Integration of the exposome in ANSES's activities

Anses opinion
Collective Expert Appraisal Report

March 2023

INVESTIGATE, EVALUATE, PROTECT

The Director General

Maisons-Alfort, 2 March 2023

OPINION
of the French Agency for Food, Environmental and Occupational Health & Safety

on the report entitled "Integration of the exposome in ANSES's activities"

ANSES undertakes independent and pluralistic scientific expert assessments.
ANSES primarily ensures environmental, occupational and food safety as well as assessing the potential health risks they may entail.
It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.
It provides the competent authorities with all necessary information concerning these risks as well as the requisite expertise and scientific and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).
Its opinions are published on its website. This opinion is a translation of the original French version. In the event of any discrepancy or ambiguity the French language text dated 2 March 2023 shall prevail.

1. BACKGROUND AND PURPOSE OF THE REQUEST

Since its emergence in 2005, the concept of the exposome has given rise to numerous research projects that form part of a continuum of questions to science about the role of environmental factors in the development of chronic diseases, which have become the leading cause of death in developed countries in recent decades. The interest shown in this concept has extended beyond research teams to convince public decision-makers, and it was included in the Act of 28 January 2016 on the modernisation of the health system.

ANSES carries out tasks in the areas of monitoring, expert appraisal, research and reference in a wide range of fields including human health, animal health and welfare, and plant health. It provides a cross-functional perspective on health issues when assessing health risks and benefits, in particular through the lens of the human and social sciences. Its monitoring, vigilance and surveillance work provides input for risk assessment. The Agency assesses a broad range of risks (chemical, biological, physical, etc.) to which a person may be exposed, intentionally or otherwise, at all ages and times of their life, whether at work, while travelling, while engaging in leisure activities, or via their diet[1]. These risks are most often assessed from a single source (air, water, food, dust, veterinary medicinal products, etc.) and a single route

[1] https://www.anses.fr/en/content/our-identity

of exposure (ingestion, inhalation, dermal contact) by making simplified assumptions about exposure over time (constant, acute, one-off exposure, etc.).

Thus, the exposome, which seeks to study the role of all the environmental factors encountered over the course of a lifetime in the development of disease, has yet to be largely implemented by ANSES, whether scientifically or methodologically. It is therefore important for the Agency to assess the practical consequences of including the exposome concept in legislation and integrating it in the deployment of its core activities. This involves identifying the opportunities, approaches and means for its implementation, as well as what is needed in terms of development and new skills to address it.

To this end, ANSES set up a working group (Exposome WG) reporting to the Scientific Board and tasked with proposing ways to strengthen integration of the exposome in the Agency's activities, particularly its expert appraisal work. In this respect, the aim was to make practical proposals via case studies on integrating the exposome in the expert appraisal work carried out by the Agency, while analysing the consequences.

Consideration of the exposome in risk assessment is still relatively unstructured. As the exposome is systemic in nature, it is made up of different components that can be studied by a variety of disciplines, using a wide range of approaches and techniques, some but not all of which are already used in risk assessment. The objective of this report is to identify the data, methods and tools needed to address the exposome and which can be put into practice, based on current risk assessment issues. It ultimately involves proposing a more comprehensive risk assessment approach, which takes account of the reality of exposures in terms of the diversity of exposure factors and sources, in a specific social and environmental context, and which integrates inter-individual and intra-individual variability over the course of a lifetime. This report focuses on all the health determinants assessed by ANSES: chemical, biological and physical agents, the psychosocial and socio-economic context, organisational constraints, etc., with the possibility of including other factors. It should be noted that the methods, data and examples relating to chemicals are more widely represented because the exposome approach was initially developed in this field. Besides expert appraisal, risk management paradigms will also need to be revised to integrate the exposome. This integration may also have an impact on all the components (assessment/monitoring/management) of risk governance. Because one of the Agency's missions is to support the players of this governance with its expertise, any changes resulting from the implementation of this WG's recommendations may then be reflected in public policies, as well as in the practices of economic players and populations.

The Agency stresses the broad scope of the questions raised by the exposome, and points out that they extend into areas (ethical, scientific, legal, etc.) that go well beyond the remit of ANSES's mission. The work undertaken with the Scientific Board has enabled an initial exploration, while remaining within ANSES's areas of competence.

2. ORGANISATION OF THE EXPERT APPRAISAL

2.1 Procedure for responding to the formal request

In the first half of 2019, ANSES drafted terms of reference for an internal request on the issue of taking the exposome into account in its activities – particularly its expert appraisal work – and put them to its Scientific Board, which would be entrusted with responding to it. There was a discussion on the objectives of this request and the way in which it was to be addressed, and a working group (WG) made up of experts from the Scientific Board (2016-2019 mandate) was formed and convened for this purpose, to share an initial overview of the situation. For internal Agency reasons, the working group (whose initial composition has changed) was only able to begin its work in early 2021. The working approach proposed by the WG was presented and discussed at the Scientific Board's meeting in March 2021.

In terms of "core activity" areas, the WG's work focused on expert appraisals in risk assessment and on research funding activities. With regard to expert appraisals, the WG made an original choice in basing its work on ongoing formal requests within the Agency, in order to consider the possibility of integrating the exposome in these specific cases of expert appraisals. These formal requests were suggested by the Agency and selected by the WG following an analysis of ANSES's work programme (2021 and 2022 versions) and the different stages of progress of the requests. Priority was given to work just beginning.

To this end, a "mirror group" was set up within the Risk Assessment Department (DER) whose members were the coordinators of the selected formal requests. Whenever possible, the ideas proposed by the WG were presented to the body tasked with responding to the formal request (WG or Expert Committee – CES).

The working group – named the Exposome WG – was therefore made up of most of the experts from the first mandate and members of the new Scientific Board (2020-2023 mandate), as well as an expert who is now retired and who was a member of the former Scientific Board, and ANSES staff members with expertise in the field of the exposome or the coordinators of the ongoing work for the selected formal requests.

The Exposome WG’s expert appraisal work was regularly submitted to the Scientific Board. Their draft report was submitted for a targeted internal and external consultation in May 2022. The report produced by the working group therefore takes account of the observations and additional information provided during this consultation and by the Scientific Board members. The report and its recommendations received final validation by the Scientific Board at its meeting on 20 September 2022.

This work was therefore conducted by a group of experts and ANSES staff with complementary skills. The expert appraisal was carried out in accordance with French Standard NF X 50-110 "Quality in Expert Appraisals – General requirements of Competence for Expert Appraisals (May 2003)".

2.2 Prevention of risks of conflicts of interest

ANSES analyses interests declared by experts before they are appointed and throughout their work in order to prevent risks of conflicts of interest in relation to the points addressed in expert appraisals.

The experts’ declarations of interests are made public on the following website: https://dpi.sante.gouv.fr/.

3. ANALYSIS AND CONCLUSIONS OF THE SCIENTIFIC BOARD

The Scientific Board adopted the following definition of the exposome, proposed by its Exposome WG in the context of its application to the Agency's work:

> "**The exposome corresponds to all the exposure to chemical, biological and physical agents, both harmful and beneficial, in interaction with the physiological status, living environment and psychosocial context, experienced by a living organism from its conception through to the end of its life, in order to explain its state of health**."

The exposome study can be broken down schematically into four modules, as shown in the figure below (Figure 1).

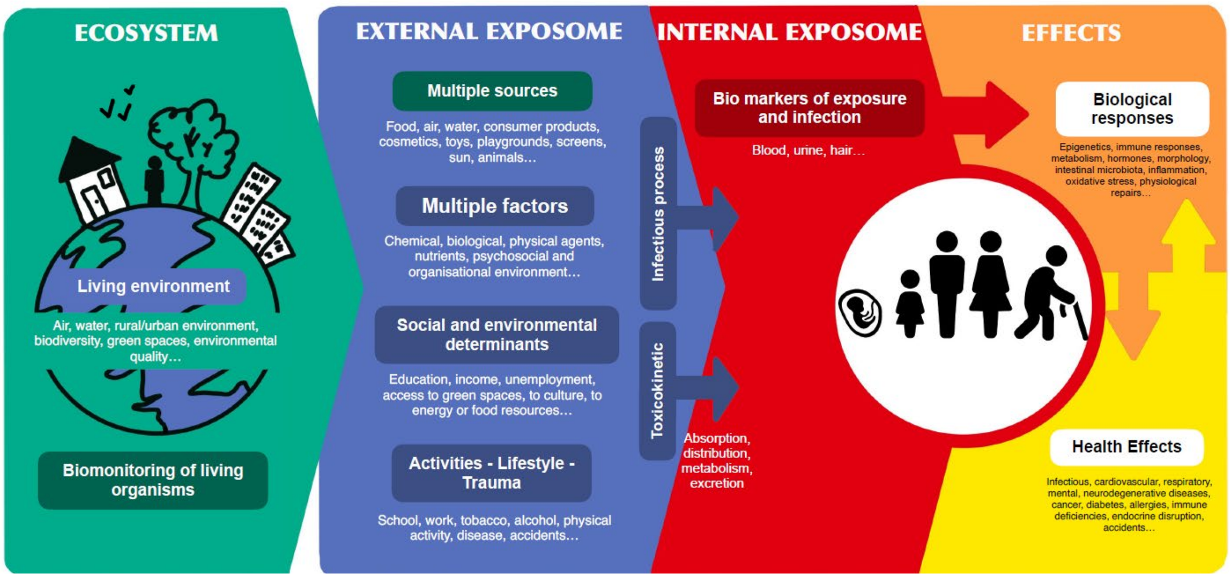


Figure 1: Representation in four modules of the study of the exposome illustrated by a few examples: from the ecosystem, which is the source of exposure, through to biological responses and health effects, and including external and internal exposure levels. The time line indicates that the exposome incorporates exposure over an entire lifetime.

The Scientific Board underlines the originality of this definition, which is suited to any living organism and includes the ecosystem and the potentially beneficial effects of exposure.

The Scientific Board notes that ANSES has already begun to take the exposome into account in its collective expert appraisal work, in particular around eight themes, presented in the diagram below (Figure 2). The case studies examined by the WG and presented in Chapter 6 of the report confirmed the applicability of integrating the exposome in the formal requests addressed by the Agency and enabled interactions to be developed between the Agency's teams, thus demonstrating their interest in moving forward on this issue.

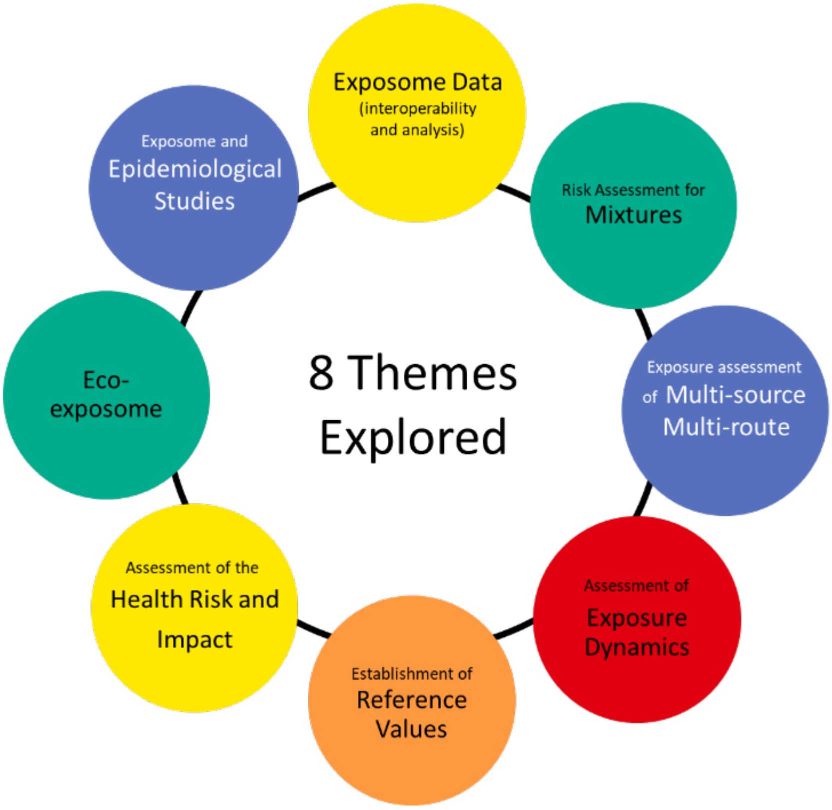


Figure 2: Themes explored at ANSES in relation to the exposome and risk assessment

The Scientific Board **recommends deploying a strategy at ANSES to progressively integrate the various components of the exposome approach into its risk assessment activities,** considering in order of priority and adapting to the context: the multi-source and multi-route of exposure, the mixtures, the multiple factors (chemical, biological, organisational, physical, psychological, etc.), the temporal dimension of exposure, the risk/benefit assessments, the social and geographical aspects, and the eco-exposome, based on the diagram below (Figure 3) proposed by the WG.

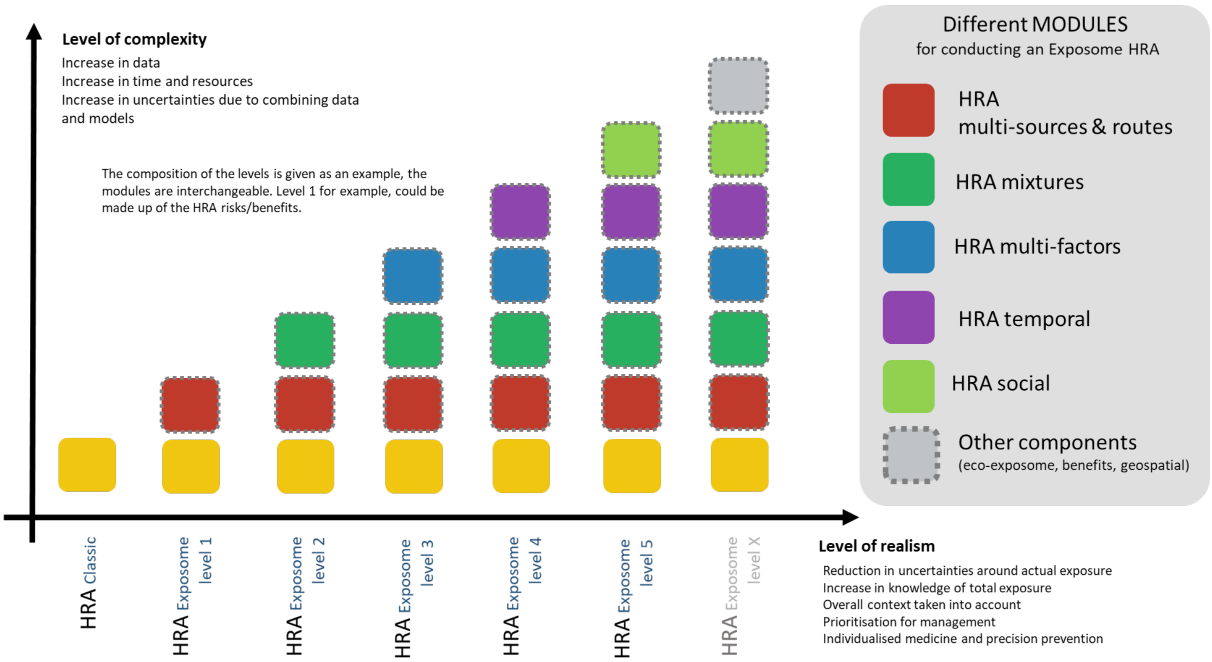


Figure 3. Diagram of a possible introduction of the different components of the exposome in health risk assessments (HRAs). The modules represent the exposome components and are added according to the question asked. As the number of modules increases, the level of consideration of the exposome components rises and is associated with a greater level of complexity and consideration of the reality of exposure.

The Scientific Board also formulates five recommendations for taking the exposome into account in ANSES's various expert appraisal activities.

3.1 Organise cross-functional links between the units of the Risk Assessment Department and with other departments

The Scientific Board recommends setting up a cross-functional activity devoted to the exposome, in order to strengthen collaboration between the various units currently organised by exposure source (food, water, air) or by agent type (physical, chemical, etc.) and grouped into fields. This cross-functional activity should, for example, make it possible to:

- systematically question the main sources and routes of exposure for all formal requests, by assessing the need to aggregate them and organise a cross-functional approach to addressing the formal request;
- systematically question the relevance and feasibility of integrating the "mixture" component into expert appraisals;
- include occupational exposure for the general population and, conversely, sources and routes of exposure in daily life for workers;
- hold a debate in order to propose comprehensive risk assessments (multi-source, multi-route, and multi-factor) integrating health impact analyses, benefits and the associated economic costs.

3.2 Acculturate ANSES's staff and expert committee members

The Scientific Board calls for:

- training of the Agency's staff and experts and greater awareness about:
  - taking the results of epidemiological studies into account in hazard identification and characterisation, and comparing epidemiological findings with experimental results for establishing lines of evidence;
  - assessing risks associated with mixtures;
  - the use of available data through national monitoring programmes and European partnerships;
  - adopting the FAIR[2] principles for data;
  - the use of spatialisation and temporal analysis tools;
  - the use of specific exposome analysis methods (omics, machine learning, etc.).

- points requiring vigilance to be inserted in ANSES opinions, where appropriate, to draw attention to components of the exposome that were not addressed in the formal request: other sources and routes that may contribute to exposure, other substances with combined effects, potential benefits of exposure, ecotoxicological impacts, etc.;

- skills of the expert committees to be strengthened in certain fields, particularly in ecology, ecotoxicology and the human and social sciences (social epidemiology, anthropology, etc.).

3.3 Organise data, make them available and analyse them

The Scientific Board advises:

- developing communication and provision of the data produced and managed by ANSES;

- consolidating the organisation of databases listing the different sources and routes of exposure, according to FAIR principles;

- contributing to the standardisation of data as well as methods and tools for their collection and storage at national (epidemiological surveillance platforms, France Exposome, the CALIS infrastructure, large cohorts such as Constances, E4N-E3N, i-Share, PSY-COHorte, etc.), European (PARC programme, etc.) and international levels;

- contributing to the acquisition and structuring of eco-exposome data (water, soil, air, biota) in interoperable databases;

- ensuring sustainable data management by minimising the environmental footprint;

- pursuing development of data analysis methods and tools such as machine learning, which allow interoperability, analysis and interpretation of data on the exposome.

---

[2] FAIR is an acronym for Findable, Accessible, Interoperable, Reusable, describing a way of working that guarantees the production of easily found, easily accessible, interoperable and reusable data

3.4 Develop operational methods and tools

The Scientific Board recommends:

- developing integrated approaches to risk assessment (multi-source, multi-route, mixtures, etc.) and working on taking the interactions between factors into account. This will involve, for example:
    - organising the methods and tools needed to carry out multi-source and multi-route risk assessments, for example by developing algorithms for combining data;
    - deploying a risk assessment strategy for chemical mixtures by prioritising mixtures according to regulatory questions, grouping substances into mixtures according to their likelihood of co-exposure, modes of action and specific effects, and using integrated approaches to testing and assessment (IATA) of their toxicity;
    - making available tools and methods devoted to multi-source and route exposures and to mixtures, such as those developed for national (Pericles, Coctell, etc.) and European (Euromix, HBM4EU, ATHLETE, PARC, etc.) research projects.
- promoting the development of spatial and temporal measures of exposure and developing indices that reflect the variety of exposures over the course of a lifetime, their occurrence, duration and sensitivity according to the time periods in question;
- improving how sensitive populations, different exposure routes and human biomonitoring data are taken into account for establishing reference values, and strengthening requirements regarding the quality of data and methods used for determining these values;
- better integrating environmental signals in human exposure assessments, and trophic and behavioural interactions between species in risk assessments.

3.5 Consolidate collaboration and partnerships

The Scientific Board strongly encourages:

- multidisciplinary collaboration, particularly in order to link epidemiological studies, experimental studies (*in chemico, in vivo* and *in vitro*), modelling (*in silico*) and risk assessment, or strengthening partnerships with ecosystem research players;
- large-scale surveys that take several sources of exposure into account, enabling the investigation of specific behaviours (vegetarianism, high consumption, addictions, etc.), sensitive populations (pregnant women, children, etc.),and local contamination, as well as integrating social and cultural aspects;
- synergies in actions rooted in the regions in question, between ANSES and other operators such as Regional Health Agencies (ARSs), local authorities and certain stakeholders (NGOs, associations). It also calls for the development of citizen science to take better account of the geographical, cultural and social characteristics of populations in exposure assessment and in the proposals for management measures.

With regard to ANSES's research funding mission, the Scientific Board would like the exposome to be maintained among the priority themes of the National Research Programme for Environmental and Occupational Health (PNR EST), targeting in particular the above-mentioned questions.

In conclusion, **this ambitious programme to integrate the exposome in ANSES's activities requires support in terms of suitable human and financial resources**.

4. AGENCY CONCLUSIONS AND RECOMMENDATIONS

Firstly, ANSES emphasises the strategic and pioneering nature at national and European level of the systemic work undertaken to determine the conditions for taking the exposome into account in the activities of a health agency. Indeed, the Agency considered it necessary, at a time when the concept is being consolidated in the scientific community and has been enshrined in French law in the Public Health Code, to investigate the conditions for its implementation in its activities. The work was carried out following an internal request, entrusted to its Scientific Board, and included analyses of specific cases of ongoing formal requests. ANSES adopts the conclusions of its Scientific Board and the Exposome WG.

The resulting recommendations are intended to strengthen and structure the process of taking the exposome into account in the Agency's different activities (expert appraisal, research and reference, vigilance and monitoring), in order to address the challenges of the "One Health" approach and tomorrow's societal issues through a comprehensive scientific approach to risk assessment. These recommendations are addressed to all the players involved in the risk assessments conducted by ANSES (researchers, assessors, experts, data producers) and to those who implement them (stakeholders, local players, funding bodies, managers, etc.).

As emphasised by its Scientific Board, this implementation of the exposome in the Agency's activities is an ambitious programme that will need to be carried out progressively and with support in terms of suitable human and financial resources. This is because deployment of the recommendations implies a change in the Agency's practices, the acculturation and upskilling of its teams and expert group members, and the further development of suitable methods and tools to ensure that the integration of the exposome in risk assessment becomes fully operational. Development work will also need to be integrated upstream, from the beginning of the exchanges with the parties commissioning the expert appraisal – ministries and authorised stakeholders – and in the early phases of reformulating the questions and planning how the formal request will be addressed. For ANSES's other core activities, implementing the exposome in its research, reference, monitoring and vigilance work should be accompanied by the systematic application of FAIR principles to optimise the management, organisation, collection and analysis of data generated or used by the Agency. This change in practices within the Agency must be supported by the establishment of a suitable organisation.

In addition to its own development, and with the aim of providing broader input to discussions on the exposome, the Agency believes it is important to share the results of its work, by disseminating the report to risk assessment players and publishing it within its scientific community and among its national, European and international partners, in order to strengthen cooperation on this issue. This effort is already under way with ANSES's contribution to research programmes on the exposome (Athlete), its participation in national and European initiatives on infectious diseases within the "One Health" framework, its participation in the Exposome Research and Expertise Group (GREEX) and its coordination of the European Partnership for the Assessment of Risks from Chemicals (PARC). In this partnership, the work packages dedicated to FAIR principles, innovative analytical and toxicological methods, and an integrated approach to risk assessment considering the development of multi-source, multi-route and multi-substance exposures over the course of a lifetime, will provide essential information for integrating the chemical exposome in the Agency's risk assessments. This project, which is bringing together 200 European partners, demonstrates ANSES's determination to be a key player in Europe in terms of innovation in risk assessment.

Lastly, as the Ministry of Health prepares to revise the national health strategy, in application of Article L.1411, which introduced the concept of the exposome into French law, the results of this work will also be mobilised by ANSES to enable it to make its own contribution.

Pr. Benoit VALLET

MOTS CLES

Évaluation des risques, multi-expositions, vie entière, santé globale, médecine systémique, approche holistique

KEY WORDS

Risk assessment, multiple-exposure, lifetime, overall health, systemic medicine, holistic approach

SUGGESTED CITATION

ANSES (2023). Opinion on the report entitled "Integration of the exposome in ANSES's activities" (Request No 2022-METH-0197). Maisons-Alfort: ANSES, 10 p.

Integration of the exposome in ANSES's activities

Request No 2022-METH-0197 "Integration of the exposome in ANSES's activities"

Collective Expert Appraisal REPORT

Exposome WG

Original version: June 2022

French Agency for Food, Environmental and Occupational Health & Safety
14 rue Pierre et Marie Curie 94701 Maisons-Alfort Cedex
Tel: +33 (0)1 49 77 13 50 — www.anses.fr

Suggested citation

ANSES. (2022). Integration of the exposome in ANSES's activities. (Request No 2022-METH-0197). Maisons-Alfort: ANSES, 197 p.

Mots clés

Evaluation des risques, multi-expositions, vie entière, santé globale, médecine systémique, approche holistique

Key words

Risk assessment, multiple-exposure, lifetime, overall health, systemic medicine, holistic approach

Presentation of the participants

PREAMBLE: The expert members of the Expert Committees and Working Groups or designated rapporteurs are all appointed in a personal capacity, *intuitu personae*, and do not represent their parent organisation.

WORKING GROUP

Chair

Mr Robert BAROUKI – University Professor, Unit Director at Inserm – Biochemistry – Toxicology – Exposome

Members

Mr Jean-Pierre CRAVEDI – Research Director, INRAe – Toxicology

Mr Philippe QUÉNEL – Honorary Professor, EHESP – Epidemiology – Environmental Health – Public Health

Ms Jeanne GARRIC – Emeritus Research Director, INRAe – Ecotoxicology – Ecological risk

Mr Alain KAUFMANN – Director of the ColLaboratoire, a unit for collaborative and participatory research-action at the University of Lausanne – Human and Social Sciences

Ms Pascale DUCHÉ – University Professor, Science and Technique of Physical and Sports Activities, Toulon University – Exercise Physiology

Mr Jean-Marc BONMATIN – Senior Research Fellow at the National Centre for Scientific Research (CNRS) in Orléans – Chemistry – Toxicology

RAPPORTEURS

Ms Isabelle MOMAS – University Professor, Public Health & Environment, University of Paris, Paris Faculty of Pharmacy – Public Health – Environmental Health – Environmental Epidemiology – Exposure science – Air pollution – Allergies

Mr Christian DUCROT – Research Director, Deputy Head of the Animal Health Department at INRAe in Montpellier – Epidemiology – Animal health – Use of antibiotics – Infectious diseases – Interdisciplinarity

EXPERT COMMITTEE

The work that is the subject of this report was monitored and adopted by the ANSES Scientific Board.

- Scientific Board – [2020-2023]

Chair

Ms Isabelle MOMAS – University Professor, Public Health & Environment, University of Paris, Paris Faculty of Pharmacy – Public Health – Environmental Health – Environmental Epidemiology – Exposure science – Air pollution – Allergies

Vice-Chairs

Mr Alain BERGERET – Retired Professor, University of Lyon 1 – Hospital practitioner in occupational medicine and health at the Hospices Civils de Lyon – Occupational diseases – Occupational risks – Epidemiology – Cancer

Mr Hein IMBERECHTS – Scientific Advisor at the Strategy and External Positioning unit at Sciensano (Belgium) – Bacteriology (*Escherichia coli* and *Salmonella*) – Zoonoses – Antimicrobial resistance – Molecular biology – Epidemiology – Risk assessment

Members

Mr Robert BAROUKI – University Professor, Unit Director at the National Institute of Health and Medical Research – Biochemistry – Toxicology – Exposome

Ms Francine BÉHAR – University Professor, University of Paris Descartes – Hospital practitioner in ophthalmology at the AP-HP – Neurosciences – Biology – Ophthalmology – Physical agents – Human health

Mr Jean-Marc BONMATIN – Senior Research Fellow at the National Centre for Scientific Research (CNRS) in Orléans – Chemistry – Toxicology

Ms Véronique COXAM – Research Director at INRAe in Theix – Nutrition – Health – Nutritional prevention of chronic diseases

Ms Catherine DARGEMONT – Research Director at the National Centre for Scientific Research (CNRS) in Montpellier – Genetics – Epigenetics – Cell biology – International scientific strategy – Assessment – Research management

Ms Marion DESQUILBET – Research Fellow at INRAe in Toulouse and at the Toulouse School of Economics – Economics, Interdisciplinarity – Environment – Food systems – Agricultural models – Socio-economic effects of GMOs

Ms Pascale DUCHÉ – University Professor, Science and Technique of Physical and Sports Activities, Toulon University – Exercise Physiology

Mr Christian DUCROT – Research Director, Deputy Head of the Animal Health Department at INRAe Montpellier – Epidemiology – Animal health – Use of antibiotics – Infectious diseases – Interdisciplinarity

Ms Jeanne GARRIC – Emeritus Research Director at INRAe, Villeurbanne – Ecotoxicology – Ecological risk

Mr Pierre-Benoit JOLY – President of INRAe Occitanie-Toulouse – Sociology of risk – Socio-economics of innovation – Biotechnologies – Seed industry – Science-society relations – Socio-ecological impacts of research

Mr Alain KAUFMANN – Director of the ColLaboratoire, a unit for collaborative and participatory research-action at the University of Lausanne – Human and Social Sciences

Ms Emeline LAGRANGE – Hospital practitioner in neurology at the Grenoble Alpes University Hospital – Medicine – Neurology – Environment, Epidemiology – Neuromuscular diseases

Mr Bruno LINA – Professor at the University of Lyon – Hospital practitioner in virology at the University Hospital of Lyon – Virology – Infectiology – Integrative approach to characterisation and monitoring of the influenza virus – Infectious diseases

Mr Marc LUCOTTE – Professor at the Department of Earth and Atmospheric Sciences of the University of Quebec (UQAM) in Montreal – Environmental sciences – Aquatic systems – Agricultural soils – Heavy metals – Pesticides – Greenhouse gases – Dynamics of environmental systems

Mr Francis MÉGRAUD – Professor emeritus at the University of Bordeaux – Practitioner assigned to the University Hospital of Bordeaux – *Helicobacter* infections – *Campylobacter* infections and other digestive infections – Stomach cancer

Ms Claire NEEMA – Professor in Plant Pathology, Montpellier Supagro – Plant health – Phytopathology – Plant epidemiology – Co-evolution – Population genetics

Ms Marie-Claude PAQUETTE – Specialised Scientific Advisor – In-house Researcher at the National Public Health Institute of Quebec – Food environment – Public policies – Food/nutrition – Processed foods – Taxation of sweetened beverages

Mr Philippe QUÉNEL – Honorary Professor at EHESP – Medicine – Epidemiology – Public Health

Mr Marc SOULAT – Professor at the University of Toulouse 3 – Hospital practitioner in occupational medicine and health at the Toulouse University Hospital – Occupational health – Occupational diseases – Environmental health – Phytopharmacovigilance – Agriculture – Exposome

Mr Noël TORDO – Head of the antiviral strategies unit at the Institut Pasteur in Paris and Director of the Institut Pasteur in Guinea – Virology – Antiviral strategies – Ebola – Animal health

Ms Florence VAL – Professor of Phytopathology, Director of the Ecology Department, Agrocampus Ouest Rennes – Plant health – Genetics of resistance in plants

Mr Xavier VAN HUFFEL – Former Director of the Risk Assessment Department at the Belgian Federal Agency for the Safety of the Food Chain (FASFC) – Animal health – Epidemiology – Risk assessment – Food chain – Research – Emerging risks

ANSES PARTICIPATION

Scientific coordination

Ms Amélie CRÉPET – Scientific Project Manager – Methodology in health risk assessment – Exposome

Mr Matthieu SCHULER – Managing Director General of the Science for Expertise Division – Health safety

Scientific contribution

Ms Amélie CRÉPET – Scientific Project Manager – Methodology in health risk assessment – Exposome

Mr Matthieu SCHULER – Managing Director General of the Science for Expertise Division – Health safety

Mr Pascal SANDERS – Scientific Director for "Exposure to and Toxicology of Chemical Contaminants" – Analytics – Toxicology

Mr Julien JEAN – Scientific Project Manager – Food risk assessment

Ms Clémence FOURNEAU – Scientific Project Manager – Occupational health

Ms Aurélie MATHIEU-HUART – Assistant to the Head of Unit – Reference values

Ms Fatoumata SISSOKO – Scientific Project Manager – Reference values

Ms Morgane BACHELOT – Scientific Expertise Coordinator – Assessment of risks associated with drinking water

Ms Emmanuelle DURAND – Scientific Project Manager – Assessment of the risks related to air environments

Ms Olivia ROTH-DELGADO – Scientific Project Manager – Safety of physical agents and new technologies

Ms Aurélie NIAUDET – Deputy Head of the Unit for Assessment of Risks Related to Physical Agents – Occupational health, Environmental health

Ms Aurélie DESBRÉE – Head of the Research Funding Unit – Research funding

Ms Laetitia DUBOIS – Director of the Research Funding & Scientific Watch Department – Research funding

Mr Laurent GUILLIER – Scientific Project Manager – Microbiological risk assessment

Ms Fanny DEBIL – Scientific Studies Coordinator – Social sciences

Ms Madeline CARSIQUE – Scientific Project Officer – Assessment of the risks associated with chemical mixtures

Collective intelligence workshops

Mr Julien JEAN – Scientific Project Manager – Food risk assessment

Ms Amélie CRÉPET – Scientific Project Manager – Methodology in health risk assessment – Exposome

Graphic facilitation

Mr Julien JEAN – Scientific Project Manager – Food risk assessment

Administrative secretariat

Ms Frieda NGOUE – Executive Assistant

Mr Régis MOLINET – Administrative Manager

HEARINGS WITH EXTERNAL PERSONS

Mr Luc MULTIGNER – Research Director – Inserm

CONTRIBUTIONS FROM OUTSIDE THE GROUP(S)

Co-exposure to chlordecone and other organochlorine compounds (Chapter 6.4.4)

Ms Paule VASSEUR – Professor Emeritus, University of Lorraine

CONTENTS

Presentation of the participants 3
Acronyms and abbreviations 12
Glossary 17
List of tables 21
List of figures 22
1. Background, purpose and procedure for carrying out the expert appraisal 24
1.1 Background and objectives 24
1.2 Procedure: means implemented and organisation 26
1.3 Prevention of risks of conflicts of interest 26
2. The exposome 27
2.1 Definition 27
2.2 Research projects and infrastructure 33
3. The exposome in ANSES's research funding mission 36
3.1 Review of exposome-related projects over the last 10 years 36
3.2 Additions to the 2022 PNR EST research questions 40
4. The exposome in ANSES's collective expert appraisal mission: overview and recommendations 42
4.1 Exposome and epidemiological studies 42
4.1.1 Background and identification of issues 42
4.1.2 What ANSES is already doing 45
4.1.3 Short-term recommendations (2023-2025) 46
4.1.4 Medium-term recommendations (2026-2029) 46
4.1.5 Long-term recommendations (2030 and beyond) 46
4.2 Interoperability and analysis of exposome data 47
4.2.1 Background and identification of issues 47
4.2.2 What ANSES is already doing 50
4.2.3 Short- and medium-term recommendations (2023-2029) 51
4.2.4 Long-term recommendations (2030) for ANSES's expert appraisal activities 51
4.3 Assessment of risks associated with mixtures 52
4.3.1 Background and identification of issues 52
4.3.2 What ANSES is already doing 54
4.3.3 Short-term recommendations (2023-2025) 55
4.3.4 Medium-term recommendations (2026-2029) 56
4.3.5 Long-term recommendations (2030 and beyond) 56
4.4 Multi-source and multi-pathway exposure assessment 57

4.4.1 Background and identification of issues....57
4.4.2 What ANSES is already doing....59
4.4.3 Short-term recommendations (2023-2025)....60
4.4.4 Medium-term recommendations (2026-2029)....60
4.4.5 Long-term recommendations (2030 and beyond)....61
4.5 Dynamic exposure assessment....61
4.5.1 Background and identification of issues....61
4.5.2 What ANSES is already doing....66
4.5.3 Short-term recommendations (2023-2025)....67
4.5.4 Medium-term recommendations (2026-2029)....68
4.5.5 Long-term recommendations (2030 and beyond)....68
4.6 Establishment of reference values....69
4.6.1 Background and identification of issues....69
4.6.2 What ANSES is already doing....71
4.6.3 Short-term recommendations (2023-2025)....71
4.6.4 Medium-term recommendations (2026-2029)....72
4.6.5 Long-term recommendations (2030 and beyond)....72
4.7 Assessment of risks and public health impact....72
4.7.1 Background and identification of issues....72
4.7.2 What ANSES is already doing....75
4.7.3 Short-term recommendations (2023-2025)....76
4.7.4 Medium-term recommendations (2026-2029)....76
4.7.5 Long-term recommendations (2030 and beyond)....77
4.8 Eco-exposome....77
4.8.1 Background and identification of issues....77
4.8.2 What ANSES is already doing....81
4.8.3 Short-term recommendations (2023-2025)....82
4.8.4 Medium-term recommendations (2026-2029)....82
4.8.5 Long-term recommendations (2030 and beyond)....83
4.8.6 Need for a cultural and structural change at ANSES....83
5. Deployment and general recommendations....84
5.1 During the planning of expert appraisals....84
5.2 Five key recommendations....86
6. Application to formal requests....89
6.1 Waste workers....89
6.1.1 Background....89

6.1.2 Purpose of the formal request 90
6.1.3 Recommendations of the Exposome WG 91
6.1.4 Actions and resources implemented 91
6.1.5 Conclusion 100
6.2 Reference values 100
6.2.1 Background 100
6.2.2 Purpose of the formal request 101
6.2.3 Recommendations of the Exposome WG 102
6.2.4 Actions and resources implemented 104
6.2.5 Conclusion 107
6.3 Microsensors to monitor the quality of indoor and outdoor air 108
6.3.1 Background 108
6.3.2 Objectives of the formal request 109
6.3.3 Recommendations of the Exposome WG 110
6.3.4 Actions and resources implemented 110
6.3.5 Conclusion 111
6.4 Chlordecone 112
6.4.1 Background 112
6.4.2 Purpose of the formal request 112
6.4.3 Recommendations of the Exposome WG 113
6.4.4 Actions and resources implemented 118
6.4.5 Conclusion 122
6.5 Digital tools and the health of children and adolescents 122
6.5.1 Background 122
6.5.2 Purpose of the formal request 123
6.5.3 Recommendations of the Exposome WG 124
6.5.4 Actions and resources implemented 124
6.5.5 Conclusion 127
6.6 Feedback on implementing recommendations in formal requests 128
6.6.1 Distribution of roles between the Exposome WG and the WGs/CESs responding to the formal requests 128
6.6.2 Difficulties encountered 128
6.6.3 Lessons learned for taking the recommendations in Chapter 4 into account in future formal requests 129
Conclusion 130
7. References 131

Annexe 1 Context, issues and terms of reference for the task that ANSES decided to entrust to a WG reporting to its Scientific Board 168

Annexe 2 List of selected PNR EST projects dealing with the exposome 172

Annexe 3 Further research for the formal request on waste workers 173

Annexe 4 Value of taking co-exposure to other contaminants into account when assessing the risk of chlordecone exposure in the French Caribbean – the example of organochlorines 175

Acronyms and abbreviations

AASQA	Approved air quality monitoring association
ADEME	French Agency for Ecological Transition
ADHD	Attention deficit hyperactivity disorder
ADME	Absorption, distribution, metabolism and excretion
ADONIS	Assessing determinants of the non-decreasing incidence of *Salmonella*
AEP	Aggregate exposure pathway
AFNOR	French Standards Institute
AFSSA	French Food Safety Agency
AMD	Age-related macular degeneration
AMPA	Aminomethylphosphonic acid
ANACT	French National Agency for the Improvement of Working Conditions
ANR	French Research Agency
ANSES	French Agency for Food, Environmental and Occupational Health & Safety
AOP	Adverse outcome pathway
APPA	Association for the Prevention of Atmospheric Pollution
ARS	Regional Health Agency
ATHLETE	Advancing Tools for Human Early Lifecourse Exposome Research and Translation
AVIESAN	French National Alliance for Life Sciences and Health
B[a]P	Benzo[a]pyrene
BAuA	*Bundesanstalt für Arbeitsschutz und Arbeitsmedizin* (German Federal Institute for Occupational Safety and Health)
BLV	Biological limit value
BPA	Bisphenol A
BRV	Biological reference value
BTEX	Benzene, toluene, ethylbenzene and xylene
CALIPSO	Dietary consumption of fish and seafood, contamination by trace elements and pollutants, and omega 3
CES	ANSES Expert Committee
CES ASE	Expert Committee on Socio-economic analysis

CES ERCA	Expert Committee on Assessment of the physical and chemical risks in foods
CHEAR	Children's health exposure analysis resource
CRÉDOC	Research Centre for the Study and Monitoring of Living Conditions
DALY	Disability-adjusted life year
DARES	Directorate for Research, Studies & Statistics
DER	ANSES Risk Assessment Department
DGAL	Directorate General for Food
DGCCRF	Directorate General for Competition, Consumer Affairs and Fraud Control
DGEC	Directorate General for Energy and the Climate
DGPR	Directorate General for Risk Prevention
DGS	Directorate General for Health
DNEL	Derived no-effect level
DTU	Denmark Technical University
DW	Drinking water
EC	European Commission
EFSA	European Food Safety Authority
EHEN	European Human Exposome Network
EHESP	School for Advanced Studies in Public Health
EQS	Environmental quality standard
Equal-Life	Early environmental quality and lifecourse mental health effects
ESFRI	European Strategy Forum on Research Infrastructures
ESTER	Epidemiology in occupational health and ergonomics
ETUI	European Trade Union Institute
EU	European Union
FAIR	Findable, Accessible, Interoperable, Reusable
FIOH	Finnish Institute of Occupational Health
FNE	*France Nature Environnement*
FSK-ML	Food safety knowledge markup language
GIS	Geographic information system
GV	Guideline value

HAS	National Authority for Health
HBGV	Health-based guidance value
HCB	Hexachlorobenzene
HGV	Health guidance value
HRA	Health risk assessment
HRMS	High-resolution mass spectrometry
HW	Household waste
IAQG	Indoor air quality guideline
IARC	International Agency for Research on Cancer
IDGV	Indoor dust guideline value
INCA	French Individual and National Food Consumption Survey
Ineris	National Institute for Industrial Environment and Risks
INRAe	National Research Institute for Agriculture, Food and the Environment
Inserm	National Institute of Health and Medical Research
IQ	Intelligence quotient
IRESP	Regional Forum for Health Education and Promotion
IRSET	Environmental and Occupational Health Research Institute
IRSN	National Research and Safety Institute
ISGlobal	*Instituto de Salud Global* (Barcelona Institute for Global Health)
iTDS	Infant Total Diet Study
ITMO	Multi-Agency Thematic Institutes
JRC	Joint Research Centre
Laberca	Laboratory for the Study of Residues and Contaminants in Food
LCSQA	Central Laboratory for Air Quality Monitoring
LERES	Laboratory for Study and Research of the Environment and Health
LOAEL	Lowest observed adverse effect level
LQ	Limit of quantification
MA	Marketing authorisation
MAF	Mixture assessment factor
MCRA	Monte Carlo risk assessment

MESRI	Ministry of Higher Education, Research and Innovation
MRL	Maximum residue limit
MSD	Musculoskeletal disorder
MSFD	Marine Strategy Framework Directive
NAF	French Classification of Activities
NGO	Non-governmental organisation
NOAEL	No observed adverse effect level
NRCWE	National Research Centre for the Working Environment
OECD	Organisation for Economic Co-operation and Development
OEL	Occupational exposure limit
OFB	French Biodiversity Agency
OH EJP	European Joint Programme on One Health
OQALI	French Food quality observatory
PAH	Polycyclic aromatic hydrocarbon
PBDE	Polybrominated diphenyl ether
PBPK	Physiologically-based pharmacokinetic
PCB	Polychlorinated biphenyl
PFOA	Perfluorooctanoic acid
PFOS	Perfluorooctanesulfonic acid
PM	Particulate matter
PNNS	National Health and Nutrition Programme
PNR EST	National Research Programme for Environmental and Occupational Health
PNSE4	Fourth National Environmental Health Action Plan
QHIA	Quantitative health impact assessment
QHRA	Quantitative health risk assessment
QSAR	Quantitative structure-Activity relationship
REACH	Registration, Evaluation and Authorisation of CHemicals
RV	Reference value
SDHI	Succinate dehydrogenase inhibitor
STIS	Space-time Information System Technologies

TDS	Total Diet Study
TK	Toxicokinetic
TK/TD	Toxicokinetic/Toxicodynamic
TRV	Toxicity reference value
UF	Uncertainty factor
UMT	Joint technology unit
VOC	Volatile organic compound
WEEE	Waste electrical and electronic equipment
WG	Working Group
WMO	World Meteorological Organization
WHO	World Health Organization

Glossary

"Career-long" approach	Takes account of all the working conditions and constraints experienced by workers during their professional career.
"Data-driven" approach	An approach based on collecting data from multiple sources without knowing *a priori* what will be done with these data, and analysing them to see whether they could help solve surveillance problems. (Chiolero and Buckeridge 2020)
"Lifelong" approach	Takes account of all health determinants over the course of a lifetime.
Biomarker of effect	A parameter that reflects the biological response (adverse or not) to an exposure. This response is an observable and/or measurable change at the molecular, biochemical, cellular, physiological or behavioural level, and reveals an individual's present or past exposure to at least one chemical, biological or physical agent. (OPERSEI 2005)
Biomonitoring	Monitoring of population exposure by measuring concentration (contamination) levels of chemicals (and their breakdown products) and environmental pollutants in a body. This is done by measuring biomarkers in biological samples of blood, urine, hair or breast milk. (Ministère des Solidarités et de la Santé 2022)
Eco-exposome	Extension of exposure science from the point of contact between stressor and receptor inward into the organism and outward to the general environment, including the ecosphere. (National Research Council 2012)
Adverse effect	A change in body function or cell structure that could lead to disease or health problems. (US Agency for Toxic Substances and Disease Registry 2018)
Epidemiology	The study of how often diseases and other health conditions occur in different groups of people and why. It includes the study of health-related measurements (e.g. pesticide exposure or vitamin deficiency) in a population and how they may influence the risk of ill health (EFSA n.d.).
Epigenetics	The study of changes in gene activity that do not involve a change in DNA sequence and can be transmitted during cell division. Unlike mutations affecting the DNA sequence, epigenetic changes are reversible. (Inserm 2017)

Total diet study	A study designed to estimate the likely consumption of harmful or beneficial substances in the diet. When undertaking such a study, commonly-consumed foods are purchased from shops in a particular country before being analysed (EFSA n.d.).
Cumulative risk assessment	A method of assessing risks to health or the environment posed by multiple substances such as chemicals (EFSA n.d.).
Weight of evidence assessment	Methodology for assessing the relevance and quality of data, and then combining heterogeneous data. (ANSES 2016b)
Risk assessment	A specialised field of applied science that involves reviewing scientific data and studies in order to evaluate risks associated with certain hazards. It involves four steps: hazard identification, hazard characterisation, exposure assessment and risk characterisation (EFSA n.d.).
Exposure science	This is the science of exposure assessment. It aims to identify and characterise contact with toxic agents and their penetration into the body, in real-life situations (Sari-Minodier et al. 2008).
Exposure	Concentration or amount of a particular substance that is taken in by an individual, population or ecosystem in a specific frequency over a certain amount of time (EFSA n.d.).
Aggregate exposure	Exposure to a chemical via all the different sources (food, water, air, consumer products, etc.) and routes (ingestion, inhalation, skin) from which it may arise (Amélie Crépet, Denys, and Hulin 2012)
Exposome	All the exposure to chemical, biological and physical agents, both harmful and beneficial, in interaction with the physiological status, living environment and psychosocial context, experienced by a living organism from its conception through to the end of its life, in order to explain its state of health. (ANSES Exposome WG)
Exposomics	Study of the exposome that relies on the application of internal and external exposure assessment methods (NIOSH 2022). "Omic" methods are used to assess internal exposure, while concentration data from different sources are combined with data on exposure factors to assess external exposure.
Exposure factor	Individual variables (e.g. behavioural, morphological, physiological, biological) that influence the internal dose of an agent to which an individual is exposed (U.S. Environmental Protection Agency (EPA) 2011).

Machine learning	A form of artificial intelligence designed to train computers to ingest and process information automatically.
Chemical mixture	Mixtures of substances in which each chemical may have a separate identifiable effect on the body and/or a combined effect (EFSA n.d.).
Meta-analysis	A statistical approach that combines the results of a series of independent studies on a given problem (ANSES 2016b).
Microbiota	Microbial communities colonising different sites. They include gut, lung or skin microbiota (Inserm 2016).
Multi-factor/factorial	Consideration of several health determinants of various kinds (chemical, biological or physical agents, psychosocial or socio-economic context, organisational constraints, etc.).
Multi-source	Consideration of several exposure sources (food, water, air, dust, consumer products, etc.).
Multi-route	Consideration of several routes of exposure (ingestion, inhalation, dermal).
Omics	High-powered technologies used for holistic analysis of the molecules that make up the cells of living organisms; for example, genomics is the study of the entire genome, while proteomics analyses the complete complement of proteins within a biological sample (EFSA n.d.). They also include metabonomics, lipidomics and transcriptomics.
At-risk population	A group of individuals with a level of exposure to a chemical, physical or biological agent that poses a risk to their health. For example, in the case of a chemical or physical agent, these may be individuals with exposure above the TRV. Similarly, it may concern a group of individuals with inadequate nutritional intakes in relation to those expected for good health. The at-risk population may (but not necessarily) include so-called sensitive or vulnerable individuals.
Sensitive population	A group of individuals for whom the response to a chemical, physical or biological agent occurs at a significantly lower level of exposure than for the general population, due to factors intrinsic to the individuals in that group. These include children, pregnant women, asthmatics, immunocompromised individuals, people who are overweight or obese, sufferers of chronic respiratory insufficiency, and people with specific conditions such as anxiety or mental illness.
Vulnerable population	Group comprising, in addition to sensitive populations, people who may be subject to higher exposure to certain chemical, biological or physical agents due to extrinsic social (e.g. isolation, cultural barriers, access to information), economic

	(e.g. financial insecurity/poverty, type of job held), environmental (e.g. housing, geographical location) or behavioural factors (e.g. dietary behaviour).
Risk	The probability that something will cause injury or harm to health. (US Agency for Toxic Substances and Disease Registry 2018)
Mental health	A state of well-being whereby individuals recognise their abilities, are able to cope with the normal stresses of life, work productively and fruitfully, and make a contribution to their communities. (World Health Organization 1985)
Thesaurus	Structured directory of terms (key words) for content analysis and document classification.
Toxicokinetics	The study of the processes by which potentially toxic substances are handled in the body. This involves an understanding of the absorption, distribution, metabolism and excretion of such substances. (EFSA n.d.)
Toxicodynamics	The process of interaction of chemical substances with the body and the subsequent reactions leading to adverse effects. (EFSA n.d.)
Toxicology	Study of the harmful effects of substances on humans or animals. (US Agency for Toxic Substances and Disease Registry 2018)
Toxicity reference value	A value defining the level of a particular substance to which people can be safely exposed over a specified period; for example, the acceptable daily intake (ADI). (EFSA n.d.)

List of tables

Table 1: Chemical emissions from non-hazardous composting or waste incineration activities where worker exposure is very likely or is above the occupational exposure limits...............92

Table 2: Mental health determinants...96

Table 3: Interactions between determinants covered by studies..97

Table 4: Results of the simple queries "mental health" and "mental health determinants" 98

Table 5: Toxicological properties common to organochlorines (chlordecone, *p,p′*-DDE, PCB, HCB and lindane)..119

Table 6: Substances referenced in the ATHLETE programme as having effects on neurodevelopment (cognitive development, behavioural disorders) or metabolism in children, which could be comparable to the effects suspected to be related to screen use 125

Table 7: Occupation codes used in connection with household waste management (2003 PCS nomenclature of occupations and socio-professional categories) 173

Table 8: Activity code chosen in connection with household waste management (2003 French NAF activity nomenclature) 173

Table 9: Agents or classes of chemical hazards for which the average intensity of exposure of household waste management workers was neither low nor very low (Sumex2 extraction)173

Table 10: Summary of the main studies measuring concentration levels (ng/g lipids) of PCB 153, PCB 180 and *p,p′*-DDE in the French Caribbean adult population compared with other populations..176

Table 11: Distribution of *p,p′*-DDE contamination in Guadeloupe/KANNARI study 2013-2014 and in Metropolitan France/ENNS 2006-2007. Ratio of contamination for the age groups 40-59 and >60 years 180

Table 12: Risk of prostate cancer in Guadeloupe related to exposure to chlordecone and/or DDE: odds ratio (OR) and 95% confidence interval (95% CI) in Multigner et al. (2010) and Emeville et al. (2015)..181

Table 13: Toxicological properties common to the organochlorines chlordecone, *p,p′*-DDE, PCB, HCB and lindane 184

List of figures

Figure 1: Number of publications and citations containing the key word "exposome" since its emergence in 2005....28

Figure 2: Distribution of publications containing the key word "exposome" according to field 28

Figure 3: Ranking of countries in the world in terms of publications containing the key word "exposome", 2016 to 2020. France is ranked second (Data from R. Slama)....29

Figure 4: Representation in four modules of the study of the exposome illustrated by a few examples: from the ecosystem, which is the source of exposure, through to biological responses and health effects, and including external and internal exposure levels. The time bubble emphasises that the exposome examines exposure over an entire lifetime. The arrows indicate the relationships between the different modules....31

Figure 5: Representation of the exposome as an example of an individual pathway with chemical, biological and physical exposure events occurring over the course of a lifetime and potentially leading to health events....32

Figure 6: Disciplines used to study the exposome showing the diversity of scientific fields required (non-exhaustive representation)....32

Figure 7: The different European H2020 projects in the EHEN cluster 34

Figure 8: Breakdown of the different epidemiological and toxicological models used in the projects funded by the PNR EST over the last 10 years. One project may study several models. 38

Figure 9: The different types of hazards considered and their proportion in exposome-related projects 38

Figure 10: Effects examined in the projects in relation to the exposome funded by the PNR EST 40

Figure 11: The eight themes underlying the WG's recommendations on taking the exposome into account in risk assessment....42

Figure 12: Recommendations for the exposome and epidemiological studies 44

Figure 13: Recommendations for exposome data 50

Figure 14: Recommendations for integrating the mixtures component in risk assessment ...54

Figure 15: Recommendations for multi-source and multi-route exposure assessment 58

Figure 16: Recommendations for dynamic exposure assessment....66

Figure 17: Recommendations for the establishment of reference values....70

Figure 18: Recommendations for assessing risks and the health impact....75

Figure 19: Relationships between chemical exposures in the environment and living beings, including humans. Any type of exogenous chemical exposure can change endogenous exposure and activate cellular toxicity pathways. The cellular level may serve as an integrator for understanding the mechanisms of adverse human health outcomes and ecosystem-level effects (Escher et al. 2017)....78

Figure 20: Recommendations for the eco-exposome 81

Figure 21: Exposome components to be progressively introduced in future risk assessments (HRAs). The choice of components depends on the subject and timetable of the formal request. 84

Figure 22: Decision tree to be used in the planning phase of the expert appraisal....85

Figure 23: Diagram of the introduction of the different components in the health risk assessments (HRAs). The modules represent the components and are added according to the question asked. As the number of modules increases, so does the degree to which the exposome components are taken into account. The level of consideration of exposome components is associated with a greater level of complexity and consideration of the reality of exposure. 86

Figure 24 The five applications to formal requests detailed in this report....89

Figure 25: Literature queries conducted on the immunological effects of chemical substances or classes frequently identified in connection with household waste management activities.94

Figure 26: Literature query on respiratory infections and waste workers 95

Figure 27: Cross-referencing of the queries "mental health" and "mental health determinants" 99

Figure 28: Literature query on mental health and waste workers....99

Figure 29: Influence of the chemical and biological context in terms of the hazard (Woodruff et al., 2008)....102

Figure 30: The four actions proposed by the Exposome WG on consideration of sensitive populations for establishing reference values....104

Figure 31: Timetable of the work on chlordecone and integration of the Exposome WG's recommendations (yellow bubbles) 114

Figure 32: *p,p'*-DDE concentration levels in the French Caribbean and in mainland France of adults over 18 years of age (in ng/g of lipids) 118

Figure 33: Free time of 11-17 year olds in France in 2009, according to INSEE's *Emploi du Temps* survey (HCFEA 2018) in hours per day 127

Figure 34: PCB 153 concentration levels in the French Caribbean and in mainland France of adults over 18 years of age (in ng/g of lipids) 177

Figure 35: PCB 180 concentration levels in the French Caribbean and in mainland France of adults over 18 years of age (in ng/g of lipids) 178

Figure 36: *p,p'*-DDE concentration levels in the French Caribbean and in mainland France of adults over 18 years of age (in ng/g of lipids) 179

Figure 37: Ratio of *p,p'*-DDE contamination in individuals over 40 years of age between Guadeloupe and Martinique and mainland France (ng/g lipids)....179

1. Background, purpose and procedure for carrying out the expert appraisal

1.1 Background and objectives

Since its emergence in 2005, the concept of the exposome has given rise to numerous research projects that form part of a continuum of questions to science about the role of environmental factors in the development of chronic diseases, which have become the leading cause of death in developed countries in recent decades. The interest shown in this concept has extended beyond research teams to convince public decision-makers, and it was included in the Act of 28 January 2016 on the modernisation of the health system.

