/toxicologists, 12% of physicians, 5% of epidemiologists, and 1% of veterinary medicine clinicians. Other disciplines were chemistry (5%), physics (4%), or mathematics and computer sciences (1%).

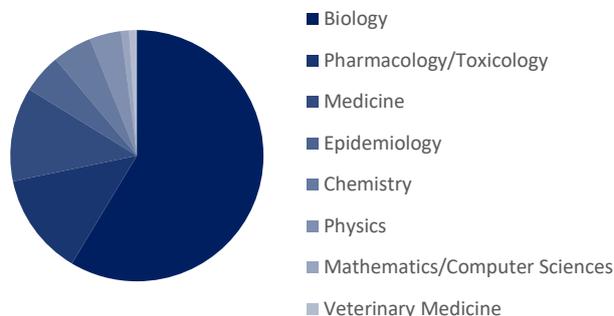
The intrinsic multidisciplinary nature of the K-Env programme was reflected in the consortia

Composition of the Consortia



project, indicating that the K-Env programme helped in attracting scientists, including biologists, toxicologists and chemists, towards research on cancer.

Discipline of the Laureates



composition. Thus, 49% of the consortia were multidisciplinary, uniting 3 or more disciplines, including mathematics, physics or chemistry. The other consortia were mainly “Biology-Medicine” or “Biology” (20 % and 15 %, respectively), “Biology-Pharmacology/Toxicology”, “Biology-Epidemiology” or “Biology/Medicine-Physics” (5 % each).

More than 20% of the laureates had little or no experience with cancer when they submitted their

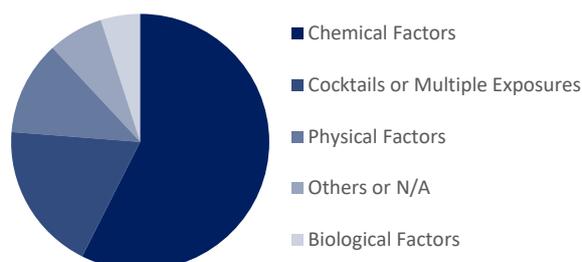
CHEMICAL FACTORS AS MAIN FOCUS

Almost 60% of the funded projects (25/43) were about chemical factors, among which endocrine disruptors (ED) or pesticides (44% and 20% of the projects on chemical factors, respectively). Slightly more than 40% of the projects on chemical factors were studying cocktails of different molecules.

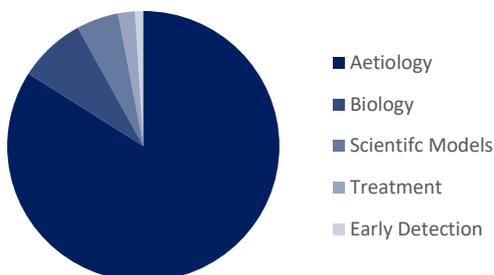
Physical and biological factors were the subject of 12% and 5% of the projects, respectively.

Projects dealing with cocktails of different types of factors or with multiple exposures (mostly epidemiological studies) were accounting for almost 20% of the projects. The important place given to cocktails of factors indicates the heed given to the reality of multiple exposures to environmental factors.

Types of Exposures



CSO Categories

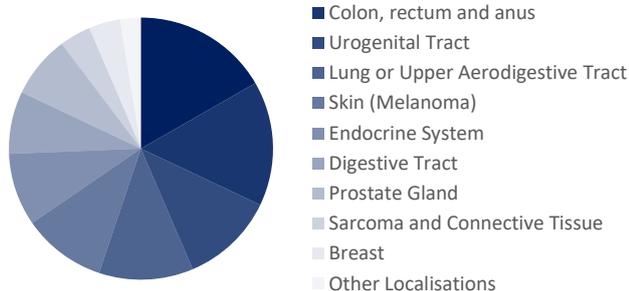


Almost 80% of the projects were focusing on one type of cancer or organ, often organs that are known to be either particularly exposed or sensitive to environmental factors. Haematological tumours (13% of the projects), colorectal (12%), urogenital (9%), lung and upper digestive tract (9%), skin (8%), or endocrine system (7%) were the most studied types of cancer.

Funded projects were in great majority (84%) belonging to the “Aetiology” CSO¹ category, in accordance with the topic of the call. “Biology” and “Scientific models” categories were accounting for 8% and 5% of the projects, respectively. “Treatment” and “Early Detection” categories were only scarcely present (2% and 1%, respectively).

A little bit more than three quarters of the projects (77%) were fundamental research projects, while the rest were epidemiologic research.

Organs studied



NEW TOOLS FOR EXPOSURE EFFECTS DETECTION AND MECHANISMS OF ACTION UNCOVERING

Many projects led to the development of detection assays or models allowing to follow the effects of environmental factor exposure, and for some to assess the level of this exposure. Some of them (e.g., methods to measure deacetylation activity or genotoxicity) have been already used by other laboratories, including in fields outside of oncology.

The knowledge advances were both on the description of environmental factors effects, including synergetic effects, and on the characterisation of mechanisms underlying known effects of factors such as endocrine disruptors. Other projects focused on the characterisation of cancers linked to environmental exposures, and on the identification of hormonal receptors ligands, including a compound used in chemotherapy.

Tools Developed in the Frame of the K-Env Programme* (31 projects over the 2012-2015 period)

- Detection assays: biological activity, DNA damages, protein of interest
- Detection assays for exposure assessment
- Mathematical models and algorithms: image processing, surgery, biological responses to exposure.

* At the date of the analysis (June 2020)

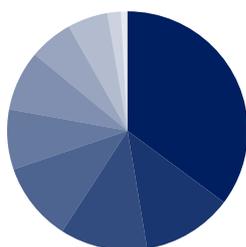
¹ The CSO (Common Scientific Outline) categories are a universal classification system covering the whole spectrum of research on cancer.