Thus, under the provisions relating to general health administration, it is written that health policy includes (Article L.1411-1, Subparagraph 1): *"The monitoring and observation of the health status of the population and the identification of its main determinants, particularly those related to education and living and working conditions. Identification of these determinants is based on the concept of the exposome, understood as the integration over an entire lifetime of all the exposures that can influence human health."* Under the provisions relating to the protection and promotion of maternal and child health, and more specifically on the general organisation and missions, Article L. 2111-1 mentions that: *"The State, local authorities and social security bodies shall participate, under the conditions laid down in this Book, in the protection and promotion of maternal and child health, which shall include in particular [...] 5° Prevention and information measures on health risks associated with environmental factors, based on the exposome concept."*

ANSES carries out tasks in the areas of monitoring, expert appraisal, research and reference in a wide range of fields including human health, animal health and welfare, and plant health. The Agency provides a cross-functional perspective on health issues when assessing health risks and benefits, in particular through the lens of the human and social sciences. Its monitoring, vigilance and surveillance work provides input for risk assessment. The Agency assesses a broad range of risks (chemical, biological, physical, etc.) to which a person may be exposed, intentionally or otherwise, at all ages and times of their life, whether at work, while travelling, while engaging in leisure activities, or via their diet[1]. These risks are most often assessed from a single source (air, water, food, dust, veterinary medicinal products, etc.) and a single route of exposure (ingestion, inhalation, dermal contact) by making simplified assumptions about exposure over time (constant, acute one-off exposure, etc.).

Thus, the exposome, which seeks to study the role of all the environmental factors encountered over the course of a lifetime in the development of disease, has yet to be largely implemented by ANSES, whether scientifically or methodologically. It is therefore important for the Agency to assess the practical consequences of including the exposome concept in legislation and integrating it in the deployment of its core activities. This involves identifying the opportunities, approaches and means for its implementation, as well as what is needed in terms of development and new skills to address it.

To this end, ANSES set up a working group (Exposome WG) reporting to the Scientific Board and tasked with proposing ways to strengthen integration of the exposome in the Agency's

[1] https://www.anses.fr/en/content/our-identity

activities, particularly its expert appraisal work. In this respect, the aim was to make practical proposals via case studies on integrating the exposome in the expert appraisal work carried out by the Agency, while analysing the consequences.

Consideration of the exposome in risk assessment is still relatively unstructured. As the exposome is systemic in nature, it is made up of different components that can be studied by a variety of disciplines, using a wide range of approaches and techniques, some but not all of which are already used in risk assessment. The objective of this report is to identify the data, methods and tools needed to address the exposome and which can be put into practice, based on current risk assessment issues. It ultimately involves proposing a more comprehensive risk assessment approach, which takes account of the reality of exposures in terms of the diversity of exposure factors and sources, in a specific social and environmental context, and which integrates inter-individual and intra-individual variability over the course of a lifetime. This report focuses on all the health determinants assessed by ANSES: chemical, biological and physical agents, the psychosocial and socio-economic context, organisational constraints, etc., with the possibility of including other factors. It should be noted that the methods, data and examples relating to chemicals are more widely represented because the exposome approach was initially developed in this field. Besides expert appraisal, risk management paradigms will also need to be revised to integrate the exposome. This integration may also have an impact on all the components (assessment/monitoring/management) of risk governance. Because one of the Agency's missions is to support the players of this governance with its expertise, any changes resulting from the implementation of this WG's recommendations may then be reflected in public policies, as well as in the practices of economic players and populations.

The Agency stresses the broad scope of the questions raised by the exposome, and points out that they extend into areas (ethical, scientific, legal, etc.) that go well beyond the remit of ANSES's mission. The work undertaken with the Scientific Board has enabled an initial exploration, while remaining within ANSES's areas of competence.

After consultation with European health organisations, it appears that the exposome is currently addressed mainly at the research level (see Chapter 2.2) and is still not widely integrated in risk assessments. However, debates are under way. EFSA, which has not formally integrated the exposome in its assessments, is currently considering this possibility, in particular through the recent organisation of a workshop on this subject. The Czech Republic's Research Centre for Toxic Compounds in the Environment (RECETOX), which is examining the exposome issue, is pushing for the integration of these new approaches and their results in national activities (monitoring and biomonitoring programmes, implementation projects, case studies, policy documents, etc.). In addition, Hungary's National Food Chain Safety Office is planning to strengthen its risk assessment activities and develop its capabilities in order to use the exposome concept. In general, these organisations state that although they are aware of the importance of the exposome, it has not been possible for them to devote more time to this topic. The main difficulties mentioned are the lack of data, in particular harmonised data, the complexity of implementing this approach and the difficulty of establishing effective coordination between the different players.

1.2 Procedure: means implemented and organisation

In the first half of 2019, ANSES drafted terms of reference for an internal request on the issue of taking the exposome into account in its activities – particularly its expert appraisal work – and put them to its Scientific Board, which would be entrusted with responding to it (Annexe 1). There was a discussion on the objectives of this request and the way in which it was to be addressed, and a working group (WG) made up of experts from the Scientific Board (2016-2019 mandate) was formed and convened for this purpose, to share an initial overview of the situation. For internal Agency reasons, the working group (whose initial composition has changed) was only able to begin its work in early 2021. The working approach proposed by the WG was presented and discussed at the Scientific Board's meeting in March 2021.

In terms of "core activity" areas, the WG's work focused on expert appraisals in risk assessment and on research funding activities. With regard to expert appraisals, the WG made an original choice in basing its work on ongoing formal requests within the Agency, in order to consider the possibility of integrating the exposome in these specific cases of expert appraisals. These formal requests were suggested by the Agency and selected by the WG following an analysis of ANSES's work programme (2021 and 2022 versions) and the different stages of progress of the requests. Priority was given to work just beginning.

To this end, a "mirror group" was set up within the Risk Assessment Department (DER) whose members were the coordinators of the selected formal requests. Whenever possible, the ideas proposed by the WG were presented to the body tasked with responding to the formal request (WG or Expert Committee – CES).

The working group – named the Exposome WG – was therefore made up of most of the experts from the first mandate and members of the new Scientific Board (2020-2023 mandate), as well as an expert who is now retired and who was a member of the former Scientific Board, and ANSES staff members with expertise in the field of the exposome or the coordinators of the ongoing work for the selected formal requests.

The Exposome WG's expert appraisal work was regularly submitted to the Scientific Board. Their draft report was submitted for a targeted internal and external consultation in May 2022. The report produced by the working group therefore takes account of the observations and additional information provided during this consultation and by the Scientific Board members. The report and its recommendations received final validation by the Scientific Board at its meeting on 20 September 2022.

This work was therefore conducted by a group of experts and ANSES staff with complementary skills. The expert appraisal was carried out in accordance with French Standard NF X 50-110 "Quality in Expert Appraisals – General requirements of Competence for Expert Appraisals (May 2003)".

1.3 Prevention of risks of conflicts of interest

ANSES analyses interests declared by experts before they are appointed and throughout their work in order to prevent risks of conflicts of interest in relation to the points addressed in expert appraisals.

The experts' declarations of interests are made public on the following website: https://dpi.sante.gouv.fr/.

2. The exposome

2.1 Definition

The concept of the exposome was put forward in 2005 by Christopher Wild (Wild 2005), epidemiologist and Director of the International Agency for Research on Cancer (IARC), to draw attention to the critical need for more complete environmental exposure assessment in epidemiological studies, with "environment" being defined in the broad sense of "non-genetic" factors that may cause disease (Wild 2012). Indeed, he pointed out at the time that whereas exquisite tools had been developed to sequence the human genome and interrogate individual susceptibility through genome-wide association studies (GWAS) (Manolio 2010), there was a relative paucity of comparable tools, or indeed investment, in relation to exposure assessment. Given that cancer and many other chronic diseases develop predominantly from a combination of environmental exposures played out on a particular genetic background, the inability to measure one part of the gene/environment combination with anything approaching the precision of the other was a limitation for epidemiology, particularly as this aims to identify relatively modest effect sizes associated with specific environmental exposures.

This concept was therefore intended to complement the genome effect by providing a complete description of the lifelong exposure history. In 2012, Wild refined his initial definition of the exposome to explicitly include three domains of investigation to be considered: internal (e.g. endogenous factors such as metabolism, morphology, etc.), specific external (e.g. environmental pollutants, radiation, micro-organisms, chemicals in the workplace) and general external (e.g. social, economic and/or psychological factors, urban/rural environment, climate, etc.) (Wild 2012).

Additional important contributions followed, developing more specific views of the exposome and reflecting different perspectives. Epidemiologist Buck Louis emphasised the importance of community and lifestyle factors (Buck Louis, Smarr, and Patel 2017), while Rappaport and Smith focused on the internal chemical exposome consisting of xenobiotics, endogenous metabolites, microbial metabolites and dietary compounds (Rappaport and Smith 2010). From a more toxicological perspective, Miller and Jones defined the exposome as including all environmental influences and associated biological responses (G. W. Miller and Jones 2014). A view based on computer modelling and highlighting the connectivity of biological processes has also been proposed (D. A. Sarigiannis 2017). The eco-exposome corresponds to the reciprocal influences between the ecosystem and human exposure (Escher et al. 2017), but different definitions have also been proposed that extend the concept to the exposure of animal and plant species in their ecosystems (Scholz et al. 2022). More recently, Vermeulen et al. advocated characterisation of the exposome on a genome-like scale to address the health challenges facing current and future generations (Vermeulen et al. 2020). A recent literature review analysed the mutually beneficial relationships between the exposome and toxicology (Barouki et al. 2021). Lastly, in order to better distinguish exposures from their biological and health effects, Price et al. (2022) suggested using the term "exposome" to describe exposures, and grouping biological and health impacts under the term "functional exposomics", by analogy with functional genomics.

Since its emergence in 2005, the exposome concept has led to an increasing number of scientific publications each year (a total of 184 results from the Web of Science Core Collection), but this still remains small (n=37 in 2021) (Figure 1).

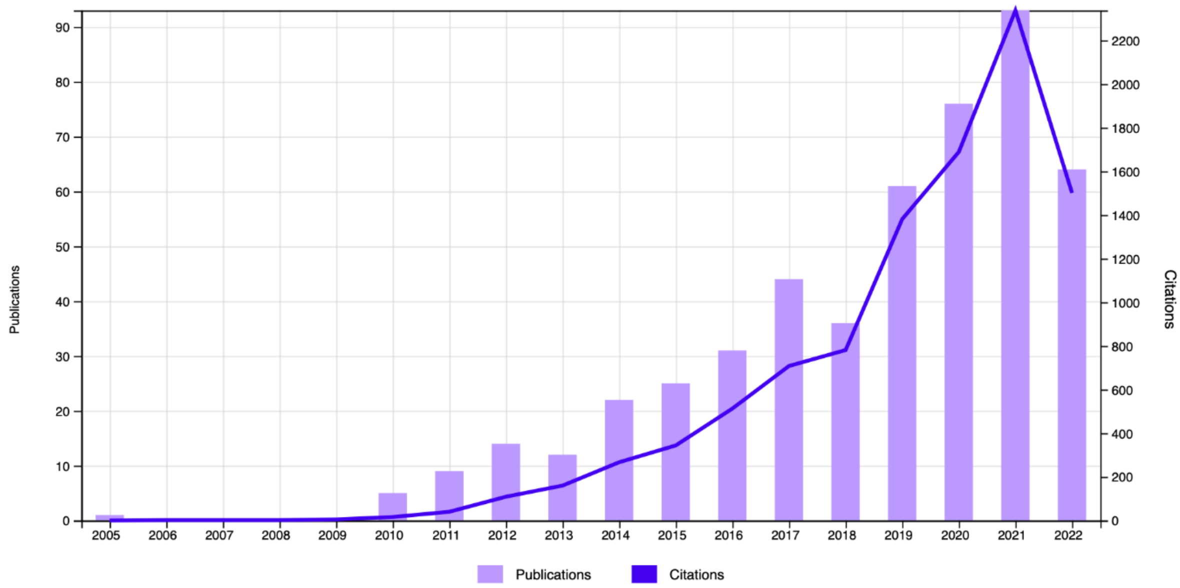


Figure 1: Number of publications and citations containing the key word "exposome" since its emergence in 2005.

These publications are mainly in the fields of environmental and occupational health, environmental sciences and toxicology (Figure 2).

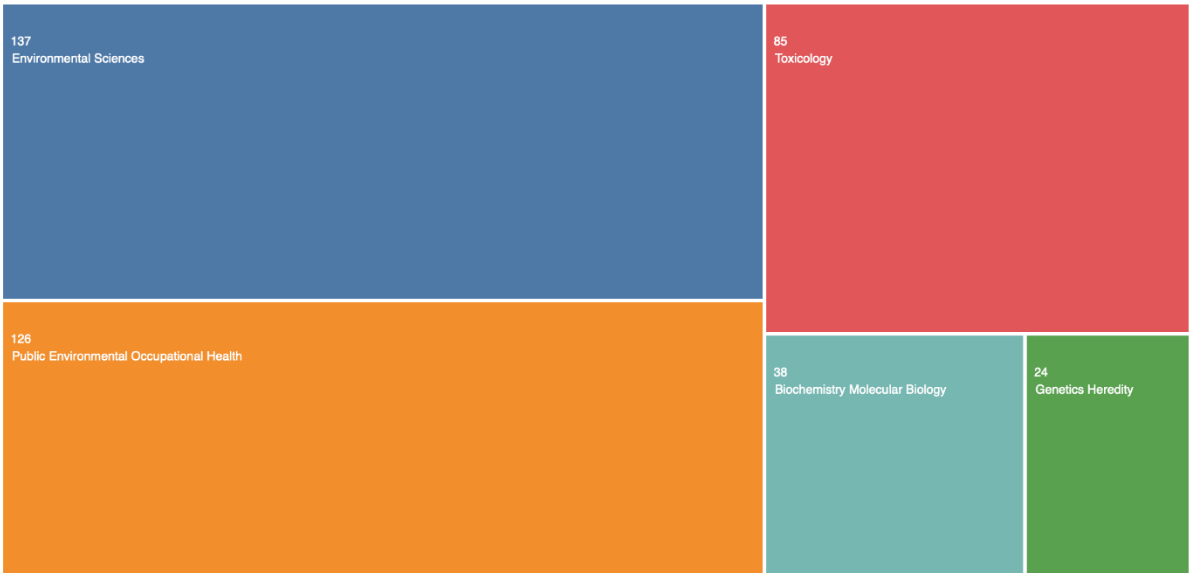


Figure 2: Distribution of publications containing the key word "exposome" according to field

France appears in a leading position in terms of research devoted to the exposome in Europe and the world, with around 20% of publications in the period 2016-2020 (second place behind the United States) (Figure 3).

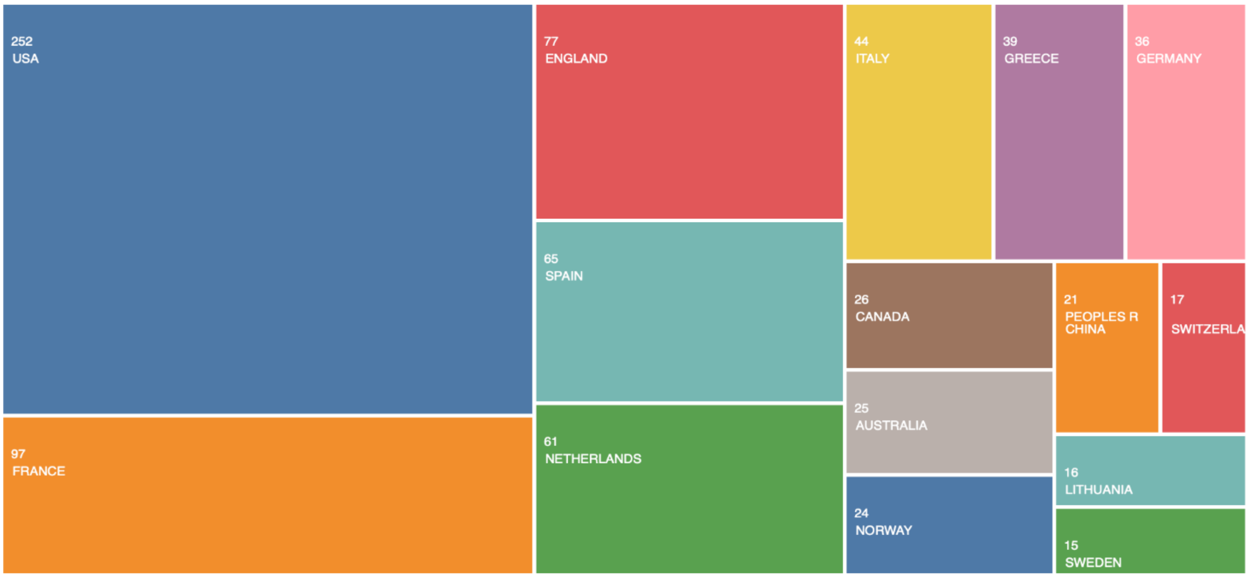


Figure 3: Ranking of countries in the world in terms of publications containing the key word "exposome", 2016 to 2020. France is ranked second (Data from R. Slama).

These views of the exposome are currently leading to studies in which 1) exposure is characterised in greater depth, mainly through the use of new tools to monitor or measure it indirectly, such as the large-scale application of "omics" approaches, 2) different types of exposure (chemical, physical, biological, social) are combined, 3) links between exposure and effects are better identified and more systematically characterised, and 4) the sequence of exposures and developmental stages over the course of a lifetime are taken into consideration. Although these objectives are ambitious and cannot yet all be achieved in a single study, they have nevertheless inspired (and will continue to inspire) epidemiological and toxicological studies, leading to a better characterisation of exposure and a better estimation of the associations with health effects (P. Vineis et al. 2017; Barouki et al. 2021). Nevertheless, some important issues remain inadequately covered, including a better assessment of causality and the mechanisms combining multiple exposures with complex health and environmental effects.

In order to facilitate the adoption and implementation of the exposome in ANSES's work, the WG suggests **the following definition of "exposome"**: the exposome corresponds to **all the exposure to chemical, biological and physical agents, both harmful and beneficial**, in interaction with **the physiological conditions, living environment and psychosocial context**, experienced by a living organism from its conception through to the end of its life, in order to explain its state of health.

This definition incorporates the different components making up the exposome: the multi-dimensional component relating to mixtures, sources and multiple exposure factors, which is represented by "all the exposure" and the diversity of agents; the health risk/benefit component; the temporal component with the study of the exposome from "conception [of a living being through to the end of its life]"; the social and environmental components represented by the "interactions with the living environment and psychosocial context". It is applicable to both human and non-human organisms (Scholz et al. 2022). Regarding the animal and plant kingdoms, the notion of "psychosocial context" will not be considered, but those of animal welfare and specific behaviour and sensitivity to their environment will be taken into account. By complementing the knowledge of the genome with which it may interact, the exposome thus helps explain the health status of populations (Barouki et al. 2018).

The WG proposes to represent the exposome study in four modules as shown in Figure 4. The first module, "ecosystem", represents the environment in which humans live, including biodiversity. An individual's surroundings will define a large part of its exposure. Monitoring its environment and the living organisms that make up its surroundings will therefore provide insights on the type and level of exposure and, more broadly, on the state of health of non-human populations living there. The second module represents all the so-called "external" exposures, which are the different agents to which individuals are liable to be exposed and which are defined by the agents' type, sources and quantity, and the social, organisational and physical environment of the individuals as well as their lifestyle and activities. The levels of these agents can be estimated by combining data on their quantities in the various sources with those on lifestyle habits (consumption of food, use of items such as toys, clothing and furniture, use of cleaning products, pursuit of sports activities, consumption of tobacco or alcohol, etc.) modulated by the physical and social environment, including the workplace.

The external exposome will then induce the type and levels of the internal exposome (third module) measured by biomarkers of exposure and infection in biological matrices such as blood, urine, hair, etc. The transition from external to internal exposure is regulated by the infectious process for biological agents and by toxicokinetics for chemical and physical agents. The external exposome and then the internal exposome will have repercussions on the human body by provoking biological responses at the molecular, cellular, tissue and organ levels (fourth module). These responses can be positive (cell repair, immune system activation, etc.) and/or negative (oxidative stress, cell death, etc.). Whether they are positive or negative depends on the duration of exposure and the body's ability to adapt. The body will react differently depending on its sensitivity and vulnerability (genetics, epigenetics, microbiota, life stage, etc.) and these responses will in some cases result in the onset of diseases (fourth module). Agents of the same type (for example a mixture of chemicals) or of a different type (for example a chemical agent and a biological agent) may combine their effects or conversely compete with each other, thus limiting their overall impact on health. It should be noted that certain factors are protective of health, such as access to healthcare, physical activity, and nutrient intakes when complying with the recommended levels. The components described above are all interrelated, illustrating the complexity of the exposome.

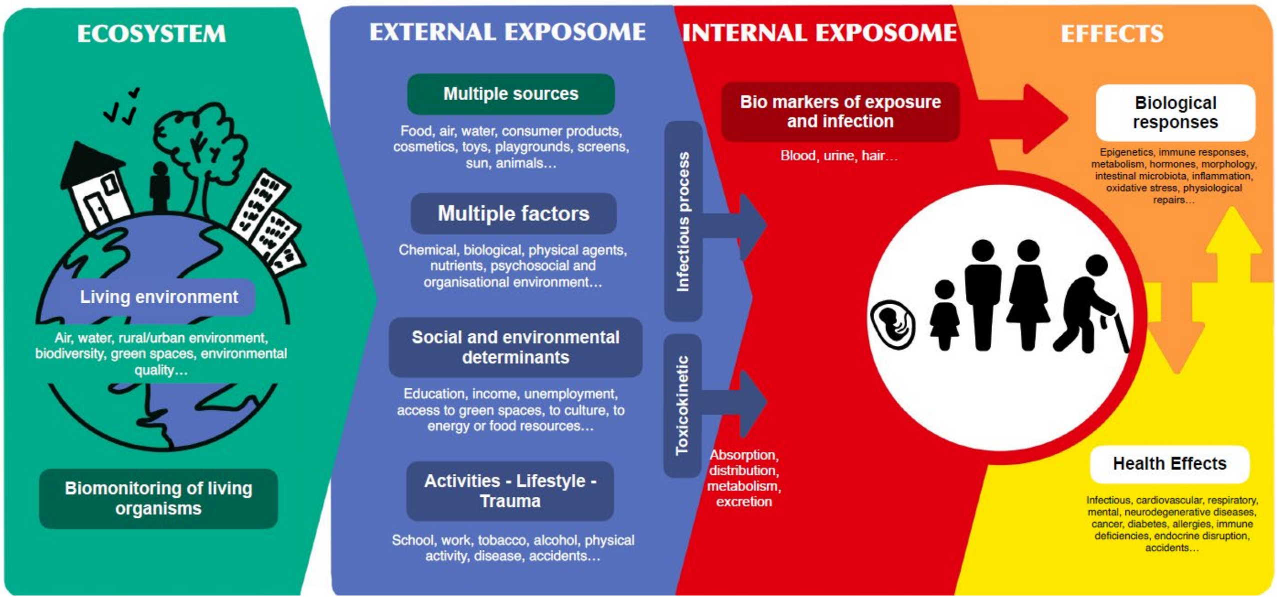


Figure 4: Representation in four modules of the study of the exposome illustrated by a few examples: from the ecosystem, which is the source of exposure, through to biological responses and health effects, and including external and internal exposure levels. The time bubble emphasises that the exposome examines exposure over an entire lifetime. The arrows indicate the relationships between the different modules.

The following example illustrates the interactions between the exposures described above. A population can be exposed to a chemical from three different sources: food, air and veterinary medicines for pets. The level of external exposure to this substance will depend on each individual's environment (e.g. urban/rural) and behaviour, in this case dietary and whether or not they have a pet. The chemical can enter the body by three routes: oral, respiratory and dermal contact, and can then be distributed to the various organs, metabolised and eliminated according to its toxicokinetics. The presence of this substance will trigger a chain of biological responses leading to the potential occurrence of a health effect, for example a decrease in immunity. If, as a result of this exposure, a virus comes into contact with the host, the two responses will combine to produce a greater response than if exposure to the virus had not been preceded by exposure to the chemical. Access to healthcare to treat the associated disease will depend on the individual's social, economic and geographical context (level of education, information, income, etc.).

Figure 5 represents the exposome as an individual pathway. With their own unique genetic and epigenetic heritage, individuals are subjected throughout their lives to several chemical, biological and physical exposure events over varying periods of time, ranging from acute exposure during a meal, for example, to chronic exposure over several years. These exposure events will potentially lead to health effects that will be triggered either immediately after the exposure event, such as allergic reactions, or months or years later, such as cancer. For example, it has been observed in recent years that specificities in genetic polymorphism may play an important role in the development of neurodegenerative diseases (Deloménie et al. 1998; Lee et al. 2018; Toselli et al. 2015).

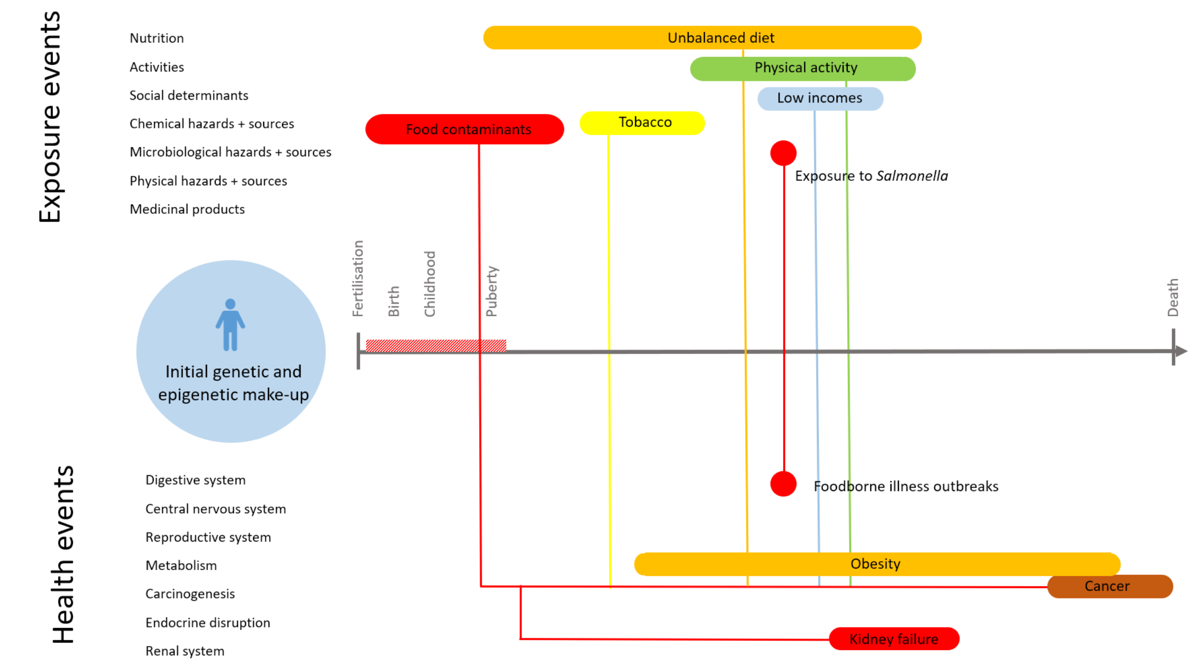


Figure 5: Representation of the exposome as an example of an individual pathway with chemical, biological and physical exposure events occurring over the course of a lifetime and potentially leading to health events

The study of the exposome requires interdisciplinary collaboration between the many scientific fields shown in Figure 6. Very close collaboration between epidemiology and other environmental health disciplines (medicine, exposure science, toxicology, microbiology, "omics" technologies, mathematics, social sciences, etc.) is needed in order to examine all the socio-environmental determinants of chronic non-genetic diseases.

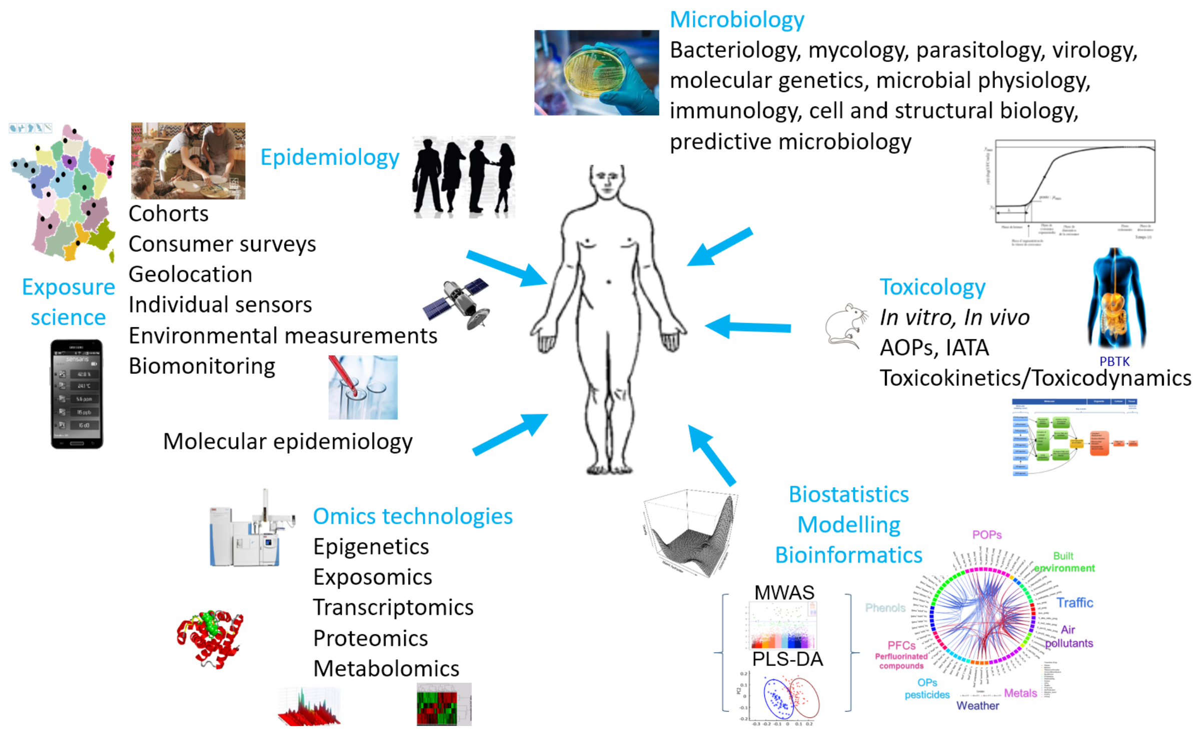


Figure 6: Disciplines used to study the exposome showing the diversity of scientific fields required (non-exhaustive representation)

2.2 Research projects and infrastructure

European projects on the exposome

Since 2012, several European projects on the exposome have been funded by the European Commission (EC), initially in the context of the FP7[2] (2007-2013) and H2020[3] (2014-2020) programmes. The European strategy initially consisted in funding multi-partner research projects with precise objectives, rather than infrastructures made available to epidemiological, clinical or toxicological programmes, as has been done in the United States since the 2010s, in particular with the following infrastructures: HERCULES[4] on the development of methods and tools for research on the exposome, CHEAR[5] to promote incorporation of the exposome into children's health studies, and LIFE[6], which focuses on the pre-conception period by characterising maternal and paternal exposure in order to assess their effects on fertility and birth. In Europe, the first three FP7 projects were HELIX[7] on the mother-child exposome (Vrijheid et al. 2014); Exposomics on the effects of air and water pollution (P. Vineis et al. 2017); and HEALS[8] on the development of methods with a strong modelling component (D. A. Sarigiannis et al. 2020). Other projects include Lifepath, which introduces notions of the social exposome throughout life (Paolo Vineis et al. 2020).

The EC has continued its efforts by funding nine projects on the exposome under the H2020 programme since 2020, grouping them together as a cluster called the European Human Exposome Network (EHEN). These projects have diverse objectives, some focusing on diseases (pulmonary, cardiovascular, immune, child neurocognitive development), others on contexts such as urban and work settings, and others on incorporating social factors and on methodologies. These projects are summarised in Figure 7 below.

[2] Seventh Framework Programme
[3] Horizon 2020
[4] Health and Exposome Research Center: Understanding Lifetime Exposures
[5] Children's Health Exposure Analysis Resource
[6] Longitudinal Investigation of Fertility and the Environment
[7] Human Early-Life Exposome
[8] Health and Environment-wide Associations based on Large population Surveys

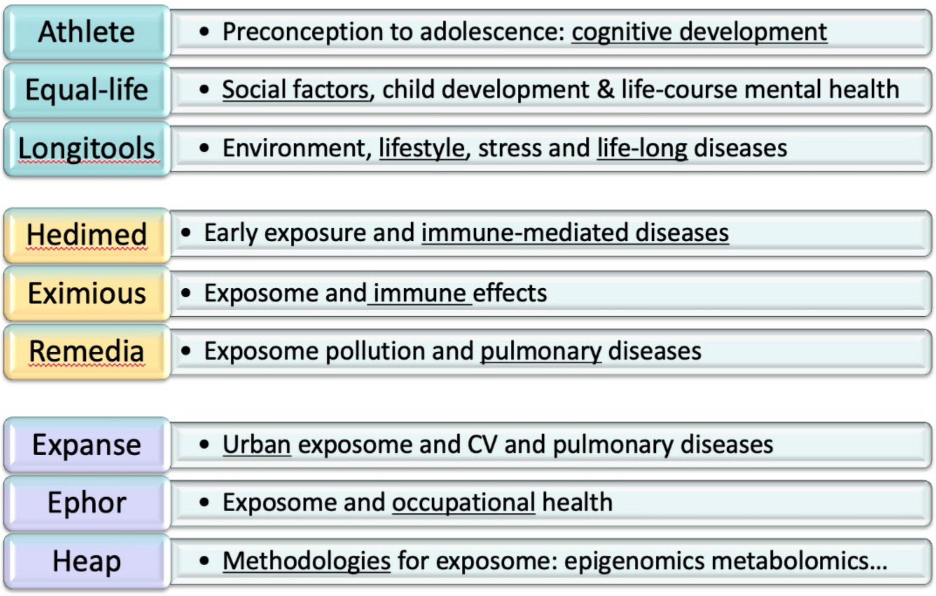


Figure 7: The different European H2020 projects in the EHEN cluster

In addition to the exposome projects themselves, there are related projects covering part of the exposome. The European biomonitoring project HBM4EU[9] (H2020, 2017-2022) aims to organise biomonitoring studies of chemical exposure at European level. Besides monitoring, this project is also seeking to better characterise the health impacts of priority chemicals and predict sources of contamination. In this sense it represents an effort to characterise the chemical exposome. The PARC[10] project, which started in 2022 and will run for seven years, is even more ambitious as it pursues and goes beyond the objectives of the HBM4EU project by including components on the toxicology of chemicals, integrated approaches to risk assessment, and environmental effects. It will be the flagship project on the link between the chemical exposome, risk assessment and public decision-making. France actively participates in European exposome programmes, often playing a leading role, such as in the REMEDIA, HELIX, ATHLETE, HBM4EU and PARC projects.

European infrastructure

In 2021, the EIRENE[11] infrastructure project was included in the European ESFRI[12] roadmap, reflecting a shift in European strategy towards establishing infrastructure. EIRENE is intended to be the future pan-European reference structure for assessing human exposure to environmental risk factors. It offers comprehensive approaches to the human and environmental chemical exposome, and omics and computational approaches to support research projects in this area. France participates in this infrastructure through the consortium that makes up the France Exposome infrastructure (see below). Other European infrastructures can also contribute to work on the exposome, in particular BBMRI-ERIC[13] and the ELIXIR[14] infrastructure on life science tools and data storage.

[9] European Human Biomonitoring for Europe
[10] Partnership for the Assessment of Risks from Chemicals
[11] Environmental Exposure Assessment Research Infrastructure
[12] European Strategy Forum on Research Infrastructures
[13] Biobanking and Biomolecular Resources Research Infrastructure
[14] European Life-Science Infrastructure

National infrastructure: France Exposome

The Laberca analytical biomonitoring platform (UMR 1329 Oniris-INRAe, Nantes) joined forces with the LERES laboratory (IRSET – UMR 1085 Inserm, Rennes) to form a national research infrastructure project called France Exposome. Its analytical activities are supplemented by toxicokinetic and systemic toxicology approaches. France Exposome, registered by the Ministry of Higher Education, Research and Innovation (MESRI) in early 2021, has been included in the national infrastructure roadmap. Oniris, EHESP and Inserm are the founding supervisory authorities, and INRAe, Université Paris Cité and Ineris are the associate authorities. France Exposome is the French branch of the European infrastructure EIRENE.

National projects

Several national projects also contribute to exposome research. They are financed, for example, by the National Research Programme for Environmental and Occupational Health (PNR EST) and the French National Research Agency (ANR). The PNR EST projects were presented at the Exposome Day[15] organised by ANSES and Inserm on 30 November 2022. Ongoing ANR projects on the exposome include GePhEx[16], which focuses on learning causal effects between phenome and exposome from large amounts of heterogeneous data in human complex diseases; SoEcoHealth, developing an approach for the evaluation of succinate dehydrogenase inhibitor (SDHI) fungicide use: exposome and hazards for biodiversity and human health; and PolluHealth on the impacts of early-life exposome on the occurrence of susceptibility factors to develop respiratory diseases at adult age.

The future-oriented investment programme (PIA) set up by the State offers opportunities for more extensive plans. For example, a project for priority exploratory research programmes and equipment (PEPR) focusing on the exposome (Expo-Dis) has just been submitted, and the ExposUM project from the University of Montpellier has just been recognised under an *Excellence sous toutes ses formes* programme.

Link to the PNSE4 and Green Data for Health

The Fourth National Environmental Health Action Plan (PNSE4) is promoting the funding of a PEPR on the exposome, which led to Expo-Dis being submitted by Inserm. In addition, the PNSE4 supports the Green Data for Health programme, which is clearly relevant to the exposome. This is because work on the exposome generates large datasets, and their storage and exploitation are at the heart of Green Data for Health. If these two objectives of the PNSE4 are achieved quickly, and if the funding agencies give priority to environmental and health issues, a genuine national strategy on the exposome will have been set in motion, which will foster the strong involvement of French teams at European level.

[15] https://www.anses.fr/en/content/anses-inserm-scientific-conference

[16] Genome, Phenome, Exposome

3. The exposome in ANSES's research funding mission

ANSES manages and implements the National Research Programme for Environmental and Occupational Health (PNR EST). This programme aims to promote sustainable research into the risks to human health associated with our environment, including our working environment, and risks to ecosystems.

PNR EST issues calls for research projects each year, in order to:

- link research and expert appraisal: the actions carried out under this programme are situated both upstream and downstream of the expert appraisal process. Upstream, it mobilises the research community in these fields, in order to provide the expert appraisal process with new data and experts; downstream, it ensures that the research needs identified during expert appraisals are incorporated in the calls for projects;
- support the production of knowledge that can be directly used for developing public prevention and precautionary policies, and for their assessment. It also contributes to their dissemination to stakeholders;
- play a leading role in fostering interactions within the scientific community, which helps ANSES mobilise researchers for its collective expert appraisals of health risks.

These general or specific[17] calls for projects are designed to finance research on priority issues linked to changes in society, raised by public policies (French Environmental Health, Occupational Health, Cancer and Ecophyto[18] plans). PNR EST is currently financed by ANSES from budgets delegated by the Ministries of the Environment, Labour and Agriculture, together with several co-funding partners, including ADEME and ITMO Cancer from the AVIESAN alliance.

Among the topics of interest in these calls for projects are risks associated with chemical agents such as endocrine disruptors, nanomaterials, biological agents, light pollution, noise and radiofrequencies. Other issues such as the impact of climate change, factors promoting cancers, and vector control are also included. To address these issues, the calls for projects encourage proposals that aim to develop multidisciplinary approaches, including human and social science approaches.

3.1 Review of exposome-related projects over the last 10 years

An average of around 35 projects have been funded each year by the PNR EST since its creation in 2006. For this review, we analysed the themes of the projects funded since 2011, the year in which the topics proposed to researchers were first structured by research question, as well as the current selection process. Since 2011, the list of funding bodies and therefore

[17] A call for projects on the theme of "Radiofrequencies and health" has been launched every year since 2013; the issue of "Antimicrobial resistance and the environment" was the subject of a specific call in 2017.
[18] The Ecophyto II+ plan supports efforts to reduce the use of plant protection products.

the scope of these calls has also stabilised, with just a few variations. In total, between 2011 and 2020, 357 projects were financed, finalised or were still in progress. Full projects generally have a budget of around €200K, and €50K for feasibility studies. Thus, the exposome cannot be studied as a single project, as this would go far beyond the limits of the allocated grants. Nevertheless, many of these projects may address one or more components of the exposome.

Projects with one of the following characteristics were considered to be related to the exposome and were therefore selected for analysis:

- Epidemiological studies enabling a "lifelong" or "career-long" approach.
- Projects with *in vitro* or *in vivo* experimental approaches, integrating either multiple-exposure aspects, mixtures or research into markers of exposure (particularly through "omics" or epigenetic studies).
- Projects dealing specifically with vulnerable populations.
- Projects taking different exposure routes into account for the same agent.
- Studies including the exposure of ecosystems for an overall approach that takes account of the health of all organisms and the human living environment: contamination of aquatic ecosystems, contaminated soil, bee health.
- Lastly, projects encompassing notions of disease burden and socio-economic components.

These criteria identified 210 projects, i.e. 59% of the projects funded by the PNR EST, 40% of which were based on epidemiological studies and 60% on experimental approaches. Annexe 2 presents the 32 projects focusing on co-exposure.

Targeted populations

Sensitive populations, especially children and pregnant women, were taken into account in 30% of these funded projects. Other categories of sensitive individuals were also addressed by specific studies (5%): hospital patients, people with asthma, allergies, overweight, chronic diseases, diabetes, age-related macular degeneration (AMD) or the elderly. A large proportion of the studies (23%) only related to workers, and 9% of the projects focused more specifically on ecosystems.

Epidemiological and toxicological models used

The breakdown of the different epidemiological and toxicological models used in the funded projects is presented in Figure 8. More than 40% of the projects involved human epidemiological studies. In a large proportion, in more than 20% of cases, cell models or three-dimensional tissues (organoids) were used. Next came the classic animal models: rats and mice. Fish and shellfish were also well represented, particularly for studying exposure associated with aquatic ecosystems.

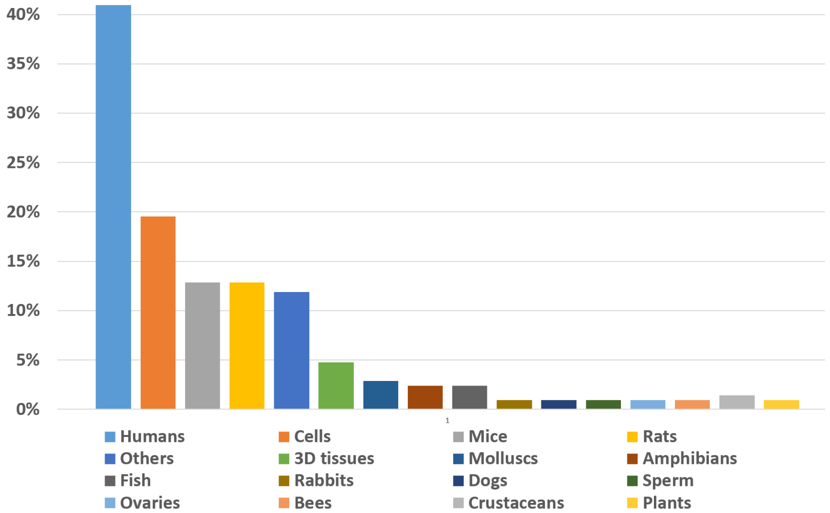


Figure 8: Breakdown of the different epidemiological and toxicological models used in the projects funded by the PNR EST over the last 10 years. One project may study several models.

Types of hazards studied

More than half of the projects dealt with chemical agents: pesticides, phthalates, phenols, endocrine disruptors, etc. The others focused on physical agents (radiofrequencies, LEDs, electromagnetic fields, etc.), air pollutants, nanoparticles or fibres, biological agents (bacteria, mould, mites, etc.), working environments (such as night work) and some took social determinants into account (socio-economic status). Figure 9 summarises the different types of factors considered and their proportions. Air pollutants addressed by specific research questions are considered separately from other types of factors.

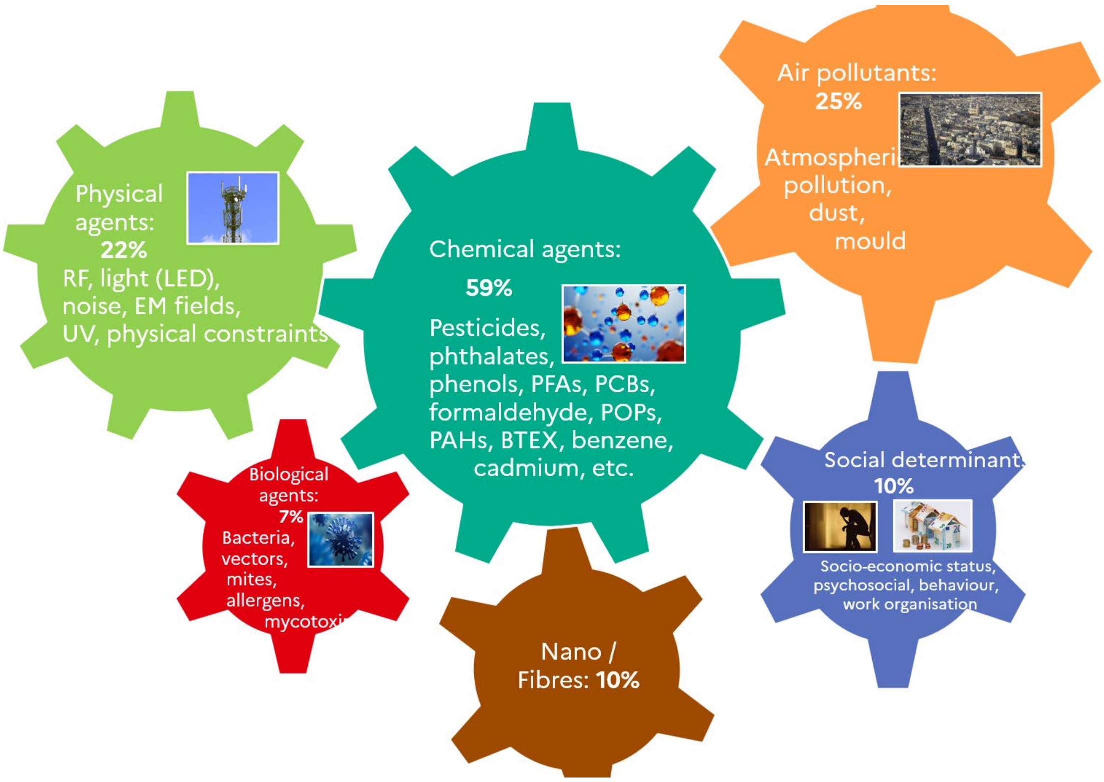


Figure 9: The different types of hazards considered and their proportion in exposome-related projects

These hazards may be studied alone or in mixtures. In the case of chemical agents, more than half of the projects studied mixtures. Studies also looked at co-exposures between different types of hazards. We were particularly interested in these projects. They are usually epidemiological or exposure studies.

Among the projects studying exposure to chemicals, including pesticides, these chemicals were studied in co-exposure with:

- both air pollution, physical agents (natural radioactivity, high-voltage power lines) and socio-economic aspects (Annexe 2 [1, 2]);
- biological agents (Zika virus) (Annexe 2 [3]);
- other physical aspects such as mechanical stress and noise (Annexe 2 [4,5]);
- socio-economic or organisational factors such as night work (Annexe 2 [6-11]).

Among the projects dealing with exposure to physical agents, this exposure was combined with:

- noise (172Annexe 2 [12]), UV radiation (Annexe 2 [13]), radiofrequencies and light pollution (Annexe 2 [14]), or air pollution;
- electromagnetic fields, asbestos fibres and tobacco (Annexe 2 [15]);
- biomechanical constraints and psychosocial and organisational aspects (Annexe 2 [16,17]);
- radiofrequencies and sociological determinants (Annexe 2 [18]).

Projects addressing issues related to air pollutants were studied in relation to biological agents (bacteria, viruses), sand haze (Annexe 2 [19]) or socio-economic determinants (Annexe 2 [20-21]).

To a lesser extent (10% of projects), co-exposures were addressed in *in vivo* and/or *in vitro* experimental studies. These projects combined the study of exposure to chemical products and physical agents (radiofrequencies, nanoparticles or LEDs, Annexe 2 [22-26]).

In projects related to ecotoxicology, ecosystem exposure and the identification of biomarkers of exposure were mainly investigated through metabolomic (Annexe 2 [27]) and transcriptomic (Annexe 2 [28-31]) studies. Epigenetic and transgenerational aspects of exposure were also explored in aquatic ecosystems (Annexe 2 [32]).

Overall, "omics" or epigenetic studies accounted for more than 30% of the projects (almost 50% of the experimental studies).

Effects on human health and ecosystems

More than a quarter of the effects on human health concerned cancer, while neurological and respiratory aspects, metabolism, reproduction, pregnancy outcomes, cardiovascular aspects and allergies completed the range of effects studied. The effects on representative ecosystem species, in particular bees, earthworms and aquatic organisms, etc. were also studied. The different effects examined are presented in Figure 10.

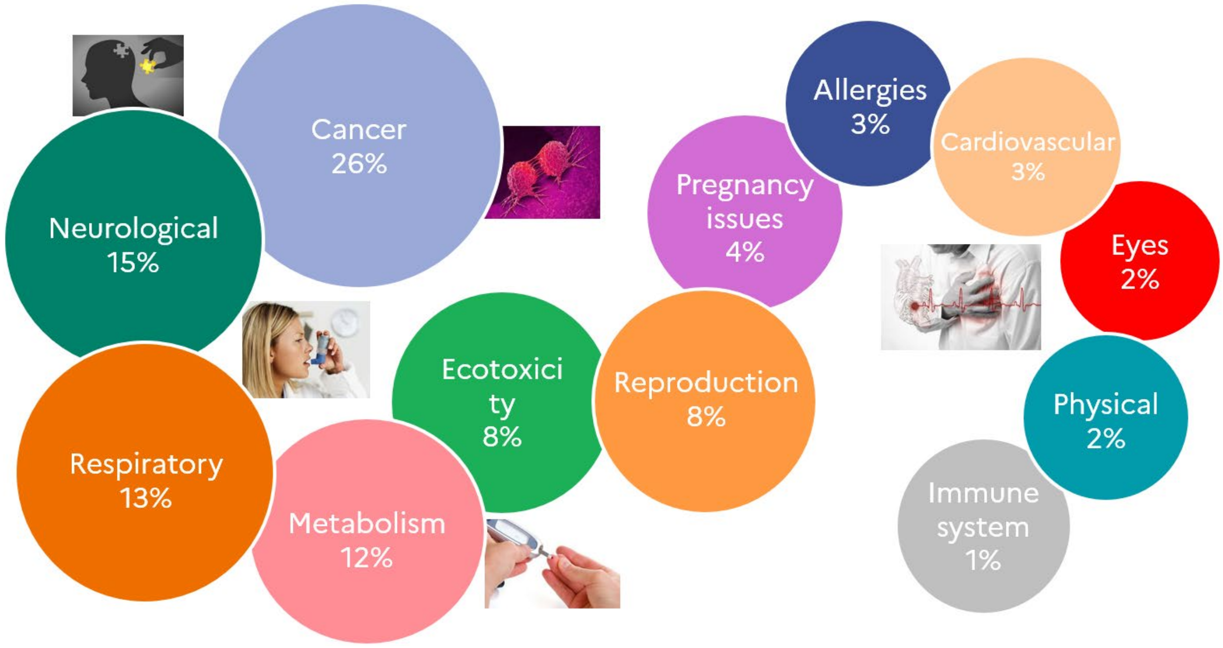


Figure 10: Effects examined in the projects in relation to the exposome funded by the PNR EST

3.2 Additions to the 2022 PNR EST research questions

A general call for projects was issued in November 2021 under the PNR EST.

This call for projects focused on priority issues in environmental and occupational health. The expected projects were required to address environmental risks to human health, in the general population or in the workplace, as well as risks to ecosystems and the quality of environments. The research questions proposed to the scientific community took into account the issues and priorities of public policies, such as exposure to chemical agents and their effects; risks associated with nanomaterials, microplastics, noise or light pollution; the link between environmental exposure and cancer; the link between biodiversity loss, ecosystem degradation and infectious diseases; worker exposure, inequalities in the face of environmental exposure, etc.

The research questions to be answered by researchers were grouped into several themes: physical agents, fibres and nanomaterials, cancer, chemical agents, endocrine disruptors, biological agents, human and social science approaches to health and environmental risks, environmental media and contamination, vectors, climate change and the associated management measures.

In the definition of the research programme's orientations, characterising the exposome and its effects on health was identified as critical and important. The notion of exposome appeared more specifically in research questions on exposure to mixtures of chemical agents or in combination with physical agents. This notion has not been explicitly expressed in the research questions until now, although many of them have contributed and continue to contribute to this notion.

The WG wished to propose additions to the research questions in the 2021 call, in order to strengthen research and production of data on certain components of the exposome. Thus, in addition to point 2 of the research question "Chemical agents", it proposed adding the following specific question:

Characterisation of exposures and study, by experimental and epidemiological means, of the health impacts on sensitive, little-studied populations (asthmatics, immunocompromised individuals, sufferers of chronic breathing difficulties, people who are overweight or obese, those suffering from psychological disorders or in a situation of social vulnerability, etc.).

In addition to point 4 of the research question "Chemical agents" and in point 4 of the research question "Biological agents", it proposed adding the question of:

Impacts on human health and ecosystems of co-exposures to microbiological and chemical agents.

Following these proposals and the discussions that took place at the steering committee meeting, it was decided that the exposome would be explicitly included in this new call under the chemical and biological agent themes.

4. The exposome in ANSES's collective expert appraisal mission: overview and recommendations

The WG proposes structuring its recommendations around eight themes related to the exposome and risk assessment (

Figure 11). For each of these themes, the context and main issues relating to risk assessment are summarised. Examples of what ANSES is already doing in relation to the issues identified are presented. Then, recommendations are provided with regard to the issues mentioned, with short- (2023-2025), medium- (2026-2029) and long-term (2030 and beyond) time scales. The dates are indicative and do not constitute a deadline as such.

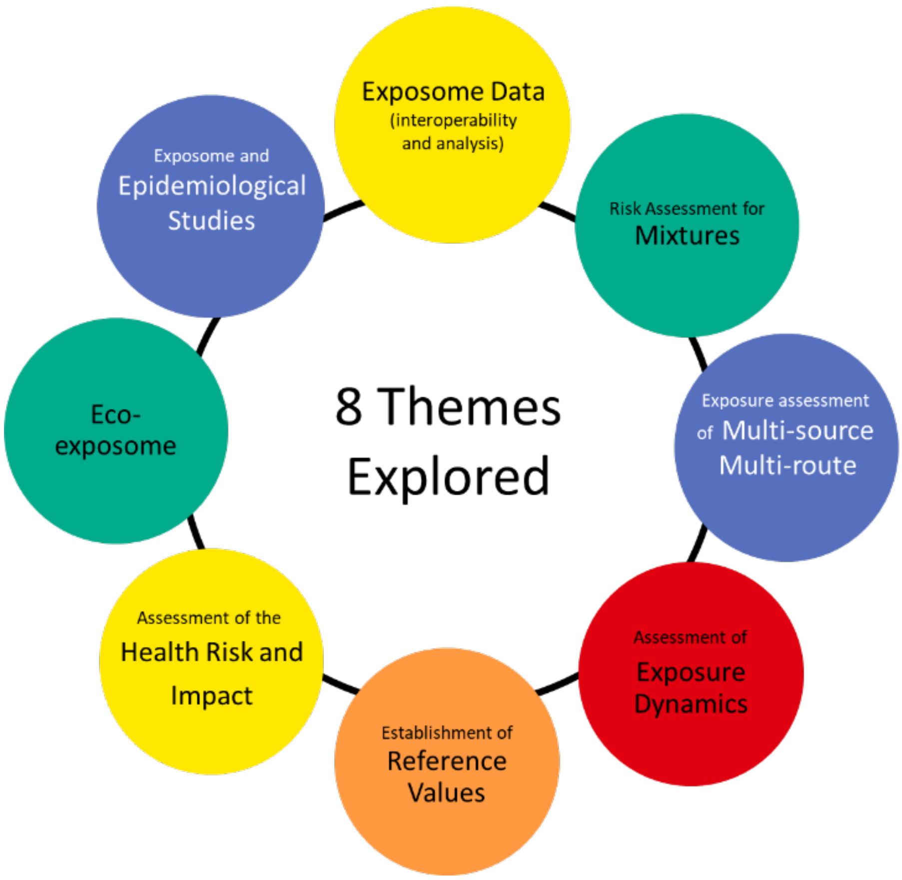


Figure 11: The eight themes underlying the WG's recommendations on taking the exposome into account in risk assessment

4.1 Exposome and epidemiological studies

4.1.1 Background and identification of issues

Since the exposome concept first emerged in 2005, many researchers in fields ranging from perinatal epidemiology to chronic diseases or psychiatry – and more recently infectious diseases such as COVID-19 – have published commentaries and reviews highlighting the potential benefits of characterising the exposome and incorporating it into epidemiological studies (Rappaport 2011; Lioy and Rappaport 2011; Buck Louis et al. 2013; G. W. Miller and Jones 2014; Vrijheid 2014; Robinson and Vrijheid 2015; Paolo Vineis 2015; Andra, Austin, and Arora 2016; DeBord et al. 2016; Guloksuz, van Os, and Rutten 2018; Rappaport 2020).

Indeed, the exposome differs from the exposure measurement paradigm used in "traditional" epidemiological studies in three ways: 1) a broader and more dynamic assessment of (lifelong) exposure taking multiple exposure routes into account; 2) integration of data on the measurement of exposure as well as on the response, across multiple scales, particularly spatio-temporal; 3) exploitation of the multidimensional information produced on the multiple exposure-response relationships, via a "data-driven" approach. The exposome represents a complement to, not a replacement for, the hypothesis-driven research that has successfully advanced the field of environmental health (Stingone et al. 2017).

A large proportion of the publications on the exposome that have appeared since 2005 consist of considerations or comments on the concept, its promise, challenges, feasibility, different methodological approaches, methods implemented, etc. However, the second wave of European EHEN projects (see Chapter 2.2) is beginning to produce practical results incorporating the components of the exposome. For example, as part of the ATHLETE project on understanding and preventing the health effects of various exposures in early life, de Prado-Bert et al. (2021) investigated the association between more than 100 exposures and epigenetic age acceleration, whereas Guillien et al. (2021) studied the role of multiple environmental and lifestyle determinants in asthma. The HEDIMED project, whose objective is to identify disease mechanisms and environmental factors related to immune-mediated diseases, has studied the link between the exposome and diabetes (Nurminen et al. 2021).

The main challenges and difficulties faced by researchers in integrating the exposome are partly due to theoretical and practical obstacles, mainly: 1) the lack of infrastructure to support the comprehensive exposure assessment activities essential to exposome research, 2) the difficulty in differentiating between normal physiological variations and environmentally induced changes in biological response measurements, 3) the lack of analytical, bioinformatics and statistical methods to process, integrate and analyse multi-dimensional data and, 4) the lack of training tailored to these new approaches and of researchers with multi-faceted training who can develop and implement them.

In 2017, Stingone et al. made recommendations based on a review of international studies proposing advances in the exposome (Stingone et al. 2017). The following issues were mentioned, based on the challenges identified by Stingone et al.:

- **Catalogue existing tools and methodologies** to facilitate exposome research and its use in epidemiological studies. For example, epidemiologists need accessible tools and approaches that can be used to characterise exogenous and endogenous factors of exposure, including exposure for which there are currently no corresponding biomarkers.
- **Develop new tools and methods to take account of specific aspects of the exposome**, such as the variation in exposure over time, particularly during critical and sensitive periods of human reproduction and development. For this, it is necessary to design studies that facilitate comparisons of the exposome over time. This can be done, for example, via ad hoc sampling taking the half-life of chemicals into account, and/or via transgenerational prospective cohort studies with repeated clinical follow-up and including several periods of biological sampling and/or dosimetry, or via cohort studies

conducted at territorial/population levels (farmers, winegrowers, firefighters, etc.) in a national or European multicentre framework.

- **Take account of** multiple exposures, in terms of agents, sources and routes, and the different associated uncertainties **in epidemiological study designs and data analysis plans**.
- **Promote data sharing and interdisciplinary collaboration**, in particular to ensure that the development of exposome assessment methods is compatible with basic epidemiological principles of study design and analysis.
- **Consider causal inference in the context of the exposome**. Causal epidemiology, such as mediation analyses that can improve understanding of the mechanistic pathway between exposure and disease, will be greatly facilitated if comprehensive data on exposure and the associated biological responses are available. The plausibility and consistency of the relationship can also be documented by complementing epidemiological studies with toxicological approaches such as adverse outcome pathway (AOP) analysis based on scientific evidence obtained through experimentation (Stingone et al. 2017; Bornehag et al. 2019). For biological agents, biological plausibility and the causal links between exposure and a health impact can also be examined through experimental studies, such as those using new models to study the microbiota. These experimental studies, coupled with epidemiological studies, provide a better understanding of the interactions between innate response, acquired immunity and inflammation. Some studies have thus revealed the complex relationships between gut microbiota, the immune system, the endocrine system and the central nervous system (Cryan and Dinan 2015; Bastiaanssen et al. 2020; Cusick, Wellman, and Demas 2021).

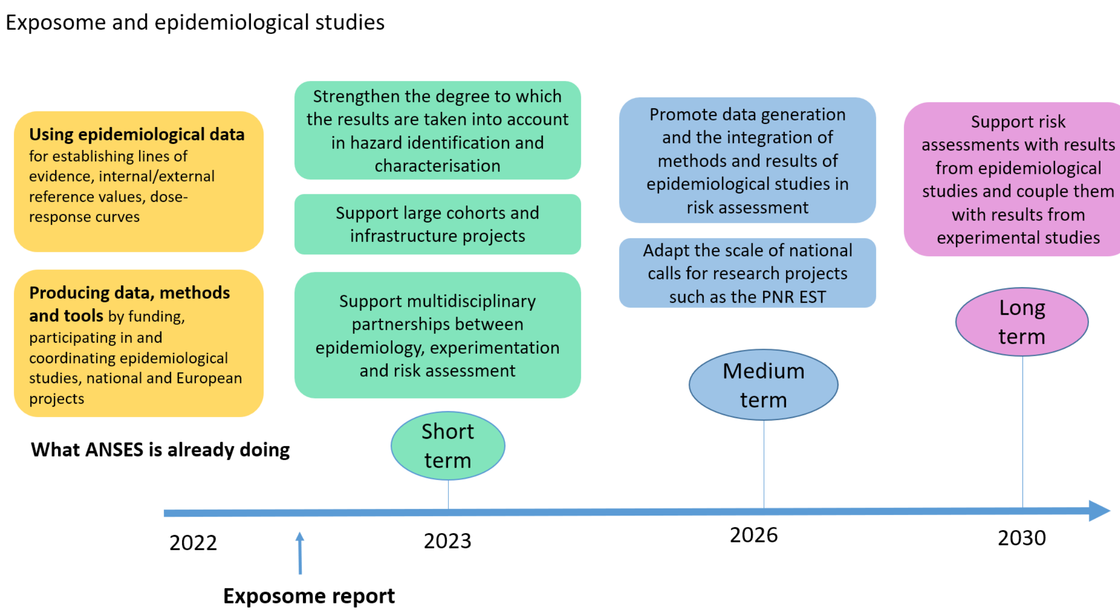


Figure 12: Recommendations for the exposome and epidemiological studies

4.1.2 What ANSES is already doing

ANSES draws on **the results of epidemiological studies** in its risk assessments, for example to:

- **Contribute establish lines of evidence** as part of an assessment of the weight of evidence at the hazard identification step. For example, in its report on the effects of outdoor ambient air particulate matter (ANSES 2019e), levels of evidence for the effects of particulate matter according to composition or particle size were established on the basis of epidemiological data. In work conducted by its WG on Occupational Diseases, epidemiological data combined with toxicological and mechanistic data were used to establish the existence of a causal link between an agent and a given effect (ANSES 2021e). In work conducted by its WG on Carcinogenic Processes, an analysis of the levels of evidence from epidemiological studies identified new target organs for the carcinogenicity of welding fumes (ANSES 2022g).
- **Establish internal or external reference values (RVs)**. For chlordecone, an internal toxicity reference value (TRV) was developed from an epidemiological study on the effects of this substance on pregnancy duration (ANSES 2021l). This new internal TRV is used to interpret the results of biomonitoring studies, in terms of risk. A new TRV for cadmium by ingestion was also established for the general population, based on epidemiological data about its effects on osteoporosis (ANSES 2019b). External reference values have also been established from epidemiological studies, for example: an 8hr-OEL for beryllium based on several epidemiological studies (ANSES 2010), an 8hr-OEL for 1,3-butadiene based on an occupational cohort for carcinogenic effects (ANSES 2011b), a chronic TRV for toluene based on an epidemiological study in workers (ANSES 2017d), and an IAQG for NO_2 based on a pool of epidemiological studies in children (ANSES 2013d).
- **Establish dose-response curves for biological agents**. Meta-analyses have been applied to epidemiological data to establish dose-response curves for biological agents (Thébault et al. 2013; Perrin et al. 2015; ANSES 2017b; 2018b).

ANSES also contributes to the production of data, methods and tools by:

- **Financing epidemiological studies** related to the exposome such as GeoCap-PAST/BIRTH, ZIP, NeuroBiomecaTMS, etc. in the framework of the PNR EST (see Chapter 3.1 and Annex 2).
- **Conducting and participating in epidemiological studies** based in part on the exposome approach, such as the PestiRiv study on pesticide exposure of people living in winegrowing and non-winegrowing areas, carried out in partnership with *Santé Publique France*.
- **Taking part in European projects** that develop the exposome approach in epidemiology, such as the HBM4EU project on the use of human biomonitoring data in establishing internal RVs (Lamkarkach et al. 2021; Ougier et al. 2021), or the ATHLETE project on the child exposome (Vrijheid et al. 2021).
- **Coordinating, under Horizon Europe**, the European PARC research and innovation partnership, which will combine an epidemiological approach, experimental studies and risk assessment.

4.1.3 Short-term recommendations (2023-2025)

The short-term recommendations, in line with what ANSES is already doing, are to:

- Strengthen the degree to which the results of epidemiological studies are taken into account in the hazard identification and characterisation steps.
- **Support the development of multidisciplinary partnerships** linking epidemiological studies, experimental studies (*in chemico*, *in vivo* and *in vitro*) and risk assessment.
- **Encourage the establishment and maintenance of large cohorts** in France such as Constances[19], E4N[20]-E3N[21], i-Share[22], Psy-COHorte[23], etc. and promote the standardisation of exposure estimates from these cohorts to enable future joint analyses.
- **Participate in and support infrastructure projects** such as France Exposome (national infrastructure to support research on the chemical exposome) and EIRENE (EU project to establish a network of analytical platforms for targeted and non-targeted assessment of substances in biological or environmental samples, which aims to support and strengthen epidemiological research in the field of environmental health).

4.1.4 Medium-term recommendations (2026-2029)

In the medium term, it is necessary to promote data generation and the integration of methods and results of epidemiological studies in risk assessment. The PARC programme will contribute to this, for example, by developing internal RVs derived from the matching of biomarkers of exposure and effect (e.g. liver enzymes, cardiotoxicity markers, etc.), by developing PBPK models to link internal exposure measured in biological matrices and external exposure obtained from data on environmental contamination and lifestyle habits, or by combining health risk and impact indicators.

Among the current research funding schemes, the PNR EST has a central role in supporting research on environmental health. However, the scale of the calls for projects (number of projects, budget allocated per project, etc.) does not allow ambitious proposals to be submitted for the development of detailed interpretation data on existing or future cohorts. It is therefore recommended that, in addition to the expected PEPR on the exposome, in the framework of the funding planned under the PNSE4, **the amounts of the grants awarded by the PNR EST should be increased** to accommodate proposals in line with this report's recommendations for deploying the exposome in expert appraisals.

4.1.5 Long-term recommendations (2030 and beyond)

In the long term, it is hoped that ANSES will **base the risk assessments** it conducts for its expert appraisals, whenever possible, on **the results of epidemiological studies** and that it will, if necessary, **combine them** with those of experimental studies, with the aim of reinforcing the establishment of lines of evidence between exposure and effects, identifying relevant

[19] Epidemiological cohort of patients consulting Social Security health clinics
[20] Epidemiological study among the children of E3N women
[21] Epidemiological study among women in the national education system
[22] Internet-based Students HeAlth Research Enterprise
[23] Cohorts in psychiatry

markers of effect, establishing quantitative dose-effect relationships, etc. In addition, further study of gene-environment interactions should, in the long term, provide important information for better identifying individual susceptibilities in populations. Integrating these susceptibilities could challenge risk assessment methods (Deloménie et al. 1998; Lee et al. 2018; Toselli et al. 2015).

4.2 Interoperability and analysis of exposome data

4.2.1 Background and identification of issues

The study of the exposome involves the use and combination of various types of data: health data, toxicological data, data on concentrations in food and the environment, data on living and working habits and conditions, etc. Advances in analytical sciences, the ability to measure a large number of analytes simultaneously, to detect and quantify them at low concentrations, and to process samples of various kinds (biological, environmental) have broadened the field of study to the individual, group or population level. In addition, the analysis concept of "omics" approaches (genomics, proteomics, transcriptomics and metabolomics) applied to the fields of chemistry and biology leads to these methods being defined as generating large amounts of the same type of information (Sillé et al. 2020).

Studies based on the exposome concept examine a multitude of environmental exposures evolving over time and space for an individual or populations. The more abundant the exposure measurements (analytes/mass spectrum, concentrations/signals, sampling conditions/matrices, subjects, temporal amplitude), the more precise and detailed the description of the exposome will be, and the more metadata (study reference, authors, period, etc.) will be available to refine their use. A great diversity of exposure measurement tools is used, ranging from analyses of biological samples using targeted (determined *a priori*) or non-targeted (no *a priori*) approaches to individual external exposure measurements using personal sampling tools or portable devices and sensors. The exposome can also be described using external exposure data from various sources such as air, water, food, consumer products, lifestyle habits, living conditions, the local environment and occupational exposure. These data can be collected via questionnaires or adapted sampling, or come from other local or wider environmental monitoring schemes (concerning air, water, soil, food, climate, artificial light) such as the GECCO[24] initiative in the Netherlands (Lakerveld et al. 2020) which use localised data (address, GIS Geographic Information System).

A recent systematic review examined the different types of published studies on the exposome (Haddad, Andrianou, and Makris 2019). It identified and analysed 78 studies. The approaches used included questionnaires and interviews in 47% of cases, biomarker measurements in 36%, use of "omics" platforms (metabolomics, 28%, genomics, 4%), access to databases available at local, government or hospital level (24%), measurements from portable sampling or measurement systems (15%), geospatial monitoring data (13%), environmental measurement data (9%) and clinical data (9%). The review of these studies demonstrates the importance of coupling classical monitoring approaches (questionnaires, targeted environmental and biological measurements) with non-targeted measurements to describe internal and external exposure over the course of a lifetime. The use of personal measuring devices is increasing, facilitating geolocated and activity measurements, and is

[24] Geoscience and hEalth Cohort COnsortium

expected to become the norm in the future. *Data mining* capabilities are being developed to better characterise the chemical exposome and improve its description and interpretation. Progress mainly concerns the annotation of metabolomic data (Meijer et al. 2021) and reconstruction of metabolic networks affected by exposure (Amara et al. 2022). Several other challenges need to be overcome, both in the analytical field for mapping the "chemical space" through combinations of extraction and separation methods, and in the field of signal processing to obtain quantitative data on levels of exposure to emerging substances (David et al. 2021). At the same time, raw data exploitation approaches are also being developed in the fields of genomics, metagenomics, transcriptomics and proteomics.

In order to jointly analyse these different types of data, statistical approaches that analyse univariate and multivariate regression models are used to highlight associations. They are not currently able to analyse complex interactions or the effects of mixtures. Other cluster analysis-based approaches to define exposure profiles and their associations with health effects are also being developed (Traoré et al. 2016; 2018; Mancini et al. 2021). Lastly, new approaches have been proposed that take into account the hierarchical structure of the different types of data obtained (Guillien et al. 2021).

The spatial data selected for the studies must be transformed into standard GIS data in order to be re-projected onto a geographic reference frame. These baseline data are then exploited according to the spatial scale needed for producing data that will be converted from environmental data into personal exposure data, or data on a geographical exposure area used for statistical analyses (Lakerveld et al. 2020).

However, the data analysis methodology for detecting and quantifying associations needs to be well established when analysing large time-series datasets from complex dynamic systems (Runge et al. 2019). Indeed, these datasets are often multidimensional and non-linear, and obtained from a limited number of samples. This creates problems related to the dimensions of these datasets, which associate a very large number of parameters with only a few individuals. In this context, the analytical methods must be able to detect the maximum number of proven causal relationships, while controlling the risk of false positives (Cadiou et al. 2021).

Lastly, the management of datasets obtained in these epidemiological studies must comply with data protection regulations and be conducted within an ethical framework, particularly in terms of informing participants and gaining consent, as well as in communicating their results to individuals.

The issues in terms of data for the exposome can be structured around the four **FAIR** principles: **Findable, Accessible, Interoperable, Reusable**. It is then necessary to:

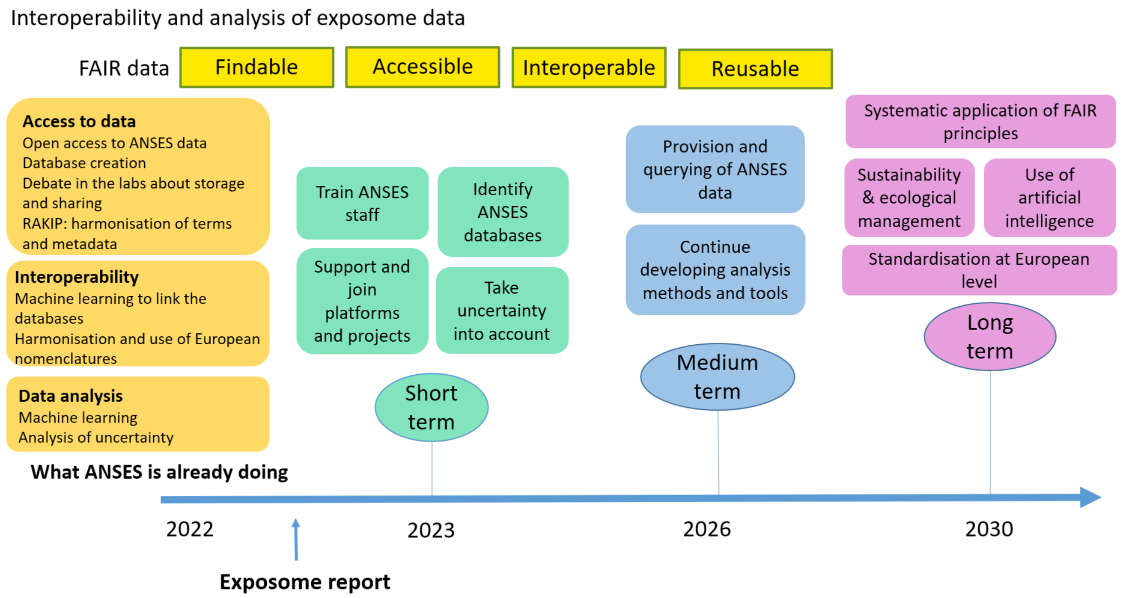
- Identify **existing datasets** from research and monitoring activities, by assigning computer identifiers and metadata to enable searches and the assessment of their relevance for use in exposome studies.
- Help **define data description standards** and thesauruses for new exposome studies in order to make them interoperable, and recommend implementing good practice and compliance with standards on metadata and data description.
- **Generate data** using harmonised or validated methods based on standards allowing their connection, with performance criteria, and which are comparable and reproducible over time.
- **Ensure the sustainability and security** of data storage conditions for future re-use.

- **Enable access to data** in line with the open data policy and the development of computer access protocols facilitating their use for research, expert appraisal or communication purposes.
- **Create** open access online **databases and platforms** to facilitate access for researchers and health agencies. The development of shared spaces for environmental data (Green Data For Health[25], GECCO[26]), health data (Health Data Hub[27]) and social data is necessary to allow them to be combined and to increase their number in order to improve the statistical power of analyses. Examples can be found in the United States in different epidemiological contexts (Senier et al. 2017).
- **Develop mathematical methods for data mining and analysis** (machine learning) or draw on methods developed in the analysis of genetic results that determine probabilities of causality of genetic variants as determinants of disease (Vermeulen et al. 2020).

More specifically, in relation to **analytical tools** for the exposome, the challenges are to:

- Develop **non-targeted approaches** to identify emerging or unexpected chemical and biological agents in a matrix.
- Include the different types of **markers of exposure** in biological matrices and environmental media (exposomics for parent substances and metabolites, genomics for micro-organisms) and **markers of effect** ("omics": metabolomics, proteomics, transcriptomics, epigenomics).
- **Develop and organise sample libraries** for performing retrospective analyses.
- For all analytical measurements, it is necessary to **ensure their metrological performance and robustness**.

Figure 13 below summarises ANSES's current actions regarding exposome data and the WG's recommendations for the future.



25 https://eig.etalab.gouv.fr/defis/green-data-for-health/
26 https://www.gecco.nl/
27 https://www.health-data-hub.fr/

Figure 13: Recommendations for exposome data

4.2.2 What ANSES is already doing

ANSES works to **make the data it collects widely available**. These data may concern food consumption (Individual and National Study on Food Consumption (INCA)), contamination and dietary exposure (Total Diet Study (TDS)), the nutritional quality of foods (Ciqual nutritional composition table and French Food Observatory (OQALI) database), the composition of tobacco and vaping products (ANSES 2020c; 2020d), nanoparticles (R-nano register), habits regarding use of consumer products (EU EPHECT[28] project), or food contamination by pathogens based on published data (PathogensInFood, www.pathogensinfood.esa.ipb.pt). The same is true for the data it manages, such as the Contamine database listing data from monitoring and control plans on the concentrations of chemicals found in food. Whenever possible, ANSES makes these data freely available for download on www.data.gouv.fr. The Agency **also creates databases** with the results of its expert appraisals, such as the database listing all the TRVs established by ANSES, which is accessible on its website[29]. It also considers **how best to store and share** the data resulting from its laboratories' work. In addition, it contributes to **European programmes** on data provision and management (EuroFIR[30], Common Open Data Platform on Chemicals[31], European Health Data Space[32], GreenData4All[33]). ANSES also participates in EFSA's work on **the harmonisation of questionnaires and the standardisation of food consumption and contamination data** at European level (FOODEX2 and SSD2 formats).

In addition to developing correspondence tables, ANSES uses **machine learning methods** to link and harmonise the different nomenclatures in its databases and to analyse and interpret them. Its methods can be integrated in operational tools such as the RSExpo software application for identifying mixtures using dimensionality reduction techniques. Lastly, in its risk assessments, ANSES provides **an analysis of the uncertainty associated with the data** (ANSES 2016c).

In order to optimise the efficient exchange of information, a scheme for **harmonising terms, concepts and metadata relating to chemical and microbiological exposure assessment models** has been proposed by ANSES in collaboration with the DTU[34], EFSA[35] and BfR[36] as part of the RAKIP[37] initiative (Plaza-Rodríguez et al. 2018). This scheme is seen as a key element in the development of a harmonised information exchange format: the Food Safety Knowledge Markup Language (FSK-ML), which defines a structure for encoding data, metadata and model scripts in a readable format.

[28] Exposure Patterns and Health Effects of Consumer Products in the EU
[29] https://www.anses.fr/en/content/toxicity-reference-values-trvs
[30] European Food Information Resource: https://www.eurofir.org/
[31] https://ec.europa.eu/info/strategy/priorities-2019-2024/europe-fit-digital-age/european-data-strategy_en
[32] https://ec.europa.eu/health/ehealth-digital-health-and-care/european-health-data-space_en
[33] https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/13170-GreenData4All-updated-rules-on-geospatial-environmental-data-and-access-to-environmental-information_en
[34] Denmark Technical University
[35] European Food Safety Authority
[36] Bundesinstitut für Risikobewertung (German Federal Institute for Risk Assessment)
[37] Risk Assessment modelling and Knowledge Integration Platform

4.2.3 Short- and medium-term recommendations (2023-2029)

In order to **apply the FAIR principles**, the Exposome WG recommends working to:

- Develop the **training of ANSES staff** in:
  - Good practice and compliance with standards;
  - The use of data available within and outside the Agency, for example via European partnerships or monitoring programmes;
  - Exposome-specific analytical methods such as omics and machine learning;
  - Taking the uncertainty associated with data into account.
- Develop **communication and the provision, interoperability and querying** of data produced and managed by ANSES. The first steps should involve identifying the available databases, developing and maintaining correspondence and reference tables, developing query interfaces, etc.
- Join, support and coordinate **initiatives and projects** such as:
  - The Ministry of Agriculture's epidemiological surveillance platforms based on FAIR principles, such as those on food-chain surveillance[38], or epidemiological surveillance in animal health[39] and plant health[40];
  - Data management platforms (Green Data for Health, Health Data Hub);
  - The European PARC partnership, where a debate will be held on metadata and data standardisation, in particular through implementation of the human biomonitoring programme on a European scale and an assessment of the resources available in the field of environmental monitoring;
  - Participation in and support for the France Exposome and EIRENE projects (see Chapter 4.1.3), which will produce data from targeted and non-targeted analysis of chemicals in biological or environmental samples, and whose sharing, analysis and long-term storage must be safeguarded.
- Continue **developing data analysis methods and tools** such as machine learning, to ensure interoperability and interpretation of data on the exposome.

4.2.4 Long-term recommendations (2030) for ANSES's expert appraisal activities

In the long term, the Exposome WG proposes that ANSES undertake work to:

- Continue developing the **standardisation** of data and the methods and tools for collecting and storing them at **national, European and international levels**.
- Contribute to **adoption of the FAIR principles** and associated tools in the various **regulatory areas**.
- Ensure **sustainable data management** by minimising the environmental footprint.
- Use **artificial intelligence** to manage and analyse large datasets.

38 https://agriculture.gouv.fr/la-plate-forme-de-surveillance-de-la-chaine-alimentaire-livre-sa-premiere-production
39 https://www.plateforme-esa.fr/
40 https://plateforme-esv.fr/

4.3 Assessment of risks associated with mixtures

4.3.1 Background and identification of issues

This chapter discusses the assessment of risks associated with mixtures of agents of the same type. It is mainly applicable to risks associated with mixtures of chemicals or mixtures of microbiological agents. The risks associated with mixtures of agents of different types, for example a chemical agent and a biological agent, are discussed in Chapter 4.7, under the term "multi-factors".

Exposure to mixtures of chemicals, whether man-made or naturally occurring in the environment, is a complex phenomenon involving multiple factors. The complexity is due to the characterisation of the mixture (composition, change over time, routes and sources of exposure), but above all to the difficulty in understanding the toxic effects of this mixture on the body, due to the possible interactions between substances (inhibition, potentiation, additivity, synergy), which may vary according to each one's respective concentration. These obstacles, together with the infinite combination of mixtures that populations may be faced with, explain why chemicals are still mostly assessed individually. However, in recent years, methods for assessing the risks of chemical mixtures have been proposed (Boobis et al. 2008; EFSA 2007; 2008; EFSA Scientific Committee et al. 2019; International Programme on Chemical Safety and Inter-Organization Programme for the Sound Management of Chemicals 2009; Fox, Brewer, and Martin 2017). They have been applied to classes of substances such as dioxins and PCBs (Marion Hulin et al. 2020), and phthalates (EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (CEP) et al. 2019; Clewell et al. 2020), or more widely to certain pesticide residues (Boon et al. 2008; EFSA, Craig, Dujardin, Hart, Hernández-Jerez, et al. 2020; EFSA, Craig, Dujardin, Hart, Hernandez-Jerez, et al. 2020; Sprong et al. 2020; Crépet et al. 2019), and are mainly based on the principle of additivity of effects, which is regarded as a conservative approach. On the other hand, very few studies combine several exposure routes (inhalation, ingestion and dermal contact combined) and/or several categories of substances (to give just the example of dietary exposure: contaminants, additives, residues, toxins or newly-formed products) (Evans et al. 2016; Amélie Crépet et al. 2021; Bopp et al. 2018; Drakvik et al. 2020).

Considering firstly that exposure to mixtures of substances is the rule for all individuals, and secondly that several studies indicate that additive or even synergistic effects can occur (European Commission. Directorate General for Health and Consumers 2012), it appears that the usual methods based on substance-by-substance risk assessment need to evolve to take these mixtures into account.

With regard to the microbiological agents that may be present in food matrices and cause infectious diseases (ANSES 2017a; 2018a) , it is generally assumed that there is no interaction between these pathogens. Two types of evidence support this hypothesis. On the one hand, the mechanisms of pathogenesis are specific to each micro-organism and on the other hand, as the prevalence is generally low, the probability of concomitant presence of several agents in a food portion is low. The risks associated with a food matrix are therefore assessed for each pathogen without interaction with the others (ANSES 2020h). Using a common risk metric – for example, the disability-adjusted life year (DALY) unit – an overall risk associated with a disease can be estimated from the sum of the risks attributed to each pathogen. However, microbiological investigations in patients can sometimes reveal co-infections, in particular viral and bacterial co-infections (Azevedo, Mullis, and Agnihothram 2017; Nagaoka et al. 2020;

Román et al. 2003). Co-infection plays a key role in the progression of a disease (Azevedo, Mullis, and Agnihothram 2017). It has also been observed that initial infection with one pathogen can indirectly contribute to infection with a second agent (Vangay et al. 2015). For example, administering antibiotics to treat respiratory infections can lead to disruption in gut microbiota composition, which no longer protects the body from pathogenic bacteria (Quévrain and Seksik 2013). Meta-analyses of case-control studies have recently shown that antibiotic use significantly increases the risk of infection with foodborne pathogens (Augustin et al. 2021; Guillier et al. 2021). The presence of several pathogens in the same food category also presents difficulties in risk management and requires consideration to be given to multiple exposure. Given the limited monitoring resources available to risk managers and professionals, it is important to be able to prioritise the different micro-organisms contributing to consumer exposure in order to optimise sampling plans and management measures.

The issues in terms of quantitative assessment of risks associated with mixtures are to:

- **Characterise priority mixtures by grouping agents into mixtures.** They can be grouped and prioritised on the basis of co-exposure obtained via external or internal exposure data, or from toxicological data on effects, or by combining the two in order to obtain an initial estimate of the risk (Crépet et al. 2019). The integration of different sources and routes of exposure is also a challenge for the assessment of mixtures. Because it requires the processing of large amounts of data and information, methods and tools need to be developed for modelling data on exposure and toxicology, such as machine learning, read-across, QSAR, etc.
- **Determine the effects and toxicokinetics of priority mixtures** by generating data on their toxicity using innovative methods. The toxicity of the mixture can be compared with that predicted for the individual substances in order to test the widely used hypotheses of additivity of doses (similar mode of action) or additivity of effects (independent mode of action). The development of high-throughput screening tools such as "omics" approaches enables a large number of tests to be carried out, which, when they can be organised around AOP networks, provide a better understanding of the nature of the effects and the mode of action of the mixture constituents. Metabolomic analysis and the characterisation of metabolic networks are now helping to explain the toxicokinetics of substances in several species (humans, livestock), particularly in terms of identifying biotransformation pathways (Viant et al. 2019; Fu et al. 2021; Jia et al. 2022). Several epidemiological studies are looking at the effects of mixtures (HELIX) or, more recently, are combining human data with experimental approaches to better establish the causal links between exposure and health effects (Braun et al. 2016; Patel 2017; Stingone et al. 2017; Jain et al. 2018; Joubert et al. 2022; Huhn et al. 2021; Dubrall et al. 2021; Bornehag et al. 2019; Caporale et al. 2022).
- **Assess the risks of priority mixtures** by developing approaches based on the various proposed methods and risk indicators (hazard index, reference point of departure, point of departure index, etc.) and **suggest management tools** such as identification of the agents contributing most to the risk or application of a protection factor such as the mixture assessment factor (MAF).

Figure 14 below summarises ANSES's current actions regarding integration of the mixtures component in risk assessment and the WG's recommendations for the future.

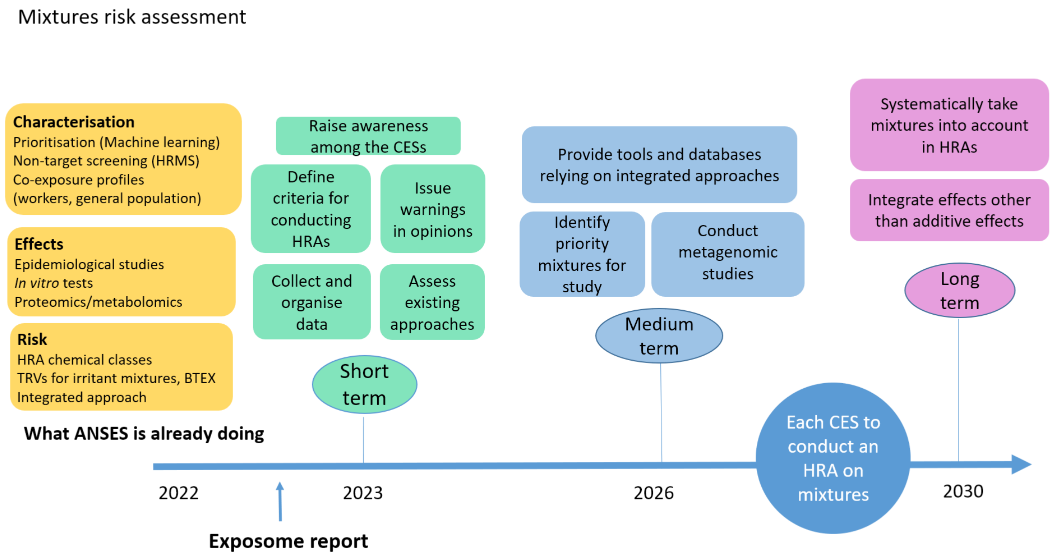


Figure 14: Recommendations for integrating the mixtures component in risk assessment

4.3.2 What ANSES is already doing

For several years now, under various research projects, ANSES has been **working on developing methods and tools as well as producing data** for assessing the risks associated with mixtures of chemicals. More recently, it has introduced the issue of chemical mixtures into its expert appraisals.

Concerning the characterisation of exposure to chemical mixtures, this work focuses on the:

- **Implementation of machine learning methods** such as dimensionality reduction, classification/clustering and network analysis to prioritise mixtures and identify homogeneous co-exposure patterns in the general population, in workers or in bees (A. Crépet et al. 2013; Traoré et al. 2016; Crépet et al. 2019). These methods have been implemented with the ANSES RSExpo software application to facilitate their use by non-statisticians.
- **Non-targeted analysis** of xenobiotics in food using high-resolution mass spectrometry (HRMS) to detect the presence of a large number of known or unknown substances in the same sample (preliminary screening step) (Martin et al. 2020).
- **Determination of homogeneous profiles of workers subject to multiple exposure**, mainly by identifying situations of exposure to several chemicals and targeting certain occupational sectors particularly concerned by combined risks (Fourneau et al. 2021).

Concerning the effects of chemical mixtures, research is under way in collaboration with teams of epidemiologists from Inserm, *Santé Publique France* and the François Baclesse Centre to **study the associations between exposure to mixtures and health effects**. For example, studies are looking at the possible link between pesticides and neurodegenerative diseases in rural populations and agricultural workers, between pesticides and prostate cancer in agricultural workers, between food contaminants and mortality in women, or between pesticides and mortality rates in bees. ANSES's laboratories are also studying the toxic effects of mixtures by means of *in vitro* tests. These tests are generally performed on human cells to assess different effects (cytotoxicity, genotoxicity, oxidative stress, inflammatory response, etc.). The mechanisms of action were recently investigated using proteomic and metabolomic analysis methods.

Concerning the risk of chemical mixtures, besides conducting risk assessments for classes of substances such as dioxins, furans and PCBs (M. Hulin et al. 2014), phthalates (Véronique Sirot et al. 2021) and pyrethroids (Vanacker, Quindroit, et al. 2020), ANSES has:

- Conducted a **literature review** on existing risk assessment methods for mixtures (ANSES 2022c).
- Developed an **approach to establishing reference values** for mixtures. This was used to establish an indoor air quality guideline (IAQG) value for a mixture of irritants in air (ANSES 2022h), and a TRV for a mixture of benzene, toluene, ethylbenzene and xylenes (BTEX) (ANSES 2022d).
- Developed **a combined prioritisation and risk assessment approach** to mixtures, which has been applied to breast milk contaminants (Amélie Crépet et al. 2022).
- Conducted case studies, since 2015, to produce **cumulative risk assessments** of pesticide mixtures using MCRA[41] (van der Voet et al. 2015) and data from food monitoring and control plans.

ANSES participates in **European working groups** to group substances according to different criteria (EFSA Scientific Committee et al. 2021), or to conduct cumulative exposure assessments (EFSA et al. 2021; ANSES et al. 2019).

Concerning microbiological agents, scientific work has been undertaken as part of the ANR's ARTISANEFOOD[42] project and a thesis co-supervised by ANSES and Centrale Supelec, in order to **optimise the sampling** to be carried out in the case of **multi-pathogen** food contamination.

4.3.3 Short-term recommendations (2023-2025)

In the short term, in order to continue taking account of mixtures in ANSES expert appraisals, the WG proposes:

- **Raising the awareness of CESs about the issue of mixtures** and questioning them on the need to integrate the mixture component in expert appraisals.
- **Defining criteria** for assessing the need and feasibility of conducting a **mixture risk assessment** when responding to a formal request.
- **Collecting and organising the data needed** to conduct mixture risk assessments. For example, in the process of establishing RVs, health effects other than the critical effect could also be identified in a database, which could then be used to search for common effects of the constituents of a mixture.
- **Issuing warnings in the ANSES opinions** by identifying the main co-exposures for each agent assessed, as well as the need and feasibility of proposing a mixture approach (World Health Organization 2019). With regard to the hazard, identifying whether the agent has potentiating properties or particular synergy situations could

[41] Monte Carlo Risk Assessment software
[42] http://www.ipb.pt/artisanefood/

open up the question of mixtures. This information on co-exposures and effects could be listed in a specific database to enable its use in future expert appraisals.

- **Assessing the different approaches proposed** by national and international health agencies such as Health Canada, EFSA, WHO, etc. and by the regulations (debate on the use of MAFs in the framework of the REACH Regulation). It will then be necessary to assess the extent to which these could be applied to ANSES's work.

4.3.4 Medium-term recommendations (2026-2029)

In the medium term, it is recommended that ANSES **develop a risk assessment strategy for mixtures based on robust data and methods**. For this purpose, it would be advisable to:

- **Develop a ranking method based on the exposome concept** to identify the mixtures to be given priority consideration in risk assessment and regulation.
- **Establish tools and databases** based on integrated approaches to testing and assessment (IATA) for grouping substances according to effects, modes of action or AOP networks and assessing their toxicity.

In order to ensure the dissemination of knowledge and the "mixture culture", it would be useful if the CESs concerned could conduct a risk assessment for at least one mixture of chemicals. In order to facilitate this initial work, it would be useful to:

- **Provide the CESs** with the tools and methods developed for national (Périclès[43], Coctell[44], etc.) and European (Euromix[45], PARC, etc.) research projects;
- **Prioritise mixtures** according to their frequency and exposure levels.

Concerning the effects of mixtures of micro-organisms, given the difficulty of elucidating the micro-organism responsible for certain foodborne illnesses (Glasset et al. 2016; Hennechart-Collette et al. 2020), it would be worthwhile to **conduct metagenomic studies** in microbiological investigations of foods (EFSA Panel on Biological Hazards et al. 2019). They may reveal possible synergies.

4.3.5 Long-term recommendations (2030 and beyond)

The long-term objective is for ANSES to be able to **systematically take mixtures into account** in its risk assessments. To do this, in addition to strengthening the work undertaken on the basis of the recommendations issued in the short and medium term, ANSES should be capable of **integrating effects other than additive ones** (synergistic, antagonistic, potentiating).

[43] Assessment of exposure to pesticide mixtures and mechanisms of toxicity of these mixtures
[44] Pre- and postnatal exposure to a wide range of substances and effects on child growth and development
[45] Assessing the health risks of combined human exposure to multiple food-related toxic substances

4.4 Multi-source and multi-route exposure assessment

4.4.1 Background and identification of issues

An individual can be exposed to a substance that may come from several sources (food, water, indoor/outdoor air, objects, consumer products, etc.) and enter the body via several routes (ingestion, inhalation, dermal contact). Overall exposure from multiple sources and routes can be estimated by measuring internal exposure using biomarkers of exposure in biological media (blood, urine, hair, etc.). Measurement of exposure through the use of biomarkers has the advantage of directly integrating the different routes of exposure and the toxicokinetics of the substance(s), and thus being able to determine the concentrations in the body. However, due to the cost and complexity of implementation, biomarker data are still limited in terms of the number of substances studied, the number of samples, etc. In addition, these data alone cannot be used to assess the contribution of different sources of exposure. Despite this, in order to define management options to mitigate exposure and the associated risk, it is essential to identify the exposure factors that contribute most to overall exposure. Another way of estimating overall exposure is to aggregate the calculated exposures by combining measurements of concentrations in the different sources with those related to the behaviour of individuals (spatio-temporal budget, food consumption, anthropomorphic data, etc.). This approach makes it possible to identify the main exposure sources and routes. However, there are many complexities in modelling overall exposure. Apart from specific cases (Cao et al. 2016), surveys rarely collect all the sources of exposure for the same individual. Therefore, determining overall exposure often requires the mathematical modelling of data from different databases, obtained on different populations and with different methodologies. The general principle of the mathematical models used for aggregate exposure assessment is to create a new population from individuals in the different surveys using Monte Carlo simulations, which are often used to combine data in risk assessment (Kennedy, van der Voet, et al. 2015; Safford et al. 2015; Paustenbach 2000; Kennedy, Butler Ellis, and Miller 2012; Kennedy, Glass, et al. 2015; Zartarian et al. 2017; Vanacker, Quindroit, et al. 2020; Vanacker, Tressou, et al. 2020). A number of tools have been developed in recent years to assess exposure from different routes and sources. The SHEDS[46] software application combines direct exposure via skin, inhalation and accidental ingestion with ingestion of food and drinking water (Isaacs et al. 2014). In Europe, Kennedy, Butler Ellis and Miller developed the BREAM[47] and BROWSE[48] (Kennedy, Butler Ellis, and Miller 2012) software applications to assess non-dietary exposure to pesticides of workers, bystanders and residents living near agricultural areas (Kennedy, van der Voet, et al. 2015; Kennedy, Glass, et al. 2015). In the Euromix project, they proposed options for aggregate exposure models combining BREAM with the MCRA[49] platform (van der Voet et al. 2015) to assess dietary exposure. Other European models assessing exposure of the general population to cosmetics (Dudzina et al. 2015), or to air and dust (RSExpo software (Vanacker, Quindroit, et al. 2020)) have been linked to dietary exposure through the MCRA platform. Approaches are also proposed in the HBM4EU project and will be pursued in the PARC programme (HBM4EU 2018).

[46] Stochastic Human Exposure and Dose Simulation
[47] Bystander and Resident Exposure Assessment Model
[48] Bystanders, Residents, Operators and Workers Exposure
[49] Monte Carlo Risk Assessment software

The issues in taking exposure from multiple sources and routes into account in risk assessment are to:

- **Determine the major sources and routes of exposure** and their contribution to overall exposure in order to implement effective management measures.
- Combine exposures from everyday life with occupational exposures.
- **Increase the use of biomarkers** as a proxy for overall exposure by organising better access to data, developing dose reconstruction methods, establishing internal TRVs, etc.
- Develop **mathematical methods for combining heterogeneous data** that can take variability and uncertainty into account.
- **Conduct surveys considering several sources** of exposure and/or collecting more specifically data on **exposure sources and routes that are less well known** (e.g. the dermal route, consumer products, physical agents such as screens, 5G or electromagnetic waves).
- Develop **bioavailability factors and physiological based pharmacokinetic (PBPK) models** to help take the different exposure routes into account, in particular the dermal route, which is less studied in the general population.
- **Develop "source to dose" models** by including transfer from soil to plants, then from plants to humans via animals (transfer kinetics and transformation in soil and animal and plant organisms), or migration from articles or indoor paints to an individual.
- Reinforce the development of TRVs for the dermal route.

Figure 15 below summarises ANSES's current actions to integrate the exposome in the assessment of multi-source and multi-route exposures and the WG's recommendations for the future.

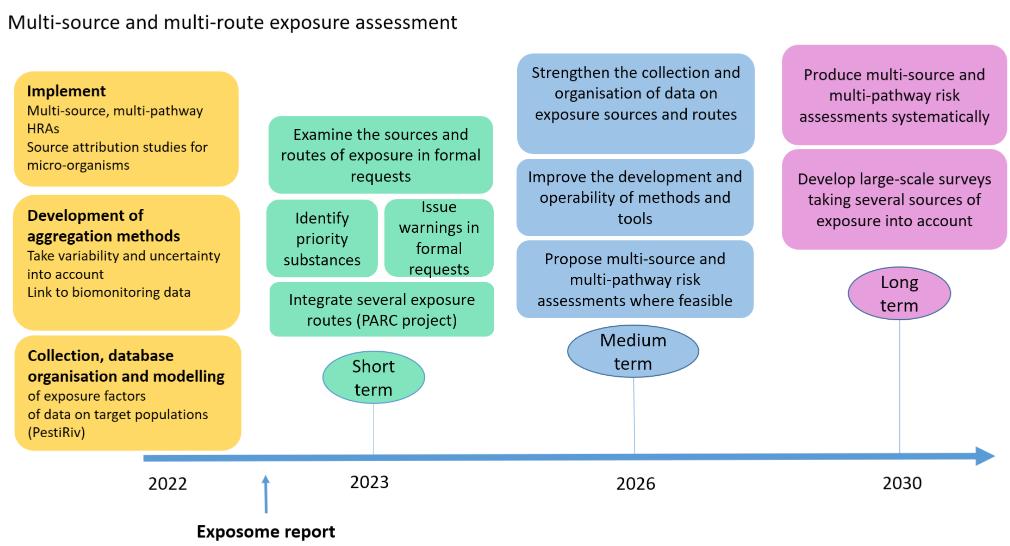


Figure 15: Recommendations for multi-source and multi-route exposure assessment

4.4.2 What ANSES is already doing

In terms of aggregating sources and routes of exposure, ANSES:

- Conducts **risk assessments that consider multiple sources and exposure routes** for chemicals such as lead (ANSES 2014), bisphenol A (ANSES 2013b), cadmium with soil-to-plant transfer modelling (ANSES 2019b; Carne et al. 2021), to identify the major sources. In the context of work on the creation/amendment of occupational disease tables, it characterises exposure by considering several exposure routes, the circumstances of the exposure (direct or indirect) and the factors liable to increase it (working conditions and environmental parameters, multiple exposure, exposure protection measures, general hygiene conditions in the workplace) (ANSES 2020f).
- Implements **source attribution studies for micro-organisms**. A meta-analysis was conducted of all the risk factors from epidemiological studies of 12 foodborne pathogens. Both food and non-food risk factors, such as person-to-person transmission, high-risk jobs, gardening, the presence of pets, etc., were considered (Gonzales-Barron et al. 2021; Kooh et al. 2021; Thébault et al. 2021; ANSES 2018a).
- **Develops methods** to combine heterogeneous data from different studies and thus aggregate exposure sources while taking variability and uncertainty into account ((Vanacker, Quindroit, et al. 2020), RSExpo software module). **It also combines aggregated external exposure data with internal exposure data** to improve the assessment of overall exposure to chemicals (Béchaux, Crépet, and Clémençon 2014; Béchaux, Bodin, et al. 2014; Béchaux, Zeilmaker, et al. 2014).
- **Collects, organises in a database and models exposure factors** to be used in health risk assessments of the French population (including workers and sensitive populations). The exposure factors currently being studied are body weight, respiratory rate and the space-time-activity budget group (Canu et al. 2021). Exposure factors are also collected for its work in connection with the exposure calculation models of the Consexpo[50] software application, mainly for toys.
- **Implements studies** conducted in collaboration with *Santé Publique France*, such as PestiRiv on environmental and biosourced measurements including geospatial data, in order to reconstruct the exposure routes and sources of people living in winegrowing areas (PestiRiv[51]), or the forthcoming study coupling the INCA4 food consumption survey and the ESTEBAN[52] biomonitoring study. ANSES also studies **specific behaviours** (for example the formal request on consumption of home-grown produce) or **local contamination** with the ChlorExpo study on chlordecone contamination of food in the French Caribbean.

In addition, prior to implementing future participatory research projects on environmental multiple exposures, the LILAS project ((Olivier Laurent et al. 2022)), which brought together staff from ANSES, IRSN and INRAe and was organised in the form of a ***living lab***, aimed to: 1) foster a common understanding of environmental health research methods and issues, as well as their strengths and limitations, and 2) identify the benefits and points requiring vigilance relating to **the introduction of participatory dimensions** into this research. This approach

[50] https://www.rivm.nl/en/consexpo
[51] https://www.anses.fr/en/content/pestiriv-study-exposure-pesticides-people-living-near-vineyards
[52] Health Study on the Environment, Biomonitoring, Physical Activity and Nutrition

can be applied to studies on exposure assessment, health risk assessment and ecosystem health, as well as to epidemiological and experimental studies, etc.

4.4.3 Short-term recommendations (2023-2025)

In the short term, **when preparing formal requests**, ANSES should **examine all the different possible sources and routes of exposure**. For each substance subject to a risk assessment, it will then be necessary to:

- **Identify its main exposure sources and routes** when formulating the problem, then **assess the need to aggregate** the different sources and routes by proposing decision criteria, and if necessary, organise a cross-functional response to the formal request by dividing the work between the different units involved and appointing a lead unit.
- **Issue warnings in ANSES opinions** to draw attention to other sources and routes that may contribute to exposure. When analysing the results of total diet studies (TDSs), "substances not of concern" should be checked to ensure they are not associated with other major sources of exposure.
- **Integrate the different sources of exposure**, particularly in the PARC programme, where occupational exposure will be combined with exposure from everyday life.

All this information will therefore enable ANSES to begin **identifying the chemicals** for which multi-source and multi-route assessments need to be proposed, along with the associated data. This identification process, which could be formalised in **a specific database**, will save time during the problem formulation phase for future assessments.

4.4.4 Medium-term recommendations (2026-2029)

In the medium term, it is recommended that ANSES **organise the data, methods and tools needed** for conducting multi-source and multi-route risk assessments.

It would also be advisable to **improve data collection, organisation and accessibility** in order to facilitate how the different exposure sources and routes are taken into account. In particular, it is important to:

- Consolidate **the organisation according to FAIR principles** of databases identifying the different sources and routes of exposure based on European ontologies describing the media and transfer methods (e.g. from plants to animal feed; from animals and plants to human food; from consumer articles to consumers).
- **Generate and/or collect data** on exposure factors, concentrations in different media, bioaccumulation parameters and transfer rates from soil to plant or drinking water, or transfer from articles (games, clothing, sofas) by dermal contact, suction or inhalation, and transfer from feed to human food, etc.
- Continue to investigate **behaviours** (vegetarianism, heavy consumption, addictions, etc.), **sensitive populations** (pregnant women, children, etc.) and local contamination, and integrate social and cultural aspects in the studies.
- Study the feasibility of **developing large-scale surveys combining several sources of exposure** in association with biomonitoring studies to create an observatory of consumption and behaviour.

Methods and tools should be further developed and **made operational** by providing user-friendly tools. For example, it will be necessary to:

- Continue working on **data combination algorithms**, calculations of exposure from different sources and routes, and different routes of PBPK models, and integrate them in the RSExpo software.
- Improve **interoperability between European software** on different sources and populations, mainly in the framework of the PARC partnership.
- Investigate efforts to **combine the aggregate exposure pathway (AEP), absorption, distribution, metabolism and excretion (ADME) and AOP approaches** in order to offer a comprehensive picture of exposures and effects, and thus assist in managing the associated risks (Clewell et al. 2020).

In order to integrate these issues in a systemic way, it would be advisable to **propose multi-source and multi-route risk assessments** where necessary and feasible. In these assessments, it will be necessary to:

- **Identify the major sources and routes** contributing to total exposure for different percentiles (median, 95^{th} and 97.5^{th}) of the population.
- **Include occupational exposure for the general population,** or at least draw attention to these additional sources of exposure.
- **Additionally include sources and routes of exposure in daily life, for occupational exposure,** when the associated exposures are liable to contribute significantly to the risk. The PARC programme will work on this topic by proposing specific examples for certain substances.

4.4.5 Long-term recommendations (2030 and beyond)

In the long term, in order to address the issues mentioned in Chapter 4.4.1, it is recommended that ANSES become able to:

- **Produce multi-source and multi-route risk assessments systematically**.
- Depending on feasibility (see Chapter 4.4.3) and associated costs, develop **large-scale surveys taking several sources of exposure into account,** created in keeping with biomonitoring studies. For example, the future INCA4 – ESTEBAN study could be extended to include additional sources of exposure other than food.

4.5 Dynamic exposure assessment

4.5.1 Background and identification of issues

The exposome concept incorporates changes in exposure over time and inequalities in environmental exposure. These may be inequalities over the course of a lifetime, with windows of increased sensitivity such as during the foetal period or the first few years of life. They can also concern spatial inequalities for populations living in sites that are highly contaminated, whether naturally (high geochemical background in arsenic, uranium, cadmium, asbestos, radon), or following natural disasters, or in connection with anthropic activities (mercury in the

Faroe Islands or along the rivers of French Guiana, contaminated sites and soil, Chernobyl, etc.). They may also relate to social inequalities, leading to higher levels of exposure to certain substances or equivalent levels of exposure but with a greater impact on health.

4.5.1.1 Assessing exposure over time

Over the course of a lifetime, a human being is exposed to various chemical and biological substances at levels that fluctuate according to their activities (physical/leisure/work/home life), living environment (rural/urban) and social context, as well as their consumption habits (food, objects, toys, clothing, furniture, cleaning products), hygiene, etc. An individual's activities, environment and consumption habits also change over time. Physical, physiological and endogenous parameters (metabolism, microbiota, etc.) also change with the age of the individual, associated with windows of increased sensitivity such as during the foetal period, the first few years of life, or puberty. The various agents encountered will either be eliminated quickly if they have a short half-life, or accumulate over time if they have a long half-life. Internal doses therefore vary from one individual to another and from one agent to another, and can lead to health effects in the longer or shorter term.

Risk assessment and management must therefore consider all these fluctuations over time and adapt to the diversity of individuals, taking the socio-demographic determinants of exposure into account. To do this, temporal modelling of exposure and new risk indices should be proposed to reflect the variety of exposures occurring over the course of a lifetime, their occurrence and duration, the sensitivity of the life period, etc. (Verger, Tressou, and Clémençon 2007; Béchaux, Zeilmaker, et al. 2014). However, today, although time is taken into account by proposing TRVs based on chronic lifelong exposure, for example, the exposure dose is still mainly considered to be constant over time.