The original articles from the projects over the 2012-2015 period (37 at the date of the analysis, thus 1,3 article per project in average) were published for over a third of them (35%) in multidisciplinary journals. The multidisciplinary component of the K-Env programme, and that of the environmental sciences in general, was reflected in the variety of domains (as determined by Web of Science) of the journals publishing the results: biology, oncology and biochemistry (a little bit more than 10% of the papers each),

**Knowledge Advances in the Frame of the K-Env Programme*
(31 projects over the 2012-2015 period)**

- Description of exposures effects (mainly endocrine disruptors and pesticides) at the cellular, tissue, or whole organism level
- Identification of synergetic effects of co-exposures (including endocrine disruptors with other contaminants)
- Description of the role of receptors or kinases involved in the effects of environmental exposures
- Characterisation of pathways or proteins involved in known effects of environmental exposures
- Description of cancers linked to environmental exposure (e.g., specific signature of radio-induced thyroid cancers)
- Identification of hormone receptors ligands (including one molecule used in chemotherapy)
- Xenobiotic-induced chemotherapy resistance mechanism identified, proof of concept of a therapeutic approach against infection-induced lymphomas, analysis of the metabolism of a contaminant in the organism

Original Articles: Publication Domains of the Journals



- Multidisciplinary
- Biology
- Oncology
- Biochemistry
- Public Health
- Medicine
- Environmental Sciences
- Computer Sciences and Engineering
- Toxicology and Pharmacology
- Chemistry

public health and medicine (8% each), environmental sciences and computer sciences/engineering (around 5% each), and toxicology/pharmacology and chemistry (2 % and 1 % of articles, respectively). Almost the three quarter of the publications (74%) are in open access, in accordance to the recommendation of the 3rd Cancer Plan action 13.5: *“Sharing knowledge and data nationally and internationally between professionals [and the lay public].”*

Conclusion

The intrinsic multidisciplinary nature of “Cancer and Environment” was translated in the generation of many multidisciplinary consortia around the projects funded by the programme. Fundamental research has been the majority of the research funded, and at the end, the tools developed and the knowledge generated have allowed the programme to reach its objectives.

A Research Open Towards Society

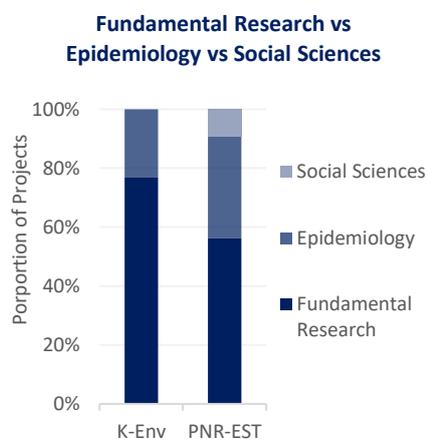
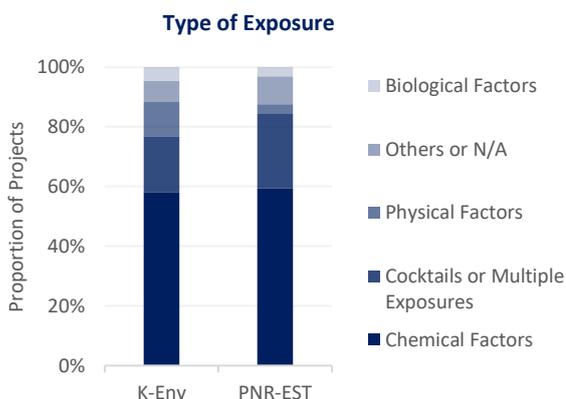
- Almost 10% of the projects has had an echo in national mainstream medias, showing the society’s interest for research on environmental risks
- One project has been carried in collaboration with stakeholders (exposed farmers)

K-Env and PNR-EST Programmes: What Complementarity?

Over the 2012-2017 period, ITMO Cancer Aviesan has funded research on cancers linked to environmental exposures via its K-Env programme (43 projects) and via the PNR-EST programme from Anses (32 projects). The latter aims at fostering research on “*development of new methods and tools on all steps of the analysis of environmental risks for health and ecosystem*”, with a focus on studies “*whose results are rapidly translatable in public policies, thus leading to long-lasting progresses in the domain of public health of the general population and at work*”.

The comparison in the field of cancer shows the complementarity between the two programmes as well as their distinct aspects:

- Only PNR-EST has supported purely descriptive epidemiologic studies or research in humanities and social sciences. The other fields were mainly shared between the two programmes;
- The communities were in good part distinct, as the three quarters of the PNR-EST laureates in cancer had not submitted any project to K-Env, and only 6% have been laureates at K-Env;
- Fundamental research was more present in K-Env (77% vs 56%), whereas PNR-EST supported more epidemiological research (34% vs 23%) and projects on social sciences (10% of the projects);



- Chemical risk factor studies were predominant in both programmes (almost 60% of the projects), but the physical risks have been more studied in K-Env (12% vs 3%), while PNR-EST has supported more projects on co-expositions of different types of factors (25% vs 19%);
- Both programmes led to new tools and knowledge on mechanisms, but only PNR-EST has

brought description of links between exposures and cancers and led to socio-economic insights;

- In relation to the multidisciplinary nature of the field, the results have been published in journals in a variety of domains for both programmes. There were however differences, namely with five times more articles in multidisciplinary journals for K-Env (35% vs 7%), and three times more publications in public health journals for PNR-EST (23% vs 8%). Publication rates per project were similar (1,3 and 1,6 for K-Env and PNR-EST, respectively).

Original Articles: Publication Domains of the Journals