To estimate lifelong exposure, it is possible to use internal exposure data, reflecting the accumulation over time of all sources of exposure, or to use a toxicokinetic (TK) model and external exposure data. TK models can be defined as "mathematical descriptions simulating the relationship between external exposure level and chemical concentration in biological matrices over time" (International Programme on Chemical Safety and Inter-Organization Programme for the Sound Management of Chemicals 2010). TK models describe the ADME process, corresponding to the absorption, distribution in the body, metabolism and excretion of chemicals and their metabolites. They thus allow exposure to be simulated over time, either by starting from external exposure events occurring over the course of a lifetime and simulating internal doses, or by reconstructing exposure from measurement data obtained in biological matrices.

The advantage of these models is that they also enable the two types of data – on external and internal exposure – to be combined to produce a refined exposure estimate. Indeed, internal and external exposure data are proxy variables providing useful but different information for estimating the real exposure, which is unknown. For substances with long half-lives, therefore, measurement data obtained in biological matrices provide information on past exposure, while external exposure data are estimates of exposure at a given time. For example, in (Béchaux, Crépet, and Clémençon 2014) and (Béchaux, Bodin, et al. 2014), biomonitoring data were used to correct the cadmium exposure estimated from external exposure data, thus allowing exposure to be modelled over time.

In addition to characterising specific exposure windows, dynamic exposure modelling is a valuable tool for risk management. It enables the impact of management measures to be assessed in the long term by predicting changes in internal exposure dose after, for example, a decrease in contamination levels in the various sources or a ban on the substance in question. It can also be used, for example, to estimate the time needed for the risk of exposure exceeding a toxicity reference value to be reduced to zero, following a new management measure.

With microbial pathogens, there is a high degree of intraspecific variability in virulence or persistence in reservoirs. Knowledge of this diversity is important for source attribution and risk assessment (ANSES 2017a; EFSA Panel on Biological Hazards et al. 2019). The dynamic nature of this diversity can be seen in numerous examples showing major changes over time in strains with a particular virulence or antimicrobial resistance profile (Ingle et al. 2021; Moura et al. 2021), as well as the emergence of new pathogens (Becker et al. 2019; Brooks et al. 2021). The monitoring of intraspecific diversity and new agents is also a central concern for One Health stakeholders (Bordier et al. 2020). The detailed characterisation of diversity is now facilitated by strain sequencing methods (EFSA Panel on Biological Hazards et al. 2019). However, linking different monitoring systems remains difficult, which limits the sensitivity and rapidity of detecting changes over time (Koch et al. 2020).

Consumer practices play a key role in the control of foodborne microbiological agents. Over 70% of the burden of foodborne illness is due to a failure to observe expiry dates, inadequate cooking of food or poor hygiene practices in the consumer's kitchen (Augustin et al. 2020). Consumer practices are recorded by ANSES in its INCA studies (Dubuisson et al. 2019). Consumer behaviour can change significantly over time due to external factors (the COVID-19 crisis (Janssen et al. 2021), the appearance of new foods, new consumption practices). It may also depend on more personal factors such as socio-professional category or a desire to reduce food waste (Guillier, Duret, et al. 2016). Analysing these factors enables different communication strategies to be defined with regard to prevention of foodborne microbiological risks (ANSES 2015b).

The issues in terms of dynamic exposure modelling are therefore to:

- **Model changes in external and internal exposures over time**, considering physiological changes, the lifestyle of individuals and the kinetics of substances.
- **Develop risk indices and reference values** that take the dynamic evolution of exposure into account.
- **Identify time windows of exposure** that may lead to a higher risk.
- **Improve the sensitivity of detecting changes** in the genetic diversity of microbiological agents by facilitating the linking of data sources.
- **Monitor changes in consumer lifestyles, consumption and hygiene practices**.

4.5.1.2 Spatialisation of exposure

Considering exposure to chemical, biological and physical agents originating from multiple processes and exposure routes in order to report on the immediate or delayed consequences of this contamination on an individual – and even sometimes their descendants – requires reliable descriptive data on the quality of the environment (air, water, soil, food, etc.) at relevant spatial and temporal scales. These data also need to be linked with information on the health of the individual (or population) studied. The social aspects related to the spatialisation of exposure are addressed in Chapter 4.5.1.3.

Furthermore, the processes of contamination are complex, with multiple sources over large geographical scales. To assess exposure at smaller spatial scales that are relevant to target populations, it is often necessary to rely on fate and transfer models to account for the spatial and temporal variability of contamination (Caudeville et al. 2021).

In practical terms, data availability and the integration of various types of information – in terms of spatial scales (from the measurement station to the geographical area) and spatial resolution, and with very different temporal frequencies of acquisition (from a single data item to several per second) – are major limitations, and potentially a source of great uncertainty when mapping exposure in time and space, compounded by the need to combine the data with information on the mobility of individuals.

French and European infrastructures and databases resulting from programmes to measure air, soil and water quality (European Norman network[53]), exposure (EIRENE[54], France Exposome[55]) and health (Health Data Hub[56]) are being developed, and will provide data and tools for research and assessment of population exposure.

Digitising georeferenced data on quality monitoring of environmental media (water, air, soil) and integrating them in geographic information systems (GISs) enables the exposure levels of a population to be represented on the scale of a study area, even if this representation is usually static. To this end, various mathematical methods and tools for improving the representativeness of the databases (in particular spatial interpolation and geostatistics) are used to include new data, increase their robustness and characterise the associated uncertainties (Caudeville et al. 2021).

In order to assess the fraction of chemicals liable to be internalised by populations, multimedia spatial exposure models (Caudeville et al. 2012) are also available for predicting the distribution of substances in different media all the way up to humans, with spatial resolutions from around ten kilometres to one kilometre.

However, the location of individuals and contamination, as well as the intensity of this contamination, varies over time. Moreover, the period of life at which exposure occurs, the onset time of a disease and individual mobility make the assessment of exposures and their consequences highly complex. Mathematical and statistical tools that can integrate such information, in space and time, are needed to calculate individual exposures more robustly. Today in particular, the application of exposure reconstruction techniques (Space-Time Information System Technologies (STIS)) and the use of new technologies such as sensor systems to monitor individual exposure in real time opens up the possibility of estimating the exposure of samples of the population in space and time with greater accuracy (Jacquez et al. 2019).

The issues in terms of spatialisation of exposure are therefore to:

- **Develop** and make available **multimedia models of contamination transfer and fate at spatial scales** tailored to the populations studied.
- **Analyse large spatial and temporal exposure datasets in a combined manner** using suitable mathematical, statistical and IT tools.
- **Adapt geovisualisation tools** (GISs) to the temporal exposure data in order to reconstruct spatial exposure over time.
- **Integrate individual exposure data**, for example via sensor systems (see Chapter 6.3), to take better account of the spatial and temporal variability of exposures.

53 https://www.norman-network.net/
54 https://www.eirene-ri.eu/
55 https://www.france-exposome.org/
56 https://www.health-data-hub.fr/

4.5.1.3 The social exposome

The distribution of individual exposomes is closely linked to social and environmental inequalities, in terms of both exposure and the availability of resources that promote physical and mental health, often referred to as "environmental amenities" (green spaces, quiet areas, high-quality built environment, social fabric, communities, etc.).

The different risk factors have particularly been documented in the urban context (urban exposome), which includes all the factors of the urban environment that are favourable and unfavourable to health, beginning with life *in utero* (Robinson et al. 2018).

The influence of socio-economic status on the exposome is manifested here in relation to a multitude of exposures such as outdoor and indoor air pollution, noise, heat, environmental resources or amenities. In addition, many studies emphasise the exposures occurring during the critical periods of the first 1000 days of life and the period of conception (Deguen, Vasseur, and Kihal-Talantikite 2022). Factors as diverse as exposure to fine particles (PM_{10} and $PM_{2.5}$), NO_2, SO_2, noise levels, tobacco smoke and the accumulation of different diseases have been found in many studies to be correlated with income, education level, being unemployed or a single woman, or belonging to certain minority groups.

Taking the social characteristics of populations into account in risk assessments would increase the relevance of the resulting management options. It has been observed that socially advantaged populations may suffer less harm at equal levels of exposure, for example because of better access to healthcare or prevention systems (UNICEF France 2021). Furthermore, although there are still few data available, besides the health impact, it seems possible to use the social exposome to assess the consequences of a poorer state of health on individual quality of life (Deguen, Vasseur, and Kihal-Talantikite 2022).

The issues in terms of taking the social exposome into account are therefore to:

- Propose an approach closely related to the issue of prevention in health. Indeed, prevention policies are often characterised by a "one size fits all" approach that does not take account of the needs and specificities of different social groups. An analogy with "personalised" or "precision" medicine could be suggested. This new approach seems to correspond to **"precision public health"** including **"geomedicine"** and should therefore be able to identify territorial risk factors and target particular social groups according to their vulnerabilities (Sandoval et al. 2018; Perroud 2018).
- Use **recent technological developments combining measurement and geolocation, coupled with research and citizen science approaches**. These developments could boost the proposed approach by vastly improving the degree of territorial coverage, data collection and the sense of "empowerment" of the populations concerned. Such an effort requires significant methodological work to ensure that the levels of precision of the measurements taken are compatible or complementary; a lower level of precision can be partially offset by a greater degree of spatio-temporal coverage, and the possibility of detecting warning signals (abrupt changes in exposure levels, spatio-temporal variations, etc.).

Figure 16 below summarises ANSES's current actions concerning dynamic exposure assessment and the WG's recommendations for the future.

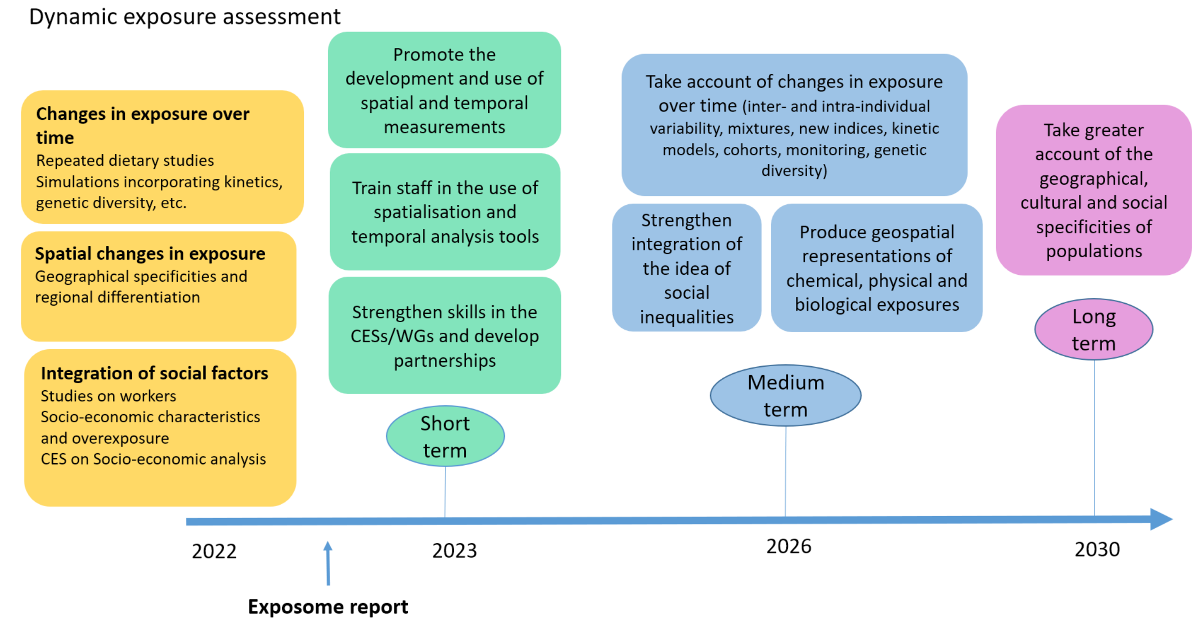


Figure 16: Recommendations for dynamic exposure assessment.

4.5.2 What ANSES is already doing

With regard to the temporal dimension, ANSES studies **trends in food consumption** (INCA 1, 2, 3) **and the associated exposures** (iTDS, TDS 1, 2) using cross-sectional surveys repeated over time. It also seeks to characterise the health impact of long-term management measures, such as recommended changes in dietary behaviour or food preparation methods, for example in the context of food contamination by chlordecone in the French Caribbean (ChlorExpo). The forthcoming study combining the INCA4 food consumption survey and the ESTEBAN biomonitoring study will be conducted on an ongoing basis, which will facilitate the study of internal exposures and food consumption over time. Research is also being carried out to **simulate changes in exposure over time** by integrating the kinetics of substances, physiological and biochemical changes, and consumption habits over the course of a lifetime (Béchaux, Zeilmaker, et al. 2014; Pruvost-Couvreur 2020). ANSES is contributing to EFSA projects on the development of a platform for **TK models** of different species (laboratory and livestock animals) including humans. ANSES also takes part in monitoring **changes over time in the genetic diversity of microbiological agents** as part of its reference activities (e.g. the *Salmonella* Network, or the Fastypers joint technological unit), or research projects such as the ANR's ClostAbat (*Clostridium*) or the One Health European Joint Programmes (OH EJP) ListAdapt (*L. monocytogenes*) and ADONIS[57] (*Salmonella*).

With regard to the spatial assessment of exposure, ANSES takes account of **regional and socio-economic differences** in food consumption and contamination in its INCA and TDS studies. It also studies **geographical specificities by carrying out targeted studies**, such as on the exposure of heavy fish consumers living mainly near the coast (CALIPSO[58],

[57] Assessing determinants of the non-decreasing incidence of *Salmonella*
[58] Dietary consumption of fish and seafood, contamination by trace elements and pollutants, and omega 3

CONSOMER[59]) (Leblanc et al. 2006; Arnich et al. 2020, 202; Lunghi et al. 2022; ANSES 2019f), on the exposure of French Caribbean populations (Kannari (ANSES 2017f) and Chlorexpo (ANSES 2021m)).

In addition, ANSES coordinates **specific studies for populations living on contaminated sites and soil** as a result of: i) agricultural activities (ANSES 2019b; 2021i), ii) industrial activities (ANSES 2021a) and iii) accidents (ANSES 2019c).

As part of the European HBM4EU programme, ANSES took part in a **study of geographical and temporal differences in exposure of the European population** to different chemical classes (PFAS, flame retardants, metals, bisphenols, etc.). With regard to noise and its effects on health, in 2013 ANSES proposed an approach for assessing the extra-auditory risks associated with exposure to environmental noise. This approach was based on the spatialisation of noise exposure established from the analysis of strategic noise maps resulting from European Directive 2002/CE/49 and the identified risk factors. It is also considering the use of data from sensor systems to characterise individual exposure to air pollutants and assess the resulting risks.

In recent years, several of ANSES's expert appraisals in risk assessment have included **the analysis of data from studies in the human and social sciences** (sociology, psychology, geography, etc.). For example, the studies carried out on sewer workers (ANSES 2016b) and waste management workers (ANSES 2019g) examined factors of increased suffering at work, in particular the exercise of an occupation with low social status, which is common to these two activities. The expert appraisal on exposure of the general population to mould in housing (ANSES, 2016c) addressed the risk of overexposure related to the socio-economic characteristics of individuals. Other expert appraisals have addressed population exposure through an analysis of the production processes that lead to substances such as nanomaterials being placed on the market. Both the increasing demands made on ANSES in the field of economics over the last few years and the need to acquire robust expertise in this field led the Agency to set up an Expert Committee on **Socio-economic analysis** (the CES ASE) in January 2022. As well as monitoring expert appraisals in its sphere of competence, this group will aim to capitalise on and structure the methodologies associated with analysing the socio-economic determinants of risk situations (which can vary exposure or effects), the economic value of a burden (health, environmental or organisational), or the assessment of management options (ANSES, Socio-economic analysis in expert appraisals). These dimensions (mainly the analysis of socio-economic determinants of exposure or effect) can be reflected in the structuring of the social exposome.

4.5.3 Short-term recommendations (2023-2025)

In order to be able to offer dynamic exposure assessments, in the short term, **the development and use of spatial and temporal measurements should be promoted**, in order to better characterise social inequalities in exposure. To this end, it will be necessary to **train staff in the use of spatialisation and temporal analysis tools** for exposure and **develop collaborations** with research institutes or teams that develop and offer these tools. Involving **experts in the field, to reinforce skills in sociology, social epidemiology, geography, demography and anthropology** in the WGs/CESs, would ensure better consideration of exposure dynamics. Concerning more specifically the study of the genetic

[59] Consumption study on seafood products: internet survey of 2500 consumers in coastal areas (2016-2017)

diversity over time of microbiological agents in the environment and in food production sectors, or strains isolated from affected patients, the lessons learned from the OH EJP projects will help identify points requiring monitoring.

4.5.4 Medium-term recommendations (2026-2029)

In the medium term, the Exposome WG recommends strengthening methodological development work that **takes account of changes in exposure over time**. In particular, it will be necessary to:

- Refine how **inter-individual and intra-individual variability over time** are taken into account by including physiological and biochemical changes and consumption habits.
- Study **changes in the composition of mixtures** over time.
- Develop **new exposure indices** that reflect the variety of exposures occurring over the course of a lifetime, their occurrence and duration, and the sensitivity of the life period.
- Strengthen the development of **kinetic models of chemical and biological agents** in living organisms and in the environment.
- Conduct **cohort studies** on consumption and lifestyle habits, exposure monitoring and health effects taking socio-cultural determinants into account in order to analyse changes and effects throughout life.
- Deploy **integrated monitoring of the genetic diversity** of microbiological agents in the environment, food production sectors and cases of human infection.

The WG also considers it would be pertinent to propose **geospatial representations of chemical, physical and biological exposures** according to the geochemical characteristics of soil, cropping practices, contaminated sites and geographical areas (coasts, islands, urban/rural) in order to identify potentially overexposed populations, and to propose suitable management measures, by associating geospatial representations with social inequalities.

With regard to the social exposome, the aim will be to strengthen integration of the idea of social inequalities in expert appraisals and study its link with health. The WG also proposes continuing the debates initiated by the Agency, and the experimental implementation of **citizen science and research** in certain regions under collaborative work undertaken (INRAe, French Natural History Museum, Inserm, IRSN, etc.).

All of these proposals could be applied to **substances of concern** in order to test the added value of considering the temporal, spatial and social dimensions in risk management.

4.5.5 Long-term recommendations (2030 and beyond)

Exposure assessments and management measures could be reviewed to **take greater account of the geographical, cultural and social specificities of populations** by involving them more closely. This greater participation could be facilitated by **synergies between the actions carried out by the Agency and other operators** such as the Regional Health Agencies (ARSs) in conjunction with local authorities, as well as certain stakeholders (NGOs, associations) based in the regions concerned. For example, in the area of air pollution, deploying sensor system networks far more widely on the ground, in a process of citizen science and research, should strengthen the population's feeling of empowerment and trust, as well as the social robustness of policy decisions on risk management.

4.6 Establishment of reference values

4.6.1 Background and identification of issues

Several types of reference values (RVs) are used to characterise the link between exposure to a chemical and occurrence of an adverse effect. Various national, European or international bodies have developed RVs. Even if the terminology may differ, the different organisations broadly follow the same methodology to establish these RVs. In France, ANSES is the reference body establishing RVs based exclusively on health criteria (ANSES 2022j). Some of the RVs developed by ANSES (TRVs, IAQGs, OELs, etc.) are used to propose management values that take socio-economic considerations into account, which are then included in French regulations.

In the general population, toxicity reference values (TRVs) are toxicological indicators used to establish a relationship between a dose and an effect (toxic with a threshold effect) or between a dose and a likelihood of effect (toxic without a threshold effect) (ANSES 2017g). They are used to assess potential risks by comparing them with exposure levels, and to help choose management measures to protect population health. They can also be used for developing health guidance values (HGVs) for drinking water, or indoor air quality guidelines (IAQGs). The HGVs for drinking water (DW) determined by ANSES correspond to the maximum concentration of a substance in DW associated with a health risk considered acceptable for the population as a whole, assuming lifelong consumption of this water by the population and taking account of possible variations in sensitivity at the different stages of life. IAQGs are numerical values, associated with an exposure time, that correspond to a concentration in air of a chemical below which no health effect or hazard with health consequences (in the case of odorous compounds) is normally expected for the general population (ANSES 2016d).

In the workplace, OELs and biological limit values (BLVs) are used to protect the health of workers (ANSES 2017c). The OELs recommended by ANSES are concentration levels of pollutants in workplace atmospheres that should not be exceeded over a determined reference period and below which the risk of impaired health is negligible. They are determined on the basis of the most recent scientific knowledge. Although reversible physiological changes are sometimes tolerated, no organic or functional damage of an irreversible or prolonged nature is accepted at this level of exposure for the large majority of workers. These concentration levels are determined while considering that the exposed population (workers, including pregnant women) is one that excludes both children and the elderly. Biological values such as BLVs and biological reference values (BRVs) are used for the biological monitoring of occupational exposure. A BLV is the limit value for the biomarkers[60] considered relevant. Just like the 8h-OEL[61], it aims to protect workers exposed to the chemical agent in question regularly and over the course of a working life from the adverse effects associated with medium- and long-term exposure. BRVs correspond to concentrations found in a general population with similar characteristics to those of the French population, or a control population not occupationally exposed to the substance in question. These values cannot be considered as providing protection from the onset of health effects, but do allow a comparison with concentrations of biomarkers of exposure and/or effects measured in exposed workers.

[60] BME: parent substance or one of its metabolites determined in a biological matrix, and whose variation is associated with exposure to the agent

[61] Level of concentration of pollutants in a workplace atmosphere not to be exceeded over an eight-hour period

In general, RVs are specific to a substance, duration and route, and apply to the entire study population (general population or workers). They are based on a critical effect (selected from the relevant adverse effects), which is the adverse effect occurring at the lowest dose in the most sensitive population (ANSES 2017g). When justified, it may be necessary to identify, from within the study population, sub-populations with greater sensitivities to certain substances, such as children or pregnant women, and take them into account when establishing the RV.

The issues identified in terms of establishment of reference values are to:

- **Develop RVs,** and their establishment methods, **that take account of exposome components** such as mixtures and the variety of exposure routes, and base RVs more on internal doses determined from measurement data obtained in biological matrices.
- **Systematically take sensitive populations into account** (foetuses, children, pregnant women), by including populations that have been less considered until now, such as the elderly, sufferers of chronic diseases (diabetes, immunodeficiency, hypo- or hyperthyroidism, respiratory and cardiovascular diseases, etc.), overweight or obese individuals, people using contraceptives, or suffering from infections, etc.
- **Strengthen the combination of different types of data**: *in silico, in vitro, in vivo* and epidemiological data to determine the link between exposure and effect and to establish RVs.
- Strengthen the consideration of specific effects in the development of RVs, such as:
  - endocrine disruption during sensitive exposure windows;
  - early effects, as recently proposed by EFSA for bisphenol A (EFSA 2022) and by ANSES for perchlorates (ANSES 2021b; 2022a);
  - respiratory and skin sensitisation.
- **Use the probabilistic approach** to incorporate inter- and intra-individual variability and uncertainty.
- **Use meta-analyses** to include multiple studies.

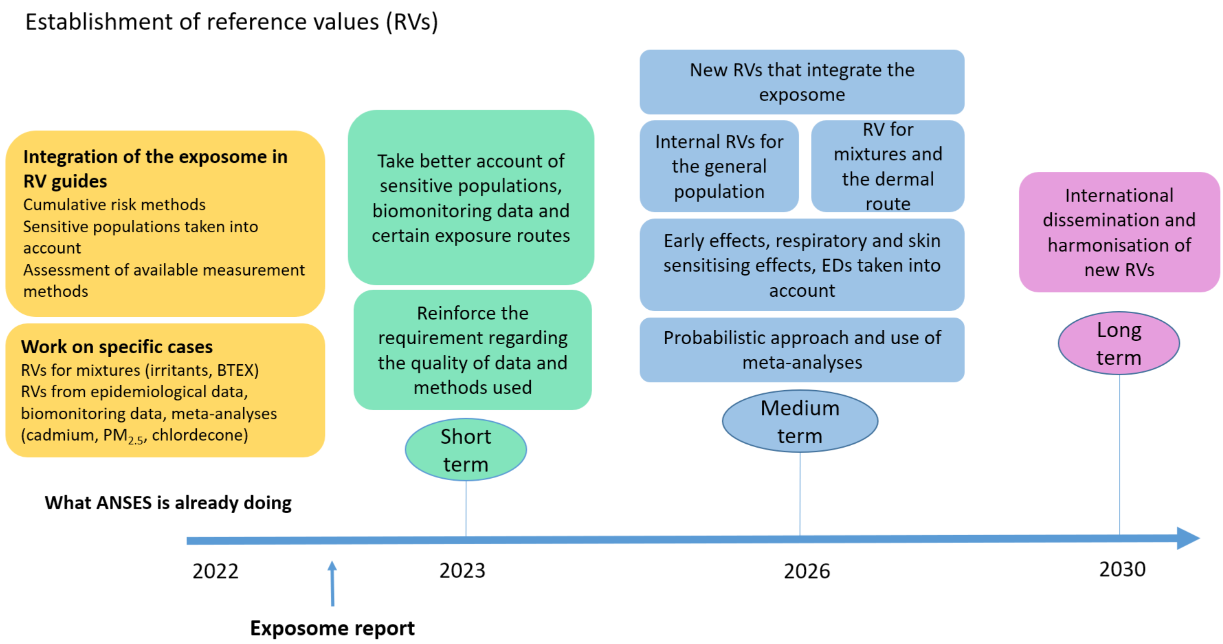


Figure 17: Recommendations for the establishment of reference values.

4.6.2 What ANSES is already doing

ANSES **already integrates some components of the exposome to establish RVs**:

By proposing **approaches** in its RV guides that:

- **Use cumulative risk methods** based on the use of survival tables, which consists in subtracting the cumulative lifetime risk of the exposed population from that of the unexposed population (e.g. $PM_{2.5}$[62] (ANSES 2022i));
- **Take sensitive populations into account**. This question is developed in Chapter 6.2;
- **Assess the available measurement methods** in order to recommend the most appropriate one(s) for measuring exposure levels in the workplace or in indoor air for comparison with an OEL or IAQG (ANSES 2020i).

By working directly on **specific cases** such as:

- **The development of an approach to establish RVs for mixtures** with application to a mixture of irritants in the air (IAQG) and to a mixture of benzene, toluene, ethylbenzene and xylenes (BTEX) (TRV) (ANSES 2022d);
- **The use of epidemiological data** to establish RVs for different substances such as cadmium (ANSES 2017e), toluene diisocyanate (ANSES 2020e) or particulate matter in ambient air ($PM_{2.5}$ (ANSES 2022i));
- **The use of meta-analyses** on epidemiological data in the case of particulate matter in ambient air ($PM_{2.5}$) for example (ANSES 2022i);
- **The use of measurement data obtained in biological matrices** to propose internal RVs such as the internal TRV for cadmium (ANSES 2017e) or chlordecone (ANSES 2021l), assessment of biomarkers of exposure with a view to recommending biological values in the workplace for trichloroethylene (ANSES 2021g) or 2-methoxy-1-propanol (ANSES 2021f).

4.6.3 Short-term recommendations (2023-2025)

In the short term, the debates held within the WGs and CESs should be pursued and new ones initiated through examples for:

- Taking better account of:
  - **Sensitive populations** by including populations that have been less considered until now (see Chapter 6.2);
  - **Measurement data obtained in biological matrices** to define internal TRVs;
  - **Certain exposure routes** for the general population by proposing, for example, TRVs for the dermal route and indoor dust guideline values (IDGVs).

- **Reinforcing the requirement regarding the quality of data and methods used** for establishing RVs, in order to limit the accumulation of uncertainties by:
  - **Assessing available measurement methods** in order to recommend the most appropriate one(s) for measuring concentrations of biomarkers of exposure to chemicals for comparison with biological values (BLVs or BRVs or internal TRVs);

[62] Ambient air particulate matter with an aerodynamic diameter <2.5 µm.

- **Combining** *in silico, in vitro, in vivo* and epidemiological **data**;
- **Using the probabilistic approach** to model uncertainty factors;
- **Using toxicokinetic/toxicodynamic (TK/TD) data** to model the inter-individual uncertainty factor.

4.6.4 Medium-term recommendations (2026-2029)

In general, in the medium term, **methods should be developed for proposing new RVs incorporating the components of the exposome**, based on the examples addressed in the short term and on the scientific literature. These new values should be accompanied by **work on their use and interpretation** by expert groups and managers. These methods will therefore help improve how co-exposures are taken into account via different routes and specific effects by:

- Developing RVs for mixtures entering the body via the same exposure route;
- Developing TRVs for the dermal route;
- Proposing internal RVs, especially for the general population;
- Taking endocrine-disrupting effects into account, especially during sensitive exposure windows;
- Taking respiratory and skin sensitising effects into account;
- Considering the impact of taking early effects into account when establishing and using RVs.

These methods could be based on **the probabilistic approach and the use of meta-analyses** to integrate variability and uncertainty, especially when modelling dose-response curves, and the use of uncertainty factors.

4.6.5 Long-term recommendations (2030 and beyond)

In the long term, efforts should be applied to **the international dissemination and harmonisation** of methods for establishing new RVs.

4.7 Assessment of risks and public health impact

4.7.1 Background and identification of issues

As detailed in the previous chapters, the exposome implies that multiple sources are identified and taken into account, and integrated in risk assessments (see Chapter 4.4). It also requires the effects of chemical and microbiological agents in mixtures to be considered (see Chapter 4.3), as recommended by the European Union's "zero pollution" ambition and Chemicals Strategy for Sustainability. These concepts of multiple exposure are currently being studied at EU level (Bopp et al. 2018; EFSA Scientific Committee et al. 2019; Drakvik et al. 2020). Another issue is the consideration of vulnerable populations, which is reflected in certain decisions regarding, for example, the presence of bisphenol A in infant feeding bottles, but which remains a major challenge.

Other implications of taking the exposome into account are more complex to implement, but are nevertheless important for risk assessment. They include the interaction between health determinants of different types (chemical, biological, physical agents, psychosocial or socio-economic context, and organisational constraints, etc.). For example, chemicals can interfere with the immune system. This interference can affect the response to an infection through several mechanisms: disruption of inflammatory mechanisms, suppression of the immune response to an infection, or even multiple and complex effects at different levels (Estaquier, Blanc, and Coumoul 2021). Many substances (PCBs and dioxins, metals, PFOA/PFOS, pesticides) have been associated with these immunosuppressive mechanisms (Dietert 2014; Ewers, Stiller-Winkler, and Idel 1982; Moore et al. 2009; Grandjean, Heilmann, Weihe, Nielsen, Mogensen, and Budtz-Jørgensen 2017; Grandjean, Heilmann, Weihe, Nielsen, Mogensen, Timmermann, et al. 2017; Di Prisco et al. 2017) while others (organochlorines, PAHs, fine particulate matter, NO_2, ozone, metals, certain plasticisers or plastics, etc.) are known to induce immunostimulation mechanisms in humans (Kim et al. 2012; Suzuki et al. 2020; Prata et al. 2020; Sharifinia et al. 2020). It has also been suggested that by promoting chronic metabolic or vascular diseases, endocrine disruptors may increase the risk of severe COVID-19, for example (Wu et al. 2021; Grandjean et al. 2020). More generally, the COVID-19 health crisis has led to the study of the link between the chemical and social exposome and severe forms of COVID-19 (Hu et al. 2021; Coker et al. 2020; Konstantinoudis et al. 2021). Another example is the emerging role of the microbiome, in particular commensal bacteria and parasites, in the occurrence of gastrointestinal cancer. It has now been added to the main risk factors for this type of cancer, which are genetics, age, smoking, alcohol consumption, obesity, and exposure to radiation and chemicals (Duijster et al. 2021).

When examining the interactions between psychosocial and chemical factors, two levels of interaction can be distinguished. On the one hand, the socio-economic situation (substandard housing, homes in polluted areas with few green spaces, etc.) can have an impact on the level of exposure to chemicals and lead to greater risks (see Chapter 4.5). On the other hand, there may be interactions between psychosocial stress and chemical stress in terms of health effects. Several epidemiological studies (Schreier et al. 2015; Tamayo y Ortiz et al. 2017) and a few experimental studies (Bouvier et al. 2017; Wright et al. 2017) have reported results on the impacts of psychosocial factors combined with exposures to chemicals such as lead, mercury, bisphenol A, etc. In this context, it should be noted that psychosocial stresses seem to have impacts on epigenetic markers, just like chemical stresses (Cao-Lei et al. 2020). Thus, the temporal dimension inherent in the exposome, which can be included by modelling exposure dynamically in risk assessment (see Chapter 4.5), can also be extended to intergenerational impacts, which are more complex to take into account but are essential for a better understanding of the risks (Nilsson, Sadler-Riggleman, and Skinner 2018).

The interactions between chemical factors and physical factors such as sunlight, heat, radiation and noise, and their impact on human health and eco-systems have also been studied, showing for example an increase in the effects of chemicals through exposure to artificial sunlight, the latter being strongly modified by recent technological developments (Mokrzyński et al. 2021; Roberts, Alloy, and Oris 2017; Rider et al. 2014; Zhao, Liu, and Lin 2013).

Another component of the exposome is the benefit (identified by a risk/benefit analysis), which may outweigh the risk. These analyses are of interest in the case of dietary exposure, for example, where a food may contain one or more substances that are harmful to the body as well as nutrients that are beneficial. A well-known example is the exposure to methylmercury via consumption of fish rich in omega-3 fatty acids (Guevel et al. 2008; V. Sirot et al. 2011).

Beyond the study of food, benefits could be taken into account more comprehensively by integrating lifestyle habits and the surrounding environment, such as whether a sport is practised, or the presence of green spaces.

Another widely developed concept related to the exposome is the Global Burden of Disease proposed by the WHO in the 1990s (Murray 1994). A population's burden of disease can be estimated using various indicators such as life expectancy, cause-specific mortality rates, the number of incident and prevalent cases of specific diseases, disability-adjusted life years (DALYs) and self-assessed health. The burden of disease thus encompasses the measurement of the impact of diseases and risk factors on physical and psychosocial health in a comprehensive and comparable manner. Extending risk assessments to include burden of disease indicators would make it possible to compare health-related harm from different types of exposure and set priorities for public health actions. The consideration of health impacts can be coupled with an economic analysis of the associated costs, in order to measure the health costs and benefits of implementing or not implementing management options, and to assist decision-makers in their choices (Ougier et al. 2021; Nedellec, Rabl, and Dab 2016).

To summarise, in addition to those presented in the previous chapters, the following issues need to be considered in order to integrate the exposome components in risk assessments:

- **Integrate multiple exposures** to estimate an overall risk: multi-substance, multi-source and exposure routes, including occupational exposure.
- **Take multiple factors into account** (chemical, biological, physical, psychosocial and organisational, etc.) as well as their interactions.
- **Consider vulnerable populations** in risk assessment and management by including a study of the social exposome.
- **Integrate the changes in exposure** throughout life and their potential impact on offspring by studying **transgenerational effects** using epigenetic markers.
- **Take account of both the risks and the benefits** for specific products or media (food, breast milk, water, etc.) and in a more comprehensive way by including lifestyle habits and the living environment.
- **Extend risk assessments with burden of disease indicators** to set priorities for public health action.
- **Assess the socio-economic impacts** of management options to reduce or eliminate health risks.

With regard to issues related to multiple exposures of the same type, dynamic exposure and consideration of vulnerable populations, the recommendations are detailed in Chapters 4.3, 4.4, 4.5 and 4.6. Only recommendations on multiple exposures of different types (multi-factors), transgenerational effects, risk/benefit analysis, health impacts and the associated socio-economic costs will be detailed here.

Figure 18 below summarises ANSES's current actions to integrate the exposome in risk assessment and the WG's recommendations for the future.

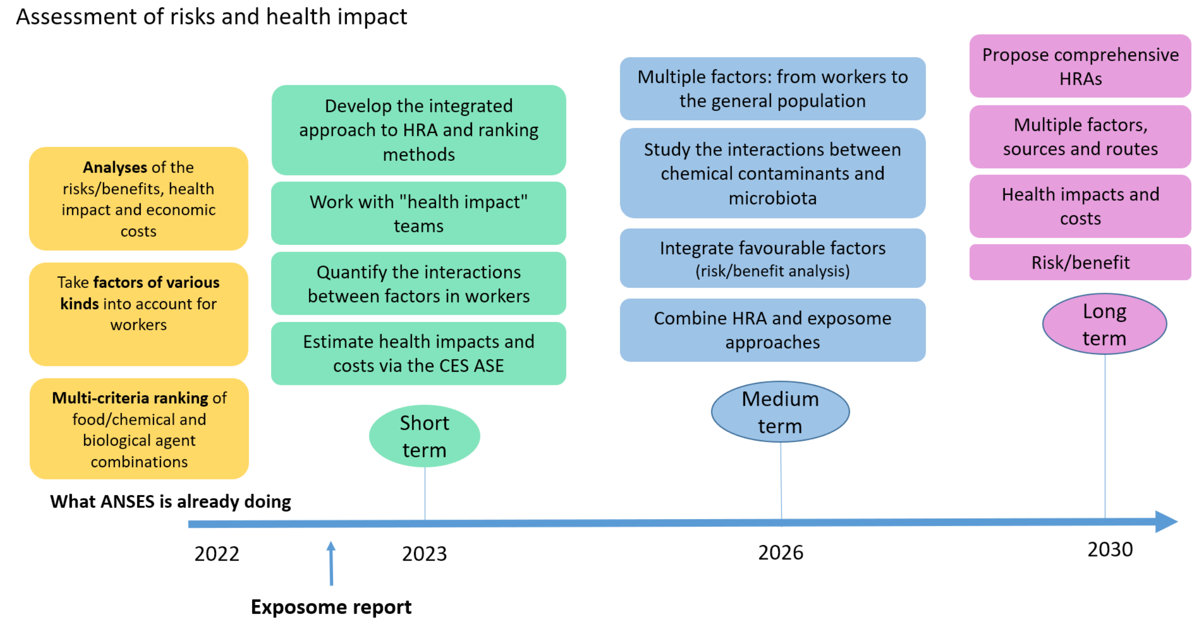


Figure 18: Recommendations for assessing risks and the health impact

4.7.2 What ANSES is already doing

In occupational health, ANSES takes account of **multiple exposures to factors of various kinds and the associated risks**. For example, when establishing occupational exposure limits (OELs), the experts discuss whether to assign an "ototoxic" (or "noise") notation in order to take account of co-exposures to chemicals and noise in the workplace (ANSES 2013a). ANSES collaborated with *Santé Publique France* and DARES on a study of occupational multiple exposures that provided an overview of the most common situations of cumulative exposure to factors of different types (chemical, biological, physical, organisational and psychosocial), depending on the area of activity or occupational category of an employee (Fourneau et al. 2021). In addition, the Agency participates in or finances research projects on the interactions between work organisation conditions and exposure to bacteria, viruses and fungi (ANR, FP7, H2020 projects on the respiratory health of poultry farmers in France), on the interactions between biological agents and chemicals (QAIHOSP[63]) and on the interactions between physical constraints and chemicals (NeuroBiomecaTMS[64]).

ANSES has long been **taking risks and benefits into account** in its work. This mainly involves balancing nutritional needs against the associated risks in order to optimise the recommendations issued under the National Health and Nutrition Programme (PNNS) (ANSES 2016a). The benefits of consuming fish containing both metals and nutrients have also been analysed, enabling optimal consumption to be determined, among other things (Guevel et al. 2008; Sirot et al. 2011; ANSES 2019d).

ANSES recently assessed the **health impact** of ragweed pollen in France, by estimating the prevalence of ragweed allergy throughout the country (ANSES 2020g). This impact was then monetised by taking account of different indicators for the costs of medical care, lost production and lost quality of life, thus combining financial and economic approaches. ANSES has also assessed the effectiveness of the beetle *Ophraella communa* as a biological control agent

63 Indoor air quality in hospitals
64 Study of the impact of co-exposure to neurotoxic chemicals and physical risk factors for musculoskeletal disorders on the occurrence of carpal tunnel syndrome in workers

against ragweed (ANSES 2015a). The **benefits** to human health and control of invasive species were taken into account and weighed against the potential **risks** to plant health and the environment. As part of the HBM4EU research programme, ANSES has assessed **the health impact and associated economic cost** of cadmium exposure and the risk of osteoporosis (Ougier et al. 2021).

Lastly, ANSES recently proposed a **methodology for multi-criteria ranking** of food/chemical and biological agent pairs according to the associated risk (ANSES 2020h) in order to help managers prioritise risk reduction efforts.

4.7.3 Short-term recommendations (2023-2025)

In the short term, it is recommended that ANSES:

- Develop **integrated approaches to risk assessment** in order to consider all multiple exposures (mixtures, sources and routes). The PARC programme will help provide methods and tools that will be applied to case studies on substances of interest to the Agency (metals, pesticides, perfluorinated substances, etc.).
- Take **account of interactions between factors** (chemical, biological and physical agents, socio-economic environment, organisational constraints, etc.), starting with well-identified situations such as those encountered in the workplace (see Chapter 6.1 on waste workers).
- Continue work on **ranking biological and chemical agents** in food in order to develop common burden of disease indicators associated with these agents.
- Investigate the **available methods for risk/benefit analysis** in the context of dietary and environmental exposures.
- Become more familiar with **health impact assessment** approaches by strengthening collaboration with specialised teams (e.g. with Inserm and *Santé Publique France*).
- Propose economic assessments of health, environmental or organisational impacts via the new Expert Committee on **Socio-economic analysis** (CES ASE).

4.7.4 Medium-term recommendations (2026-2029)

In the medium term, in order to develop risk assessment, it will be necessary to **extend the study of interactions between factors** – which at present are mainly only taken into account in occupational exposure – to everyday life. Multi-determinant approaches could be proposed that enable health effects to be cross-referenced according to interactions between the factors (e.g. digital technology, nutrition, chemicals, physical activity, etc.) and the social context. Furthermore, encouraging **the analysis of the relationship between exposures and the health and social situation** of populations would enable a better analysis of the causes of diseases. Integrating the notion of **health-promoting factors such as nutritional factors, physical activity or green spaces** could complement risk assessments with aspects relating to benefits.

As the gut microbiota is both a target of and an essential bulwark against chemical and biological stressors entering the body via the oral route, it would be wise to **explore the impact of these agents on the nature and functioning of this microbiota,** as well as the consequences of a possible imbalance on health (Elmassry, Zayed, and Farag 2022).

Risk assessment approaches should also be combined with those used in studying the exposome by **extending risk assessments to include health impact analyses, and the study of the associated costs**, for high-risk substances such as metals. The methods and indicators used to estimate the global burden of disease (morbidity, mortality, premature mortality, DALYs, QALYs) could be used, while including a debate on multiple exposures (Benichou 2007). The feasibility of **comparing the results of risk assessments, often based on toxicological data, with the incidence of the diseases in question** when the time span between exposure and the onset of effects allows it (foetal exposure and IQ) could be studied. This work is being considered within the framework of PARC. Dose-response curves could also be used to explain the risk beyond the TRV.

4.7.5 Long-term recommendations (2030 and beyond)

In the longer term, it will be necessary to propose **comprehensive risk assessments** (mixtures, multi-factors, multi-sources and routes) **integrating** analyses of **health impacts, health benefits and the associated economic costs**.

4.8 Eco-exposome

4.8.1 Background and identification of issues

Biodiversity and the functioning of ecosystems are severely threatened by anthropogenic environmental changes (stressors), which mainly include chemical pollution, habitat loss or modification, climate change and invasive species. These stressors are liable to interact with each other, often in unpredictable ways, with combined effects that may be greater (synergy) or smaller (antagonism) than those expected from their individual impact alone. The impacts of multiple stressors in ecology and ecotoxicology have long been studied, with a view to considering the reality of exposures and increasing the predictive power of assessments. However, the methodologies and terminologies used and the major stressors studied (chemicals, nutrients, temperature, physical habitat, food, etc.) vary according to the disciplines (aquatic or terrestrial ecotoxicology or ecology) and the ecosystems considered (aquatic, marine, terrestrial, etc.). Based on a bibliometric analysis and literature review, Orr et al. (2020), noted that this division between disciplines, as well as between the studied media, is not yet conducive to the emergence of approaches and results that can be generalised on the nature and intensity of interactions between stressors that can be expected at the different scales of biological organisation, including the temporal dynamics of exposure (Orr et al. 2020). They also emphasised the need to deepen our understanding of the mechanisms of action of stressors, and also of the mechanisms of interactions between stressors and at different levels (physico-chemical, organisms, ecosystems).

The concept of the eco-exposome was introduced in the report entitled "Exposure Science in the 21st Century: A Vision and a Strategy" (National Research Council 2012), which proposed an extended notion of the exposome that broadens the concept of stressor-receptor contact not only to internal exposure but also to external exposure, including the ecosphere, with markers of both internal and external exposure. It extends the exposome concept, which is based on exposure science, by defining the eco-exposome as "the extension of exposure science from the point of contact between stressor and receptor inward into the organism and outward to the general environment, including the ecosphere", relative to all the qualitative and quantitative information needed to understand the nature of the contact between receptors, such as individuals or ecosystems, and physical, chemical and biological stressors.

The advantage of this eco-exposome concept is that it implies considering the external interactions of an organism (human or other species) with the multiple sources of pollution and stressors to which it is subjected, with the ensuing consequences on the control (feedback, management) of these "stress" sources, and on the need for research and tools to understand this complexity. The dynamics of exposure include spatio-temporal changes in both stressors and targets for the analysis of biological consequences.

The eco-exposome complements the "One Health" initiative created in the early 2000s. This concept has been considerably strengthened with the COVID-19 pandemic, as it can help better address emerging diseases posing a pandemic risk. To this end, it proposes an integrated, systemic and unified approach to public, animal and environmental health at local, national and global levels.

In 2017, Escher et al. extended the exposome concept to ecotoxicology and exposure to ecosystems (Escher et al. 2017). Similar to the "human exposome", the eco-exposome is characterised by internal and external measurements of exposure to which each organism in a species may be subjected. Assuming that some molecular targets of substances are conserved at the cellular level, and relying mainly on AOP-type approaches, this descriptive approach to chemical exposure can be a major help in establishing links between effects from the cell to the population, and in better understanding the links between organism health, ecosystem status and human health. Figure 19 shows the different types of chemical exposure from the environment and their link via environmental media and the food chain to human exposure. Despite the complexity of such an ecosystem-wide approach, the authors emphasise that knowledge of the mechanisms of action and adaptation to stressors, which are shared between species, and variations in metabolic and functional traits of organisms, can also help to explain the differences.

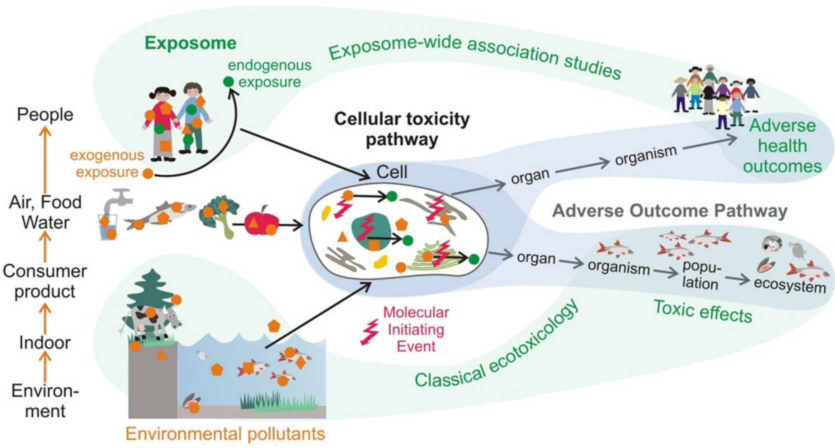


Figure 19: Relationships between chemical exposures in the environment and living beings, including humans. Any type of exogenous chemical exposure can change endogenous exposure and activate cellular toxicity pathways. The cellular level may serve as an integrator for understanding the mechanisms of adverse human health outcomes and ecosystem-level effects (Escher et al. 2017).

More recently, Scholz et al. (2022) proposed a definition that limits the scope of the eco-exposome to the internal exposure of individuals within their ecosystem (internal chemical environment including endogenous molecules), similar to the one that predominates in human health (Scholz et al. 2022). Consequently, the eco-exposome becomes one of the building blocks of risk assessment, enabling complex external exposure scenarios (Hines, Conolly, and Jarabek 2019) to be linked with toxicological effects via an AOP approach.

In ecotoxicology, the term exposome is beginning to appear as a key word, particularly in studies on aquatic environments (freshwater or marine), to describe the exposure of populations (fish, invertebrates). This relates to either environmental chemistry work (Bessonneau et al. 2017), or broader approaches combining measurements in environmental media with measurements of endogenous metabolites and exogenous substances (David et al. 2017; T. H. Miller et al. 2019; Roszkowska et al. 2019) in order to predict the associated toxic risk.

Several approaches that can be related to the exposome concept had previously been explored. They involved the development of biomarkers of disruption or adaptation, some of which are now routinely used for monitoring environmental media and identifying associated chemical stressors (Garric, Morin, and Vincent-Hubert 2010), or the measurement of contaminants and exogenous metabolites in order to characterise bioavailable contaminants and assess the toxic danger for the population, establish limit values for environmental quality (Ciliberti et al. 2017), or characterise contamination sources (Sarkis et al. 2020). The most recent analytical techniques in molecular biology (metabolomics, proteomics, transcriptomics, genomics) are now widely used in the field of ecotoxicology, as well as in health. They open up vast prospects for a better understanding of eco-exposome dynamics and the associated effects, and offer the possibility of investigating the effects of multiple stressors in a wide range of animal and plant species, and including interactions between species, including humans (Escher et al. 2017; Gao 2021).

These effects, measured on individuals or on the scale of populations in terrestrial and aquatic ecosystems (biomarkers, bioindicators), are invaluable signals that could potentially provide information on the type and level of pressure, particularly chemical pressure in environmental media, thereby inferring the possible exposure of local human populations (via air, water, food) to chemicals. As an example, the work carried out on sentinel species in the environment, such as birds, molluscs, fish, amphibians and reptiles (Purdom et al. 1994; Fry 1995; Guillette et al. 1994; Hayes et al. 2006; Trudeau et al. 2020; Caporale et al. 2022), has revealed exposure to endocrine-disrupting substances and given early warning of the associated effects, well before those now also widely demonstrated in humans (Bortone and Davis 1994).

The development of citizen observation of the environment (identification of the presence/absence of species, photographs, etc.), now part of a coordinated approach and sometimes associated with standardised protocols produced by researchers, has led to an increase in the amount of information available on the state of environmental media and the behaviour of common or rare species (Loïs 2014). Thanks to progress in computing, masses of data from naturalists can be made usefully available to researchers, managers and the public, even if their processing and scientific interpretation may require adaptations (Arazy and Malkinson 2021). As in the field of human health, the vulnerability of populations and communities is recognised as a major variable, at least in the field of research, for defining ecotoxicological values that are truly relevant for reducing the impact of contamination and ensuring the long-term functioning of populations and ecosystems. Thus, according to De Lange et al. (2010), the vulnerability of a population, subjected to specific environmental conditions, can be described by three major components: susceptibility of the species to chemical and biological exposure, in relation to the traits of the individuals (biological, such as developmental stage, and ecological, such as nutritional or reproductive behaviour – strictly aquatic or hybrid, for example); the sensitivity of the population to exposure (structure, function and trophic relations), and lastly the ability of populations to recover (adaptation, positive feedback loop, etc.) (De Lange et al. 2010).

Co-exposures to chemical and biological stressors should also be considered in ecosystem risk assessment. They have been addressed in research that shows they can have definite consequences for the most widely studied animal populations (amphibians, pollinators, fish), even if the interaction mechanisms (toxicity, behavioural disruption, feeding, etc.) are not necessarily explained (Harwood and Dolezal 2020). Moreover, these interactions can have various consequences that are either positive, with for example the reduction or suppression of infection by the pathogen (Botías et al. 2021; Cuco et al. 2017), or negative, such as immunosuppressive or immunotoxic effects (Schlüter-Vorberg and Coors 2019) or an increase in the frequency of malformations in amphibians (Haas et al. 2018).

Nevertheless, it should be noted that with regard to the regulatory assessment of chemical agents and their effects on animal and plant species and, more broadly, on aquatic and terrestrial ecosystems, the norm remains the standardisation of assessment conditions rather than an examination of the diversity of environmental media and conditions to be considered. An approach based on the concept of the eco-exposome, integrating all chemical, biological and physical pressures, is not yet in use. Only a certain degree of biological diversity is considered through the integration of threshold values for several animal, plant or microbial species.

The issues in terms of the eco-exposome for environmental risk assessment are as follows:

- **Develop a comprehensive view** of the contamination of living environments and populations (animal and plant), taking account of the multiple stressors, particularly chemical, and their interactions, as for example in the work by Atugoda et al. (2021) on interactions between microplastics, pharmaceuticals and personal care products (Atugoda et al. 2021), Gauthier et al. (2014) on the effects of a mixture of metals and PAHs in the aquatic environment (Gauthier et al. 2014), or Hutton et al. (2021) on the effects of salinity on pesticide toxicity in fish (Hutton et al. 2021), or on the interactions between chemical and biological agents (Haas et al. 2018; Bailey et al. 2018; Schlüter-Vorberg and Coors 2019; Billet et al. 2021).
- **Develop analytical platforms** tailored to the study of the exposome for ecosystems and able to combine non-targeted and targeted analyses.
- **Adopt a systemic approach to pressures and impacts on the quality and functioning** of environmental media and on human health, based on multi- and inter-disciplinarity.
- **Take the vulnerability of animal and plant populations, along with its indirect effects, into account in risk assessment processes** (Fleeger 2020)**.** This vulnerability may be due, for example, to the structure and contamination levels of habitats (Sánchez, Altizer, and Hall 2020) or food webs (Windsor et al. 2020).
- **Develop acceptable values in environmental matrices and organisms** that are truly protective of ecosystems, based on realistic exposure scenarios (time and space).
- **Study the consequences of the adaptation of animal and plant species and micro-organisms** to anthropogenic pressures, including climate change, on the interactions between these species and with human populations (e.g. COVID, larvae, tiger mosquitoes).

Figure 20 below summarises ANSES's current actions concerning the eco-exposome and the WG's recommendations for the future.

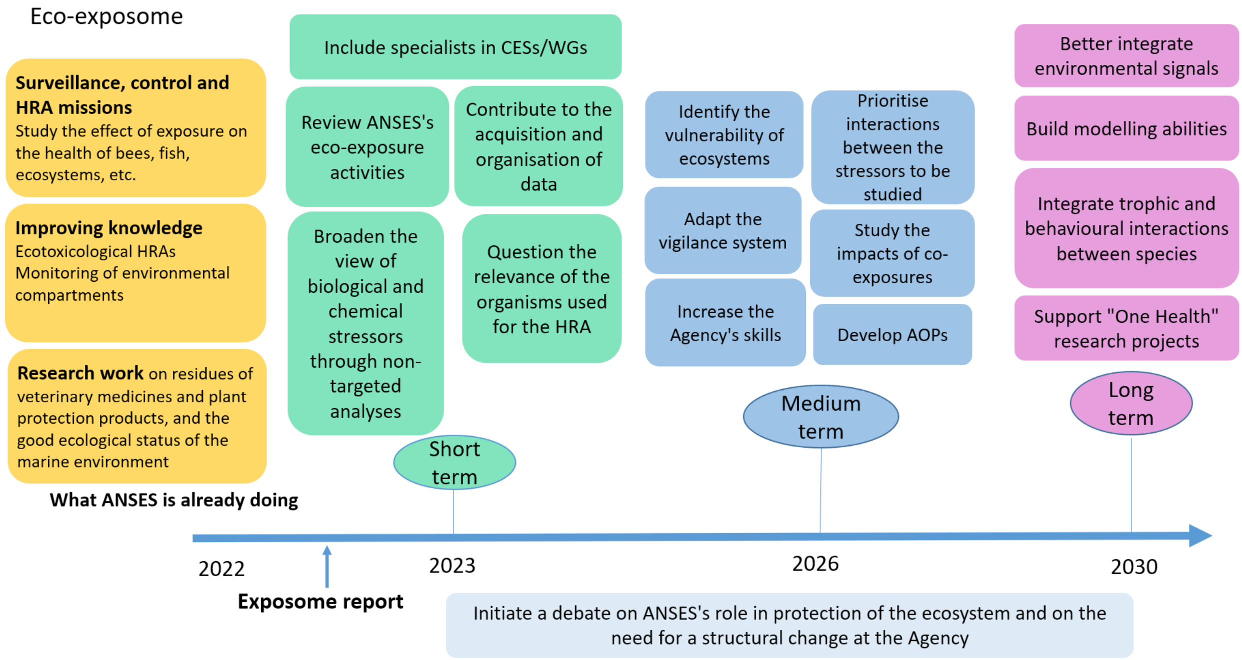


Figure 20: Recommendations for the eco-exposome

4.8.2 What ANSES is already doing

ANSES is currently involved in improving knowledge of the environment through two missions:

- **Assessing the ecotoxicological risks** of plant protection products, biocides, veterinary medicines and animal feed additives before they are placed on the market. The aim of this mission is to assess the risks to ecosystems on the basis of data obtained mainly from single-species tests and, more rarely, from more complex experimental systems such as micro- or mesocosms.
- **Monitoring different environmental compartments**, mainly with a view to protecting human health but also that of livestock or agricultural production.

ANSES therefore participates in various surveillance, control and risk assessment missions for:

- Residues of veterinary drugs and plant protection products in aquaculture, and for terrestrial animals and bees (ANSES 2021j; 2019a).
- Contaminants in fishery products (biogenic amines, plastics, pollutants, marine biotoxins, etc.) (Kazour et al. 2020; Guillier, Berta-Vianrullen, et al. 2016; ANSES 2019f; 2021h; Arnich and Thébault 2018).
- Effects on human or environmental health of plant protection product residues (phytopharmacovigilance) (ANSES 2020b).
- Impact of chemicals (UV filters, pesticides, hydrocarbons, heavy metals, pharmaceuticals, etc.) on French tropical coral reefs (ANSES, to be published).
- Transfer of biological agents (bacteria, viruses, parasites) from livestock and wildlife to humans (ANSES 2021c; 2021d; 2021n).
- Antibiotic use in veterinary medicine and antimicrobial resistance (ANSES 2020k).

- Microbiological aggressors of agricultural production identified in the epidemiological surveillance platform for plant health (ANSES 2020j; 2020j).
- Good ecological status of the marine environment (Marine Strategy Framework Directive (MSFD)) (Saïbi-Yedjer et al. 2018).

ANSES **laboratories also carry out research** in collaboration with other research teams to study the effect of chemical exposure on fish or bee health, or to characterise the fate of pesticides or microplastics in ecosystems (Havard, Laurent, and Chauzat 2020; Coulon et al. 2019; Le Du-Carrée, Boukhari, et al. 2021; Le Du-Carrée, Saliou, et al. 2021; Le Du-Carrée et al. 2022; Dupuy et al. 2019; Slaby et al. 2022; Hermabessiere et al. 2019).

4.8.3 Short-term recommendations (2023-2025)

In order to move forward on the more systematic integration of the eco-exposome concept in ANSES's activities, the Exposome WG recommends firstly **making progress with the existing scheme**, starting by **optimising the use of available data** and promoting the establishment of a **favourable cultural environment** within the Agency. This would include:

- Drawing up a **comprehensive review of ANSES's activities** in relation to the eco-exposome concept.
- **Broadening the view of biological and chemical stressors** present in the studied environments by using tailored tools such as non-targeted analysis.
- **Questioning the relevance of the environmental organisms targeted** besides those identified by the current OECD guidelines for ecotoxicological risk assessment.
- **Including more ecologists and ecotoxicologists in the expert committees** and in the PNR EST call for projects and selection committee.
- **Contributing to the acquisition and structuring of eco-exposome data** (water, soil, air, biota) in interoperable databases.
- **Beginning to develop a strategic debate** on the role that ANSES could play in terms of **ecosystem protection and restoration** in initiatives like the Green Deal.

4.8.4 Medium-term recommendations (2026-2029)

The second step necessary for the deployment of the eco-exposome concept at ANSES will be the implementation of **a multi-partner action plan designed to integrate the new approaches both in the laboratories and in the expert appraisal and regulatory activities**. This would enable ANSES to engage more actively in a paradigm shift.

To support this, the Exposome WG recommends:

- **Identifying and ranking the vulnerability of plant and animal communities** to exposure to multiple factors (chemical, biological agents, etc.), taking climate change into account.
- **Adapting the vigilance system**, in particular with new digital tools (sensors, signal processing, satellite surveillance, etc.), to detect signals useful for monitoring the health of the environment itself, as well as the health of livestock and agricultural production.
- **Integrating metadata that better describe the vulnerability of animal, plant and microbiological populations** in the environment (e.g. degraded habitat from excessive temperatures) in environmental monitoring, in order to refine risk assessment and management measures.

- **Prioritising the stressor interactions** to be considered for populations of environmental species in ecosystem risk assessment.
- **Contributing to the development of AOPs** for sentinel species in ecosystems.
- **Strengthening the Agency's skills** in understanding the population dynamics of environmental species.
- **Strengthening the study of the impact of co-exposures** on the offspring of various species by studying **transgenerational effects**.

4.8.5 Long-term recommendations (2030 and beyond)

In the longer term, it would be desirable for ANSES to acquire the ability to conduct **systemic risk assessments that integrate the notion of eco-exposome**. This would require:

- **Strengthening modelling abilities**, to make better use of future models combining mechanistic approaches of the AEP/AOP type. This combination is already in place in some areas. There is a perceived strong need for staff training.
- **Integrating trophic and behavioural interactions between environmental species and humans** in risk assessments.
- **Better integrating environmental signals** in human exposure assessment, as has been done with endocrine disruptors and their observed effects on ecosystems (Akhbarizadeh et al. 2021; Lathers 2002).
- **Supporting research projects** seeking to identify new environmental signals of interest to contribute to the sustainability of ecosystems according to a "One Health" approach.

4.8.6 Need for a cultural and structural change at ANSES

If ANSES wishes to integrate the eco-exposome concept in its activities, by applying more effort to taking environmental targets into account, the Exposome WG sees a number of major developments:

A cultural change through the acquisition of a new sphere of competence related to the environment. This change will be achieved through the gradual deployment of this competence among ANSES staff and the expert committees. Including ecology experts (population and community dynamics) in the committees will require a support phase, similar to that experienced by experts in the human and social sciences. Similarly, the idea of circularity of consumer products (recycling) and its integration in risk assessments will require some time to be adopted.

A structural change with an essential clarification of the spheres of competence between ANSES and its partner agencies. A partnership with the French Biodiversity Agency (OFB) is under discussion.

5. Deployment and general recommendations

This chapter proposes a strategy for deploying the exposome at the planning phase of expert appraisals, in relation to the eight themes presented in Chapter 4. The general recommendations needed for deploying the exposome at ANSES are also detailed.

5.1 During the planning of expert appraisals

For a health risk assessment as conducted today, Figure 21 outlines the different components of the exposome that can be introduced.

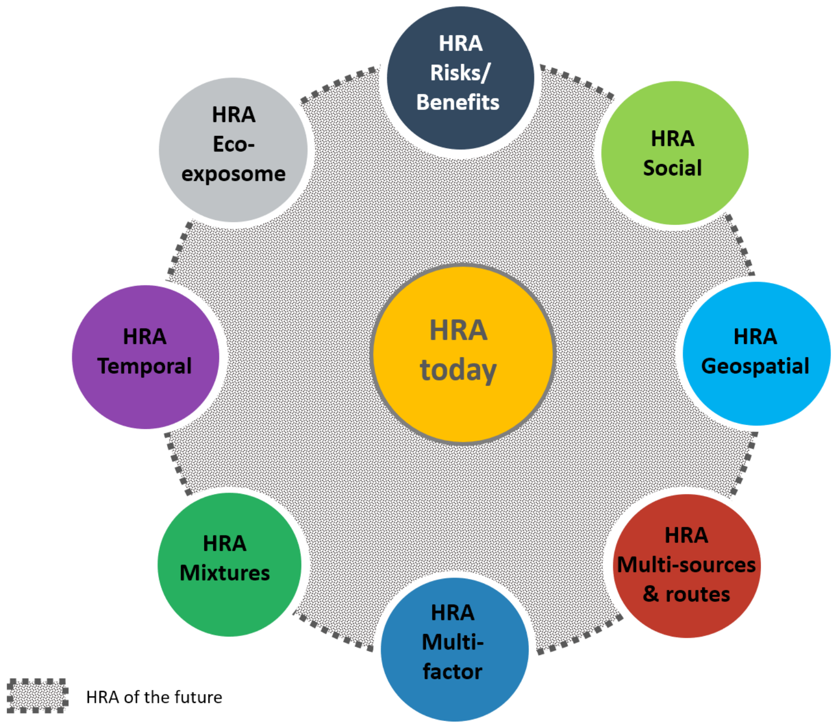


Figure 21: Exposome components to be progressively introduced in future risk assessments (HRAs). The choice of components depends on the subject and timetable of the formal request.

The different exposome components should be introduced progressively during the planning phase of an expert appraisal. This planning phase contains three steps, which consist in defining: 1) the context of the formal request, 2) the question being asked and if necessary, its reformulation, and 3) the data, methods and tools used. The WG proposes adding during this planning phase a questioning step on the relevance of using an exposome approach to address the question being asked. This will be introduced progressively according to the subject of the formal request, the available data and methods, and the associated timetable. The decision tree in Figure 22 can be used when framing an expert appraisal, in order to review the different components that can be introduced. For each component, the level at which it will be addressed in the expert appraisal will depend on the progress made in implementing the recommendations in Chapter 4 for the associated theme. For example, for taking mixtures into account: 1) if the expert appraisal takes place when the recommendations in Chapter 4 are at the "short-term" stage, it will be necessary, for example, to issue an alert in the ANSES opinion and suggest collecting the data needed to take this mixture into account, 2) if the expert appraisal takes place in the longer term, it could then be proposed that an HRA of mixtures be conducted on the basis of the data and methods organised following the recommendations in Chapter 4. If the decision tree leads to one or other or several of these components being taken into consideration, they should be integrated in step 2 of the reformulation of the question(s) asked, and also in step 3 on the choice of methods used.

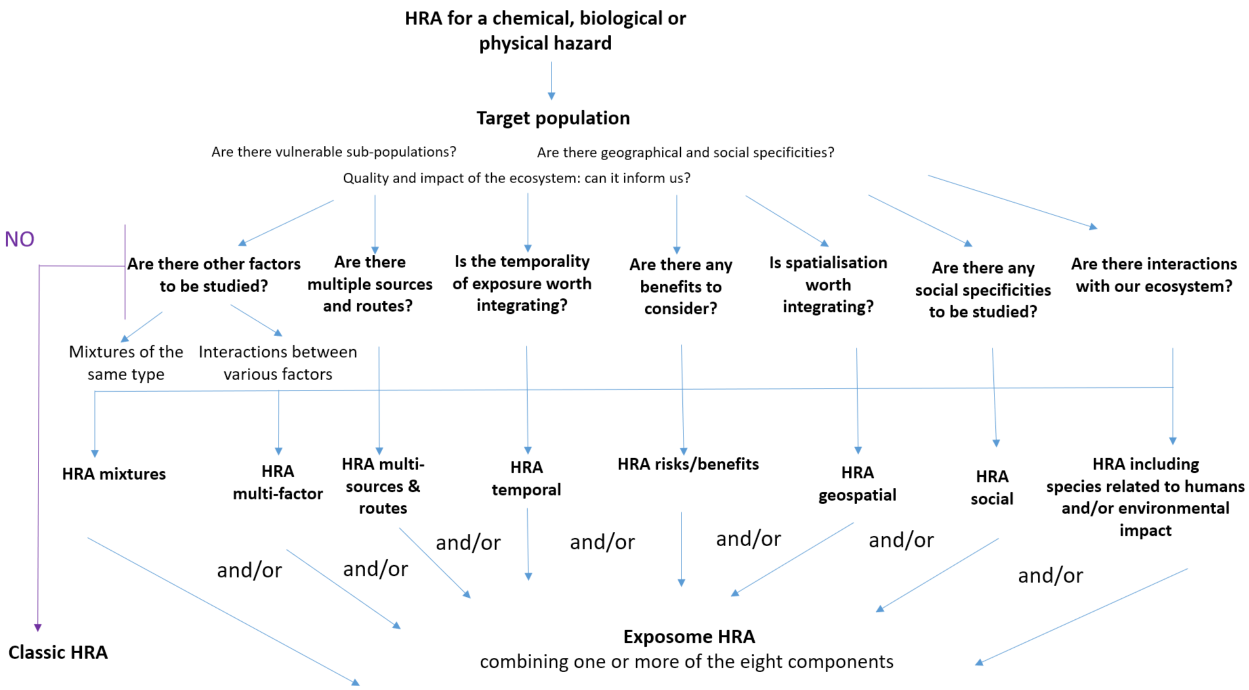


Figure 22: Decision tree to be used in the planning phase of the expert appraisal

Figure 23 outlines the possible introduction of the different components in risk assessments and its impact on their levels of complexity and consideration of the reality of exposures. The modules represent those components that can be added in a number and order that is appropriate to the question asked and the time available. As the number of modules increases, so does the degree to which the exposome components are taken into account. The integration of exposome components is associated with a level of complexity that aims to get as close as possible to reality. The y-axis groups together the events that contribute to an increasing level of complexity. Taking exposome components into account requires greater resources in terms of data, time and people. Proposals are made in the next section (see Chapter 5.2) to address this. Taking exposome components into account is also accompanied by an increase in the uncertainties due to combining data and models, which must be quantified using suitable methods (ANSES 2016c). However, the difficulties associated with increasing complexity must be weighed against the benefits of integrating exposome components. The x-axis groups together the events that increase the level of realism. The more the exposome components are taken into account, the closer the resulting HRA will be to the reality of exposures and risks, by reducing some of the uncertainties and proposing a more integrative approach. This more comprehensive approach can also be used to identify priority sources, substances and populations, and thus to guide management measures. Since the exposome also takes individual, geographical and social specificities into account, it could eventually help develop a public health policy that is more targeted and tailored to specific sub-groups of the population.

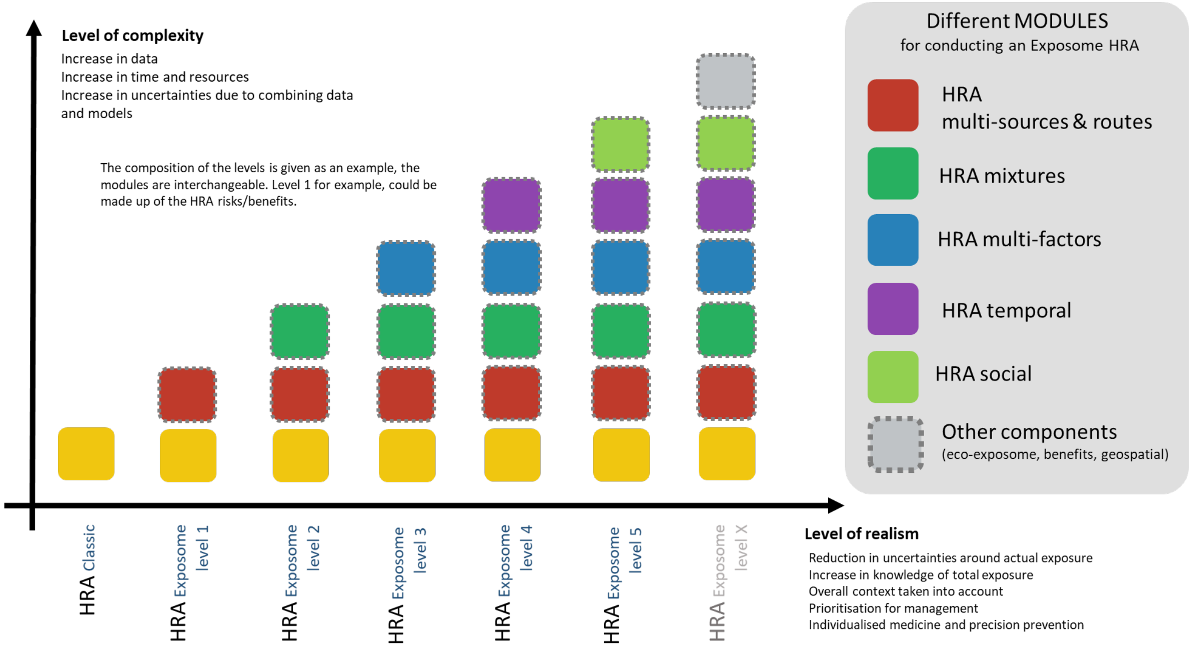


Figure 23: Diagram of the introduction of the different components in the health risk assessments (HRAs). The modules represent the components and are added according to the question asked. As the number of modules increases, so does the degree to which the exposome components are taken into account. The level of consideration of exposome components is associated with a greater level of complexity and consideration of the reality of exposure.

5.2 Five key recommendations

The WG has identified five key elements to enable ANSES to successfully take the exposome into account in its expert appraisal work and more generally in all its activities.

1. Develop a cross-functional activity tasked with implementing and following up the recommendations

Risk assessment calls on a number of different skills requiring a multidisciplinary team to be organised for the work. The DER units cover several disciplines, including toxicology, chemistry, microbiology, nutrition, epidemiology, medicine, statistics and mathematical modelling. These disciplines are reflected in the different skills of ANSES staff and are deployed in the work carried out by several units. The WG proposes setting up a cross-functional activity devoted to the exposome, spanning the DER units, in order to strengthen cooperation between them around this approach. These units are currently organised by exposure source (food, water, air) or agent type (physical, chemical, microbiological, etc.) and are grouped into three main areas, two of which are related to expert appraisal: "Food, animal and plant health", "Environmental and occupational health", and one which covers "Observatories, methods and data". The objectives of this cross-functional activity would be to strengthen collaboration between the DER units, reinforce the link between research and expert appraisal, and assist with implementing the WG's recommendations. It would also be responsible for disseminating information and providing training to ANSES staff and expert committees. Lastly, it would also strengthen the link between the work of the DER and the laboratories, to support the coordination efforts of the scientific directors. A strong link with the Social Sciences, Expertise & Society Unit (MiSSES) would also be necessary to take the social HRA and socio-economic impacts into account.

2. Acculturate ANSES staff and expert committee members

Strengthening the way in which the exposome is taken into account in the Agency's activities requires a phase of acculturation of ANSES staff and experts, and of the members of its expert committees and working groups. Presentations, specific training and workshops could therefore be offered to the Agency's staff and experts.

Dissemination of the WG's objectives and work has already started, with their presentation to the different CESs and DER units. The involvement of ANSES staff in research projects related to the exposome is also recommended, in order to contribute to staff training on this subject.

Lastly, the integration of new skills, particularly in ecology, ecotoxicology and modelling (more specifically spatial modelling) in the expert committee panels would enable these components to be better integrated.

3. Data organisation, provision and analysis

The exposome requires the use of a large quantity of different types of data. Their accessibility, collection, management and interoperability therefore play a central role in taking the exposome into account in risk assessment. Chapter 4.2 presents the issues related to data. These issues are grouped around the FAIR principles. The WG considers that the actions currently being taken on the collection, provision, organisation and analysis of data should be strengthened, in particular through the introduction of human resources with expertise in IT, data management and data science. These new skills will complement those of the scientists who produce and use the data, to make their access and use more efficient.

4. Development of operational methods and tools

Taking the exposome into account generates additional costs in terms of time to respond to formal requests and human resources to be mobilised, which can be offset by the development and use of operational tools to apply the methods needed for taking the various components into account. For example, the RSExpo software was developed by the DER to identify priority mixtures based on co-exposures, calculate the cumulative risk for a given mixture, and aggregate different sources and exposure routes, while taking uncertainties into account. Its RShiny interface makes it easy for a non-statistical user to operate the associated models. At the European level, numerous software packages are available or under development, such as MCRA[65] for food risk assessment, the EFSA TK/TD platform (TK plate) for toxicokinetic and toxicodynamic models (Testai et al. 2021), the VEGA platform[66] for QSAR models, TREXMO[67] for worker exposure models, etc. The WG recommends developing expertise and use of existing software and strengthening the development of operational tools within the Agency.

5. Consolidate collaborations and partnerships with research teams

[65] https://mcra.rivm.nl/Select
[66] https://www.vegahub.eu/portfolio-item/vega-qsar/
[67] https://www.seco.admin.ch/seco/fr/home/Arbeit/Arbeitsbedingungen/Chemikalien-und-Arbeit/Exposition/TREXMO.html

To achieve its objective of integrating the exposome and eco-exposome in its activities, ANSES will need to rely on specialised research teams at national and European level. In addition to its funding activities, such as the PNR EST (see Chapter 3), or research and development contracts, the Agency should continue to strengthen its participation in national and European projects and platforms related to the exposome. The PARC programme, with more than 200 European partners working on different aspects of chemical risk assessment, will be an opportunity to combine the advances made in the various disciplines related to the exposome and apply them to future expert appraisals. Lastly, it seems important for ANSES to support the idea of taking the exposome into account in risk assessment (as proposed in this report and beyond) at European and international level.

6. Application to formal requests

Five of the formal requests from ANSES's 2021 and 2022 work programmes were selected by the WG as examples of the application of the recommendations made in Chapter 4 (Figure 1Figure 24). This chapter details each one's background and objectives, along with the recommendations made by the WG for integrating one or more components of the exposome. Some of these recommendations were implemented by the coordinators and the WGs/CESs tasked with responding to the formal requests, when the timetable allowed it, and the work undertaken to implement these recommendations is detailed. A final paragraph provides feedback on the difficulties and needs encountered during implementation.

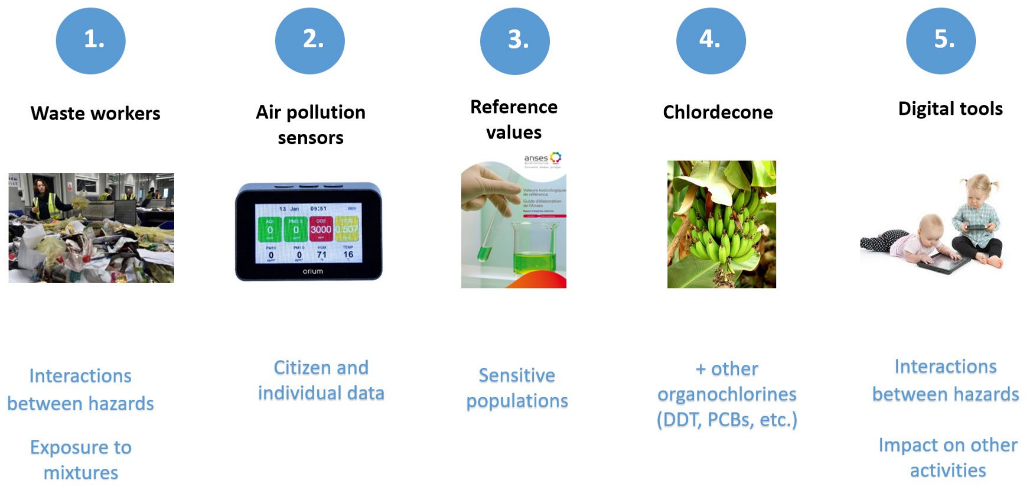


Figure 24 The five applications to formal requests detailed in this report

6.1 Waste workers

Selected because of this formal request's diversity in terms of factors addressed, as well as exposure to chemical mixtures. The psychosocial dimension linked to this type of occupation is also an interesting example of taking the social component of the exposome into account.

6.1.1 Background

The waste management and recycling sector is growing rapidly and constantly evolving. This sector is a driver for action in the circular economy as it ensures that waste is treated while producing resources such as raw materials or energy. The obligation to recycle is regulated at both European and French levels. There is no specific health component; or if there is one, it is more focused on the environmental aspects. In view of the key occupational health issues identified, ANSES issued an internal request in 2016 to investigate the health risks for professionals in the waste management and recycling sector in France.

In an initial expert appraisal phase (ANSES 2019g), the Agency produced a general picture of the sector in France, describing the organisation of waste collection, sorting and treatment (recycling and disposal) activities, the associated regulatory framework, workers' health and future prospects regarding socio-economic dynamics. In order to provide an overview of the sector without claiming to be exhaustive, the study examined a list of 28 "waste" management processes including extended producer responsibility, household and similar waste, organic waste and construction waste, as well as "materials" processes (glass, plastics, metals, etc.), and proposed that they be grouped according to the potential health risks for workers and, in particular, the level of knowledge of the risks. Each of these categories was associated with specific recommendations for prevention, assessment and/or characterisation of health risks for workers. Three processes – "construction waste", "wood" and "household packaging" – were deemed to be of particular interest for the second phase of this expert appraisal, aimed at conducting an occupational health risk assessment (HRA).

In addition to the finding that data on health risks are lacking, this initial expert appraisal highlighted numerous occupational exposures to a wide variety of factors (toxic chemicals, mould, bacteria, high temperatures, intense noise, mechanical vibrations, sources of fire or explosions, work near mechanical or electrical equipment, presence of sharp objects, vehicle traffic/driving, etc.), in addition to arduous working conditions (heavy lifting, repetitive movements, night or shift work, etc.) and risks to mental health (working alone, violence or incivility, and a lack of recognition).

Following on from this initial work, the Agency proposed conducting a health risk assessment targeting workers involved in the collection, sorting and treatment of household waste. The scope of the expert appraisal would include a study of the "household packaging" process (paper, cardboard, plastics and glass), which was identified as a potentially high-risk process in phase 1.

When searching for case studies designed to test the specific conditions for integrating the exposome concept in the Agency's expert appraisals, this topic attracted the attention of the WG for its diversity in terms of the factors addressed and the workers' exposure to mixtures. Considering also the benefits of initiating its debates as early as the framing phase of the expert appraisal, the WG decided to examine this second phase of the expert appraisal as a case study.

6.1.2 Purpose of the formal request

The purpose of this second phase of the expert appraisal was to conduct a health risk assessment for workers involved in the collection, sorting and treatment of household waste. The work was to be carried out in two stages.

Household waste (HW) results from the daily domestic activity of households and is collected through normal (residual household waste) or separate (glass, household packaging and biowaste) collections. Residual household waste refers to the part of the waste that remains after the separate collections, and is also called "non-recyclable waste". HW also includes non-household waste collected under the same conditions as HW.

To begin with, the factors to which workers involved in the collection, sorting and processing of household waste are exposed will be documented and analysed. This question will incorporate a study of the process aimed at characterising the target occupational population and defining the exposure (type of substances, materials or products, concentrations, duration, etc.) according to the occupational activities and tasks concerned and, more broadly, the organisation of the process and work. This study will include a definition of the legal framework in which these activities take place, as well as an analysis of the structure of the HW market, its dynamics and the players involved. As an initial approach, all types of health constraints for workers (chemical, biological, physical, organisational and relational) will be considered. In addition, this overall characterisation of health risks will take the effects on psychological health into account.

The knowledge available on the factors thus identified will be used to assess the feasibility of conducting a qualitative and/or quantitative health risk assessment, which will be carried out subsequently.

6.1.3 Recommendations of the Exposome WG

The management of waste raises a series of questions:

- Waste contains a multitude of different chemicals exposing the people handling it to a mixture of substances and raising the question of the associated health risks.
- Waste contains chemicals and biological organisms, also raising the question of interactions between chemical and biological agents.
- Waste handlers are often in difficult personal and professional socio-economic situations, to which can be added the significant organisational constraints of this type of work. All this can therefore affect their mental health. The links between chemical, biological and psychological factors also raise concerns.

When framing the second phase of this work, two main lines of investigation were proposed by the WG experts:

1. The study of the interactions between chemicals and biological agents, and in particular their impact on the modulation of immune responses.
2. The study of the interactions between the different determinants (organisational, relational, chemical and physical constraints) responsible for occupational stress.

The question of the combined effects of chemical mixtures is one of the issues of the exposome. As it is on the work programme of the WG on Household Waste Workers, it will not be developed here, in order to focus on the two lines of investigation mentioned above. For an example of co-exposure to a mixture of chemicals and their effects, see the formal request on chlordecone presented in Chapter 6.4.

6.1.4 Actions and resources implemented

The WG on Household Waste Workers tasked with conducting this work was only set up in March 2022. Certain information and aids to reflection were therefore collected prior to its establishment and are set out below.

6.1.4.1 Interactions between chemical and biological substances

Working assumptions

Some environmental chemicals can interfere with immune response mechanisms and may make the body more vulnerable to infectious biological agents. Exposure of humans to organochlorines, dioxins and PCBs (Dietert 2014), certain metals (Ewers, Stiller-Winkler, and Idel 1982; Moore et al. 2009) or organofluorines (perfluorooctanesulfonic acid (PFOS) and perfluorooctanoic acid (PFOA)) has been associated with immunosuppressive mechanisms (reduced concentration of immune cells), thought to favour infectious episodes (otitis, bronchitis, pneumonia), particularly in children (Grandjean, Heilmann, Weihe, Nielsen, Mogensen, and Budtz-Jørgensen 2017; Grandjean, Heilmann, Weihe, Nielsen, Mogensen, Timmermann, et al. 2017). Many chemicals (organochlorines, PAHs, fine particulate matter, NO_2, ozone, metals, certain plasticisers or plastics, etc.) are also known to induce immunostimulation mechanisms in humans (induction of inflammatory phenomena) involving different activation pathways (Kim et al. 2012; Suzuki et al. 2020; Prata et al. 2020; Sharifinia et al. 2020). These chemicals could potentially increase the risk of disrupting the immune response to exposure to a biological infectious agent and promote certain infections, particularly respiratory infections (influenza, measles, SARS-CoV-2).

Workers involved in household waste management activities are potentially exposed to chemicals and biological agents. It therefore seems relevant to investigate whether the chemicals to which these workers are exposed could interact with the immune system and potentiate their risk of developing infections when exposed to biological agents.

Identification of chemicals of interest

In a first "macroscopic" approach, several summary reports describing different stages of household waste management were consulted in order to identify the chemicals to which the workers targeted by the expert appraisal were liable to be exposed. The first reports identified concerned incineration of household waste and composting (INRS 2010; 2015; 2019). With regard to composting activities, the compounds that seem to be of interest from a health point of view – because they exceed the reference values or are frequently encountered in the working environment – were ammonia and inhalable dust. For incineration activities, exposure to several metals (lead, chromium, cadmium, copper, iron, vanadium, arsenic), dust (inhalable and respirable), B[a]P and dioxins was estimated to be very likely (Table 1).

Table 1: Chemical emissions from non-hazardous composting or waste incineration activities where worker exposure is very likely or is above the occupational exposure limits

Substances found in workplace atmospheres	Treatment steps involved	References
Respirable dust	Composting, Incineration	INRS (2010; 2015)
Alveolar dust	Incineration	INRS (2015)
Ammonia (NH_3)	Composting	INRS (2010)
Lead compounds	Incineration	INRS (2015; 2019)
Hexavalent chromium (chromium VI) and compounds	Incineration	INRS (2015; 2019)
Cadmium and compounds	Incineration	INRS (2015; 2019)
Aluminium	Incineration	INRS (2015)
Calcium	Incineration	INRS (2015)
Copper	Incineration	INRS (2015)
Iron	Incineration	INRS (2015)
Vanadium (V_2O_5)	Incineration	INRS (2015)
Nickel compounds	Incineration	INRS (2019)

Beryllium compounds	Incineration	INRS (2019)
Cobalt compounds	Incineration	INRS (2019)
Inorganic arsenic compounds	Incineration	INRS (2019)
B[a]P	Incineration	INRS (2015)
Refractory ceramic fibres (RCFs)	Incineration	INRS (2019)
Dioxin-like polychlorinated biphenyls	Incineration	INRS (2019)

Source: INRS (2010) Approaching chemical and microbiological risks in the composting sector; INRS (2015) *Installations de traitements thermique des déchets non dangereux et DASRI* [Thermal treatment facilities for non-hazardous waste and infectious clinical waste]; INRS (2019) – *Fiche aide au repérage de produits cancérogènes – Incinération d'ordures ménagères* [Fact sheet for identifying carcinogenic products – Incineration of household waste]

In addition, exploration of the Sumex2 job-exposure matrices identified other agents or classes of chemical hazards to which drivers are exposed more widely during household waste collection and treatment activities, without specifying the management step concerned (Annexe 2 , Table 7 and Table 8). As ammonia and dust have already been identified in the previous list, and as the other substances belong to rather broad families (surfactants and ketones, etc.), these results were not considered in the remainder of the work.

A literature search was also carried out to gather some information on biomonitoring in the field of waste management. A simple query was run on the Scopus database using the following equation *(TITLE-ABS-KEY (waste) AND TITLE-ABS-KEY ("occupational health" OR workers) AND TITLE-ABS-KEY (biomonitoring)).* It found 66 results, which were subjected to a qualitative content analysis based on the reading of the title. This analysis shows that three main themes of interest for our work are addressed in the publications:

- Exposure to metals, phthalates, BPA and analogues, dioxins, PAHs and pesticides during the incineration of household waste and the recycling of waste electrical and electronic equipment (WEEE).
- Use of cytotoxicity/genotoxicity tests for biomonitoring of waste management workers.
- Exposure to metals and metal dust during informal WEEE recycling in China, Ghana or Brazil.

Immunological effects of the identified chemicals

On the basis of these observations, bibliometric analyses were conducted in order to determine the immunological effects of the frequently identified substances or chemical classes. Test queries were conducted in Scopus by cross-referencing several groups of key words relating to immunological effects – including the development of respiratory infections – and to chemical exposure. The queries selected for the bibliometric analysis are shown in Figure 25.

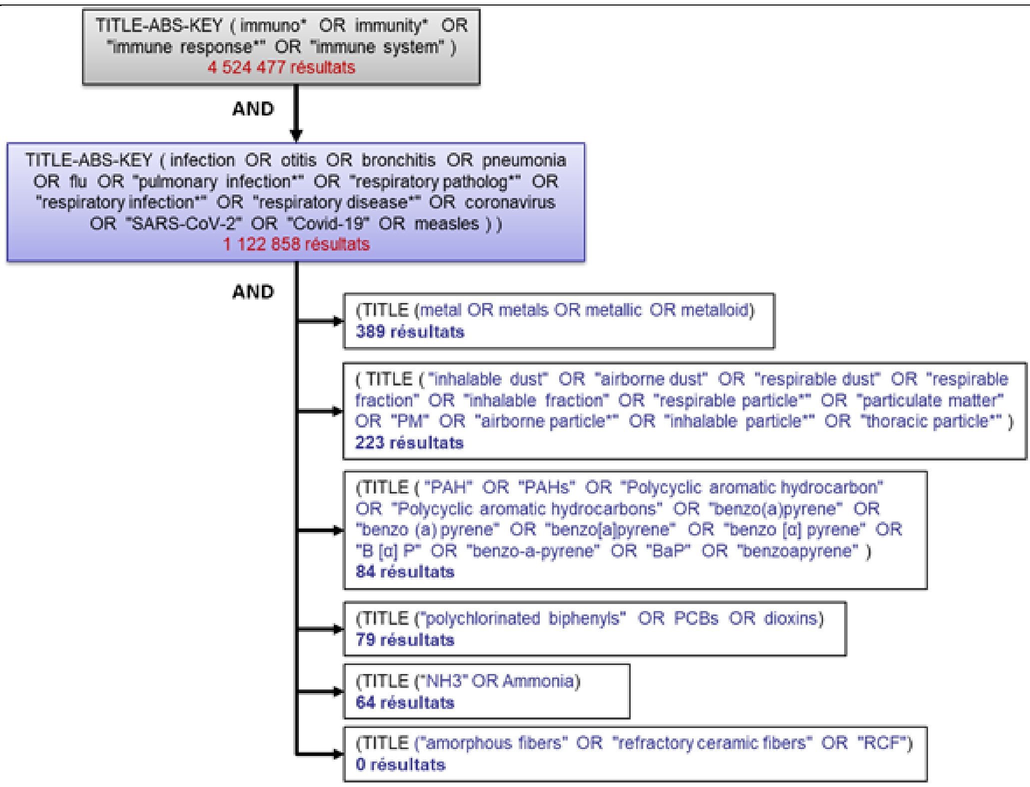


Figure 25: Literature queries conducted on the immunological effects of chemical substances or classes frequently identified in connection with household waste management activities

Consistent with the preliminary findings, scientific articles reported immunological effects of metals, particles/dust, PAHs or dioxins. Publications relating to ammonia gas exposure also seem to be available. However, there does not seem to be any literature on this type of effect for refractory fibres.

As regards metallic elements, additional analyses by type of metal show varying results. Substances such as chromium VI, lead, beryllium, vanadium, cobalt or nickel were all associated with fewer than 50 publications. For aluminium, arsenic, iron, cadmium, copper or calcium, the results exceeded a hundred publications, and even a thousand in the case of iron.

In addition, a bibliometric analysis cross-referencing key words related to respiratory infections with key words related to waste management occupations suggested that this topic is covered in the literature (Figure 26).

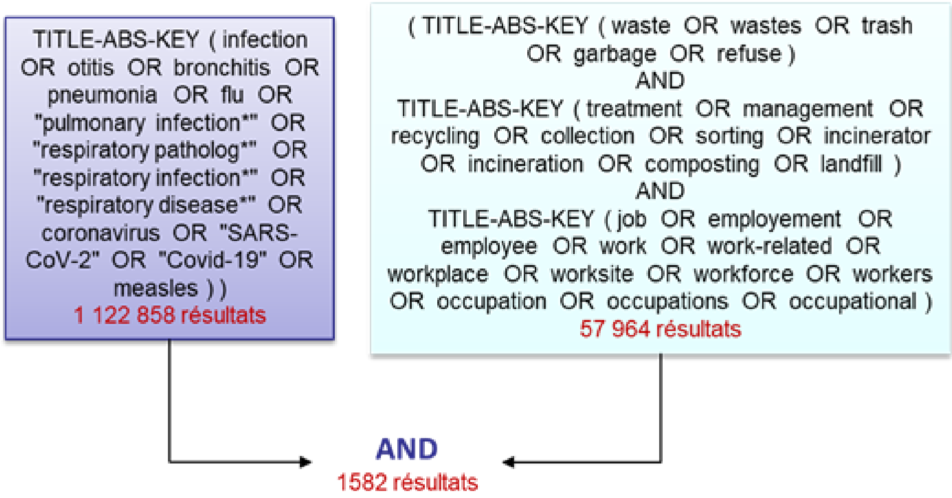


Figure 26: Literature query on respiratory infections and waste workers

Outlook

These initial investigations suggest that some of the chemicals to which waste workers are exposed may interact with the immune system and potentially play a role in promoting infection. If co-exposures to chemicals and biological agents at certain workstations were demonstrated during the expert appraisal process, this could justify an in-depth study of this type of interaction. Observation of the development of infections in workers, particularly respiratory infections, in connection with certain activities could also be grounds for a debate on these possible interactions.

6.1.4.2 Interactions between determinants of mental health

Why focus on addressing the issue of mental health rather than stress?

The notion of "stress" can be scientifically mobilised to describe psychological stimuli or problems, particularly in the workplace (Loriol 2014; Lhuilier 2010). Nevertheless, this notion remains limited in its ability to grasp all the social and subjective dynamics that drive individuals in work situations. Notions of mental health or psychological health seem better placed to reflect this.

Mental health

Depending on the discipline or institution, there are many definitions, approaches or "entry points" into mental health and illness. Without accounting for this diversity here, it is worth reiterating the intellectual and social importance of an approach to mental health that is as integrated as possible. This all-encompassing understanding is regularly found in the WHO's expert appraisals (World Health Organization 1985; 2014; World Health Organization Europe 2009).

According to the WHO, mental health is "a state of well-being whereby individuals recognize their abilities, are able to cope with the normal stresses of life, work productively and fruitfully, and make a contribution to their communities". It should not be seen only as the absence of mental disorders but as an integral part of health in the broadest sense. This approach echoes the definition of health generally given by the WHO in its Constitution, namely a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.

It is thus possible to distinguish three dimensions of mental health, namely positive mental health, reactive psychological distress (or suffering), and psychiatric (or mental) disorders. This distinction was proposed at the first WHO European Ministerial Conference on Mental Health in Helsinki in January 2005. Taking these dimensions into account, the field of mental health can be modelled at the intersection of two continuums: a "mental health continuum", which extends from psychological distress to optimal mental health, and a "mental illness continuum", which extends from the absence of symptoms of mental illness to severe mental illness.

Many factors play a role in determining the degree of mental health of an individual at a given time. These determinants can be socio-economic, biological and environmental, including the work environment. Working conditions are an important determinant of mental health. Again according to the WHO, "*Mental health and well-being is influenced not only by individual attributes, but also by the social circumstances in which persons find themselves and the environment in which they live; these determinants interact with each other dynamically, and may threaten or protect an individual's mental health state* (World Health Organization 2012).

There are many classifications of the determinants of mental health, including social, socio-economic, biological, psychosocial, personal, (extra)occupational, demographic and socio-emotional. When the interrelationships are complex between the social and the economic, or between the individual and the social, as illustrated by the question of gender (Allen et al. 2014) or of addictions, they remain schematic and their boundaries porous. From the perspective of typologisation, and therefore simplification, these categorisations can nevertheless be used as a first step.

Mental health determinants

The determinants can be categorised through the "biopsychosocial" model, according to which mental health is a dynamic process resulting from biological, psychological and social factors that are constantly interacting and may change throughout life. On the basis of this approach, we propose making a distinction between two main groups of determinants: "personal" and "social" (Table 2).

Table 2: Mental health determinants

"Personal" determinants	**"Social" determinants**
➢ Age ➢ Sex ➢ Genetics ➢ Pre-existing state of health ➢ Individual behaviours	➢ Childhood events ➢ Socio-demographic characteristics: gender, ethnicity ➢ Education ➢ Living environment*: housing, transport, food, hygiene, medical care ➢ Family and social fabric ➢ Social norms ➢ Socio-professional factors: occupational trajectories and situations*, income, employment (existence, type), exposure, working conditions and organisation, professional fabric

**These aspects must be considered both in terms of their access and "quality"*

Some documented interactions

A brief literature search identified publications on the interactions between some of the above-mentioned determinants and their links to physical and/or mental health effects. The table below describes the interactions that have been addressed by studies (Table 3).

Table 3: Interactions between determinants covered by studies

Organisational and psychosocial factors	
DARES: Analysis of the "Sumer" and "Working Conditions" surveys. The accumulation of organisational constraints (lack of autonomy, time pressure) combined with socio-economic insecurity leads to a lower level of psychological well-being and more frequent functional limitations.	(Coutrot and Sandret 2015; Beque and Mauroux 2018; Waltisperger 2007; Beque 2014; Holman 2013; Parent-Thirion et al. 2016; Coutrot 2018; DREES and Santé publique France 2017)
NRCWE: Study of potential interactions between ergonomic factors (heavy lifting) and psychosocial factors (stress) at work and their effects on pregnancy and foetal development	(Sejbaek et al. 2018)
Organisational, psychosocial and physical factors (postural constraints)	
Environmental and Occupational Health Research Institute (IRSET Angers) *Ester Team (epidemiology in occupational health and ergonomics)*: In the French wage-earning population, industrial constraints and production standards, as well as lack of flexibility, hierarchical supervision and versatility of workstations are positively associated with exposure to postural constraints, regardless of gender. A harmful psychosocial environment (low social support, low skill use and development, and high psychological demand) is associated with an increased risk of exposure to postural constraints. Postural constraints are themselves associated with musculoskeletal disorders (MSDs).	(Bertin et al. 2018)
BAuA: Study of the role of interactions between specific risk factors related to the nature of the work (e.g. large forces applied to the body, repetitive manual activities, unfavourable postures or forced physical inactivity), work-related psychosocial factors and work organisation issues in the genesis of MSDs.	(BAuA 2014)
NRCWE: Study of potential interactions between ergonomic/physical and occupational psychosocial factors and their role in the development of MSDs	(Karstad, Rugulies, et al. 2018; Karstad, Jørgensen, et al. 2018)
ETUI: Musculoskeletal disorders and psychosocial factors at work	(Roquelaure 2018)
Personal and socio-professional factors	
BAuA: Study of potential occupational risk factors for cardiovascular disease (CVD) encompassing psychosocial factors (including stress), physical workload and physical/chemical factors	(BAuA 2014)

FIOH: Assessment of psychosocial factors at work and associations with depression and low back pain. Proposed job-exposure matrix.	(Solovieva et al. 2014)
NRCWE: Study of the effects on offspring of concomitant exposure to work-related stress and stress in private life during pregnancy	(Liu et al. 2019; Pape et al. 2021)
ANACT: Study of the cumulative effects of exposure to risks in the reality of work for populations in fragile (or insecure) employment situations. Proposed explanatory model of risk exposure and its accumulation, integrating the characteristics of exposed persons: age, gender, experience, status, etc.	(Burens et al. 2011)

Bibliometric analysis of interactions between determinants

In addition, literature queries were tested in Scopus.

✓ **"Simple" queries, by groups of key words**

This firstly involved listing different groups of English key words related to mental health and the "personal" and social determinants. The key words chosen refer to general categories, without any breakdown according to specific diseases, problems or risk factors.

In terms of the key words selected and the associated data volumes, the following results can be observed (Table 4):

Table 4: Results of the simple queries "mental health" and "mental health determinants"

Group	Key words	Field	Number of publications
Mental health	((mental W/0 health OR mental W/0 condition) OR (mental W/0 disorder OR mental W/0 disease OR mental W/0 distress OR psychological W/0 hardship OR psychological W/0 distress AND psychological W/0 strain OR psychological W/0 disorder OR psychic W/0 distress OR psychic W/0 disorder OR psychic W/0 disease OR psychic W/0 hardship OR psychic W/0 strain OR brain W/0 disorder) OR (psychiatric OR neuropsychiatric))	TITLE ABSTRACT KEYWORDS	414,409
Occupational status	((work* W/0 situation) OR (professional W/0 situation) OR (professional W/0 status) OR (employment W/0 status) OR (employment W/0 situation) OR (occupation*) OR (job) OR (work*))	TITLE ABSTRACT KEYWORDS	7,995,192
"Personal" determinants	((personal W/0 risk W/0 factor) OR (genetics OR age OR sex OR ethnic*) OR (health W/0 status OR existing W/0 condition OR health W/0 condition OR state AND of AND health) OR (behaviour OR behavior))	TITLE ABSTRACT KEYWORDS	12,702,814
Social determinants	((socioeconomic W/0 status) OR (social W/0 status) OR (social W/0 determinant) OR (community W/0 factor) OR (social W/0 factor) OR (economic W/0 status) OR (economic W/0 determinant) OR (economic W/0 factor))	TITLE ABSTRACT KEYWORDS	265,127

✓ Queries by cross-referencing groups of key words

Multiple cross-referencing of queries was then carried out. The most relevant are shown in Figure 27:

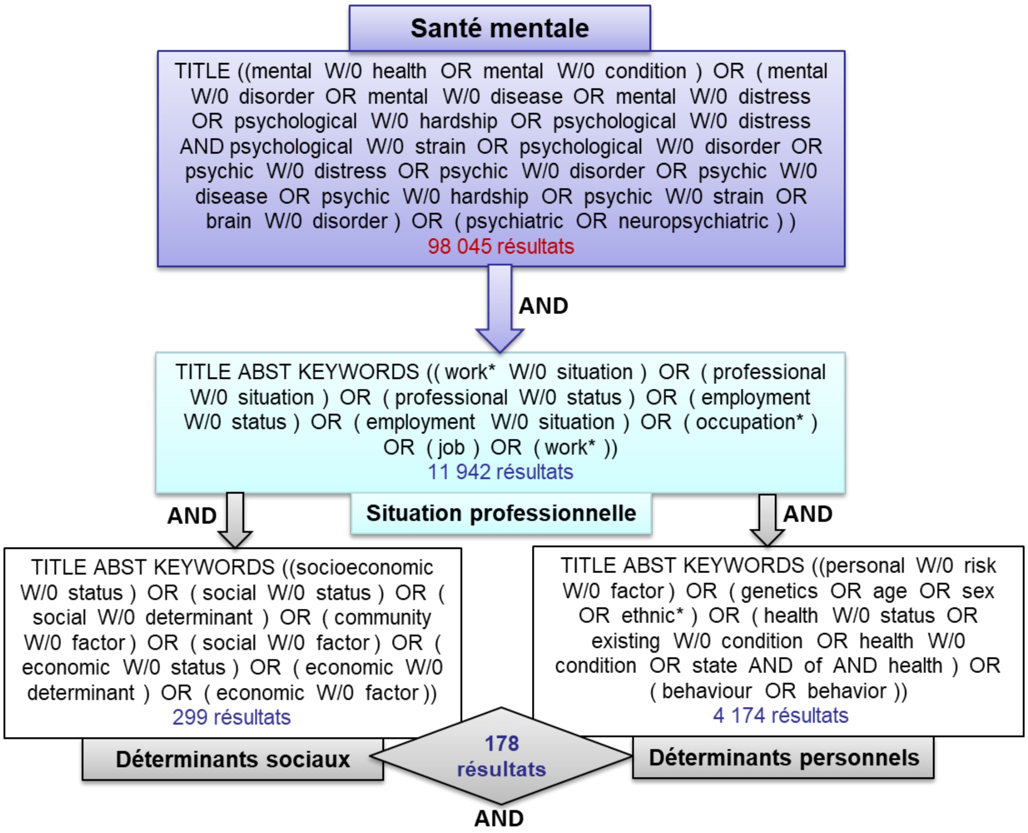


Figure 27: Cross-referencing of the queries "mental health" and "mental health determinants"

✓ Test queries incorporating "waste workers" key words

In addition, the key word group "mental health" was cross-referenced with key words related to waste management occupations (Figure 28). The small number of publications obtained suggests that this subject is relatively rarely addressed in the literature through the specific prism of the workers in our study.

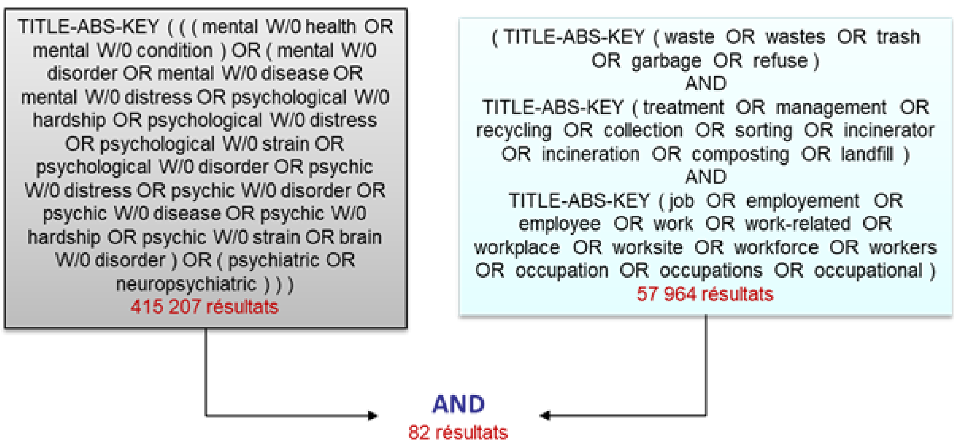


Figure 28: Literature query on mental health and waste workers

Outlook

These results are at first sight complicated to understand. With regard to the volume, however, cross-referencing queries with various fields significantly reduces the number of certain articles (to fewer than 500 publications).

In any case, it is necessary to read at least the titles and abstracts to determine the level of relevance of the publications, and establish a possible link between the volume of publications and the level of actual documentation of the subject.

Moreover, the body of articles constituted is of considerable interest. Even if they do not address a specific sector such as the waste industry, and thus question the degree to which the results can be transposed, they could provide useful information for understanding the interactions between mental health and biological factors, for example.

6.1.5 Conclusion

This formal request analysing the factors to which workers involved in collecting, sorting and treating household waste are exposed raised several questions related to the exposome. In particular, it considered the impacts on physical and/or mental health of exposure to chemical mixtures; of an interaction between chemical and biological agents; of an interaction between chemical agents, biological agents and psychological factors. This last type of interaction reveals the interweaving of personal, social and professional rationales. On this last point, waste management professions are characterised by major organisational and relational constraints. An initial study of the literature has shown that an exposome approach could be useful for better understanding the health status of these workers, who are exposed to various hazards. For example, it has been observed that some of the chemicals to which waste workers are exposed may interact with the immune system and potentially play a role in promoting infection. An in-depth study of this type of interaction could be carried out during the expert appraisal on the basis of these initial data. With regard to interactions involving organisational and relational constraints in addition to chemical and physical exposures, the body of data, although disparate, encourages the study of their link with the mental health and, more broadly, the overall health status of these workers.

6.2 Reference values

Selected for the possibility of integrating the exposome concept when creating a single methodological guide for selecting and developing reference values in the general and occupational populations.

6.2.1 Background

As mentioned in Chapter 4.6, ANSES is responsible for establishing reference values (RVs). To this end, it has produced several methodological guides for selecting (ANSES 2012) and establishing RVs:

- The TRV development guide (ANSES 2017g).
- The method for developing IAQGs (ANSES 2016d).
- The reference document for establishing occupational exposure limits (OELs and BLVs/BRVs) for chemical agents (ANSES 2017c).

- The guide for assessing health risks associated with situations where the quality limits and references for DW have been exceeded (ANSES 2007b), and the method for assessing health risks associated with the presence of drug residues in DW (ANSES 2013c).
- Work on proposing TRVs and IAQGs for mixtures of substances is currently under way.

When developing RVs, sensitive populations are considered through selection of the critical effect and the key study (data showing effects for sensitive populations when available), and by adding an inter-individual uncertainty factor. This takes into account the potential variability in response in the human population, which may be due to genetic make-up, age, sex, lifestyle, health status, differences in toxicokinetic responses (e.g. genetic polymorphisms in metabolic enzymes) or in toxicodynamic responses (different target sensitivities, hereditary disease resulting in deficient DNA repair). This factor therefore takes account of the differences in response between an average person and a sensitive person in the population of interest. Specific recommendations on choosing this factor when children are regarded as a sensitive population are given in the "TRV" guide (ANSES 2017g). For example, several RVs have been developed based on critical effects observed in sensitive populations, when the data were available:

- For NO_2 (ANSES 2013d):
  - Short-term IAQG: ANSES adopted the IAQG developed by the WHO (World Health Organization Europe 2010) based on changes in respiratory function and an increase in airway responsiveness in asthmatics.
  - Long-term IAQG based on the occurrence of respiratory symptoms in children.
- For cadmium (ANSES 2017e), the chronic TRV was based on the risk of osteoporosis or bone fractures observed in postmenopausal women.
- For sodium valproate (ANSES 2021k): reprotoxic TRVs for the oral and respiratory routes and an 8hr-OEL were developed for major birth defects in newborns of epileptic mothers exposed during pregnancy.

It should be noted that although these guides share common guidelines, there are differences in terms of methodologies and terminologies, etc., which are partly related to the application of these RVs to different areas (general population/workers, water/air guideline values, etc.).

6.2.2 Purpose of the formal request

In 2020, ANSES therefore issued an internal request to propose a single methodological guide for selecting and developing reference values for the general population (TRVs, IAQGs, GVs in drinking water) and in the workplace (OELs, BLVs/BRVs). This guide will be compiled by merging the existing guides (ANSES 2007b; 2012; 2013d; 2016d; 2017c; 2017g) and harmonising the development methods as much as possible, and will be updated as new methodological work is developed. For example, ANSES recently carried out expert appraisals in relation to reference values for substance mixtures, and will integrate this methodology in the new guide.

6.2.3 Recommendations of the Exposome WG

When this new guide is produced, the Exposome WG believes it important to systematically identify sensitive populations and take them into account in the establishment of RVs, thus including populations that have been less considered until now. It also recommends taking a broader look at how sensitive populations are taken into account in risk assessments and when making the associated recommendations. The literature presented below highlights the fact that, although sensitive populations are now considered in the selection and establishment of RVs, changes are needed to take them more fully into account in practice.

For many chemical agents, children and pregnant women are identified as sensitive populations and are therefore subject to specific hazard and/or exposure analyses. However, other populations – such as the elderly, or those suffering from chronic diseases, nutritional disorders, or kidney, respiratory or heart failure – who may have even greater sensitivities to certain substances, are rarely considered for the determination of RVs because of the lack of data to identify them or to establish the RVs. Several examples illustrate this deficiency. Fluoride, whose ability to bond to bone tissue and teeth has long been known, also has neurotoxic, nephrotoxic and hepatotoxic properties (Grandjean 2019; Dharmaratne 2019; Malin et al. 2019; Perera et al. 2018). Several studies in animals and humans have shown that in adults and children with renal disease, circulating fluoride levels can increase fivefold and the toxic effects are much greater (Ibarra-Santana et al. 2007; Lucas and Roberts 2005). Some of these studies also show potentiating effects of heavy metals and aluminium on fluoride toxicity. It should be noted that in its opinion of 4 January 2005 on fluorides in water, AFSSA mentioned that "as fluoride is mainly eliminated via the urinary tract, particular attention should be paid to people suffering from kidney failure", but that this group was not taken into account in developing the TRV (6 mg/d, as was also the case with the value proposed by the WHO) (ANSES 2007b).

As highlighted in the Lautenberg Toxic Substances Control Act in the United States (Koman et al. 2019), both the sensitivity of sub-populations (in addition to children and pregnant women) and the co-exposure of these sub-populations to several chemicals that may interact with each other should therefore be taken into account in chemical risk assessment. The need to integrate exposure to several chemical stress factors, as well as variability in biological susceptibility, in risk assessment had already been highlighted in the past (Woodruff et al. 2008) (Figure 29).

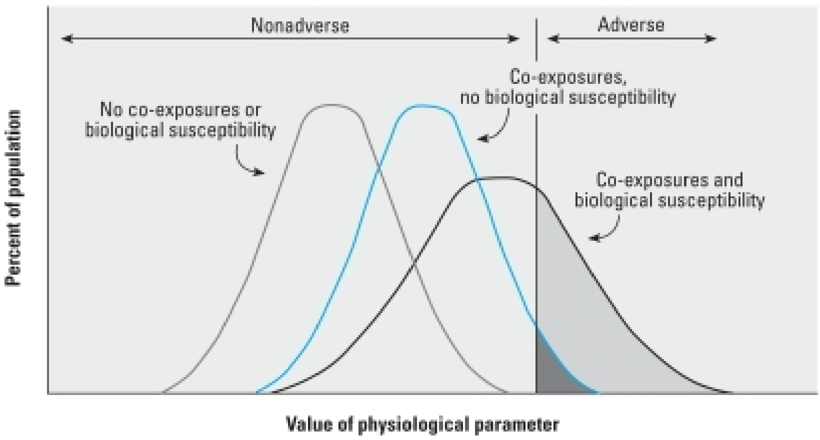


Figure 29: Influence of the chemical and biological context in terms of the hazard (Woodruff et al., 2008)

The question that arises is whether there are sensitive populations who have not been taken into account until now, and for whom the uncertainty factors used are inadequately protective.

In a study to determine whether asthmatic people (about 1/10 of the general population in Europe) were protected by derived no-effect levels (DNELs) for acute inhalation exposure adopted under the REACH regulation for general and occupational populations, Johansson et al. (2016) indicated that (1) there was a general lack of data on asthmatics; (2) the available data on asthmatics were not used as much as they could be to derive DNELs; (3) several of the selected DNELs for inhalation exceeded or were close to the NOAEC and/or LOAEC values for asthmatics, indicating small or non-existent safety margins. In conclusion, these authors regretted that asthmatics were excluded as a group of interest in the establishment of many RVs, especially occupational ones (Johansson et al. 2016).

Johanson (2020) investigated the extent to which asthma was taken into account when setting acute RVs in the general and occupational populations (Johanson 2020). He found that experimental studies comparing healthy and asthmatic subjects were often inconclusive, and that the available studies were under-utilised by both expert committees and industry. Data for some irritants suggest that asthmatics are up to three times more sensitive than healthy subjects. The most abundant data, which relate to sulphur dioxide, show a ninefold increase in sensitivity for asthmatics, suggesting that a default factor of 10 should be applied when setting RVs for irritants. In a recent review of the literature on the link between the exposome and asthma, Guillien et al. (2021) reported the higher sensitivity of asthmatic individuals to several families of air pollutants such as suspended particles, nitrogen or sulphur dioxides, and ozone, and stressed the lack of data on the complex interactions and effects of mixtures (Guillien et al. 2021).

More generally, in its report entitled "Study for the strategy for a non-toxic environment of the 7th Environment Action Programme – Sub-study c: Protection of children and vulnerable groups from harmful exposure to chemicals" published in August 2017 (European Commission. Directorate General for the Environment et al. 2017), the European Commission pointed to shortcomings in risk assessment, stating in particular:

- "Inconsistencies in the protection of vulnerable groups in relation to specific categories of relevant chemicals legislation, e.g., legislation related to work, food, products, and environment. In each of these categories, there are pieces of legislation that consider vulnerable groups, while other legislation sharing the same objectives does not consider vulnerable groups in its provisions."
- "EU risk assessments typically focus on single substances and do not consider the risks to children and other vulnerable groups from combined exposure to toxic chemicals. Therefore, a regulatory approach for cumulative risk assessment needs to be developed."
- "Current risk assessment methodologies do not cater for the diverse circumstances of vulnerable populations, whose consumption patterns and exposure levels may differ significantly due to factors such as age, geographical location and lifestyle factors."

While the emphasis of the last point is on exposure, the WG considers that the comment also applies to hazard characterisation and thus to the determination of RVs.

6.2.4 Actions and resources implemented

The WG proposes the following four actions to better integrate sensitive populations when establishing RVs and conducting health risk assessments:

1. Propose a definition of sensitive, vulnerable and at-risk populations to be included in the glossary of the new guide, and in other documents of a more general scope on the principles of expert appraisals.
2. Introduce a step to identify sensitive populations in the RV development process. The new guide should make reference to the Exposome WG's report, the points in Chapter 6.2.4.2 below should be added to the template for RV development reports and this step should appear in the summary for developing reference values associated with the guide. In addition, it is recommended that a chapter be systematically devoted to this in all RV development reports.
3. Develop an approach for taking sensitive populations into account in the establishment of RVs.
4. Propose a debate on taking sensitive populations into account when assessing risks and making recommendations.

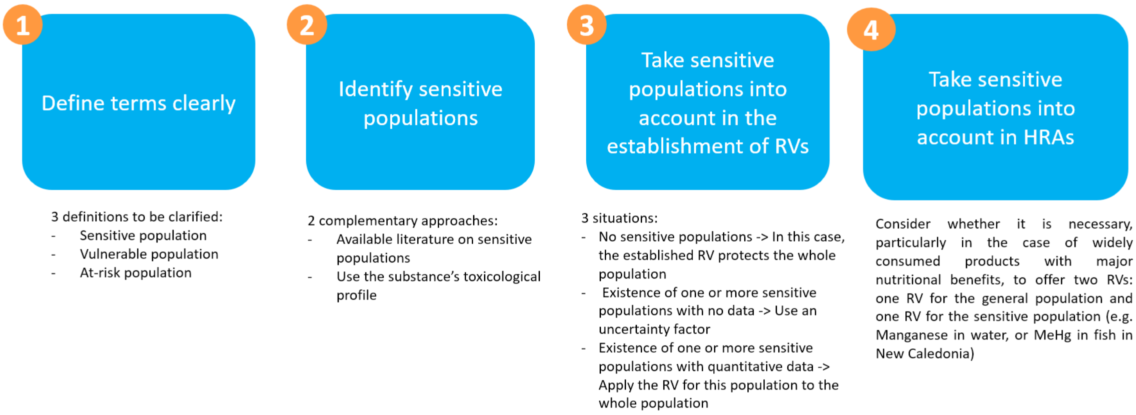


Figure 30: The four actions proposed by the Exposome WG on consideration of sensitive populations for establishing reference values

6.2.4.1 Proposed definitions

It was noted that in ANSES's various publications (guides, opinions, reports, scientific and technical support notes), different terms such as "vulnerable population" and "at-risk population" are used to designate sensitive populations. After an internal debate and discussion, the WG recommends harmonisation with the definitions below:

Sensitive population*: a group of individuals for whom the response to a chemical, physical or biological agent occurs, due to factors intrinsic to the individuals in that group, at a significantly lower level of exposure than for the general population. These include children, pregnant women, asthmatics, immunocompromised individuals, people who are overweight or obese, sufferers of chronic respiratory insufficiency, and people with specific conditions such as anxiety or mental illness.

Vulnerable population*: this group comprises, in addition to sensitive populations, people who, due to extrinsic factors that can be social (e.g. isolation, cultural barriers, access to information), economic (e.g. financial insecurity/poverty, type of job held), environmental (e.g.

housing, geographical location) or behavioural (e.g. dietary behaviour), may be subject to higher exposure to certain chemical, biological or physical agents

*For greater clarity, where only intrinsic factors are involved, the WG recommends the use of **sensitive population** rather than **vulnerable population**.

At-risk population: a group of individuals with a level of exposure to a chemical, physical or biological agent that poses a risk to their health. For example, in the case of a chemical or physical agent, these may be individuals with exposure above the TRV. Similarly, it may concern a group of individuals with inadequate nutritional intakes in relation to those expected for good health. The at-risk population may (but not necessarily) include so-called sensitive or vulnerable individuals.

6.2.4.2 Identification of sensitive populations

Sensitive populations should systematically be identified when establishing RVs by adding a specific chapter in all expert appraisals. This chapter should describe the data available in the scientific literature or, on the other hand, state that there are none. Analysing sensitive populations in a separate single chapter has multiple advantages. It makes it possible to:

- Study all the different sensitive populations and estimate, if possible, their respective extent within the French population,
- Justify which sensitive population is most relevant for developing the RV (depending on its degree of sensitivity and extent),
- Raise points requiring vigilance for risk assessment on sensitive populations that were not necessarily included for establishing the TRV,
- Highlight the data to be acquired to describe any sensitive populations,
- If necessary, establish several RVs (a specific RV for the sensitive population versus an RV for the population of interest).

Two complementary approaches described below are proposed to substantiate this chapter.

Approach based on the available literature on the study of sensitive populations

This approach is based on the analysis of scientific knowledge available in the literature in which, for a given effect, sensitive populations have been identified and studied for the substance of interest. In addition to the pregnant women and children generally considered, this analysis should be extended to other sensitive populations, identified as such according to the substance, for example asthmatics, immunocompromised people, overweight and obese people, those suffering from chronic respiratory insufficiency, or people with specific characteristics such as anxiety or mental illness. The following elements could be included:

- Identify and describe the available studies on the effects of the substance in different sensitive populations.
- Information on the prevalence of the sensitive population.
- Assess and if possible quantify the risk associated with this sensitivity. For example, a relative risk level that is twice as high in asthmatics as in the general population.
- Assess the robustness of the data and indicate any missing data.

Approach based on the toxicological profile of the substance

In the absence of data for the first approach – or in addition to it – this second approach involves the search for potential sensitive populations based on the toxicity of the substance. It consists in using data on, for example, chemical structure, kinetics and biotransformation pathway(s), mode of action of the substance, etc., to estimate the variability of toxic responses, toxicity windows and possible sensitive populations. This analysis may require new data to be generated for suspected sensitive populations.

6.2.4.3 Taking sensitive populations into account in the establishment of TRVs

The step to identify sensitive populations may result in:

- None of the data showing the existence of any sensitive populations. In this case, the established RV protects the whole population of interest.
- The existence of one or more sensitive populations with no data, or data that cannot be used for establishing an RV. In this case, the use of a UF_D uncertainty factor for lack of data should be considered on a case-by-case basis to take this uncertainty into account.
- The existence of one or more sensitive populations with quantitative data. In this case, an RV should be established from this population and applied to the whole population.

However, establishment of the TRV should be considered with a view to the most appropriate public policy for prevention by including any possible secondary health consequences of its use in risk management (see Chapter 6.2.4.4). Thus, for RVs related to the general population, the Exposome WG recommends establishing an RV that protects the whole population based on data from a sensitive population or incorporating an uncertainty factor, while conducting a broader debate on the consequences of its application to the population, and if necessary proposing one or more specific RVs for sensitive populations.

6.2.4.4 Taking sensitive populations into account when assessing risks and making recommendations

The deployment of a quantitative health risk assessment approach aims to make recommendations on managing the risks by the players concerned (national or local authorities, consumers, economic players, etc.).

In order to provide protection for the whole population, RVs are established based on data from studies on the most sensitive population, when available. However, by applying this approach to "practical cases", the Agency has identified cases where it has limitations or even generates difficulties, as it could lead to recommendations with broader impacts than on the substance and/or the population considered, thus raising questions in terms of an overall approach to health.

This is particularly the case where:

- there are two thresholds, a minimum threshold to be reached for good health and a maximum threshold not to be exceeded. For example, some nutrients (such as manganese) may be necessary for the proper functioning of our metabolism, resulting in a nutritional reference or intake level to be reached, but may at the same time have an upper intake level that should not be exceeded (acute or chronic). These two thresholds may differ for some parts of the population. For example, children have a maximum threshold which, if it is not to be exceeded, requires the implementation of management measures that are incompatible with the nutritional needs of adults.

Protecting sensitive populations may therefore mean reduced benefits for non-sensitive populations.

- When consumption or an activity can have both health risks and benefits. For example: consumption of fish containing methylmercury has proven toxicological risks, but these fish also have long-chain polyunsaturated fatty acids with important nutritional benefits. Acting to protect the population from a harmful substance may lead to adverse effects elsewhere, such as a reduction in nutritional intake or substitution by foods containing other harmful substances, thus causing an exposome "switch" (e.g. New Caledonia formal request or exposome switch for chlordecone, see 6.4.3.3).

In both cases, applying a threshold to the general population that is derived from a fraction of the population with proven sensitivity may lead to the non-sensitive part of the population being deprived of benefits. In addition to an absence of benefits (in this case nutritional), the search for substitutes (e.g. meat as a substitute for fish, or bottled water in the event of a decision to suspend distribution of tap water) may also prove to be non-neutral in health, economic or environmental terms.

It is difficult – at first sight – to identify the need to make this distinction at the time of establishing the RV, in the absence of any expert context. On the other hand, with this in mind, the RV development reports should fully document any information that will enable the recommendations to be adjusted in due time. This refers to the concept of proportionate universalism, in which actions should be universal, but with a scope and intensity proportionate to the level of social disadvantage. Proportionate universalism enables a universal and targeted approach to be integrated, offering intervention to all, but with conditions or intensity that vary according to need (Poissant 2014). In connection with the previous section, 6.2.4.3, it may therefore be useful, particularly in the case of widely consumed products with major nutritional benefits, to offer two RVs: one for the general population and another for the sensitive population.

6.2.5 Conclusion

The merging of the guides on the development and selection of reference values (RVs) for the general and occupational populations was an opportunity for the Exposome WG to recommend better integration of sensitive populations in the establishment of RVs and in health risk assessments. In this respect, the following were proposed: 1/ a definition of sensitive, vulnerable and at-risk populations, 2/ systematic integration of a step to identify sensitive populations in the RV development process; this should appear in the summary for developing RVs and be the subject of a specific chapter in the ad hoc reports, 3/ an approach for taking sensitive populations into account when establishing RVs, and 4/ ideas for taking sensitive populations into account when assessing risks and making the resulting recommendations. This example illustrated a more comprehensive approach in terms of taking inter-individual variability within a population into account. It also highlighted the necessary balancing of a) the positive impact of risk reduction recommendations in the sensitive population, with b) the possible negative impact of recommendations for the non-sensitive population.

6.3 Microsensors to monitor the quality of indoor and outdoor air

Selected for the debate on the use of individual and citizen data to improve the study of the exposome

6.3.1 Background

The development of sensor systems for air quality monitoring, also known as microsensors or low-cost sensors (LCSs), has grown rapidly in recent years. Several factors can explain the growing popularity of these microsensors:

- The relatively low initial purchase cost of these technologies compared with the measuring instruments used in reference methods.
- Their ease of use and adaptability, which offer a variety of application areas to a broad range of users.
- Growing public awareness of air pollution and its health impact.
- The development of "crowdsourcing"[68] citizen research and a growing interest among the population in producing and sharing data.
- Growing demand and interest in connected objects (the Internet of Things[69]) from parts of the population.
- A need to improve knowledge of the large-scale spatio-temporal distribution of air pollution, and to cover different microenvironments.
- Advances in electronic engineering and computer science to manage the large amounts of data generated.

Because of their characteristics, these technologies offer many potential advantages and can be used in the context of regulatory air quality monitoring, mainly through mapping, investigating emission sources, improving temporal coverage, temporal resolution and spatial coverage, searching for and establishing measurement sites, assessing model output, assessing individual exposure, process management (e.g. tunnel ventilation control, building ventilation, etc.), raising awareness/communicating on air quality issues.

Because of these numerous areas of application, air microsensors have an increasingly wide pool of users: institutional players involved in air quality monitoring, research organisations, local authorities, citizens or citizens' associations.

However, the use of microsensors raises several questions, such as their metrological reliability, the management, use and interpretation of data and, ultimately, their relevance in addressing air quality issues. In 2018, the World Meteorological Organization (WMO) published a report on the possible use of low-cost sensors (Crotwell et al. 2018). The scientific literature available in late 2017 showed that this type of sensor has both advantages and disadvantages compared with traditional methods: the more compact and/or less expensive devices are often less sensitive, less accurate and less suited to the chemical characteristics

[68] Crowdsourcing is the outsourcing of a task to amateur contributors

[69] Manifestation of the Internet in the real world concerning objects, cars, buildings and other elements connected to a physical Internet network by an electronic chip, sensor or sensor system. This network connectivity enables the retrieval, storage, transfer and processing (without discontinuity between the physical and virtual worlds) of the related data, regardless of its geographical origin. Abbreviated to IoT (AFNOR 2021).

of the variable under consideration, although this can be offset by the greater density of the observation network that can be obtained with these sensors.

Many studies using microsensors have been carried out or are under way in France and abroad to answer these questions. Among the various applications of microsensors, the assessment of individual exposure is currently the least studied.

6.3.2 Objectives of the formal request

In this context, the Directorate General for Health (DGS), Directorate General for Energy and Climate (DGEC) and Directorate General for Risk Prevention (DGPR) made a formal request to ANSES on 21 December 2018 to:

1. Conduct a review of studies using microsensors and the profiles of their users.
2. Assess the strengths and limitations, and the complementarity with respect to conventional measurement, of data from microsensors used by citizens to characterise exposure in order to interpret the health implications.
3. Discuss the legal status of the data generated by microsensors.

In the remainder of this document, the term "sensor system" will be used instead of microsensor, in line with the definitions proposed by the French Standards Institute (AFNOR) (AFNOR 2021).

A working group of nine experts in metrology, geography, sociology, epidemiology and IT was set up to conduct this expert appraisal. This WG on Microsensors reported to the CES on "Assessment of risk related to air environments". The WG worked between January 2020 and March 2022 supported by consultations, hearings and interviews with various national and international stakeholders: institutions (ISGlobal, IRSN, Inserm, JRC, AASQA, ADEME, etc.), associations (APPA, FNE, Respire), manufacturers, distributors, users of sensor systems and legal experts, as well as a literature review and an extraction from the LCSQA "Capt'Air" database, which lists projects using sensor systems and documents their technical characteristics.

In response to the three objectives of the formal request, the WG drafted two expert appraisal reports published jointly in April 2022 with an opinion (ANSES 2022b) on the "Use of microsensors to monitor the quality of indoor and outdoor air" (2022).

The first expert appraisal report (Volume 1) (ANSES 2022e, 1) sought to:

- Propose definitions and prerequisite knowledge on sensor systems, the data generated and the stakeholders involved in their implementation.
- Provide an overview of projects relating to the assessment of sensor systems and projects involving citizens, drawing on literature reviews and reference reports on the topic.
- Focus on the specific case of carbon dioxide (CO_2) sensor systems, because of the recommendations on measuring CO_2 in indoor public spaces as a means of combating the spread of COVID-19, and the variety of equipment available.
- Conduct a review of studies specifically on the use of sensor systems for individual exposure assessment, with a discussion of the potential advantages and limitations of using sensor systems in studies.

- Identify key points to consider to ensure that data generated by a sensor system can contribute to the assessment of individual exposure.
- Discuss the use of sensor systems for assessing the health effects of air pollution once the data generated have been deemed "valid", i.e. they comply with the key points of the previous step.
- Discuss the specific case of private users of sensor systems.
- Discuss the legal status of data generated by sensor systems.

The second expert appraisal report (Volume 2) provides a review of the profiles and motivations of sensor system users (ANSES 2022f, 2).

6.3.3 Recommendations of the Exposome WG

During presentation of the formal request to the Exposome WG, two lines of investigation were proposed: 1) examine exposome projects liable to deploy air sensor systems, and 2) reflect on the added value for ANSES's expert appraisals of using individual exposure data generated by sensor systems.

6.3.4 Actions and resources implemented

With regard to point 1, a questionnaire was developed by the WG on Microsensors in order to set up an international consultation on exposome projects liable to deploy air sensor systems. This questionnaire was sent to four exposome research projects: ATHLETE, REMEDIA, EXPANSE and LongITools. Only one response, from the ATHLETE project team, was sent to ANSES, and its data were therefore analysed by the WG on Microsensors. As part of the ATHLETE project's "urban intervention" study, Atmotube Pro® portable sensor systems will be deployed among 40 children aged 9-11 years in the cities of Barcelona and Bradford, to characterise their exposure to particulate matter (PM_1, $PM_{2.5}$ and PM_{10}) and volatile organic compounds (VOCs), and propose actions to reduce this exposure. These sensor systems were selected because they are light and compact (and therefore suitable for children), inexpensive, and their metrological reliability has already been proven. More generally, according to ISGlobal, air sensor systems offer multiple advantages in the study of the exposome: real-time exposure measurement and the possibility of linking individual exposure to specific locations ("exposure tracing"), the possibility of measuring different parameters with a single device, or multiplying sensor systems to get a more complete picture of exposure to air pollution, the possibility of studying specific populations, etc. On the other hand, sensor systems provide information on the exposure of participants that cannot be generalised to the general population. In addition, these sensor systems provide data on short time intervals and cannot be used to study the long-term effects of air pollution. Lastly, the metrological trueness of these sensor systems is a critical element to consider.

With regard to point 2, the expert appraisal work presented in Volume 1 aims in part to answer these questions: what are the advantages and limitations of sensor systems for assessing exposure to air pollution? How can the data generated be used to assess health effects? A review of these chapters was carried out by the Exposome WG. Some of the conclusions and recommendations of this report are set out below.

In general, the CES on "Assessment of the risks related to air environments" concluded that "Sensor systems offer many opportunities in the area of individual exposure assessment.

Thanks to miniaturisation, portable sensor systems can easily be worn by individuals during their daily activities. This enables the devices to integrate the different microenvironments frequented and the exposure conditions specific to each individual, with measurements in near real time. On a larger scale, the initial purchase cost and small size of the sensor systems also leads to a multitude of measurement points and devices being deployed in microenvironments that have been overlooked or rarely studied to date. However, the metrological quality of the pollutant concentration measurements remains the main limitation of these systems [...] Sensor systems are therefore seen as devices that complement the data sources or exposure assessment methods already used in exposure science studies. In addition, sensor systems could help optimise mapping (on spatial and temporal scales) and large-scale models, thus helping to improve the estimation of exposure to air pollution."

For use in risk assessment, the CES concluded that "The use of exposure data generated by sensor systems (deemed valid) with a view to conducting a qualitative health risk assessment (QHRA) or qualitative health impact assessment (QHIA) requires consideration of whether these data are aligned with the dose-response relationships established for hourly, daily or annual exposure that will be used to quantify the health risk. Suitable use therefore requires that measurements from sensor systems be integrated over the same interval as that used to establish the dose-response relationship. In addition, these measurements need to be repeated over the year in order to be representative of the exposure studied over the medium or long term. Furthermore, data generated by a portable sensor system, integrating the different sources to which an individual is exposed, cannot be considered as representative of population exposure. It is therefore important to ensure that the sensor systems are deployed in sufficient numbers to be representative of the study population.

Moreover, while sensor systems are particularly relevant for studying the short-term effects of air pollution at the individual level, they can also contribute to assessing the effects of air pollution on larger scales (fixed sensor systems and/or via improved mapping and models)."

To improve the quality of the data generated, recommendations for manufacturers of sensor systems were provided.

Concerning knowledge on the health risks associated with air pollution, the CES "recommended that the opportunities offered by sensor systems be considered for:

- Improving estimates of individual exposure.
- Acquiring exposure data in places that have been overlooked or rarely documented.
- Studying the contribution of different microenvironments to the overall exposure of individuals.
- Studying the determinants of exposure.
- Studying the links between exposure and health."

It also stressed "that sensor systems can be coupled with devices measuring heart rate or respiratory rate to enable a more detailed study of additional exposure indicators such as the inhaled dose."

6.3.5 Conclusion

This formal request was an opportunity to examine the new tools for measuring individual exposure and their use in risk assessment. It concluded that sensor systems are proving valuable in making the exposome concept operational in environmental health studies, by improving knowledge of individual exposure. Indeed, despite their limited metrological quality, sensor systems offer many opportunities for addressing the various issues related to indoor and outdoor air pollution, particularly through improved spatio-temporal coverage and the possibility of studying the various microenvironments contributing to an individual's total exposure. These sensor systems are not suited to communicating at the individual level about a potential health risk to the user from air pollution. On the other hand, it may be possible to use huge volumes of privately produced data to improve air pollution modelling, with the data produced by monitoring networks and the resulting population exposure maps, thus contributing to the assessment of health risks from air pollution at larger – or smaller – territorial scales.

6.4 Chlordecone

This example illustrates how the exposome can contribute to placing a classical risk analysis in a broader framework: combined effects with other substances (organochlorines), eco-exposome (fishing areas, soil), changes in agricultural practices, dietary behaviours and food preparation methods (type of cooking), long-term impacts of consumption recommendations and health effects including a risk/benefit analysis.

6.4.1 Background

Chlordecone was used to combat weevils in the banana plantations of Martinique and Guadeloupe from 1972 to 1993. This pesticide, which poses hazards and risks to humans, is now banned, but local populations remain exposed. This is because of its chemical structure, which makes it highly persistent in the environment: chlordecone is still present in the soil and can be found in certain plant- and animal-based foodstuffs, as well as in water at certain catchment areas used for drinking water and in estuaries. For many years, the Agency has been involved in assessing the dietary risks posed by chlordecone for the French Caribbean population. The Agency's activities in this area are conducted as part of the "Chlordecone" action plans first established in 2008 by the Ministries of Health and the Overseas Territories.

In December 2017, ANSES published an opinion on the updating of dietary exposure data as part of the Kannari project on "Health, nutrition and chlordecone exposure in the French Caribbean", in order to assess the risks for French Caribbean populations and issue consumption recommendations (ANSES 2017f). On 10 July 2018, ANSES received a formal request from the Directorate General for Food (DGAL), Directorate General for Health (DGS) and Directorate General for Competition, Consumer Affairs and Fraud Control (DGCCRF) to update the chronic (external) oral toxicity reference value (TRV) for chlordecone in light of the latest toxicological and epidemiological studies and to propose, if possible, an internal TRV. An initial expert appraisal was published on 11 February 2021, proposing an external TRV of 0.17 µg/kg bw/d and an internal TRV of 0.4 µg/L plasma (ANSES 2021l).

6.4.2 Purpose of the formal request

As part of the formal request of 10 July 2018, ANSES was asked to reassess the risks based on the external and internal exposure data from the Kannari study (ANSES 2017f) and the external and internal TRVs published in the November 2021 opinion (ANSES 2021l). This work was conducted by the ERCA CES through the appointment of expert rapporteurs. In a second formal request dated 17 December 2019, ANSES was asked to assess the contribution of differentiated management measures for contaminated soil used for cultivation or livestock farming, in order to achieve "zero chlordecone" in food. The Exposome WG was consulted in the context of these two formal requests.

6.4.3 Recommendations of the Exposome WG

As the main route of exposure to chlordecone is through food, the "classical" risk management approach is to: 1) assess the "external" exposure of the population via dietary habits and food contamination data, 2) assess the risks (for different subgroups) on the basis of this exposure and an external TRV, 3) establish maximum residue limits (MRLs) to be transposed into regulations, 4) carry out checks on the products distributed. This is essentially what was done in the French Caribbean with regard to chlordecone in the 2000s.

However, this risk management approach to chlordecone faces several problems, including: 1) the frequent consumption of home-grown food and/or products from short "informal" supply chains that are not subject to any regulatory controls, 2) a problem of scale, particularly in terms of time, because of the asynchronous change in chlordecone concentrations between biological and environmental concentrations, making it difficult to assess changes in the situation over time using only environmental data.

An exposome approach therefore has a dual advantage in this situation:

- In terms of exposure assessment, it leads to the use of measurement data obtained in biological matrices within the population, in order to obtain an integrated measurement (all sources combined, including the various food sources) of internal exposure (if necessary including other chlorine compounds), and the ability to monitor this exposure at "close" frequencies enabling management measures to be assessed.
- In terms of risk management, it leads to: 1) "participatory" management measures being developed to reduce contaminated products through appropriate land use, by the populations most at risk of high exposure (members of agricultural cooperatives or JaFa family garden programmes[70] for the home-production population) 2) individual measures being promoted to reduce exposure via a "responsible" diet, with the aim of reducing high-risk foods while still favouring a "local" diet, 3) in the long term, and depending on the future opinion of the French National Authority for Health (HAS), support measures, or even biomedical monitoring, being implemented for the people most at risk of developing disorders or diseases linked to high chlordecone contamination.

In a way, with the exposome, risk management moves from a preventive and prescriptive State approach to an approach rooted in a "health promotion" public health practice involving the populations concerned.

The WG makes seven recommendations for integrating an "exposome" approach in these two formal requests, which are presented in Figure 31. The first five recommendations listed below are related to the formal request on the update of the HRA. The last two relate to the formal request on the management of contaminated soil.

[70] https://jafa.ireps.gp/

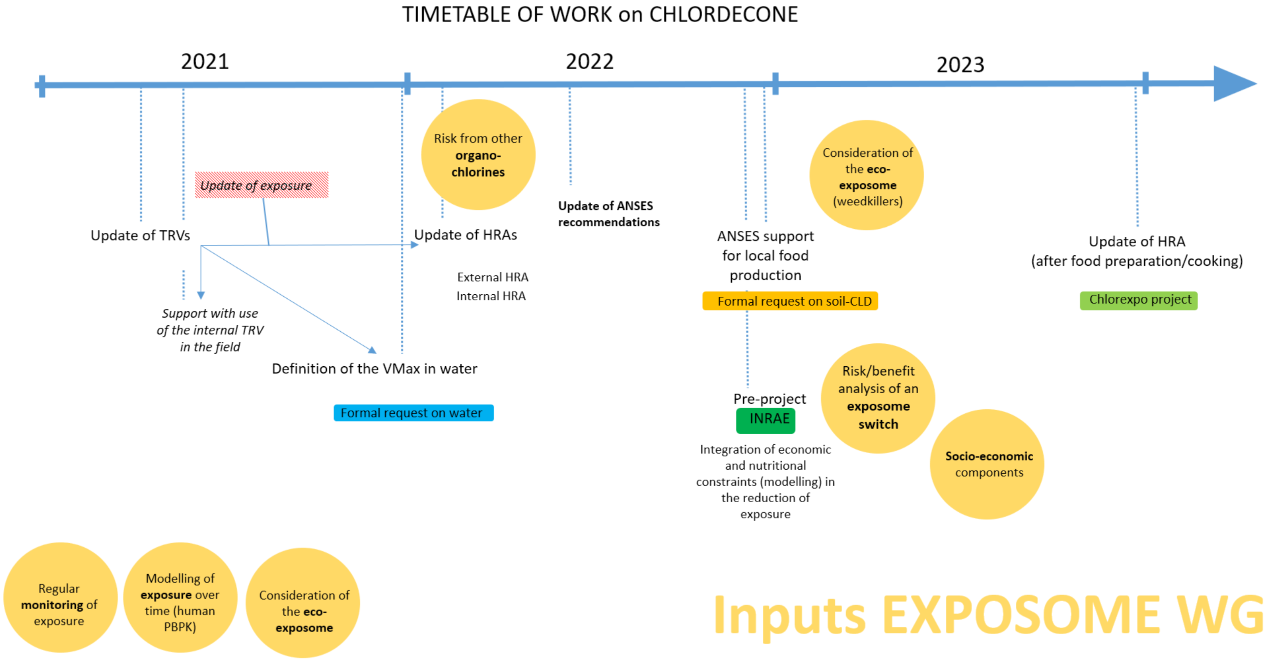


Figure 31: Timetable of the work on chlordecone and integration of the Exposome WG's recommendations (yellow bubbles)

6.4.3.1 Regularly monitor the biological chlordecone concentration levels of the population

With reference to the early 2000s, a decrease in the level of biological chlordecone concentration levels was observed in different sub-populations. On the other hand, it is not possible to observe changes in chlordecone concentrations in the French Caribbean environment on the same time scale, as its half-life in soil is extremely long (several hundred years) compared with its half-life in the body (between 60 and 160 days). There is therefore a "disconnect" between the changes in chlordecone levels in the French Caribbean population and in their environment, probably amplified by the steps taken in the French Caribbean to limit exposure to chlordecone (dietary recommendations, reinforced food controls, agricultural practices, etc.). It is therefore not appropriate to assess the change over time in the population's exposure to chlordecone based on environmental data alone.

The Exposome WG considers that regular analysis of biomonitoring data is essential for assessing the short-term impact of management measures. In addition, these data are useful indicators for improving the targeting of preventive actions to be taken (e.g. production or consumption recommendations aimed at the most at-risk populations, such as consumers of home-grown produce, or proposals for biomedical monitoring if necessary). Furthermore, a management strategy developed and implemented on the basis of these biomonitoring data could lead to greater involvement of the population in resolving this environmental pollution (development of responsible individual approaches to home production and consumption, personalised medical care).

6.4.3.2 Model chlordecone exposure over time

As chlordecone blood levels only reflect the last few months of exposure (half-life between 60 and 160 days), they provide no information on longer-term exposure, such as that of agricultural workers in banana plantations before 1993 (the official date of the chlordecone ban). In this respect, the WG supports the approach of reconstructing the changes in chlordecone exposure over time using a PBPK model tailored to humans. This model could also be used to predict the impact of management scenarios on chlordecone blood levels in the French Caribbean population.

6.4.3.3 Conduct a risk/benefit analysis of different risk reduction strategies

All the management actions taken to date aim to continue decreasing chlordecone blood levels in the French Caribbean population. One of the questions raised by the Exposome WG is whether there is a risk that the changes in the current dietary behaviour of the French Caribbean population as a result of these management measures could lead to a significant change in their dietary exposome, moving from a "traditional or local" context associated with majority consumption of "local" (i.e. French Caribbean) products to a new context, more linked to processed and/or imported food products. This change could lead to increased exposure to other chemicals and/or a nutritional imbalance with the consumption of more fatty and sugary foods. Analysing the benefit/risk balance of management measures targeting chlordecone is therefore a crucial component to be taken into account in future proposals for management measures.

It is currently difficult to objectively assess a possible change in this dietary exposome, as the most recent data on French Caribbean dietary habits were collected between 2013 and 2014. The following questions therefore remain open: Has an exposome shift already taken place? Is it ongoing? Will it happen? Indeed, the overall policy of preventing risks associated with exposure to chlordecone seeks to maintain as far as possible the consumption of local food, associated with a healthy nutritional balance. Economic issues such as employment and food accessibility also depend on this local production being maintained.

It is therefore necessary to examine the changes in the food exposome of the French Caribbean population and the future health benefits/consequences.

6.4.3.4 Integrate the socio-economic components

Regulatory prevention and verification measures to limit chlordecone contamination of commercial products do not apply to home-grown produce, which is widespread in the French Caribbean. In order to supplement the regulatory measures and move towards a "zero chlordecone" diet, the regional health agencies (ARS), via the regional forums for health education and promotion (IREPS) of Guadeloupe and Martinique, are conducting programmes under the Chlordecone Plan, designed to protect the health of consumers of home-grown plant, animal and fishery products by reducing their exposure to chlordecone.

Two programmes run by the IREPS, which are based on a health promotion approach[71], aim to:

[71] Environmental health promotion is a process by which individuals and communities become aware of the link between their environment and their health, and acquire the skills, capacity for reflection and critical thinking, as tools for developing the will and power to act, that will enable them to work as

- create a favourable climate for the emergence of positive and constructive responses to chlordecone.
- make the complexity of the chlordecone issue in the French Caribbean living environment more understandable.
- not divert people to a diet too high in fat, sugar and/or salt.
- These programmes are the JaFa family garden programme, launched in 2008, which concerns food from kitchen gardens and family holdings. It is mainly aimed at people who regularly eat root vegetables from their own or their neighbours' Creole gardens, or root vegetables purchased from roadside sellers. The solutions proposed to reduce exposure to chlordecone are based on AFSSA's recommendations and on agronomic research conducted by CIRAD and INRA. Initially, JaFa advisers provide support to willing households. They make home visits, provide personalised follow-up on agronomy and nutrition, and offer thematic workshops. In addition, knowledge of the level of soil pollution enables the families concerned to choose suitable crops. Indeed, the presence of chlordecone in the soil does not mean that all garden production has to be abandoned: there are still crops that can be grown without risk and adjustments can be made to small areas to avoid pollution. Diversification of the diet, for example by introducing more green vegetables, can reduce exposure and has other nutritional benefits. For family holdings, amateurs raising livestock are also given advice on how to avoid producing contaminated meat or eggs, as poultry flocks on contaminated land are particularly vulnerable. Agronomic and nutritional workshops are offered to improve gardening practices and reinforce knowledge of balanced nutrition.
- The TITIRI Programme[72], launched in Guadeloupe in 2019, concerns freshwater and seafood products. It aims to help reduce the risks of exposure to chlordecone by recommending fishing areas and fish species with low levels of contamination, and by guiding the population towards the consumption of fish products (molluscs, fish, shellfish) with little or no contamination.

Preventing contamination of the populations of the French Caribbean must indeed be based on a reinforced community dynamic. This can only work if it succeeds in establishing a relationship of trust between prevention operators and the population, in a social context marked by a high level of mistrust of the authorities, which is particularly clear in the current pandemic and vaccination context. Chlordecone contamination could be an opportunity to strengthen more comprehensively the actions in favour of health promotion/prevention in the French Caribbean. This would require the establishment of ambitious mechanisms for listening to and involving the population, in order to take protective measures rooted in local culinary, agricultural, fishing and animal husbandry traditions. Only such a community health approach can help restore a sense of control and equity among the population (Desgroseillers et al. 2016).

6.4.3.5 Broaden knowledge to other substances with possible co-exposure and common effects with chlordecone

Current management measures focus on chlordecone and mainly target ways of producing food with low residual levels of chlordecone contamination, or aim to target individuals for

responsible citizens, individually and collectively, to solve current and future environmental, health and related problems (source: Languedoc Roussillon environmental health education network).

[72] https://titiri.ireps.gp/

whom measures to reduce their exposure should be implemented, or investigate the possible effects induced by this exposure (HAS formal request, 2022 in progress). However, some dimensions of the local chemical exposome are still unknown, particularly with regard to exposure to other organochlorines that may have similar biological targets to chlordecone[73]. The Exposome WG therefore recommends investigating the relevance and value of taking co-exposure to other substances into account in the assessment and management of risks associated with chlordecone.

6.4.3.6 Consider the eco-exposome in order to better anticipate and manage human exposure

Nearly a quarter of the utilised agricultural land in the two French Caribbean *départements* of Guadeloupe and Martinique is considered to be moderately or heavily contaminated by chlordecone. At the same time, a national survey initiated in 2008 in French Caribbean slaughterhouses revealed contamination of animal products. The work carried out under the ANR INSSICCA project[74] particularly illustrated the need to understand, explain and model the processes of contamination transfer and bioavailability, from contaminant sinks such as soil and water to the matrices to which animals and humans are then exposed.

Exposure of livestock via the ingestion of crops or grasses growing on polluted soil is directly dependent on the supply of feed. This results in livestock becoming contaminated, making them unfit for consumption. The ability to analyse free and conjugated chlordecone and its metabolite (chlordecol) made it possible to monitor the toxicokinetics of the compound in the animal's body and specify toxicokinetic parameters such as the half-life of chlordecone, which was assessed to be between 20 and 55 days depending on the species. The results show that decontamination of animals (sheep, pigs) can be achieved by removing them from contaminated plots of land over time intervals compatible with farming practices.

In addition, methods are being developed for the chemical analysis of chlordecone and its metabolite (5b-hydrochlordecone) in sea and river water. In particular, passive samplers can now achieve limits of quantification of around ten pg/L[75] for detecting very low concentrations of this pollutant, required particularly in sea water. These tools now help trace and provide information on the presence of this compound and its metabolites in surface and coastal waters (Gonzalez et al. 2019), thus highlighting risks of human exposure. Chlordecone measurements in the environment, as well as in organisms in Galion Bay (Martinique), show significant variations in contamination depending on the site, due to several factors (de Rock et al. 2020): wet season versus dry season, system hydraulics, type of sampling station, species concerned, etc.

Recent studies (Sabatier et al. 2021) have focused on a retrospective analysis of marine sediments collected at sea in areas influenced by inflows from two watersheds in Guadeloupe (Pérou) and Martinique (Galion), which are known for their large banana-growing areas and soil contamination by chlordecone. The results showed a large increase in sediment concentrations of chlordecone and its metabolite (chlordecol) simultaneously in Guadeloupe and Martinique. These high concentrations were associated with the increase in erosion following the sharp growth in the use of weedkillers (glyphosate and AMPA) from the 1990s. This work shows the need to integrate cropping practices and how they change over time, especially in a context of climate change, in

[73] The TDS Antilles project, whose scope was refocused on chlordecone only, would have enabled exposure data on other substances to be obtained.
[74] Report on the end of the ANR INSSICCA project: Innovative strategies to establish safe livestock rearing systems in chlordecone-contaminated areas. Project ANR-16-CE21-0008.
[75] This LQ is nevertheless insufficient to meet the requirements of the new regulation (EQS: 0.5 pg/L).

order to understand and predict the risks of remobilisation of contaminants initially trapped in soil, towards inland and marine surface waters and groundwater, and the consequences in terms of transfer to humans. With the increase in erosion of cultivated soil in response to changing cropping practices, soil that was originally a contaminant sink can become a source of substances and metabolites, and thus contaminate other environmental media that are vectors of exposure for humans.

These examples, in the case of chlordecone, highlight the need to combine knowledge of the spatio-temporal changes in the eco-exposome with general data on the exposure of human populations in order to assess the risks of contamination as accurately as possible, particularly in relation to food, and to identify tools for managing the key variables of this contamination and for preventing exposure.

6.4.4 Actions and resources implemented

The proposals on the eco-exposome in 6.4.3.6 could be addressed directly in the context of the formal request on assessing the contribution of differentiated management measures for contaminated soil used for cultivation or livestock farming, in order to achieve "zero chlordecone" in food (planned for 2023).

Regarding the proposal in 6.4.3.5, the WG assisted with the exploratory work carried out by a rapporteur member of the ERCA CES on the issue of co-exposure to chlordecone and other substances, such as organochlorines. A summary of this work is presented below. All the information is available in Annex 4 and will be integrated in the expert appraisal currently under way on updating the risk assessment of exposure to chlordecone, carried out by the ERCA CES.

A- Co-exposure of the French Caribbean population to organochlorines

PCB 153, PCB 180 and *p,p'*-DDE concentration levels in the French Caribbean adult population were compared with those observed in mainland France, the United States and Canada (Figure 32 and Annexe 4 Table 10 and Table 11, and Figure 33 to Figure 37). Even if these comparisons are difficult to make (there is no overlap in the populations and periods studied), the data support a possible French Caribbean specificity with regard to high *p,p'*-DDE concentration levels in individuals over 60 years of age, particularly in Guadeloupe (between 1.2 and 1.5 times higher for concentrations measured in ng/g lipids).

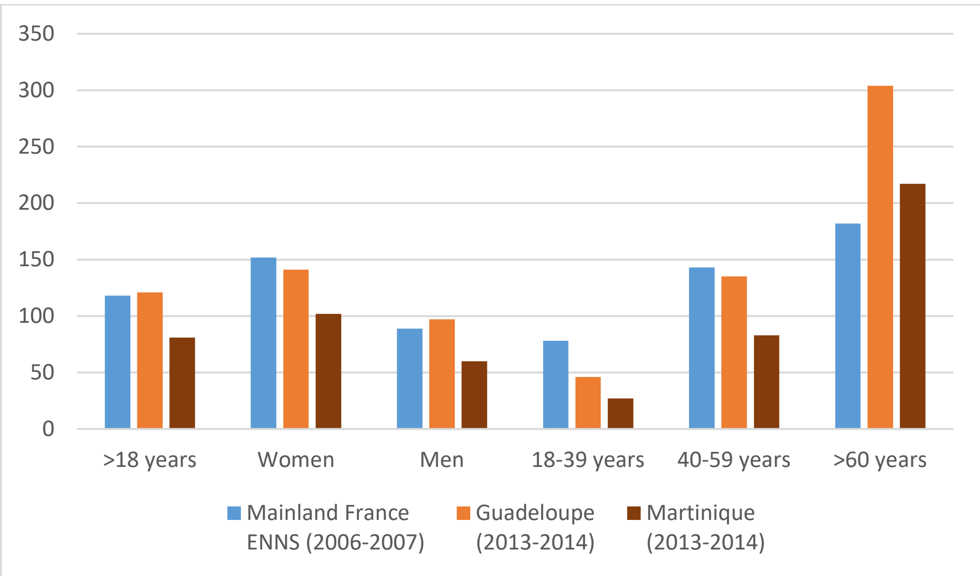


Figure 32: *p,p'*-DDE concentration levels in the French Caribbean and in mainland France of adults over 18 years of age (in ng/g of lipids)

B- Sources of exposure to organochlorines (DDE and PCBs)

Although we have no precise data on the sources of exposure to PCBs and DDT (and its metabolite DDE) in the French Caribbean, several reports (ANSES 2011a; Fréry et al. 2013; Weitekamp et al. 2021) have shown that, in general, since these substances were banned, food is the main source of exposure for the general population in all the territories studied. Apart from food, a possible source of exposure to DDT could be the relatively recent use of dicofol in agriculture. Indeed, dicofol, which can contain up to 25% DDT (Qiu et al. 2005), was used in combination with tetradifon in Martinique and Guadeloupe until 2008 as a mite-control treatment for banana trees, and thus contaminated the soil (Gentil et al. 2018).

C- Effects of organochlorines

Epidemiological studies conducted in recent years (on the French Caribbean population and other populations) have revealed a number of health effects in individuals exposed to organochlorine compounds. Table 5 gives a summary of the most common effects described for some of these compounds.

Table 5: Toxicological properties common to organochlorines (chlordecone, *p,p'*-DDE, PCB, HCB and lindane)

Toxicity	CLD	***p,p'*-DDE** *ATSDR 2004*	**PCB** *ATSDR 2004*	**HCB** *ATSDR 2004*	**Lindane (γ-HCH)** **ATSDR 2005**
Half-life	63-165 d	6.9 years[a]	3-9 years (7-14)[b] 3-10 years (work)[c]		1-25 d[d] 7 years β-HCH
Nephrotoxicity	x				x
Hepatotoxicity	x	x	x	x	x
Immunosuppression		x	x	x	x
Thyroid hormone alterations		x	x	x	
Reprotoxicity	x	x	x	x	x
Neurotoxicity	x	x	x	x	x
Neurodevelopment	x Timoun	x EPA 2004, Timoun	x		
Foetotoxicity Malformations		x	x	x	x (animal)
IARC classification	2B 1987	2A (DDT) 2018	1 2016	2B 2001	1 2018
Endocrine disruptor	Binds to ERα, ERβ	Antiandrogenic	Oestrogenic or Antioestrogenic depending on the congeners*		Antiandrogenic Antioestrogenic
Other					Haematoxicity

[a](Ritter et al. 2009); [b](Grandjean et al. 2008); [c](Shirai and Kissel 1996); [d](US Agency for Toxic Substances and Disease Registry 1994); * in addition to alterations of thyroid activities by some PCB metabolites

***p,p'*-DDE, PCBs and prostate cancer:** Emeville et al. (2015) identified a significant association between plasma *p,p'*-DDE concentrations and prostate cancer in Guadeloupe (Annexe 4 and Table 12). On the other hand, the association between PCB 153 concentrations and prostate cancer was not significant (Emeville et al. 2015).

***p,p'*-DDE, PCBs and neurodevelopmental toxicity:** studies carried out as part of the TIMOUN mother-child cohort in Guadeloupe, which measured *p,p'*-DDE and PCB 153 concentrations in parallel with those of chlordecone in the umbilical cord, revealed a significant sex-dependent decrease in thyroxine associated with prenatal exposure to *p,p'*-DDE. Given the role of thyroid function in neurodevelopment, exposure to *p,p'*-DDE is liable to affect the health of the child population in the same way as chlordecone. Indeed, *p,p'*-DDE has a similar toxicological profile to that of chlordecone. The most significant effects of DDT and DDE have been observed on neurocognitive and behavioural development, which may persist in childhood (Eskenazi et al. 2006; Ribas-Fitó et al. 2006; Torres-Sánchez et al. 2007; van den Berg et al. 2017).

With regard to PCBs, neurodevelopmental toxicity (along with immunotoxicity) was one of the two criteria used to establish guideline values for PCBs, by the WHO (Faroon et al. 2003) and by AFSSA in 2007 (ANSES 2007a). Numerous epidemiological studies report reduced cognitive performance and motor and psychomotor deficits, associated with pre- and postnatal exposure (Tilson, Jacobson, and Rogan 1990; Jacobson and Jacobson 1996; Trnovec et al. 2008; Lynch et al. 2012), but not all are convergent.

Thus, exposure to *p,p'*-DDE and PCBs could cause neurodevelopmental effects and thus affect the development of the child population in the same way as exposure to chlordecone.

Other effects of organochlorines in animals and humans: the organochlorines often encountered in contamination studies include *p,p'*-DDE (active metabolite of DDT), PCBs, hexachlorobenzene (HCB), β-HCH (degradation or contamination product of lindane or γ-HCH). Their toxicity in animals and humans has been summarised by the ATSDR (US Agency for Toxic Substances and Disease Registry 2019; 2000; 2015; 2005; 2020), the WHO (WHO/IPCS 1984; 1991; 1997; Faroon et al. 2003; World Health Organization 2011) and the IARC, the latter of which re-assessed the carcinogenicity of PCBs in 2016, and that of DDT/DDE/DDD and lindane in 2018 (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2016; 2018). A qualitative analysis of their toxicity shows a common toxicological profile: hepatotoxicity, neurotoxicity and neurodevelopmental toxicity, reprotoxicity and endocrine disruption (Table 5).

The mechanisms of endocrine disruption by substances found alongside chlordecone differ according to the compounds. DDT and its metabolites induce oestrogen-dependent cell proliferation (Soto et al. 1995), and while *o,p*'-DDT is a weak agonist of the ERα and Erβ oestrogen receptors (Kuiper et al. 1998), *o,p*'-DDT, *p,p'*-DDT and especially *p,p'*-DDE are androgen receptor antagonists, with *p,p'*-DDE being the most potent antiandrogen among them (Kelce et al. 1995; 1997). At the thyroid level, a significant inverse relationship has been noted between DDE concentrations and thyroid hormone levels in umbilical cord blood, in several mother-child cohort studies in China (Luo et al. 2017) and Europe (Maervoet et al. 2007; Krönke et al. 2022). *p,p'*-DDE contamination was significantly associated with an increased incidence of *diabetes* (T2D) (Turyk et al. 2009; Cox et al. 2007; Everett et al. 2007). Prenatal exposure was associated with childhood obesity in twelve prospective studies (Vrijheid et al. 2016), with significant sex-dependent effects in boys, compared with girls (Warner et al. 2014). The endocrine activity of PCBs on steroid sex hormones is more complex, as their antioestrogenic or antiandrogenic activity depends on the degree of chlorination of the congeners, the position of the chlorines in the structure, and the activity of their metabolites (Bonefeld-Jørgensen et al. 2001): highly chlorinated congeners are antioestrogens and their hydroxylated metabolites are more active than the parent compound. On the other hand, low-chlorinated PCBs and their hydroxylated metabolites are generally oestrogenic. It is therefore difficult to predict the activity of a PCB contamination cocktail given the variety and diversity of these contaminants. Note that Goncharov et al. (2010) found a decrease in testosterone levels in the Native American (Mohawk) male population, significantly associated with four congeners (PCB 74, 99, 153 and 206) and four congener groups (mono-ortho-substituted, di-ortho-substituted, tri- and tetra-ortho-substituted, and dioxin-like TEQs), which supports the above assertions. The thyroid is the main target organ for PCBs after the liver (Goncharov et al. 2010). They interfere at different levels of thyroid function: binding to the thyroid receptor (agonists), competing with thyroid hormones for transporter proteins to the target tissues and decreasing thyroid hormone levels (Krönke et al. 2022). These effects on thyroid function may have been responsible for the cognitive, motor or psychomotor deficits recorded during *in utero* and/or postnatal exposure as mentioned above (Tilson, Jacobson, and Rogan 1990; Jacobson and Jacobson 1996; Trnovec et al. 2008; Lynch et al. 2012). *Cardiovascular disorders* in the form of an increased incidence in *hypertension* were demonstrated in the population of Anniston (Alabama, US), which had suffered from longstanding exposure to industrial PCB pollution (Goncharov et al. 2010). Epidemiological studies are now able to identify exposure to persistent organic pollutants, especially PCBs, as a risk factor for hypertension, diabetes and obesity, all of which result from the genesis and progression of cardiovascular disorders (Perkins et al. 2016). Numerous cases of gestational diabetes (Vafeiadi et al. 2017) and childhood obesity (Tang-Péronard et al. 2014; Lignell et al. 2013; Dallaire et al. 2014) are attributed to PCB exposure. The neurodevelopmental, cognitive and behavioural effects of *p,p'*-DDE and PCBs, which may persist in childhood, explain why the female population of childbearing age and the infant population are considered targets of their toxicity (Eskenazi et al. 2009; World Health Organization 2011). In addition, the involvement of prenatal exposure to DDE and PCBs in childhood obesity needs to be explored in the French Caribbean. More broadly, the involvement of these organochlorines as factors in hypertension, type 2 diabetes and obesity in the general adult population should be studied.

Combined effects of chlordecone and other organochlorines: there are currently no data on possible interactions between chlordecone and other organochlorines in terms of combined effects.

Conclusion on the effects of organochlorines: Chlordecone and other organochlorines share common toxicological effects and targets. However, there are currently no data on possible interactions between chlordecone and other organochlorines in terms of combined effects. It therefore seems necessary to investigate the combined effects of chlordecone and other persistent organic pollutants, such as DDE and PCBs, in particular with regard to the effects on metabolic syndrome with multiple consequences, neurodevelopmental effects in the child population, and prostate cancer in the male population.

D- Conclusion on the need to consider other contaminants in assessing the risk of chlordecone exposure

The example of organochlorines in the context of persistent chlordecone contamination in the French Caribbean shows the need to extend the risk assessment of chlordecone to other environmental contaminants. Although the available data are currently insufficient to carry out a quantitative assessment of the risks associated with exposure to other organochlorines, they converge in showing the advantage of considering these substances in the same way as chlordecone.

In addition to organochlorines, other contaminants present in the Caribbean environment such as PAHs, dioxins and furans, hexachlorobenzene, pentachlorobenzene and DDE are liable to have combined effects with chlordecone.

The Exposome WG therefore recommends broadening the scope of investigation of exposure to chemical contaminants of interest in the French Caribbean beyond chlordecone, in order to assess the risks more comprehensively and better adapt management measures. For this, it may be necessary to carry out a total diet study in the French Caribbean, coupled with a biomonitoring study. The next biomonitoring study (Kannari 2) will be an opportunity to conduct such an integrated study in order to update and collect contamination data on other contaminants of interest and better document their dietary sources. Monitoring of organochlorine contamination should cover the whole population and not be limited to adults heavily contaminated by chlordecone, so as not to neglect long-term and multi-generational metabolic diseases, which may affect the child population, women of childbearing age and the population in general (Gore et al. 2015). Lastly, toxicological and epidemiological studies are needed to investigate the combined effects of chlordecone and other contaminants in the French Caribbean environment.

6.4.5 Conclusion

Taking the exposome into account as recommended by the WG makes it possible to propose a holistic and systemic approach to the issue of chlordecone contamination in the French Caribbean in terms of both risk assessment and risk reduction. Thus, in addition to the HRA on exposure of the population to this substance alone, it was proposed to study and take into account the combined effects with other organochlorines and substances of interest present in the French Caribbean, and conduct an analysis of the risks and benefits of the various exposure reduction strategies for humans and ecosystems, taking the social and geographical specificities of the French Caribbean into account. It was also recommended that the biological concentration levels in the population be monitored regularly and their changes over time modelled. Lastly, the WG insists on the need to develop prevention and health promotion actions, based mainly on a community approach and participatory prevention and monitoring actions.

6.5 Digital tools and the health of children and adolescents

6.5.1 Background

The growth in information and communication technologies, along with the development of a digital culture, has led in recent years to the widespread distribution of connected tools and the expansion of their uses, both in the private and professional spheres, and in all age groups. These changes raise many questions, concerns and controversies, particularly regarding the potential health effects of using these digital tools. The examples mentioned include addiction, developmental disorders in children, and burnout at school or work. However, the scientific evidence on these concerns has still not been stabilised. Certain individual and social factors (age, household size, socio-economic profile, etc.) could also act as determinants of exposure to digital technologies (equipment rate, duration of exposure, type of use, etc.) and vary both the nature and severity of the potential health effects (Bach et al. 2013).

In 2016, on the occasion of its expert appraisal on exposure to radiofrequencies and children's health, ANSES had identified certain studies showing a link between "problematic use of mobile phones[76]" and the onset of cognitive disorders or impaired well-being in children and adolescents. ANSES had concluded that: "Three large studies show an association between intensive and inappropriate phone use by adolescents or pre-adolescents and mental health problems. They investigated the consequences of the use of the mobile phone and not of the radiofrequencies it emits. In light of this information, there may be an association worth exploring between such use of mobile telephones and changes in mental health."

In 2020, ANSES warned about the increase in sedentary behaviour and physical inactivity among young people, due in particular to the passive use of screens for recreation. The COVID-19 health crisis has led to increased exposure to screens and the use of new technologies among the population (ANSES 2020a).

6.5.2 Purpose of the formal request

All of the above-mentioned points justified ANSES conducting an expert appraisal to identify the direct and indirect health effects for children and adolescents associated with screen-based technological devices in all their dimensions: physical, mental and cognitive, psychosocial, family. The expert appraisal also sought to understand how health determinants modulate these effects depending on exposure.

A working group, the Digital Tools WG, was formed with 16 experts from a wide range of disciplines: sociology, information sciences, philosophy, paediatrics, child psychiatry, psychology, epidemiology (including social epidemiology), cognitive neuroscience (memory, sleep, learning) and addiction. This WG reported to the CES on "Physical agents and new technologies". The expert appraisal was initiated in 2020 for a period of 36 months.

In order to organise the WG's reasoning, an analytical framework was initiated. This overall analytical framework for the expert appraisal sought to describe individually the parameters of exposure, the categories of adverse health effects, and the technical and human determinants that can vary both. It illustrated the complexity of the interactions involved in assessing the health risks associated with the use of digital technologies.

The exposure situations identified as potentially playing a role in the occurrence of health risks were:

- The context of the exposure (alone, with peers, with parents, etc.), which could involve a discussion on the content viewed.
- The times and places of exposure (end of day/morning; school/home, etc.), which may have a different impact, especially on sleep.

[76] The notion of "problematic use" was put forward in the study by Bianchi and Phillips (2005). The authors developed a specific questionnaire, the Problematic Cellular Phone Use Questionnaire (PCPU-Q), comprising 12 items. The first seven questions ask participants whether they have experienced symptoms of problematic mobile phone use in the past year, and the next five questions investigate the consequences of problematic phone use on five real-life examples.

- The type of content viewed, and whether it was appropriate for the age and sensitivity of the child.
- The media used (mobile or fixed devices).

Among the "modulating" or "moderating" parameters, which can act on both hazard and exposure, the plan was to:

- study attention-grabbing strategies/techniques;
- characterise the factors modulating both exposure and health effects (social vulnerabilities, biological, psychosocial and psychological sensitivities).

Lastly, as mentioned above, it was important that the health consequences of exposure take health into account in its broadest definition: physical, physiological (including neurological), social and psychological effects.

6.5.3 Recommendations of the Exposome WG

The Exposome WG recommends working on the following areas:

1. Take into account the potential effects on the psychomotor development of young children, and in particular the impact on fine motor skills.
2. Investigate interactions with other factors:
    a. Study the combined effects of exposure to screens and to chemical and microbiological agents.
    b. Study the possible change in the exposure profile of children to indoor environmental pollutants and to artificial and blue light since the massive use of digital tools.
3. Assess the impact of exposure to screens on other activities, and understand the mechanisms promoting this exposure.
4. Assess the beneficial effects of the use of digital tools for children with autistic disorders, or with socialisation difficulties.

It should be noted that numerous studies show that the consequences of exposure to screens and the intensity of digital practices are largely modulated by the social context and the diversity of individual cultural practices (Lieury, Lorant, and Champault 2014; Kassam and Ferrari 2020).

6.5.4 Actions and resources implemented

Among the recommendations of the Exposome WG, the feasibility of both parts of Recommendation 2 above was studied.

6.5.4.1 Assess the risks associated with the combined effects of exposure to screens and to chemical and microbiological agents

Certain types of chemical exposure could cause the same suspected adverse health effects as the use of certain digital tools. For example, the recreational use of screens by young children is suspected to have consequences for their physical (risk of overweight, sleep disorders) and cognitive development (HCSP 2019, 2019). As an example, Table 6 shows the substances for which the weight of evidence was seen as likely or very likely for their effects on neurodevelopment and metabolism, based on a literature review carried out for the ATHLETE project (see Chapter 2). It is therefore relevant to ask whether the effects induced by exposure to screens and to chemicals could be combined. However, to our knowledge, no data are available on health effects associated with co-exposure to screens and chemical and microbiological agents. Specific studies should therefore be set up to investigate the combined effects of chemical exposure and screen use on child development.

Table 6: Substances referenced in the ATHLETE programme as having effects on neurodevelopment (cognitive development, behavioural disorders) or metabolism in children, which could be comparable to the effects suspected to be related to screen use

Substances	Effects	Institution/Authors
Lead	Cognitive outcomes, behavioural outcomes	(US EPA 2014; ATSDR 2020)
Cadmium	Cognitive outcomes	(Lamkarkach et al. 2021; ANSES 2019b; US Agency for Toxic Substances and Disease Registry 2012a; Rodríguez-Barranco et al. 2013; Branca et al. 2020)
Chlorpyrifos	Cognitive outcomes, behavioural outcomes (including ADHD)	(European Food Safety Authority (EFSA) 2019)
Benzo(a)pyrene	Behavioural outcomes (including ADHD), head circumference	(US EPA 2017)
Bisphenol A	Obesity, hormonal effects	(EFSA CEF Panel 2015)
Bisphenol A	Cognitive outcomes	(ECHA 2017a)
Bisphenol S	Anxiety-related behaviour (Toxicological data)	(HBM4EU 2021, 4)
Organophosphate pesticides	Cognitive outcomes, behavioural outcomes (including ADHD), autism	(US EPA 2015)
Methylmercury	Cognitive outcomes, behavioural outcomes (including ADHD)	(ECHA 2017b)
PBDE	Behavioural outcomes	(US Agency for Toxic Substances and Disease Registry 2017)
PBDE	Cognitive outcomes	(National Academies of Sciences, Engineering, and Medicine et al. 2017)
Arsenic (inorganic)	Cognitive outcomes and various neurodevelopmental effects	(U.S. Food and Drug Administration 2016; US Agency for Toxic Substances and Disease Registry 2016; EFSA Panel on Contaminants in the Food Chain 2009)
Manganese	Behavioural outcomes	(Santé Canada 2019; US Agency for Toxic Substances and Disease Registry 2012b)
HCB	Neurological effects and social behaviour	(US Agency for Toxic Substances and Disease Registry 2015)

6.5.4.2 Study the possible change in the exposure profile of children to indoor environmental pollutants and to artificial and blue light since the massive use of digital tools

According to a survey by the French High Council for the Family, Childhood and Age (HCFEA), 32% of children's time is spent on school activities (school or homework), 30% on "doing things together as a family" (meals, travel, family activities), in addition to time at home with no family activities, and 25% for "other" times and places (activities, recreation) (HCFEA 2018). The exposure profile of children therefore differs according to the activities with the family and those carried out during these "other" times. Already in 2009, screen time accounted for the vast majority of children's free time (Figure 33). In addition, the amount of time spent in front of screens has been increasing over the years. In its digital barometer, the CRÉDOC observed an increase in the time spent watching television and, on the internet, of an average of one hour per week for each, between 2018 and late 2020, which means that two additional hours per week are being devoted to screen time. On the internet, 36% of children aged 12-17 are even heavy consumers, spending more than 8 hours a week watching videos, films and other audiovisual content (Crédoc 2021). Assuming that in the majority of cases the devices used are not portable, children may therefore be spending more and more time indoors, which could change their exposure profile and increase the time they are exposed to chemicals and microbiological substances in indoor air, as well as to artificial light and, in any case, to blue light from screens. Moreover, the increase in time spent indoors induces a change in behaviour: snacking, decreased physical activity and increased sedentary behaviour (ANSES 2020a), as well as a decrease in the quantity and quality of sleep (HCSP 2020). This is an important change to consider in an exposome approach in future child-specific risk assessments.

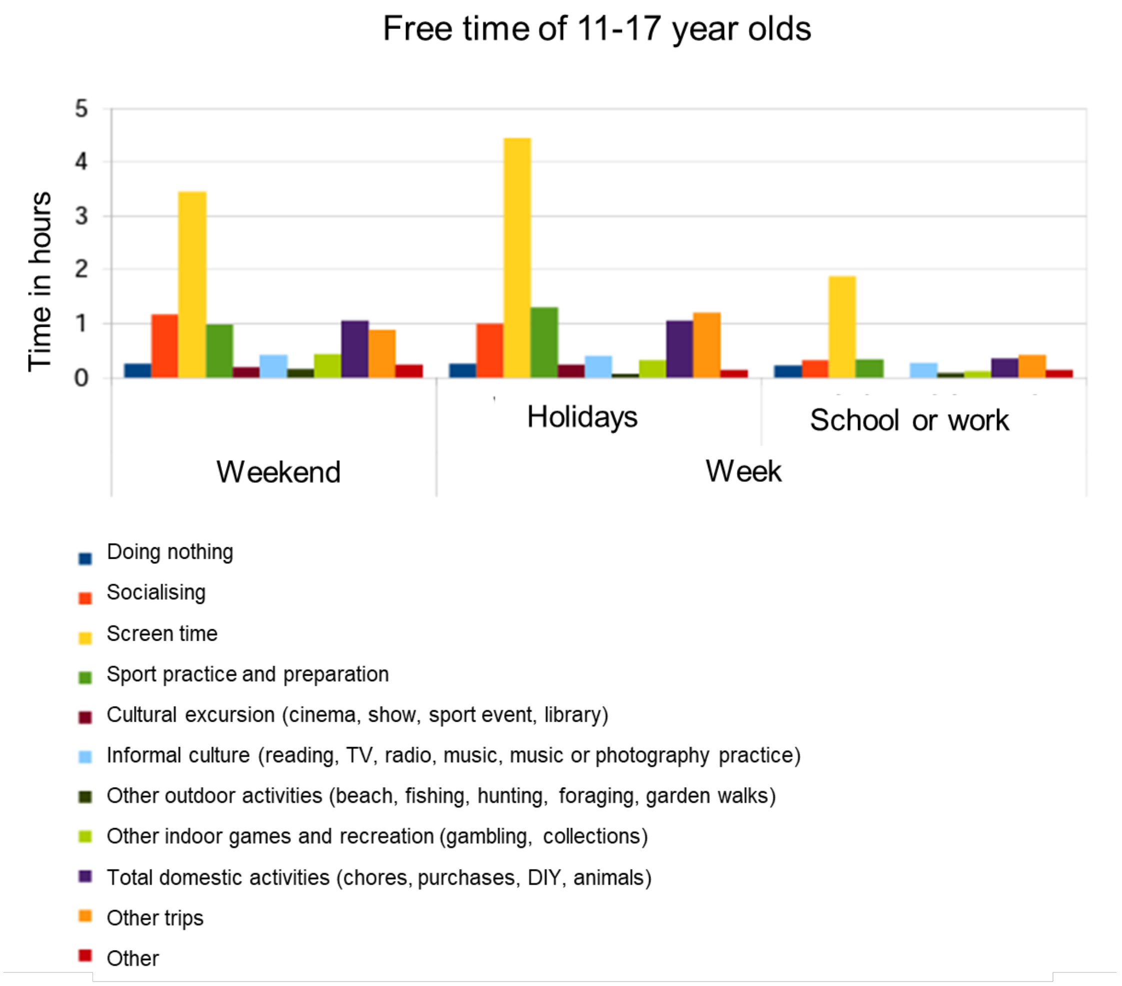


Figure 33: Free time of 11-17 year olds in France in 2009, according to INSEE's *Emploi du Temps* survey (HCFEA 2018) in hours per day

6.5.5 Conclusion

For this formal request, the WG proposed to investigate the combined effects of exposure to screens and to chemical and microbiological agents, while taking account of possible changes in user behaviour and the impact on their exposure profiles and other activities, as well as any benefits that may be derived from the use of these digital tools. The initial literature searches identified some chemicals that may cause hazards in common with those associated with exposure to screens, but no studies have investigated their possible combined effects. It should be noted, however, that the hazards associated with the use of screens alone have yet to be characterised and confirmed, which currently makes a multi-hazard risk assessment difficult. However, it was also observed that screen use led to an increase in the amount of time spent indoors, which could lead to an increase in exposure to 1) chemical and microbiological substances in indoor air, 2) artificial and blue light, as well as to 3) a change in behaviour in terms of snacking, reduced physical activity, and quantity and quality of sleep. These points suggest that an exposome approach should be favoured in future risk assessments of children's exposure to digital screens.

6.6 Feedback on implementing recommendations in formal requests

6.6.1 Distribution of roles between the Exposome WG and the WGs/CESs responding to the formal requests

One of the first steps was to define the roles of the Exposome WG and the WGs/CESs tasked with conducting the selected expert appraisals, and their interactions in implementing the recommendations. It was established that the Exposome WG, on the basis of the presentation of the formal requests by the ANSES coordinators, would issue recommendations for integrating certain components of the exposome in the formal requests selected as case studies. From these recommendations, the WG/CES tasked with responding to the formal request could then choose to apply them by including them directly in their work (6.2 Reference values, 6.3 Microsensors, 6.4 Chlordecone) or by including them in the outlook of the formal request (e.g. 6.1 Waste workers, 6.5 Digital tools). There was also an option not to consider these recommendations when addressing the formal request for reasons of timing. The level of involvement of the Exposome WG members in implementing the recommendations varied according to the formal request. In the case of the internal request on reference values, an expert from the Exposome WG worked on an initial reflection based on the literature to assess the relevance of a recommendation to take better account of sensitive populations. The proposals and actions were then implemented entirely by the ANSES coordinators and two experts from the Exposome WG. In the case of chlordecone, an expert rapporteur seconded from the CES responding to the formal request, assisted by the ANSES coordinators and two experts from the Exposome WG, conducted the work on the question of combined exposure with other organochlorines. There was also the question of the validation circuit for the results of the actions taken. In the case of the three formal requests that directly incorporated certain recommendations, they were validated by consensus between the Exposure WG and the members of the WGs or rapporteurs tasked with responding to the formal requests via the ANSES coordinators. In order to inform and bring together the ANSES coordinators and experts, the general objectives of the Exposome WG and the proposals for application to the formal requests had been presented beforehand to all the CESs in the DER by the Exposome WG coordinator, assisted in some cases by an Exposome WG member.

6.6.2 Difficulties encountered

Some difficulties were encountered in implementing the recommendations, such as the divergence between the timetables of the two WGs, the lack of data, and the lack of specific expertise for applying the Exposome WG's recommendations to the expert appraisal in question. For example, when the Exposome WG issued its recommendations, the work of the Digital Tools WG was already under way, so the Exposome WG's recommendations relating to early childhood could not be implemented because the Digital Tools WG had focused its expert appraisal on adolescents. Furthermore, it was not possible to further develop the recommendations on the combined effects of different exposures due to a lack of microbiological and toxicological expertise in the Digital Tools WG. Lastly, the absence of longitudinal data precisely documenting the time spent in indoor and outdoor environments and the time available for this work meant that it was not possible to reach a decision on the changes in the exposure profile of children and adolescents related to the use of digital tools.

Similarly, the WG on Microsensors was in the process of finalising its work, so the Exposome WG was only able to participate in the final phase of reviewing the conclusions. In the case of the formal request on waste workers, which only began very recently (March 2022), literature research was carried out by the ANSES coordinator before the establishment of the WG and will be proposed to the WG for possible further study.

Despite the difficulties mentioned above and a perceptible apprehension due largely to the complex topic of the exposome and the tight timeframe for the formal requests, it is clear from this experience that implementing the Exposome WG's recommendations has been a successful experiment. Indeed, thanks to major efforts and communication on the part of the ANSES coordinators, the Exposome WG members and the members of the CESs/WGs of the case studies, it was possible to implement the recommendations in a short time and at satisfactory levels for most of the selected formal requests. Moreover, the fact that it was possible to adapt the level of implementation (choice between integrating the recommendations directly or including them in the outlook) according to the timetable and the means available in terms of staff and methodological and data resources, enabled all the players to commit to the project and gradually incorporate the various exposome components into the work carried out.

6.6.3 Lessons learned for taking the recommendations in Chapter 4 into account in future formal requests

This initial experience helped identify some operational points to facilitate implementation of the recommendations in Chapter 4 in future formal requests to the Agency. Choices need to be made from among all the recommendations proposed in Chapter 4, based on relevance to the subject and the data and methods available at the time of responding to the formal request.

Some recommendations can be implemented quickly, while others will require further groundwork, for example those related to data organisation or methodological development work. It appears essential to include the latter in the Agency's work programme and, if necessary, create specific internal or external working groups. In all these cases, additional resources are needed in terms of time and people, as well as support and training for ANSES staff. It is also proposed that the progress made by ANSES in the area of the exposome be viewed over time through regular reviews (which could be carried out every two years), in order to boost and sustain the approach, and benefit from feedback. Lastly, it is important to ensure that the expert appraisal work remains intelligible and operational for managers.

Conclusion

Introducing the exposome in risk assessment allows for a holistic and systemic approach. Holistic in the sense that several components of the risk are considered, and systemic because an overall approach is favoured.

This ANSES report on the exposome proposes a series of recommendations and actions, detailed in Chapters 4, 5 and 6.6, to guide the Agency in taking the exposome into account in health risk assessment. These actions should be integrated and adapted as progress is made. This report also highlights, through the case studies it proposes, the possibility of integrating certain exposome components in ongoing formal requests right away, and stresses the advantages of doing so.

For example, integrating the exposome when addressing the risk associated with chlordecone showed the benefits of proposing an overall approach that considers the specificities of the local population and is able to include a series of risk factors (co-exposure to other organochlorines, potential changes in the exposome due to a decrease in traditional nutritional intake and an increase in the consumption of products rich in saturated fatty acids, taking the eco-exposome into account).

Application to the formal requests on waste workers and digital tools showed the need to study the possible interactions between chemical, biological, physical and psychosocial agents with common effects, while the formal request on microsensors suggested new tools for collecting the individual data needed for the exposome.

Lastly, application to the internal request on TRVs raised the question of the value of considering all sensitive populations, and of applying reference values based on these specific populations to the whole population. Indeed, the overall approach made possible by the exposome can reveal differentiated positive or negative effects – for certain substances, for example, that are also sources of nutritional intake – between sensitive and non-sensitive populations.

Integrating the exposome concept in the Agency's activities requires training for staff and experts. It generates additional costs in terms of time and resources, due to the complexity of this issue. Some of these costs should be considered as an investment in the future, enabling ANSES to better prepare for the issues of tomorrow. In addition, the assistance provided to the groups' work by cross-functional teams in data management and organisation, as well as in the development of operational methods and tools, will help offset some of these costs.

If ANSES is to fulfil its missions and meet the high expectations of society, it must start adopting the exposome approach as of today. ANSES is already well on its way in this change, and even has a certain lead over other agencies in Europe in terms of the subjects explored, the methodologies developed and the lessons learned from the specific cases already examined.

7. References

AFNOR. 2021. 'Norme : Atmosphères ambiantes - Capteurs pour la qualité de l'air - Concepts relatifs à l'utilisation de dispositifs de type « capteur » / « système-capteur » FD X43-121'. https://norminfo.afnor.org/norme/pr-fd-x43-121/atmospheres-ambiantes-capteurs-pour-la-qualite-de-lair-concepts-relatifs-a-lutilisation-de-dispositifs-de-type-capteur/194518.

Akhbarizadeh, Razegheh, Giacomo Russo, Sergio Rossi, Katarina Golianova, Farid Moore, Marco Guida, Maria De Falco, and Lucia Grumetto. 2021. 'Emerging Endocrine Disruptors in Two Edible Fish from the Persian Gulf: Occurrence, Congener Profile, and Human Health Risk Assessment'. *Marine Pollution Bulletin* 166 (May): 112241. https://doi.org/10.1016/j.marpolbul.2021.112241.

Allen, Jessica, Reuben Balfour, Ruth Bell, and Michael Marmot. 2014. 'Social Determinants of Mental Health'. *International Review of Psychiatry (Abingdon, England)* 26 (4): 392–407. https://doi.org/10.3109/09540261.2014.928270.

Amara, Adam, Clément Frainay, Fabien Jourdan, Thomas Naake, Steffen Neumann, Elva María Novoa-Del-Toro, Reza M. Salek, Liesa Salzer, Sarah Scharfenberg, and Michael Witting. 2022. 'Networks and Graphs Discovery in Metabolomics Data Analysis and Interpretation'. *Frontiers in Molecular Biosciences* 9: 841373. https://doi.org/10.3389/fmolb.2022.841373.

Andra, Syam S., Christine Austin, and Manish Arora. 2016. 'The Tooth Exposome in Children's Health Research'. *Current Opinion in Pediatrics* 28 (2): 221–27. https://doi.org/10.1097/MOP.0000000000000327.

ANSES. 2007a. 'Avis relatif à l'établissement de teneurs maximales pertinentes en polychlorobiphényles qui ne sont pas de type dioxine (PCB « non dioxin-like », PCB-NDL) dans divers aliments'. Avis de l'ANSES. Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/RCCP2006sa0305b.pdf.

———. 2007b. 'Evaluation des risques sanitaires liés aux situations de dépassement des limites et références de qualité des eaux destinées à la consommation humaine'. Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/EAUX-Ra-LimitesRef.pdf.

———. 2010. 'Le Béryllium et Ses Composés'. Valeurs limites d'exposition en milieu professionnel. Avis de l'ANSES. Rapport d'expertise Collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/VLEP-Ra-beryllium.pdf.

———. 2011a. 'Etude de l'Alimentation Française 2 (EAT2) - Tome 1 : Contaminants Inorganiques, Minéraux, Polluants Organiques Persistants, Mycotoxines, Phyto-Estrogènes'. Saisine n°2006-SA-0361. Avis de l'ANSES. Rapport d'expertise Collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/PASER2006sa0361Ra1.pdf.

———. 2011b. 'Le 1,3-Butadiène'. Valeurs limites d'exposition en milieu professionnel Saisine n°2007-SA-0419. Avis de l'ANSES. Rapport d'expertise Collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/VLEP2007sa0419Ra.pdf.

———. 2012. 'Valeurs sanitaires de référence (VR)'. Guide des pratiques d'analyse et de choix Saisine n°2011-SA-0355. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/CHIM2011sa0355Ra.pdf.

———. 2013a. ‘Coexposition Professionnelle Au Bruit et Aux Substances Chimiques’. Valeurs limites d’exposition en milieu professionnel Saisine n°2012-SA-0047. Rapport d’expertise Collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l’alimentation, de l’environnement et du travail. https://www.anses.fr/fr/system/files/VLEP2012sa0047Ra.pdf.

———. 2013b. ‘Évaluation des risques du bisphénol A (BPA) pour la santé humaine. Tome 1’. Saisines n°2009-SA-0331 et 2010-SA-0197. Avis de l’ANSES. Rapport d’expertise collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l’alimentation, de l’environnement et du travail. https://www.anses.fr/fr/system/files/CHIM2009sa0331Ra-0.pdf?msclkid=7e60ef88bb3611eca8f900badb61d6b0.

———. 2013c. ‘Évaluation des risques sanitaires liés à la présence de résidus de médicaments dans les eaux destinées à la consommation humaine: méthode générale et application à la carbamazépine et à la danofloxacine’. Saisine n°2009-SA-0210. Avis de l’ANSES. Rapport d’expertise collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l’alimentation, de l’environnement et du travail. https://www.anses.fr/fr/system/files/EAUX2009sa0210Ra.pdf.

———. 2013d. ‘Proposition de Valeurs Guides de Qualité d’air Intérieur. Le Dioxyde d’azote’. Saisine n°2011-SA-0021. Avis de l’ANSES. Rapport d’expertise Collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l’alimentation, de l’environnement et du travail. https://www.anses.fr/fr/system/files/AIR2011sa0021Ra.pdf.

———. 2014. ‘Exposition agrégée au plomb : prise en compte des différents voies d’exposition. Appui à la saisine 2013-SA-0092’. Rapport d’appui scientifique et technique. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l’alimentation, de l’environnement et du travail. https://www.anses.fr/fr/system/files/AUT2013sa0092Ra.pdf.

———. 2015a. ‘Evaluation des risques pour la santé des végétaux liés à Ophraella communa, un insecte ravageur de l’ambroisie à feuilles d’armoise’. Saisine n°2014-SA-0199. Avis de l’ANSES. Rapport d’expertise collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l’alimentation, de l’environnement et du travail. https://www.anses.fr/fr/system/files/SANTVEG2014SA0199Ra.pdf.

———. 2015b. ‘Information des consommateurs en matière de prévention des risques biologiques liés aux aliments Tome 2 - Évaluation de l’efficacité des stratégies de communication’. Saisine n°2012-SA-0118. Avis de l’ANSES. Rapport d’expertise collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l’alimentation, de l’environnement et du travail. https://www.anses.fr/fr/system/files/BIORISK2012sa0118Ra-02.pdf.

———. 2016a. ‘Actualisation des repères du PNNS : Révision des repères de consommations alimentaires’. Saisine n°2018-SA-0248. Avis de l’ANSES. Rapport d’expertise collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l’alimentation, de l’environnement et du travail. https://www.anses.fr/fr/system/files/NUT2012SA0103Ra-1.pdf.

———. 2016b. ‘Évaluation du poids des preuves à l’ANSES : revue critique de la littérature et recommandations à l’étape d’identification des dangers’. Saisine n°2019-SA-0097. Avis de l’ANSES. Rapport d’expertise collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l’alimentation, de l’environnement et du travail. https://www.anses.fr/fr/system/files/AUTRE2015SA0089Ra.pdf.

———. 2016c. ‘Prise En Compte de l’incertitude En Évaluation Des Risques : Revue de La Littérature et Recommandations Pour l’ANSES’. Rapport d’étape Saisine n°2015-SA-0090. Avis de l’ANSES. Rapport d’expertise Collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l’alimentation, de l’environnement et du travail. https://www.anses.fr/fr/system/files/AUTRE2015SA0090Ra.pdf.

———. 2016d. 'Proposition de Valeurs Guides de Qualité d'air Intérieur. Méthode d'élaboration de Valeurs Guides d'air Intérieur. Seconde Édition.' Saisine n°2010-SA-0307. Avis de l'ANSES. Rapport d'expertise Collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/AIR2010SA0307Ra.pdf.

———. 2017a. 'Attribution des sources des maladies infectieuses d'origine alimentaire. Partie 1 : Revue des méthodes et inventaire des données.' Saisine n° 2015-SA-0162. Avis de l'ANSES. Rapport d'expertise collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/BIORISK2015SA0162Ra.pdf.

———. 2017b. 'Avis relatif aux produits de charcuterie crue contaminés par Trichinella spp.' Saisine n°2016-SA-0040. Avis de l'ANSES. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/BIORISK2016SA0040.pdf.

———. 2017c. 'Document de Référence Pour l'élaboration de Valeurs Limites d'exposition à Des Agents Chimiques En Milieu Professionnel'. Valeurs limites d'exposition en milieu professionnelabeil Saisine n°2016-SA-0248. Rapport d'expertise Collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/VLEP2016SA0248Ra.pdf.

———. 2017d. 'Élaboration de VTR Par Voie Respiratoire Pour Le Toluène'. Saisine n°2007-SA-0102. Avis de l'ANSES. Rapport d'expertise Collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/SUBSTANCES2017SA0102Ra.pdf.

———. 2017e. 'Exposition au cadmium Propositions de valeurs toxicologiques de référence par ingestion, de valeurs sanitaires repères dans les milieux biologiques (sang, urines, …)'. Saisine n°2015-SA-0140. Rapport d'expertise collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/VSR2015SA0140Ra-1.pdf.

———. 2017f. 'Exposition des consommateurs des Antilles au chlordécone, résultats de l'étude Kannari'. Saisines n°2014-SA-0109 et 2017-SA-0029. Avis de l'ANSES. Rapport d'expertise collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/ERCA2014SA0029Ra.pdf.

———. 2017g. 'Valeurs Toxicologiques de Référence. Guide d'élaboration de l'ANSES'. Saisine n° 2017-SA-0016. Rapport d'expertise Collective. Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/SUBSTANCES2017SA0016Ra.pdf.

———. 2018a. 'Attribution des sources des maladies infectieuses d'origine alimentaire. Partie 2 : Analyse des données épidémiologiques'. Saisine n°2015-SA-0162. Avis de l'ANSES. Rapport d'expertise collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/BIORISK2015SA0162Ra-2.pdf.

———. 2018b. 'Avis relatif aux mesures de maîtrise des salmonelles en filière porcine : état des connaissances et appréciation quantitative des risques'. Saisine n° 2016-SA-0037. Avis de l'ANSES. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/BIORISK2016SA0037Ra.pdf.

———. 2019a. 'Avis relatif à l'évolution de la méthodologie d'évaluation du risque vis-à-vis des abeilles domestiques et des insectes pollinisateurs sauvages dans le cadre des dossiers de demande d'autorisation de mise sur le marché des produits phytopharmaceutiques'. Saisine n°2019-SA-0097. Avis de l'ANSES. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/PHYTO2019SA0097.pdf.

———. 2019b. 'Avis relatif à l'Exposition au cadmium (CAS n°7440-43-9) – Propositions de valeurs toxicologiques de référence (VTR) par ingestion, de valeurs sanitaires repères dans les milieux biologiques (sang, urine, …) et de niveaux en cadmium dans les matières fertilisantes et supports de culture permettant de maîtriser la pollution des sols agricoles et la contamination des productions végétales.' Saisine n°2015-SA-0140. Avis de l'ANSES. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail.

———. 2019c. 'Avis relatif aux évaluations de risques post-accidentelles liées à l'incendie de l'usine Lubrizol en Seine-Maritime'. Saisine n°2019-SA-0165. Avis de l'ANSES. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/ERCA2019SA0165-4.pdf.

———. 2019d. 'Avis relatif aux risques et bénéfices associés à la consommation de poissons pélagiques contaminés par le mercure en Nouvelle-Calédonie'. Saisine n°2016-SA-0041. Avis de l'ANSES. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/ERCA2016SA0041.pdf.

———. 2019e. 'Effets sanitaires des particules de l'air ambiant extérieur selon les composés, les sources et la granulométrie'. Saisine n°2014-SA-0156. Rapport d'expertise collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/AIR2014SA0156Ra-Sante.pdf.

———. 2019f. 'Risques liés aux pinnatoxines dans les coquillages'. Saisine n°2016-SA-0013. Avis de l'ANSES. Rapport d'expertise collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/ERCA2016SA0013Ra.pdf.

———. 2019g. 'Risques sanitaires pour les professionnels de la gestion des déchets en France'. Saisine n°2016-SA-0137. Avis de l'ANSES. Rapport d'expertise collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/CONSO2016SA0137Ra.pdf.

———. 2020a. 'Avis relatif à l'évaluation des risques liés aux niveaux d'activité physique et de sédentarité des enfants et des adolescents'. Saisine n°2017-SA-0064_a. Avis de l'ANSES. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/NUT2017SA0064-a.pdf.

———. 2020b. 'Campagne nationale exploratoire des pesticides dans l'air ambiant. Premières interprétations sanitaires'. Saisine n°2020-SA-0030. Rapport d'appui scientifique et technique révisé. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/AIR2020SA0030Ra.pdf.

———. 2020c. 'Déclaration des produits du tabac et produits connexes en France. Produits du tabac : bilan 2016-2020'. Saisine n°2018-SA-0189. Rapport d'appui scientifique et technique. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/CONSO2018SA0189Ra-1.pdf.

———. 2020d. 'Déclaration des produits du tabac et produits connexes en France. Produits du vapotage : bilan 2016-2020'. Saisine n°2018-SA-0189. Rapport d'appui scientifique et technique. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/CONSO2018SA0189Ra-1.pdf.

———. 2020e. 'Draft. Expert Appraisal on Recommending Occupational Exposure Limits for Chemical Agents- Assessment of Health Effects and Methods for the Measurement of Exposure Levels in Workplace Atmospheres for Toluene Diisocyanate Mixed Isomers (TDI) CAS N° 26471-62-5'. Document de consultation Saisine n°2012-SA-0080. Rapport d'expertise Collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/REC_NEC_VLEP_TDI_pourconsult_paraphV3.pdf.

———. 2020f. 'Guide méthodologique pour l'élaboration de l'expertise en vue de la création ou de la modification de tableaux de maladies professionnelles, ou de recommandations aux comités régionaux de reconnaissance des maladies professionnelles'. Rapport d'expertise collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/AIR2019SA0220Ra.pdf.

———. 2020g. 'Impacts sanitaires et coûts associés à l'ambroisie à feuilles d'armoise en France'. Saisine n°2018-SA-0088. Rapport d'expertise collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/AIR2018SA0088Ra.pdf.

———. 2020h. 'Méthodologie de hiérarchisation des dangers biologiques et chimiques dans les aliments'. Saisine n°2016-SA-0153. Avis de l'ANSES. Rapport d'expertise collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/BIORISK2016SA0153Ra.pdf.

———. 2020i. 'Méthodologie d'évaluation des méthodes de mesure dans l'air des lieux de travail et l'air intérieur'. Autosaisine n°2020-SA-0050. Rapport d'expertise collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/AIR2020SA0050Ra.pdf.

———. 2020j. 'Stratégie de lutte vis-à-vis de Xylella fastidiosa Phase 2'. Saisine n°2018-SA-0248. Avis de l'ANSES. Rapport d'expertise collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/SANTVEG2018SA0248Ra-1.pdf.

———. 2020k. 'La résistance aux antibiotiques, une problématique majeure pour les animaux et les humains'. ANSES - Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. 17 November 2020. https://www.anses.fr/fr/content/la-r%C3%A9sistance-aux-antibiotiques-une-probl%C3%A9matique-majeure-pour-les-animaux-et-les-humains.

———. 2021a. 'Avis relatif à la mise en œuvre d'un plan de contrôle orienté sur les denrées alimentaires d'origine animale et végétale produites sur le pourtour du golfe de Fos-sur-Mer'. Saisine n°2018-SA-0104. Avis de l'ANSES. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/ERCA2019SA0165-4.pdf.

———. 2021b. 'Avis relatif à la pertinence de la ré-évaluation des risques sanitaires liés à la présence d'ions perchlorate dans les eaux destinées à la consommation humaine à la lumière des travaux de l'US EPA publiés le 23 mai 2019'. Saisine n°2019-SA-0116. Avis de l'ANSES. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/VSR2019SA0116.pdf.

———. 2021c. 'Avis relatif à la surveillance sanitaire à mettre en œuvre pour le SARS-CoV-2 au sein des élevages de visons et lien avec la santé des travailleurs auprès des visons'.

Saisine n°2020-SA-0158. Avis de l'ANSES. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/SABA2020SA0158.pdf.

———. 2021d. 'Avis relatif à une demande d'avis sur les mesures de gestion en santé animale et en sécurité sanitaire des aliments lors de suspicions et de confirmations de cas de fièvre charbonneuse'. Saisine n°2010-SA-0007. Avis de l'ANSES. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/SANT2010sa0007.pdf.

———. 2021e. 'Cancer de la prostate en lien avec les pesticides incluant le chlordécone'. Saisine n°2018-SA-0267. Avis de l'ANSES. Rapport d'expertise collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/2018SA0267Ra.pdf.

———. 2021f. 'Evaluation des indicateurs biologiques d'exposition en vue de la recommandation de valeurs biologiques de référence pour le 2-méthoxy-1-propanol (1PG2ME ou PGMEβ ; CAS 1589-47-5) et l'acétate de 2-méthoxypropyle (1PG2MEA ou PGMAβ ; CAS 70657-70-4)'. Valeurs limites d'exposition en milieu professionnel Saisine n°2012-SA-0073. Avis de l'ANSES. Rapport d'expertise collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/VSR2013SA0105Ra.pdf.

———. 2021g. 'Evaluation des indicateurs biologiques d'exposition en vue de la recommandation de valeurs limites biologiques et de valeurs biologiques de référence pour le trichloroéthylène (n° CAS 79-01-6)'. Valeurs limites d'exposition en milieu professionnel Saisine n°2013-SA-0105. Avis de l'ANSES. Rapport d'expertise collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/VSR2013SA0105Ra.pdf.

———. 2021h. 'Les brévétoxines. Exposition par consommation de coquillages, par inhalation d'embruns ou par contact en cas de baignade ou d'activités nautiques'. Saisine n°2020-SA-0020. Avis révisé et avis de l'ANSES. Rapport d'expertise collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/ERCA2016SA0013Ra.pdf.

———. 2021i. 'Note relatif à la recommandation de niveaux en cadmium dans les matières fertilisantes permettant de maîtriser la contamination en cadmium des sols et des productions agricoles et l'exposition de la population humaine'. Demande n°2021-AST-0120. Appui scientifique et technique de l'ANSES. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/ERCA2021AST0120.pdf.

———. 2021j. 'Surveillance des médicaments vétérinaires en post-AMM'. Rapport annuel. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/ANMV-Ra-Pharmacovigilance2020.pdf.

———. 2021k. 'Valeurs sanitaires de référence. Le valproate de sodium'. Valeurs sanitaires de référence Saisine n°2018-SA-0214. Avis de l'ANSES. Rapport d'expertise collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/VSR2018SA0214Ra.pdf.

———. 2021l. 'Valeurs sanitaires de référence pour le chlordécone'. Valeurs sanitaires de référence Saisine n°2018-SA-0166. Avis révisé de l'ANSES. Rapport révisé d'expertise collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/ERCA2018SA0166Ra.pdf.

———. 2021m. ‘ChlorExpo, une étude affinée de l’exposition alimentaire au chlordécone de la population des Antilles’. ANSES - Agence nationale de sécurité sanitaire de l’alimentation, de l’environnement et du travail. 28 June 2021. https://www.anses.fr/fr/content/chlorexpo-une-%C3%A9tude-affin%C3%A9e-de-l%E2%80%99exposition-alimentaire-au-chlord%C3%A9cone-de-la-population-des.

———. 2021n. ‘Appel à candidatures d’experts pour la constitution d’un Groupe de travail (GT). GT Grippe porcine’. Agence nationale de sécurité sanitaire de l’alimentation, de l’environnement et du travail. https://www.anses.fr/fr/system/files/APC_GT_Grippe_porcine_Role_et_missions.pdf.

———. 2022a. ‘Avis relatif à la pertinence de la ré-évaluation de la VTR chronique par voie orale pour les ions perchlorate’. Saisine n°2019-SA-0116. Avis de l’ANSES. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l’alimentation, de l’environnement et du travail. https://www.anses.fr/fr/system/files/VSR2019SA0116-1.pdf.

———. 2022b. ‘Avis relatif à l’utilisation de micro-capteurs pour le suivi de la qualité de l’air intérieur et extérieur DOUBLON ?’ Saisine n° 2018-SA-0271. Avis de l’ANSES. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l’alimentation, de l’environnement et du travail.

———. 2022c. ‘État des connaissances sur les approches existantes pour la prise en compte des mélanges. Réflexion pour l’élaboration de valeurs de référence’. Autosaisine n°2016-SA-0101 et Sasine n°2018-SA-0152. Rapport d’expertise collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l’alimentation, de l’environnement et du travail. https://www.anses.fr/fr/system/files/Rapport_VGAI_melange_phase1_vconsult.pdf.

———. 2022d. ‘Méthode d’élaboration de VTR Pour Un Mélange de Substances et Application Au Mélange Toluène, Xylène, Éthylbenzène et Benzène (BTEX)’. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l’alimentation, de l’environnement et du travail.

———. 2022e. ‘Micro-capteurs pour le suivi de la qualité de l’air intérieur et extérieur. Volume 1. De l’usage des micro-capteurs à des fins d’évaluation de l’exposition individuelle’. Saisine n°2018-SA-0271. Rapport d’expertise collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l’alimentation, de l’environnement et du travail.

———. 2022f. ‘Micro-capteurs pour le suivi de la qualité de l’air intérieur et extérieur. Volume 2. Mesures citoyennes de qualité de l’air. Figures, Savoirs, Actions’. Saisine n° 2018-SA-0271. Rapport d’expertise collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l’alimentation, de l’environnement et du travail.

———. 2022g. ‘Travaux exposant aux fumées de soudage à inscrire à la liste des substances, mélanges et procédés cancérogènes’. Valeurs sanitaires de référence Saisine n°2017-SA-0237. Avis de l’ANSES. Rapport d’expertise collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l’alimentation, de l’environnement et du travail. https://www.anses.fr/fr/system/files/VSR2017SA0237Ra-2.pdf.

———. 2022h. ‘Valeur Guide de Qualité d’air Intérieur (CGAI). Construction de VGAI Mélange : Etude de Cas Pour Un Mélange de Substances Irritantes.’ Autosaisine n°2016-SA-0101. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l’alimentation, de l’environnement et du travail.

———. 2022i. ‘Valeurs Toxicologiques de Référence (VTR). VTR Par Voie Respiratoire Pour Les Particules de l’air Ambiant Extérieur. Recommandation de VTR Long Terme Pour Les PM2,5 et Extrapolation Aux PM10. Faisabilité d’élaboration de VTR Pour Le Carbone Suie et Pour Les Particules Ultrafines’. Autosaisine n°2019-SA-0198. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l’alimentation, de l’environnement et du travail.

———. 2022j. 'Les valeurs de référence'. ANSES - Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. 5 April 2022. https://www.anses.fr/fr/content/les-valeurs-de-r%C3%A9f%C3%A9rence.

———. à paraître. 'Impacts des substances chimiques sur les récifs coralliens'. Avis de l'ANSES. Rapport d'expertise collective. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail.

ANSES, E Chatzidimitriou, A Mienne, S Pierlot, L Noel, and X Sarda. 2019. 'Assessment of Combined Risk to Pesticide Residues through Dietary Exposure'. *EFSA Journal* 17 (EU-FORA: Series 2). https://doi.org/10.2903/j.efsa.2019.e170910.

Arazy, Ofer, and Dan Malkinson. 2021. 'A Framework of Observer-Based Biases in Citizen Science Biodiversity Monitoring: Semi-Structuring Unstructured Biodiversity Monitoring Protocols'. *Frontiers in Ecology and Evolution* 9 (July): 693602. https://doi.org/10.3389/fevo.2021.693602.

Arnich, Nathalie, Eric Abadie, Nicolas Delcourt, Valérie Fessard, Jean-Marc Fremy, Vincent Hort, Emmeline Lagrange, et al. 2020. 'Health Risk Assessment Related to Pinnatoxins in French Shellfish'. *Toxicon* 180 (June): 1–10. https://doi.org/10.1016/j.toxicon.2020.03.007.

Arnich, Nathalie, and Anne Thébault. 2018. 'Dose-Response Modelling of Paralytic Shellfish Poisoning (PSP) in Humans'. *Toxins* 10 (4): 141. https://doi.org/10.3390/toxins10040141.

ATSDR. 2020. 'Minimum Risk Levels for Hazardous Substances'.

Atugoda, Thilakshani, Meththika Vithanage, Hasintha Wijesekara, Nanthi Bolan, Ajit K. Sarmah, Michael S. Bank, Siming You, and Yong Sik Ok. 2021. 'Interactions between Microplastics, Pharmaceuticals and Personal Care Products: Implications for Vector Transport'. *Environment International* 149 (April): 106367. https://doi.org/10.1016/j.envint.2020.106367.

Augustin, Jean-Christophe, Pauline Kooh, Thomas Bayeux, Laurent Guillier, Thierry Meyer, Nathalie Jourdan-Da Silva, Isabelle Villena, Moez Sanaa, Olivier Cerf, and null On Behalf Of The ANSES Working Group On Consumer Information On Foodborne Biological Risks. 2020. 'Contribution of Foods and Poor Food-Handling Practices to the Burden of Foodborne Infectious Diseases in France'. *Foods (Basel, Switzerland)* 9 (11): E1644. https://doi.org/10.3390/foods9111644.

Augustin, Jean-Christophe, Pauline Kooh, Lapo Mughini-Gras, Laurent Guillier, Anne Thébault, Frédérique Audiat-Perrin, Vasco Cadavez, Ursula Gonzales-Barron, and Moez Sanaa. 2021. 'Risk Factors for Sporadic Infections Caused by Shiga Toxin-Producing Escherichia Coli: A Systematic Review and Meta-Analysis'. *Microbial Risk Analysis*, Risk factors for sporadic foodborne diseases by meta-analysis of observational studies, 17 (April): 100117. https://doi.org/10.1016/j.mran.2020.100117.

Azevedo, Marli, Lisa Mullis, and Sudhakar Agnihothram. 2017. 'Viral and Bacterial Co-Infection and Its Implications'. *SciFed Virology Research Journal* 1 (1): 10.23959/sfjv-1000002.

Bach, Jean-François, Olivier Houdé, Pierre Léna, and Serge Tisseron. 2013. *L'enfant et les écrans: un avis de l'Académie des sciences*. Éducation. Paris: Le Pommier. https://www.academie-sciences.fr/pdf/rapport/avis0113.pdf.

Bailey, Christyn, Aurélie Rubin, Nicole Strepparava, Helmut Segner, Jean-François Rubin, and Thomas Wahli. 2018. 'Do Fish Get Wasted? Assessing the Influence of Effluents on Parasitic Infection of Wild Fish'. *PeerJ* 6 (November): e5956. https://doi.org/10.7717/peerj.5956.

Barouki, Robert, Karine Audouze, Christel Becker, Ludek Blaha, Xavier Coumoul, Spyros Karakitsios, Jana Klanova, Gary W Miller, Elliott J Price, and Denis Sarigiannis. 2021. 'The Exposome and Toxicology: A Win–Win Collaboration'. *Toxicological Sciences*, December, kfab149. https://doi.org/10.1093/toxsci/kfab149.

Barouki, Robert, Karine Audouze, Xavier Coumoul, Florence Demenais, and Dominique Gauguier. 2018. 'Integration of the Human Exposome with the Human Genome to Advance Medicine'. *Biochimie* 152 (September): 155–58. https://doi.org/10.1016/j.biochi.2018.06.023.

Bastiaanssen, Thomaz F. S., Sofia Cussotto, Marcus J. Claesson, Gerard Clarke, Timothy G. Dinan, and John F. Cryan. 2020. 'Gutted! Unraveling the Role of the Microbiome in Major Depressive Disorder'. *Harvard Review of Psychiatry* 28 (1): 26–39. https://doi.org/10.1097/HRP.0000000000000243.

BAuA. 2014. 'Research and Development Programme 2014-2017'. Www.Baua.De. 2014. https://www.baua.de/EN/Tasks/Research/Research-and-development-programme-2014-2017/Research-and-development-programme-2014-2017.html.

Béchaux, Camille, Laurent Bodin, Stéphan Clémençon, and Amélie Crépet. 2014. 'PBPK and Population Modelling to Interpret Urine Cadmium Concentrations of the French Population'. *Toxicology and Applied Pharmacology* 279 (3): 364–72. https://doi.org/10.1016/j.taap.2014.06.026.

Béchaux, Camille, Amélie Crépet, and Stéphan Clémençon. 2014. 'Improving Dietary Exposure Models by Imputing Biomonitoring Data through ABC Methods'. *The International Journal of Biostatistics* 10 (2): 277–87. https://doi.org/10.1515/ijb-2013-0062.

Béchaux, Camille, Marco Zeilmaker, Mathilde Merlo, Bas Bokkers, and Amélie Crépet. 2014. 'An Integrative Risk Assessment Approach for Persistent Chemicals: A Case Study on Dioxins, Furans and Dioxin-like PCBs in France'. *Regulatory Toxicology and Pharmacology: RTP* 70 (1): 261–69. https://doi.org/10.1016/j.yrtph.2014.07.004.

Becker, Daniel J., Alex D. Washburne, Christina L. Faust, Erin A. Mordecai, and Raina K. Plowright. 2019. 'The Problem of Scale in the Prediction and Management of Pathogen Spillover'. *Philosophical Transactions of the Royal Society B: Biological Sciences* 374 (1782): 20190224. https://doi.org/10.1098/rstb.2019.0224.

Benichou, Jacques. 2007. 'Biostatistics and Epidemiology: Measuring the Risk Attributable to an Environmental or Genetic Factor'. *Comptes Rendus Biologies*, L'épidémiologie : une science en développement / Epidemiology : a developing science, 330 (4): 281–98. https://doi.org/10.1016/j.crvi.2007.02.015.

Beque, Maryline. 2014. 'Les risques psychosociaux au travail : Un panorama d'après l'enquête Santé et itinéraire professionnel 2010'. *Dares Analyses*, no. 31: 11p.

Beque, Maryline, and Amélie Mauroux. 2018. 'Conditions de travail : une autonomie en recul mais une ambiance de travail moins tendue. Enquête Conditions de travail et risques psychosociaux 2016'. *Bulletin Epidémiologique Hebdomadaire*, no. 12–13: 221–27.

Berg, Martin van den, Karin Kypke, Alexander Kotz, Angelika Tritscher, Seoung Yong Lee, Katarina Magulova, Heidelore Fiedler, and Rainer Malisch. 2017. 'WHO/UNEP Global Surveys of PCDDs, PCDFs, PCBs and DDTs in Human Milk and Benefit-Risk Evaluation of Breastfeeding'. *Archives of Toxicology* 91 (1): 83–96. https://doi.org/10.1007/s00204-016-1802-z.

Bertin, M., N. Fouquet, M. Léonard, E. Chazelle, and Y. Roquelaure. 2018. 'Facteurs de risque organisationnels et psychosociaux associés aux contraintes posturales en milieu professionnel. Résultats à partir de l'enquête SUMER 2010'. *Archives des Maladies Professionnelles et de l'Environnement* 79 (4): 564–65. https://doi.org/10.1016/j.admp.2018.05.012.

Bessonneau, Vincent, Jennifer Ings, Mark McMaster, Richard Smith, Leslie Bragg, Mark Servos, and Janusz Pawliszyn. 2017. 'In Vivo Microsampling to Capture the Elusive Exposome'. *Scientific Reports* 7 (1): 44038. https://doi.org/10.1038/srep44038.

Billet, Logan S., Vanessa P. Wuerthner, Jessica Hua, Rick A. Relyea, and Jason T. Hoverman. 2021. 'Population-level Variation in Infection Outcomes Not Influenced by Pesticide

Exposure in Larval Wood Frogs (*Rana Sylvatica*)'. *Freshwater Biology* 66 (6): 1169–81. https://doi.org/10.1111/fwb.13708.

Bonefeld-Jørgensen, Eva Cecilie, Helle Raun Andersen, Thomas Høj Rasmussen, and Anne Marie Vinggaard. 2001. 'Effect of Highly Bioaccumulated Polychlorinated Biphenyl Congeners on Estrogen and Androgen Receptor Activity'. *Toxicology* 158 (3): 141–53. https://doi.org/10.1016/S0300-483X(00)00368-1.

Boobis, Alan R., Bernadette C. Ossendorp, Ursula Banasiak, Paul Y. Hamey, Istvan Sebestyen, and Angelo Moretto. 2008. 'Cumulative Risk Assessment of Pesticide Residues in Food'. *Toxicology Letters* 180 (2): 137–50. https://doi.org/10.1016/j.toxlet.2008.06.004.

Boon, P.E., H. Van der Voet, M.T.M. Van Raaij, and J.D. Van Klaveren. 2008. 'Cumulative Risk Assessment of the Exposure to Organophosphorus and Carbamate Insecticides in the Dutch Diet'. *Food and Chemical Toxicology* 46 (9): 3090–98. https://doi.org/10.1016/j.fct.2008.06.083.

Bopp, Stephanie K., Robert Barouki, Werner Brack, Silvia Dalla Costa, Jean-Lou C. M. Dorne, Paula E. Drakvik, Michael Faust, et al. 2018. 'Current EU Research Activities on Combined Exposure to Multiple Chemicals'. *Environment International* 120 (November): 544–62. https://doi.org/10.1016/j.envint.2018.07.037.

Bordier, Marion, Theethawat Uea-Anuwong, Aurélie Binot, Pascal Hendrikx, and Flavie L. Goutard. 2020. 'Characteristics of One Health Surveillance Systems: A Systematic Literature Review'. *Preventive Veterinary Medicine* 181 (August). https://doi.org/10.1016/j.prevetmed.2018.10.005.

Bornehag, Carl-Gustaf, Efthymia Kitraki, Antonios Stamatakis, Emily Panagiotidou, Christina Rudén, Huan Shu, Christian Lindh, Joelle Ruegg, and Chris Gennings. 2019. 'A Novel Approach to Chemical Mixture Risk Assessment—Linking Data from Population-Based Epidemiology and Experimental Animal Tests'. *Risk Analysis* 39 (10): 2259–71. https://doi.org/10.1111/risa.13323.

Bortone, Stephen A., and William P. Davis. 1994. 'Fish Intersexuality as Indicator of Environmental Stress'. *BioScience* 44 (3): 165–72. https://doi.org/10.2307/1312253.

Botías, Cristina, Julia C. Jones, Tobias Pamminger, Ignasi Bartomeus, William O. H. Hughes, and Dave Goulson. 2021. 'Multiple Stressors Interact to Impair the Performance of Bumblebee *Bombus Terrestris* Colonies'. Edited by Rebecca Morris. *Journal of Animal Ecology* 90 (2): 415–31. https://doi.org/10.1111/1365-2656.13375.

Bouvier, E, F Brouillard, J Molet, D Claverie, J-H Cabungcal, N Cresto, N Doligez, et al. 2017. 'Nrf2-Dependent Persistent Oxidative Stress Results in Stress-Induced Vulnerability to Depression'. *Molecular Psychiatry* 22 (12): 1701–13. https://doi.org/10.1038/mp.2016.144.

Branca, Jacopo J. V., Claudia Fiorillo, Donatello Carrino, Ferdinando Paternostro, Niccolò Taddei, Massimo Gulisano, Alessandra Pacini, and Matteo Becatti. 2020. 'Cadmium-Induced Oxidative Stress: Focus on the Central Nervous System'. *Antioxidants* 9 (6): 492. https://doi.org/10.3390/antiox9060492.

Braun, Joseph M., Chris Gennings, Russ Hauser, and Thomas F. Webster. 2016. 'What Can Epidemiological Studies Tell Us about the Impact of Chemical Mixtures on Human Health?' *Environmental Health Perspectives* 124 (1). https://doi.org/10.1289/ehp.1510569.

Brooks, Daniel R., Eric P. Hoberg, Walter A. Boeger, and Valeria Trivellone. 2021. 'Emerging Infectious Disease: An Underappreciated Area of Strategic Concern for Food Security'. *Transboundary and Emerging Diseases*, February. https://doi.org/10.1111/tbed.14009.

Buck Louis, Germaine M., Melissa M. Smarr, and Chirag J. Patel. 2017. 'The Exposome Research Paradigm: An Opportunity to Understand the Environmental Basis for Human

Health and Disease'. *Current Environmental Health Reports* 4 (1): 89–98. https://doi.org/10.1007/s40572-017-0126-3.

Buck Louis, Germaine M., Edwina Yeung, Rajeshwari Sundaram, S. Katherine Laughon, and Cuilin Zhang. 2013. 'The Exposome - Exciting Opportunities for Discoveries in Reproductive and Perinatal Epidemiology: Exposome and Reproductive and Perinatal Epidemiology'. *Paediatric and Perinatal Epidemiology* 27 (3): 229–36. https://doi.org/10.1111/ppe.12040.

Burens, Isabelle, Pascale Mercieca, Charles Parmentier, and Jack Bernon. 2011. 'Comprendre les effets cumulatifs des risques pour les populations en situation de travail fragile. Convention ANSES - ANACT, n°06 CRD 31. Rapport final (CONDIDENTIEL)'. Editions de l'Anact. https://veille-travail.anact.fr/osiros/result/notice.php?queryosiros=id%3A%2828722%29&from=panier&osirosstart=0&sort_define=tri_annee&sort_order=1#.

Cadiou, Solène, Xavier Basagaña, Juan R. Gonzalez, Johanna Lepeule, Martine Vrijheid, Valérie Siroux, and Rémy Slama. 2021. 'Performance of Approaches Relying on Multidimensional Intermediary Data to Decipher Causal Relationships between the Exposome and Health: A Simulation Study under Various Causal Structures'. *Environment International* 153 (August): 106509. https://doi.org/10.1016/j.envint.2021.106509.

Canu, Irina Guseva, Benjamin Guinhouya, Roseline Bonnard, Jérémie Botton, Frédéric Clerc, Anne Sophie Ficheux, Youssef Oulhote, et al. 2021. 'Towards Establishing the National Referential on Exposure Factors in France'. *ISEE Conference Abstracts*, August. https://doi.org/10.1289/isee.2021.P-004.

Cao, S., X. Duan, X. Zhao, Y. Chen, B. Wang, C. Sun, B. Zheng, and F. Wei. 2016. 'Health Risks of Children's Cumulative and Aggregative Exposure to Metals and Metalloids in a Typical Urban Environment in China'. *Chemosphere* 147 (March): 404–11. https://doi.org/10.1016/j.chemosphere.2015.12.134.

Cao-Lei, L., S. R. de Rooij, S. King, S. G. Matthews, G. a. S. Metz, T. J. Roseboom, and M. Szyf. 2020. 'Prenatal Stress and Epigenetics'. *Neuroscience and Biobehavioral Reviews* 117 (October): 198–210. https://doi.org/10.1016/j.neubiorev.2017.05.016.

Caporale, Nicolò, Michelle Leemans, Lina Birgersson, Pierre-Luc Germain, Cristina Cheroni, Gábor Borbély, Elin Engdahl, et al. 2022. 'From Cohorts to Molecules: Adverse Impacts of Endocrine Disrupting Mixtures'. *Science* 375 (6582): eabe8244. https://doi.org/10.1126/science.abe8244.

Carne, G., S. Leconte, V. Sirot, N. Breysse, P. M. Badot, A. Bispo, I. Z. Deportes, C. Dumat, G. Rivière, and A. Crépet. 2021. 'Mass Balance Approach to Assess the Impact of Cadmium Decrease in Mineral Phosphate Fertilizers on Health Risk: The Case-Study of French Agricultural Soils'. *Science of The Total Environment* 760 (March): 143374. https://doi.org/10.1016/j.scitotenv.2020.143374.

Caudeville, Julien, Roseline Bonnard, Céline Boudet, Sébastien Denys, Gérard Govaert, and André Cicolella. 2012. 'Development of a Spatial Stochastic Multimedia Exposure Model to Assess Population Exposure at a Regional Scale'. *The Science of the Total Environment* 432 (August): 297–308. https://doi.org/10.1016/j.scitotenv.2012.06.001.

Caudeville, Julien, Corentin Regrain, Frederic Tognet, Roseline Bonnard, Mohammed Guedda, Celine Brochot, Maxime Beauchamp, et al. 2021. 'Characterizing Environmental Geographic Inequalities Using an Integrated Exposure Assessment'. *Environmental Health: A Global Access Science Source* 20 (1): 58. https://doi.org/10.1186/s12940-021-00736-9.

Chiolero, Arnaud, and David Buckeridge. 2020. 'Glossary for Public Health Surveillance in the Age of Data Science'. *Journal of Epidemiology and Community Health*, April, jech-2018-211654. https://doi.org/10.1136/jech-2018-211654.

Ciliberti, Alexandre, Arnaud Chaumot, Rémi Recoura-Massaquant, André Chandesris, Adeline François, Marina Coquery, Martial Ferréol, and Olivier Geffard. 2017. 'Caged Gammarus as Biomonitors Identifying Thresholds of Toxic Metal Bioavailability That Affect Gammarid Densities at the French National Scale'. *Water Research* 118 (July): 131–40. https://doi.org/10.1016/j.watres.2017.04.031.

Clewell, Rebecca A., Jeremy A. Leonard, Chantel I. Nicolas, Jerry L. Campbell, Miyoung Yoon, Alina Y. Efremenko, Patrick D. McMullen, et al. 2020. 'Application of a Combined Aggregate Exposure Pathway and Adverse Outcome Pathway (AEP-AOP) Approach to Inform a Cumulative Risk Assessment: A Case Study with Phthalates'. *Toxicology in Vitro* 66 (August): 104855. https://doi.org/10.1016/j.tiv.2020.104855.

Coker, Eric S., Laura Cavalli, Enrico Fabrizi, Gianni Guastella, Enrico Lippo, Maria Laura Parisi, Nicola Pontarollo, Massimiliano Rizzati, Alessandro Varacca, and Sergio Vergalli. 2020. 'The Effects of Air Pollution on COVID-19 Related Mortality in Northern Italy'. *Environmental and Resource Economics* 76 (4): 611–34. https://doi.org/10.1007/s10640-020-00486-1.

Coulon, Marianne, Frank Schurr, Anne-Claire Martel, Nicolas Cougoule, Adrien Bégaud, Patrick Mangoni, Gennaro Di Prisco, et al. 2019. 'Influence of Chronic Exposure to Thiamethoxam and Chronic Bee Paralysis Virus on Winter Honey Bees'. *PLOS ONE* 14 (8): e0220703. https://doi.org/10.1371/journal.pone.0220703.

Coutrot, Thomas. 2018. 'Travail et bien-être psychologique : l'apport de l'enquête CT-RPS 2016'. *Dares Analyses* Document d'études de la Dares (217): 53p.

Coutrot, Thomas, and Nicolas Sandret. 2015. 'Pilotage Du Travail et Risques Psychosociaux'. *Dares Analyses*, no. 003: 10.

Cox, Shanna, Amanda Sue Niskar, K.M. Venkat Narayan, and Michele Marcus. 2007. 'Prevalence of Self-Reported Diabetes and Exposure to Organochlorine Pesticides among Mexican Americans: Hispanic Health and Nutrition Examination Survey, 1982–1984'. *Environmental Health Perspectives* 115 (12): 1747–52. https://doi.org/10.1289/ehp.10258.

Crédoc. 2021. 'Baromètre du numérique : Enquête sur la diffusion des technologies de l'information et de la communication dans la société française'. Edition 2021. Centre de Recherche pour l'Étude et l'Observation des Conditions de Vie.

Crépet, A., J. Tressou, V. Graillot, C. Béchaux, S. Pierlot, F. Héraud, and J. Ch Leblanc. 2013. 'Identification of the Main Pesticide Residue Mixtures to Which the French Population Is Exposed'. *Environmental Research* 126 (October): 125–33. https://doi.org/10.1016/j.envres.2013.03.008.

Crépet, Amélie, Sébastien Denys, and Marion Hulin. 2012. 'Exposition Agrégée, Combinée, Cumulées à Des Substances Chimiques et Risques Associés'. *Environnement, Risques & Santé* 11 (5): 424–25. https://doi.org/10.1684/ers.2012.0570.

Crépet, Amélie, The Minh Luong, Janis Baines, Polly E. Boon, Julie Ennis, Marc Kennedy, Isabelle Massarelli, et al. 2021. 'An International Probabilistic Risk Assessment of Acute Dietary Exposure to Pesticide Residues in Relation to Codex Maximum Residue Limits for Pesticides in Food'. *Food Control* 121 (March): 107563. https://doi.org/10.1016/j.foodcont.2020.107563.

Crépet, Amélie, Paule Vasseur, Julien Jean, Pierre-Marie Badot, Fabrice Nesslany, Jean-Paul Vernoux, Cyril Feidt, and -Kodja Sakina Mhaouty. 2022. 'Integrating Selection and Risk Assessment of Chemical Mixtures: A Novel Approach Applied to a Breast Milk Survey'. *Environmental Health Perspectives* 130 (3): 35001. https://doi.org/10.1289/EHP8262.

Crépet, Marie Vanacker, Corinne Sprong, Waldo de Boer, Urska Blaznik, Marc Kennedy, Chris Anagnostopoulos, et al. 2019. 'Selecting Mixtures on the Basis of Dietary Exposure and Hazard Data: Application to Pesticide Exposure in the European Population in Relation to Steatosis'. *International Journal of Hygiene and Environmental Health* 222 (2): 291–306. https://doi.org/10.1016/j.ijheh.2018.12.002.

Crofton, Kevin M., Da-Lian Ding, Robert Padich, Michele Taylor, and Donald Henderson. 2000. ‘Hearing Loss Following Exposure during Development to Polychlorinated Biphenyls: A Cochlear Site of Action’. *Hearing Research* 144 (1–2): 196–204. https://doi.org/10.1016/S0378-5955(00)00062-9.

Crotwell, Andrew, M. Steinbacher, World Meteorological Organization (WMO), and Other Greenhouse Gases and Related Measurement Techniques (GGMT-2017) 19th WMO/IAEA Meeting on Carbon Dioxide. 2018. ‘19th WMO/IAEA Meeting on Carbon Dioxide, Other Greenhouse Gases and Related Measurement Techniques (GGMT-2017)’. GAW 242. Technical Publications. Geneva: WMO.

Cryan, John F., and Timothy G. Dinan. 2015. ‘More than a Gut Feeling: The Microbiota Regulates Neurodevelopment and Behavior’. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology* 40 (1): 241–42. https://doi.org/10.1038/npp.2014.224.

Cuco, Ana P., Nelson Abrantes, Fernando Gonçalves, Justyna Wolinska, and Bruno B. Castro. 2017. ‘Interplay between Fungicides and Parasites: Tebuconazole, but Not Copper, Suppresses Infection in a Daphnia-Metschnikowia Experimental Model’. *PLOS ONE* 12 (2): e0172589. https://doi.org/10.1371/journal.pone.0172589.

Cusick, Jessica A., Cara L. Wellman, and Gregory E. Demas. 2021. ‘The Call of the Wild: Using Non-Model Systems to Investigate Microbiome–Behaviour Relationships’. *Journal of Experimental Biology* 224 (10): jeb224485. https://doi.org/10.1242/jeb.224485.

Dallaire, Renée, Éric Dewailly, Pierre Ayotte, Nadine Forget-Dubois, Sandra W. Jacobson, Joseph L. Jacobson, and Gina Muckle. 2014. ‘Growth in Inuit Children Exposed to Polychlorinated Biphenyls and Lead during Fetal Development and Childhood’. *Environmental Research* 134 (October): 17–23. https://doi.org/10.1016/j.envres.2014.06.023.

David, Arthur, Jade Chaker, Elliott J. Price, Vincent Bessonneau, Andrew J. Chetwynd, Chiara M. Vitale, Jana Klánová, et al. 2021. ‘Towards a Comprehensive Characterisation of the Human Internal Chemical Exposome: Challenges and Perspectives’. *Environment International* 156 (November): 106630. https://doi.org/10.1016/j.envint.2021.106630.

David, Arthur, Anke Lange, Alaa Abdul-Sada, Charles R. Tyler, and Elizabeth M. Hill. 2017. ‘Disruption of the Prostaglandin Metabolome and Characterization of the Pharmaceutical Exposome in Fish Exposed to Wastewater Treatment Works Effluent As Revealed by Nanoflow-Nanospray Mass Spectrometry-Based Metabolomics’. *Environmental Science & Technology* 51 (1): 616–24. https://doi.org/10.1021/acs.est.6b04365.

De Lange, H.J., S. Sala, M. Vighi, and J.H. Faber. 2010. ‘Ecological Vulnerability in Risk Assessment — A Review and Perspectives’. *Science of The Total Environment* 408 (18): 3871–79. https://doi.org/10.1016/j.scitotenv.2009.11.009.

DeBord, D. Gayle, Tania Carreón, Thomas J. Lentz, Paul J. Middendorf, Mark D. Hoover, and Paul A. Schulte. 2016. ‘Use of the “Exposome” in the Practice of Epidemiology: A Primer on -Omic Technologies’. *American Journal of Epidemiology* 184 (4): 302–14. https://doi.org/10.1093/aje/kwv325.

Deguen, Séverine, Pauline Vasseur, and Wahida Kihal-Talantikite. 2022. ‘Inégalités sociétales et exposome urbain - Des origines sociales pour des expositions différentes’. *médecine/sciences* 38 (1): 75–80. https://doi.org/10.1051/medsci/2021149.

Deloménie, C, Dm Grant, R Krishnamoorthy, and Jm Dupret. 1998. ‘Les Arylamine N-Acétyltransférases : Du Polymorphisme Génétique à La Susceptibilité Aux Xénobiotiques.’ *Médecine/Sciences* 14 (1): 27. https://doi.org/10.4267/10608/880.

Dereumeaux, Clémentine, and Abdesattar Saoudi. 2018. ‘Imprégnation de La Population Antillaise Par La Chlordécone et Certains Composés Organochlorés En 2013-2014 : Étude Kannari’. Saint-Maurice, France: Santé publique France.

https://www.santepubliquefrance.fr/regions/antilles/documents/rapport-synthese/2018/impregnation-de-la-population-antillaise-par-la-chlordecone-et-certains-composes-organochlores-en-2013-2014-etude-kannari.

Desgroseillers, Valérie, Nicolas Vonarx, Anne Guichard, Bernard Roy, and Didier Fassin. 2016. *La santé communautaire en 4 actes. Repères, acteurs, démarches et défis - Valérie ,Nicolas Vonarx,Anne Guichard,Bernard Roy,Didier Fassin*. Infirmières, communautés, sociétés. Québec, Canada: PUL, Presses de l'Université Laval diffusion Chronique sociale. https://www.decitre.fr/livres/la-sante-communautaire-en-4-actes-9782763721750.html.

Dharmaratne, R. W. 2019. 'Exploring the Role of Excess Fluoride in Chronic Kidney Disease: A Review'. *Human & Experimental Toxicology* 38 (3): 269–79. https://doi.org/10.1177/0960327118814161.

Di Prisco, Gennaro, Marco Iannaccone, Flora Ianniello, Rosalba Ferrara, Emilio Caprio, Francesco Pennacchio, and Rosanna Capparelli. 2017. 'The Neonicotinoid Insecticide Clothianidin Adversely Affects Immune Signaling in a Human Cell Line'. *Scientific Reports* 7 (1): 13446. https://doi.org/10.1038/s41598-017-13171-z.

Dietert, Rodney R. 2014. 'Developmental Immunotoxicity, Perinatal Programming, and Noncommunicable Diseases: Focus on Human Studies'. *Advances in Medicine* 2014: 867805. https://doi.org/10.1155/2014/867805.

Drakvik, Elina, Rolf Altenburger, Yasunobu Aoki, Thomas Backhaus, Tina Bahadori, Robert Barouki, Werner Brack, et al. 2020. 'Statement on Advancing the Assessment of Chemical Mixtures and Their Risks for Human Health and the Environment'. *Environment International* 134 (January): 105267. https://doi.org/10.1016/j.envint.2019.105267.

DREES and Santé publique France. 2017. *L'état de santé de la population en France: rapport 2017*. https://drees.solidarites-sante.gouv.fr/sites/default/files/2021-01/Rapport-ESPF-2017.pdf.

Dubrall, Diana, René Pflock, Joanna Kosinska, Matthias Schmid, Markus Bleich, Nina Himmerkus, Stefan Offermanns, Markus Schwaninger, and Bernhardt Sachs. 2021. 'Do Dimethyl Fumarate and Nicotinic Acid Elicit Common, Potentially HCA_2 -mediated Adverse Reactions? A Combined Epidemiological-experimental Approach'. *British Journal of Clinical Pharmacology* 87 (10): 3813–24. https://doi.org/10.1111/bcp.14787.

Dubuisson, Carine, Ariane Dufour, Sandrine Carrillo, Peggy Drouillet-Pinard, Sabrina Havard, and Jean-Luc Volatier. 2019. 'The Third French Individual and National Food Consumption (INCA3) Survey 2014-2015: Method, Design and Participation Rate in the Framework of a European Harmonization Process'. *Public Health Nutrition* 22 (4): 584–600. https://doi.org/10.1017/S1368980018002896.

Dudzina, Tatsiana, Christiaan J. E. Delmaar, Jacqueline W. H. Biesterbos, Martine I. Bakker, Bas G. H. Bokkers, Paul T. J. Scheepers, Jacqueline G. M. van Engelen, Konrad Hungerbuehler, and Natalie von Goetz. 2015. 'The Probabilistic Aggregate Consumer Exposure Model (PACEM): Validation and Comparison to a Lower-Tier Assessment for the Cyclic Siloxane D5'. *Environment International* 79 (June): 8–16. https://doi.org/10.1016/j.envint.2015.03.006.

Duijster, Janneke W., Eelco Franz, Jacques Neefjes, and Lapo Mughini-Gras. 2021. 'Bacterial and Parasitic Pathogens as Risk Factors for Cancers in the Gastrointestinal Tract: A Review of Current Epidemiological Knowledge'. *Frontiers in Microbiology* 12: 790256. https://doi.org/10.3389/fmicb.2021.790256.

Dupuy, Célie, Joëlle Cabon, Lénaïg Louboutin, Stéphane Le Floch, Thierry Morin, and Morgane Danion. 2019. 'Cellular, Humoral and Molecular Responses in Rainbow Trout (Oncorhynchus Mykiss) Exposed to a Herbicide and Subsequently Infected with Infectious Hematopoietic Necrosis Virus'. *Aquatic Toxicology (Amsterdam, Netherlands)* 215 (October): 105282. https://doi.org/10.1016/j.aquatox.2019.105282.

ECHA. 2017a. ‘Annex XV Report - Proposal for Identification of a Substance of Very High Concern on the Basis of the Criteria Set out in Reach Article 57’. European Chemicals Agency.

———. 2017b. ‘Opinion Proposing Harmonised Classification and Labelling at EU Level of Methylmercuric Chloride’. Helsinki, Finlande: European Chemicals Agency. Committee for Risk Assessment. https://echa.europa.eu/documents/10162/80dbdd45-67a2-10ef-0e89-58ba5927c882.

EFSA. 2007. ‘Scientific Colloquium: Cumulative Risk Assessment of Pesticides to Human Health: The Way Foward’. Summary Report. 27-28 Novembrer 2006. Parma, Italy. https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/sp.efsa.2007.EN-117.

———. 2008. ‘Opinion of the Scientific Panel on Plant Protection Products and Their Residues to Evaluate the Suitability of Existing Methodologies and, If Appropriate, the Identification of New Approaches to Assess Cumulative and Synergistic Risks from Pesticides to Human Health with a View to Set MRLs for Those Pesticides in the Frame of Regulation (EC) 396/2005’. *EFSA Journal* 6 (5): 705. https://doi.org/10.2903/j.efsa.2008.705.

———. 2022. ‘Draft Opinion. Re-Evaluation of the Risks to Public Health Related to the Presence of Bisphenol A (BPA) in Foodstuffs’. European Food Safety Agency. https://connect.efsa.europa.eu/RM/s/publicconsultation2/a0l1v00000E8BRD/pc0109.

———. n.d. ‘Glossaire’. Accessed 23 May 2022. https://www.efsa.europa.eu/fr/glossary-taxonomy-terms.

EFSA, Maria Anastassiadou, Judy Choi, Tamara Coja, Bruno Dujardin, Andy Hart, Antonio F Hernandez-Jerrez, et al. 2021. ‘Cumulative Dietary Risk Assessment of Chronic Acetylcholinesterase Inhibition by Residues of Pesticides’. *EFSA Journal* 19 (2). https://doi.org/10.2903/j.efsa.2021.6392.

EFSA CEF Panel. 2015. ‘Scientific Opinion on the Risks to Public Health Related to the Presence of Bisphenol A (BPA) in Foodstuffs’. *EFSA Journal* 13 (1): 3978. https://doi.org/10.2903/j.efsa.2015.3978.

EFSA, Peter S Craig, Bruno Dujardin, Andy Hart, Antonio F Hernández-Jerez, Susanne Hougaard Bennekou, Carsten Kneuer, et al. 2020. ‘Cumulative Dietary Risk Characterisation of Pesticides That Have Acute Effects on the Nervous System’. *EFSA Journal* 18 (4): 76pp. https://doi.org/10.2903/j.efsa.2020.6087.

EFSA, Peter S Craig, Bruno Dujardin, Andy Hart, Antonio F Hernandez-Jerez, Susanne Hougaard Bennekou, Carsten Kneuer, et al. 2020. ‘Cumulative Dietary Risk Characterisation of Pesticides That Have Chronic Effects on the Thyroid’. *EFSA Journal* 18 (4): e06088. https://doi.org/10.2903/j.efsa.2020.6088.

EFSA Panel on Biological Hazards, Kostas Koutsoumanis, Ana Allende, Avelino Alvarez-Ordóñez, Declan Bolton, Sara Bover-Cid, Marianne Chemaly, et al. 2019. ‘Whole Genome Sequencing and Metagenomics for Outbreak Investigation, Source Attribution and Risk Assessment of Food-Borne Microorganisms’. *EFSA Journal* 17 (12): e05898. https://doi.org/10.2903/j.efsa.2019.5898.

EFSA Panel on Contaminants in the Food Chain. 2009. ‘Scientific Opinion on Arsenic in Food’. *EFSA Journal*, no. 10 (September): 199. https://doi.org/10.2903/j.efsa.2009.1351.

EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (CEP), Vittorio Silano, José Manuel Barat Baviera, Claudia Bolognesi, Andrew Chesson, Pier Sandro Cocconcelli, Riccardo Crebelli, et al. 2019. ‘Update of the Risk Assessment of Di-butylphthalate (DBP), Butyl-benzyl-phthalate (BBP), Bis(2-ethylhexyl)Phthalate (DEHP), Di-isononylphthalate (DINP) and Di-isodecylphthalate (DIDP) for Use in Food Contact Materials’. *EFSA Journal* 17 (12). https://doi.org/10.2903/j.efsa.2019.5838.

EFSA Scientific Committee, Simon John More, Vasileios Bampidis, Diane Benford, Susanne Hougaard Bennekou, Claude Bragard, Thorhallur Ingi Halldorsson, et al. 2019.

‘Guidance on Harmonised Methodologies for Human Health, Animal Health and Ecological Risk Assessment of Combined Exposure to Multiple Chemicals’. *EFSA Journal* 17 (3): e05634. https://doi.org/10.2903/j.efsa.2019.5634.

EFSA Scientific Committee, Simon John More, Vasileios Bampidis, Diane Benford, Claude Bragard, Antonio Hernandez-Jerez, Susanne Hougaard Bennekou, et al. 2021. ‘Guidance Document on Scientific Criteria for Grouping Chemicals into Assessment Groups for Human Risk Assessment of Combined Exposure to Multiple Chemicals’. *EFSA Journal* 19 (12). https://doi.org/10.2903/j.efsa.2021.7033.

Elmassry, Moamen M., Ahmed Zayed, and Mohamed A. Farag. 2022. ‘Gut Homeostasis and Microbiota under Attack: Impact of the Different Types of Food Contaminants on Gut Health’. *Critical Reviews in Food Science and Nutrition* 62 (3): 738–63. https://doi.org/10.1080/10408398.2020.1828263.

Emeville, Elise, Arnaud Giusti, Xavier Coumoul, Jean-Pierre Thomé, Pascal Blanchet, and Luc Multigner. 2015. ‘Associations of Plasma Concentrations of Dichlorodiphenyldichloroethylene and Polychlorinated Biphenyls with Prostate Cancer: A Case–Control Study in Guadeloupe (French West Indies)’. *Environmental Health Perspectives* 123 (4): 317–23. https://doi.org/10.1289/ehp.1408407.

Escher, Beate I., Jörg Hackermüller, Tobias Polte, Stefan Scholz, Achim Aigner, Rolf Altenburger, Alexander Böhme, et al. 2017. ‘From the Exposome to Mechanistic Understanding of Chemical-Induced Adverse Effects’. *Environment International* 99 (February): 97–106. https://doi.org/10.1016/j.envint.2016.11.029.

Eskenazi, Brenda, Jonathan Chevrier, Lisa Goldman Rosas, Henry A. Anderson, Maria S. Bornman, Henk Bouwman, Aimin Chen, et al. 2009. ‘The Pine River Statement: Human Health Consequences of DDT Use’. *Environmental Health Perspectives* 117 (9): 1359–67. https://doi.org/10.1289/ehp.11748.

Eskenazi, Brenda, Amy R. Marks, Asa Bradman, Laura Fenster, Caroline Johnson, Dana B. Barr, and Nicholas P. Jewell. 2006. ‘In Utero Exposure to Dichlorodiphenyltrichloroethane (DDT) and Dichlorodiphenyldichloroethylene (DDE) and Neurodevelopment Among Young Mexican American Children’. *Pediatrics* 118 (1): 233–41. https://doi.org/10.1542/peds.2005-3117.

Estaquier, J, E Blanc, and X Coumoul. 2021. ‘Que Sait-on de l’action Des Perturbateurs Endocriniens Sur Le Système Immunitaire ?’ *La Revue Du Praticien* 71 (7): 729–34.

European Commission. Directorate General for Health and Consumers. 2012. *Toxicity and Assessment of Chemical Mixtures*. LU: Publications Office. https://data.europa.eu/doi/10.2772/21444.

European Commission. Directorate General for the Environment, Milieu Ltd., Ökopol., Risk & Policy Analysts (RPA)., and RIVM. 2017. *Study for the Strategy for a Non-Toxic Environment of the 7th Environment Action Programme: Final Report.* EU Publications, KH-02-17-928-EN-N. LU: Publications Office. https://data.europa.eu/doi/10.2779/025.

European Food Safety Authority (EFSA). 2019. ‘Statement on the Available Outcomes of the Human Health Assessment in the Context of the Pesticides Peer Review of the Active Substance Chlorpyrifos’. *EFSA Journal* 17 (8). https://doi.org/10.2903/j.efsa.2019.5809.

Evans, Richard M., Olwenn V. Martin, Michael Faust, and Andreas Kortenkamp. 2016. ‘Should the Scope of Human Mixture Risk Assessment Span Legislative/Regulatory Silos for Chemicals?’ *Science of The Total Environment* 543 (February): 757–64. https://doi.org/10.1016/j.scitotenv.2015.10.162.

Everett, Charles J., Ivar L. Frithsen, Vanessa A. Diaz, Richelle J. Koopman, William M. Simpson, and Arch G. Mainous. 2007. ‘Association of a Polychlorinated Dibenzo-p-Dioxin, a Polychlorinated Biphenyl, and DDT with Diabetes in the 1999–2002 National Health and Nutrition Examination Survey’. *Environmental Research* 103 (3): 413–18. https://doi.org/10.1016/j.envres.2006.11.002.

Ewers, U., R. Stiller-Winkler, and H. Idel. 1982. 'Serum Immunoglobulin, Complement C3, and Salivary IgA Levels in Lead Workers'. *Environmental Research* 29 (2): 351–57. https://doi.org/10.1016/0013-9351(82)90036-6.

Faroon, Obaid M, L Samuel Keith, Cassandra Smith-Simon, Christopher T De Rosa, World Health Organization, and International Programme on Chemical Safety. 2003. 'Polychlorinated Biphenyls : Human Health Aspects', Concise international chemical assessment document ; 55, . https://apps.who.int/iris/handle/10665/42640.

Fleeger, John W. 2020. 'How Do Indirect Effects of Contaminants Inform Ecotoxicology? A Review'. *Processes* 8 (12): 1659. https://doi.org/10.3390/pr8121659.

Fourneau, Clémence, Valérie Pernelet Joly, Margaux Sanchez, Henri Bastos, Guillaume Boulanger, Guillaume Perouel, Thomas Coutrot, Nadine Fréry, and Catherine Galey. 2021. 'Profils homogènes de travailleurs polyexposés'. Maisons-Alfort, France: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. https://www.anses.fr/fr/system/files/PST3_ProfilTravailleursExposes_Polyexposition.pdf.

Fox, Mary, L. Brewer, and Lawrence Martin. 2017. 'An Overview of Literature Topics Related to Current Concepts, Methods, Tools, and Applications for Cumulative Risk Assessment (2007–2016)'. *International Journal of Environmental Research and Public Health* 14 (4): 389. https://doi.org/10.3390/ijerph14040389.

Fréry, N., L. Guldner, A. DSaoudi, Garnier R, Zeghnoun A, and M. L. Bidondo. 2013. 'Exposition de La Population Française Aux Substances Chimiques de l'environnement. Tome 2: Polychlorobiphényles (PCB-NDL) et Pesticides'. Saint-Maurice, France: Insitut de Veille Sanitaire (InVS). https://www.santepubliquefrance.fr/determinants-de-sante/exposition-a-des-substances-chimiques/pesticides/documents/rapport-synthese/exposition-de-la-population-francaise-aux-substances-chimiques-de-l-environnement.-tome-2-polychlorobiphenyles-pcb-ndl-.-pesticides.

Fry, D M. 1995. 'Reproductive Effects in Birds Exposed to Pesticides and Industrial Chemicals.' *Environmental Health Perspectives* 103 (Suppl 7): 165–71.

Fu, Qiuguo, Andreas Scheidegger, Endre Laczko, and Juliane Hollender. 2021. 'Metabolomic Profiling and Toxicokinetics Modeling to Assess the Effects of the Pharmaceutical Diclofenac in the Aquatic Invertebrate Hyalella Azteca'. *Environmental Science & Technology* 55 (12): 7920–29. https://doi.org/10.1021/acs.est.0c07887.

Ganzleben, Catherine, Jean-Philippe Antignac, Robert Barouki, Argelia Castaño, Ulrike Fiddicke, Jana Klánová, Erik Lebret, et al. 2017. 'Human Biomonitoring as a Tool to Support Chemicals Regulation in the European Union'. *International Journal of Hygiene and Environmental Health* 220 (2): 94–97. https://doi.org/10.1016/j.ijheh.2017.01.007.

Gao, Peng. 2021. 'The Exposome in the Era of One Health'. *Environmental Science & Technology* 55 (5): 2790–99. https://doi.org/10.1021/acs.est.0c07033.

Garric, Jeanne, Soizic Morin, and Françoise Vincent-Hubert. 2010. 'Les biomarqueurs en écotoxicologie : définition, intérêt, limite, usage'. *Sciences Eaux Territoires* 1 (1): 12–17.

Gauthier, Patrick T., Warren P. Norwood, Ellie E. Prepas, and Greg G. Pyle. 2014. 'Metal–PAH Mixtures in the Aquatic Environment: A Review of Co-Toxic Mechanisms Leading to More-than-Additive Outcomes'. *Aquatic Toxicology* 154 (September): 253–69. https://doi.org/10.1016/j.aquatox.2014.05.026.

Gentil, C, J Spinosi, L Cahour, L Chaperon, and M El Yamani. 2018. 'Document Technique Pour La Construction de La Matrice Culture Exposition de La Banane Dessert Aux Antilles : Projet Matphyto DOM'. Saint-Maurice, France: Santé publique France. https://www.santepubliquefrance.fr/regions/antilles/documents/rapport-synthese/2018/document-technique-pour-la-construction-de-la-matrice-culture-exposition-de-la-banane-dessert-aux-antilles-projet-matphyto-dom.

Glasset, Benjamin, Sabine Herbin, Laurent Guillier, Sabrina Cadel-Six, Marie-Léone Vignaud, Joel Grout, Sylvie Pairaud, et al. 2016. 'Bacillus Cereus-Induced Food-Borne Outbreaks in France, 2007 to 2014: Epidemiology and Genetic Characterisation'. *Euro Surveillance: Bulletin Europeen Sur Les Maladies Transmissibles = European Communicable Disease Bulletin* 21 (48): 30413. https://doi.org/10.2807/1560-7917.ES.2016.21.48.30413.

Goncharov A, Rej R, Negoita S, Schymura M, Santiago-Rivera A, Morse G; Akwesasne Task Force on the Environment; Carpenter DO. 2009. Lower serum testosterone associated with elevated polychlorinated biphenyl concentrations in Native American men. *Environ Health Perspect.* 117(9):1454-60. doi: 10.1289/ehp.0800134. Epub 2009 May 20.

Goncharov, Alexey, Michael Bloom, Marian Pavuk, Irina Birman, and David O Carpenter. 2010. 'Blood Pressure and Hypertension in Relation to Levels of Serum Polychlorinated Biphenyls in Residents of Anniston, Alabama'. *Journal of Hypertension* 28 (10): 2053–60. https://doi.org/10.1097/HJH.0b013e32833c5f3e.

Gonzales-Barron, Ursula, Anne Thébault, Pauline Kooh, Laurence Watier, Moez Sanaa, and Vasco Cadavez. 2021. 'Strategy for Systematic Review of Observational Studies and Meta-Analysis Modelling of Risk Factors for Sporadic Foodborne Diseases'. *Microbial Risk Analysis*, Risk factors for sporadic foodborne diseases by meta-analysis of observational studies, 17 (April): 100082. https://doi.org/10.1016/j.mran.2019.07.003.

Gonzalez, Jean-Louis, Jean-Pierre Allenou, Anne Togola, Julien Guyomarch, Nathalie Tapie, and Hélène Budzinski. 2019. 'Synthèse des actions de développement et de validation de méthodes d'analyse opérationnelles du chlordécone dans les eaux littorales de Martinique par les techniques d'échantillonnage passif: POCIS, SBSE et membrane silicone'. Rapport final. Livrable du contrat RSP-EIP 2018-2019-Lot E et de l'action AQUAREF_2018_G2b7.

Gore, A. C., V. A. Chappell, S. E. Fenton, J. A. Flaws, A. Nadal, G. S. Prins, J. Toppari, and R. T. Zoeller. 2015. 'Executive Summary to EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals'. *Endocrine Reviews* 36 (6): 593–602. https://doi.org/10.1210/er.2015-1093.

Grandjean, Philippe. 2019. 'Developmental Fluoride Neurotoxicity: An Updated Review'. *Environmental Health* 18 (1): 110. https://doi.org/10.1186/s12940-019-0551-x.

Grandjean, Philippe, Esben Budtz-Jørgensen, Dana B. Barr, Larry L. Needham, Pal Weihe, and Birger Heinzow. 2008. 'Elimination Half-Lives of Polychlorinated Biphenyl Congeners in Children'. *Environmental Science & Technology* 42 (18): 6991–96. https://doi.org/10.1021/es800778q.

Grandjean, Philippe, Carsten Heilmann, Pal Weihe, Flemming Nielsen, Ulla B. Mogensen, and Esben Budtz-Jørgensen. 2017. 'Serum Vaccine Antibody Concentrations in Adolescents Exposed to Perfluorinated Compounds'. *Environmental Health Perspectives* 125 (7): 077018. https://doi.org/10.1289/EHP275.

Grandjean, Philippe, Carsten Heilmann, Pal Weihe, Flemming Nielsen, Ulla B. Mogensen, Amalie Timmermann, and Esben Budtz-Jørgensen. 2017. 'Estimated Exposures to Perfluorinated Compounds in Infancy Predict Attenuated Vaccine Antibody Concentrations at Age 5-Years'. *Journal of Immunotoxicology* 14 (1): 188–95. https://doi.org/10.1080/1547691X.2017.1360968.

Grandjean, Philippe, Clara Amalie Gade Timmermann, Marie Kruse, Flemming Nielsen, Pernille Just Vinholt, Lasse Boding, Carsten Heilmann, and Kåre Mølbak. 2020. 'Severity of COVID-19 at Elevated Exposure to Perfluorinated Alkylates'. *PLOS ONE* 15 (12): e0244815. https://doi.org/10.1371/journal.pone.0244815.

Guevel, Marie-Renée, Véronique Sirot, Jean-Luc Volatier, and Jean-Charles Leblanc. 2008. 'A Risk-Benefit Analysis of French High Fish Consumption: A QALY Approach'. *Risk Analysis: An Official Publication of the Society for Risk Analysis* 28 (1): 37–48. https://doi.org/10.1111/j.1539-6924.2008.01001.x.

Guillette, L J, T S Gross, G R Masson, J M Matter, H F Percival, and A R Woodward. 1994. ‘Developmental Abnormalities of the Gonad and Abnormal Sex Hormone Concentrations in Juvenile Alligators from Contaminated and Control Lakes in Florida.’ *Environmental Health Perspectives* 102 (8): 680–88.

Guillien, Alicia, Solène Cadiou, Rémy Slama, and Valérie Siroux. 2021. ‘The Exposome Approach to Decipher the Role of Multiple Environmental and Lifestyle Determinants in Asthma’. *International Journal of Environmental Research and Public Health* 18 (3): 1138. https://doi.org/10.3390/ijerph18031138.

Guillier, Laurent, Isabelle Berta-Vianrullen, Laurence Rudloff, Diane Cuzzucoli, Mathilde Saussac, and Guillaume Duflos. 2016. ‘Surveillance de l’histamine dans les poissons réfrigérés à forte teneur en histidine en France (2010 à 2012 et 2015)’. *Bulletin épidémiologique, santé animale et alimentation*, no. 77: 88–92.

Guillier, Laurent, Steven Duret, Hong-Minh Hoang, Denis Flick, Christophe Nguyen-Thé, and Onrawee Laguerre. 2016. ‘Linking Food Waste Prevention, Energy Consumption and Microbial Food Safety: The next Challenge of Food Policy?’ *Current Opinion in Food Science*, Food safety, 12 (December): 30–35. https://doi.org/10.1016/j.cofs.2016.06.006.

Guillier, Laurent, Anne Thébault, Philippe Fravalo, Lapo Mughini-Gras, Nathalie Jourdan-da Silva, Julie David, Pauline Kooh, Vasco Cadavez, and Ursula Gonzales-Barron. 2021. ‘Risk Factors for Sporadic Salmonellosis: A Systematic Review and Meta-Analysis’. *Microbial Risk Analysis*, Risk factors for sporadic foodborne diseases by meta-analysis of observational studies, 17 (April): 100138. https://doi.org/10.1016/j.mran.2020.100138.

Guloksuz, Sinan, Jim van Os, and Bart P. F. Rutten. 2018. ‘The Exposome Paradigm and the Complexities of Environmental Research in Psychiatry’. *JAMA Psychiatry* 75 (10): 985. https://doi.org/10.1001/jamapsychiatry.2018.1211.

Haas, Sarah E., Mari K. Reeves, Alfred E. Pinkney, and Pieter T. J. Johnson. 2018. ‘Continental-Extent Patterns in Amphibian Malformations Linked to Parasites, Chemical Contaminants, and Their Interactions’. *Global Change Biology* 24 (1): e275–88. https://doi.org/10.1111/gcb.13908.

Haddad, Nadine, Xanthi D. Andrianou, and Konstantinos C. Makris. 2019. ‘A Scoping Review on the Characteristics of Human Exposome Studies’. *Current Pollution Reports* 5 (4): 378–93. https://doi.org/10.1007/s40726-019-00130-7.

Harwood, Gyan P., and Adam G. Dolezal. 2020. ‘Pesticide–Virus Interactions in Honey Bees: Challenges and Opportunities for Understanding Drivers of Bee Declines’. *Viruses* 12 (5): 566. https://doi.org/10.3390/v12050566.

Havard, Tiphaine, Marion Laurent, and Marie-Pierre Chauzat. 2020. ‘Impact of Stressors on Honey Bees (Apis Mellifera; Hymenoptera: Apidae): Some Guidance for Research Emerge from a Meta-Analysis’. *Diversity* 12 (1): 7. https://doi.org/10.3390/d12010007.

Hayes, Tyrone B., Paola Case, Sarah Chui, Duc Chung, Cathryn Haeffele, Kelly Haston, Melissa Lee, et al. 2006. ‘Pesticide Mixtures, Endocrine Disruption, and Amphibian Declines: Are We Underestimating the Impact?’ *Environmental Health Perspectives* 114 (Suppl 1): 40–50. https://doi.org/10.1289/ehp.8051.

HBM4EU. 2018. ‘Additional Deliverable 12.4 - Conceptual Design of the Integrated Computational Platform’. HBM4EU Deliverable Report AD12.4. https://www.hbm4eu.eu/work-packages/additional-deliverable-12-4-conceptual-design-of-the-integrated-computational-platform/.

———. 2021. ‘Deliverable Report 5.9 - 3rd Substance Specific Derivation of EU-Wide Health-Based Guidance Values’. HBM4EU Deliverable Report D5.9. https://www.hbm4eu.eu/work-packages/deliverable-5-9-3rd-substance-specific-derivation-of-eu-wide-health-based-guidance-values/.

HCFEA. 2018. 'Les Temps et Les Lieux Tiers Des Enfants et Des Adolescents Hors Maison et Hors Scolarité'. https://www.hcfea.fr/IMG/pdf/rapport_temps_et_lieux_tiers_des_enfants.pdf.

HCSP. 2019. 'Avis relatif aux effets de l'exposition des enfants et des jeunes aux écrans'. *Rapport de l'HCSP*. Avis de la HCSP. Paris, France: Haut Conseil de la Santé Publique. https://www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=759.

———. 2020. 'Analyse des données scientifiques : effets de l'exposition des enfants et des jeunes aux écrans'. *Rapport de l'HCSP*. Rapport du Haut Conseil de la santé publique. Paris, France: Haut Conseil de la Santé Publique. https://www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=759.

Hennechart-Collette, Catherine, Sandra Martin-Latil, Audrey Fraisse, Florian Niveau, and Sylvie Perelle. 2020. 'Virological Analyses in Collective Catering Outbreaks in France between 2012 and 2017'. *Food Microbiology* 91 (October): 103546. https://doi.org/10.1016/j.fm.2020.103546.

Hermabessiere, Ludovic, Ika Paul-Pont, Anne-Laure Cassone, Charlotte Himber, Justine Receveur, Ronan Jezequel, Maria El Rakwe, et al. 2019. 'Microplastic Contamination and Pollutant Levels in Mussels and Cockles Collected along the Channel Coasts'. *Environmental Pollution* 250 (July): 807–19. https://doi.org/10.1016/j.envpol.2019.04.051.

Hines, David E., Rory B. Conolly, and Annie M. Jarabek. 2019. 'A Quantitative Source-to-Outcome Case Study To Demonstrate the Integration of Human Health and Ecological End Points Using the Aggregate Exposure Pathway and Adverse Outcome Pathway Frameworks'. *Environmental Science & Technology* 53 (18): 11002–12. https://doi.org/10.1021/acs.est.9b04639.

Holman, David. 2013. 'Job Types and Job Quality in Europe'. *Human Relations* 66 (4): 475–502. https://doi.org/10.1177/0018726712456407.

Hu, Hui, Yi Zheng, Xiaoxiao Wen, Sabrina S. Smith, Javlon Nizomov, Jennifer Fishe, William R. Hogan, Elizabeth A. Shenkman, and Jiang Bian. 2021. 'An External Exposome-Wide Association Study of COVID-19 Mortality in the United States'. *The Science of the Total Environment* 768 (May): 144832. https://doi.org/10.1016/j.scitotenv.2020.144832.

Huhn, Sebastian, Beate I. Escher, Martin Krauss, Stefan Scholz, Jörg Hackermüller, and Rolf Altenburger. 2021. 'Unravelling the Chemical Exposome in Cohort Studies: Routes Explored and Steps to Become Comprehensive'. *Environmental Sciences Europe* 33 (1): 17. https://doi.org/10.1186/s12302-020-00444-0.

Hulin, M., N. Bemrah, A. Nougadere, J. L. Volatier, V. Sirot, and J. C. Leblanc. 2014. 'Assessment of Infant Exposure to Food Chemicals: The French Total Diet Study Design'. *Food Additives and Contamiants: Part A* 31 (7): 1226–39. https://doi.org/10.1080/19440049.2014.921937.

Hulin, Marion, Véronique Sirot, Paule Vasseur, Aurelie Mahe, Jean-Charles Leblanc, Julien Jean, Philippe Marchand, Anaïs Venisseau, Bruno Le Bizec, and Gilles Rivière. 2020. 'Health Risk Assessment to Dioxins, Furans and PCBs in Young Children: The First French Evaluation'. *Food and Chemical Toxicology* 139 (May): 111292. https://doi.org/10.1016/j.fct.2020.111292.

Hutton, Sara J., Scott J. St. Romain, Emily I. Pedersen, Samreen Siddiqui, Patrick E. Chappell, J. Wilson White, Kevin L. Armbrust, and Susanne M. Brander. 2021. 'Salinity Alters Toxicity of Commonly Used Pesticides in a Model Euryhaline Fish Species (Menidia Beryllina)'. *Toxics* 9 (5): 114. https://doi.org/10.3390/toxics9050114.

IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. 2016. *Polychlorinated Biphenyls and Polybrominated Biphenyls*. Vol. 107. International Agency for Research on Cancer. https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Polychlorinated-Biphenyls-And-Polybrominated-Biphenyls-2015.

———. 2018. *DDT, Lindane, and 2,4-D*. Vol. 113. Place of publication not identified: International Agency for Research on Cancer. https://www.ncbi.nlm.nih.gov/books/NBK507424.

Ibarra-Santana, Claudia, Ma del Socorro Ruiz-Rodríguez, Ma del Pilar Fonseca-Leal, Francisco Javier Gutiérrez-Cantú, and Amaury de J. Pozos-Guillén. 2007. 'Enamel Hypoplasia in Children with Renal Disease in a Fluoridated Area'. *The Journal of Clinical Pediatric Dentistry* 31 (4): 274–78. https://doi.org/10.17796/jcpd.31.4.m97777625k278261.

Ingle, Danielle J., Rebecca L. Ambrose, Sarah L. Baines, Sebastian Duchene, Anders Gonçalves da Silva, Darren Y. J. Lee, Miriam Jones, et al. 2021. 'Evolutionary Dynamics of Multidrug Resistant Salmonella Enterica Serovar 4,[5],12:I:- In Australia'. *Nature Communications* 12 (1): 4786. https://doi.org/10.1038/s41467-021-25073-w.

INRS. 2010. 'Approches des risques chimiques et microbiologiques dans le secteur du compostage'. *Hygiène et sécurité du travail*, no. 221: 14p.

———. 2015. 'Installations de Traitements Thermique Des Déchets Non Dangereux et DASRI'. https://www.inrs.fr/media.html?refINRS=ED%206222.

———. 2019. 'Incinération d'ordures ménagères'. Fiche d'aide au repérage de produit cancérogène. https://www.inrs.fr/media.html?refINRS=FAR%2011.

Inserm. 2016. 'Glossaire Microbiote'. *Médecine/Sciences* 32 (11): 922–922. https://doi.org/10.1051/medsci/20163211003.

———. 2017. 'Epigénétique : Un génome, plein de possibilité !' Inserm. 2017. https://www.inserm.fr/dossier/epigenetique/.

International Programme on Chemical Safety and Inter-Organization Programme for the Sound Management of Chemicals. 2009. 'Assessment of Combined Exposures to Multiple Chemicals : Report of a WHO/IPCS International Workshop on Aggregate/Cumulative Risk Assessment', IPCS harmonization project document ; no. 7, , 75.

———. 2010. 'Characterization and Application of Physiologically Based Phamacokinetic Models in Risk Assessment', IPCS harmonization project document ; no. 9, . https://apps.who.int/iris/handle/10665/44495.

Isaacs, Kristin K., W. Graham Glen, Peter Egeghy, Michael-Rock Goldsmith, Luther Smith, Daniel Vallero, Raina Brooks, Christopher M. Grulke, and Halûk Özkaynak. 2014. 'SHEDS-HT: An Integrated Probabilistic Exposure Model for Prioritizing Exposures to Chemicals with Near-Field and Dietary Sources'. *Environmental Science & Technology* 48 (21): 12750–59. https://doi.org/10.1021/es502513w.

Jacobson, Joseph L., and Sandra W. Jacobson. 1996. 'Intellectual Impairment in Children Exposed to Polychlorinated Biphenyls in Utero'. *New England Journal of Medicine* 335 (11): 783–89. https://doi.org/10.1056/NEJM199609123351104.

Jacquez, G.M., J.R. Meliker, R.R. Rommel, and P.E. Goovaerts. 2019. 'Exposure Reconstruction Using Space–Time Information Technology'. In *Encyclopedia of Environmental Health*, 793–804. Elsevier. https://doi.org/10.1016/B978-0-12-409548-9.01704-8.

Jain, Pooja, Paolo Vineis, Benoît Liquet, Jelle Vlaanderen, Barbara Bodinier, Karin van Veldhoven, Manolis Kogevinas, et al. 2018. 'A Multivariate Approach to Investigate the Combined Biological Effects of Multiple Exposures'. *Journal of Epidemiology and Community Health* 72 (7): 564–71. https://doi.org/10.1136/jech-2017-210061.

Janssen, Meike, Betty P. I. Chang, Hristo Hristov, Igor Pravst, Adriano Profeta, and Jeremy Millard. 2021. 'Changes in Food Consumption During the COVID-19 Pandemic: Analysis of Consumer Survey Data From the First Lockdown Period in Denmark, Germany, and Slovenia'. *Frontiers in Nutrition* 8: 635859. https://doi.org/10.3389/fnut.2021.635859.

Jia, Wei, Pan Zhuang, Qiao Wang, Xuzhi Wan, Lei Mao, Xinyu Chen, Hong Miao, Dawei Chen, Yiping Ren, and Yu Zhang. 2022. 'Urinary Non-Targeted Toxicokinetics and Metabolic Fingerprinting of Exposure to 3-Monochloropropane-1,2-Diol and Glycidol from Refined Edible Oils'. *Food Research International* 152 (February): 110898. https://doi.org/10.1016/j.foodres.2021.110898.

Johanson, Gunnar. 2020. 'Are Asthmatics More Sensitive to Irritants?' *International Journal of Hygiene and Environmental Health* 226 (May): 113488. https://doi.org/10.1016/j.ijheh.2020.113488.

Johansson, Mia K. V., Gunnar Johanson, Mattias Öberg, and Linda Schenk. 2016. 'Does Industry Take the Susceptible Subpopulation of Asthmatic Individuals into Consideration When Setting Derived No-Effect Levels?' *Journal of Applied Toxicology: JAT* 36 (11): 1379–91. https://doi.org/10.1002/jat.3352.

Joubert, Bonnie R., Marianthi-Anna Kioumourtzoglou, Toccara Chamberlain, Hua Yun Chen, Chris Gennings, Mary E. Turyk, Marie Lynn Miranda, et al. 2022. 'Powering Research through Innovative Methods for Mixtures in Epidemiology (PRIME) Program: Novel and Expanded Statistical Methods'. *International Journal of Environmental Research and Public Health* 19 (3): 1378. https://doi.org/10.3390/ijerph19031378.

Karstad, Kristina, Anette F B Jørgensen, Birgit A Greiner, Alex Burdorf, Karen Søgaard, Reiner Rugulies, and Andreas Holtermann. 2018. 'Danish Observational Study of Eldercare Work and Musculoskeletal DisorderS (DOSES): A Prospective Study at 20 Nursing Homes in Denmark'. *BMJ Open* 8 (2): e019670. https://doi.org/10.1136/bmjopen-2017-019670.

Karstad, Kristina, Reiner Rugulies, Jørgen Skotte, Pernille Kold Munch, Birgit A. Greiner, Alex Burdorf, Karen Søgaard, and Andreas Holtermann. 2018. 'Inter-Rater Reliability of Direct Observations of the Physical and Psychosocial Working Conditions in Eldercare: An Evaluation in the DOSES Project'. *Applied Ergonomics* 69 (May): 93–103. https://doi.org/10.1016/j.apergo.2018.01.004.

Kassam, Shanoor, and Romina Ferrari. 2020. 'Les Effets de l'exposition Aux Écrans Des Enfants et Des Adolescent-e-S : Concepts-Clés, Revue de Littérature et État Des Lieux Des Pratiques.' 20.2. Fribourg: Institut de recherche et de documentation pédagogique.

Kazour, Maria, Sharif Jemaa, Maria El Rakwe, Guillaume Duflos, Ludovic Hermabassiere, Alexandre Dehaut, Florane Le Bihanic, et al. 2020. 'Juvenile Fish Caging as a Tool for Assessing Microplastics Contamination in Estuarine Fish Nursery Grounds'. *Environmental Science and Pollution Research* 27 (4): 3548–59. https://doi.org/10.1007/s11356-018-3345-8.

Kelce, William R., Christy R. Lambright, L.Earl Gray, and Kenneth P. Roberts. 1997. 'Vinclozolin and p,P′-DDE Alter Androgen-Dependent Gene Expression:In Vivo Confirmation of an Androgen Receptor-Mediated Mechanism'. *Toxicology and Applied Pharmacology* 142 (1): 192–200. https://doi.org/10.1006/taap.1996.7966.

Kelce, William R., Christy R. Stone, Susan C. Laws, L. Earl Gray, Jon A. Kemppainen, and Elizabeth M. Wilson. 1995. 'Persistent DDT Metabolite p,p'–DDE Is a Potent Androgen Receptor Antagonist'. *Nature* 375 (6532): 581–85. https://doi.org/10.1038/375581a0.

Kennedy, Marc C., M. Clare Butler Ellis, and Paul C. H. Miller. 2012. 'BREAM: A Probabilistic Bystander and Resident Exposure Assessment Model of Spray Drift from an Agricultural Boom Sprayer'. *Computers and Electronics in Agriculture* 88 (October): 63–71. https://doi.org/10.1016/j.compag.2012.07.004.

Kennedy, Marc C., C. Richard Glass, Bas Bokkers, Andy D. M. Hart, Paul Y. Hamey, Johannes W. Kruisselbrink, Waldo J. de Boer, Hilko van der Voet, David G. Garthwaite, and Jacob D. van Klaveren. 2015. 'A European Model and Case Studies for Aggregate Exposure Assessment of Pesticides'. *Food and Chemical Toxicology*, Toxicity testing and model development for estimating cumulative and aggregate exposure to pesticide residues in Europe, 79 (May): 32–44. https://doi.org/10.1016/j.fct.2014.09.009.

Kennedy, Marc C., Hilko van der Voet, Victoria J. Roelofs, Willem Roelofs, C. Richard Glass, Waldo J. de Boer, Johannes W. Kruisselbrink, and Andy D. M. Hart. 2015. 'New Approaches to Uncertainty Analysis for Use in Aggregate and Cumulative Risk Assessment of Pesticides'. *Food and Chemical Toxicology*, Toxicity testing and model development for estimating cumulative and aggregate exposure to pesticide residues in Europe, 79: 54–64. https://doi.org/10.1016/j.fct.2015.02.008.

Kim, Min Ji, Véronique Pelloux, Erwan Guyot, Joan Tordjman, Linh-Chi Bui, Aline Chevallier, Claude Forest, Chantal Benelli, Karine Clément, and Robert Barouki. 2012. 'Inflammatory Pathway Genes Belong to Major Targets of Persistent Organic Pollutants in Adipose Cells'. *Environmental Health Perspectives* 120 (4): 508–14. https://doi.org/10.1289/ehp.1104282.

Koch, Lionel, Anne-Aurelie Lopes, Avelina Maiguy, Sophie Guillier, Laurent Guillier, Jean-Nicolas Tournier, and Fabrice Biot. 2020. 'Natural Outbreaks and Bioterrorism: How to Deal with the Two Sides of the Same Coin?' *Journal of Global Health* 10 (2): 020317. https://doi.org/10.7189/jogh.10.020317.

Koman, Patricia D., Veena Singla, Juleen Lam, and Tracey J. Woodruff. 2019. 'Population Susceptibility: A Vital Consideration in Chemical Risk Evaluation under the Lautenberg Toxic Substances Control Act'. Edited by Linda S. Birnbaum. *PLOS Biology* 17 (8): e3000372. https://doi.org/10.1371/journal.pbio.3000372.

Konstantinoudis, Garyfallos, Tullia Padellini, James Bennett, Bethan Davies, Majid Ezzati, and Marta Blangiardo. 2021. 'Long-Term Exposure to Air-Pollution and COVID-19 Mortality in England: A Hierarchical Spatial Analysis'. *Environment International* 146 (January): 106316. https://doi.org/10.1016/j.envint.2020.106316.

Kooh, Pauline, Anne Thébault, Vasco Cadavez, Ursula Gonzales-Barron, and Isabelle Villena. 2021. 'Risk Factors for Sporadic Cryptosporidiosis: A Systematic Review and Meta-Analysis'. *Microbial Risk Analysis*, Risk factors for sporadic foodborne diseases by meta-analysis of observational studies, 17 (April): 100116. https://doi.org/10.1016/j.mran.2020.100116.

Krönke, Anna A., Anne Jurkutat, Maike Schlingmann, Tanja Poulain, Matthias Nüchter, Anja Hilbert, Hannu Kiviranta, et al. 2022. 'Persistent Organic Pollutants in Pregnant Women Potentially Affect Child Development and Thyroid Hormone Status'. *Pediatric Research* 91 (3): 690–98. https://doi.org/10.1038/s41390-021-01488-5.

Kuiper, George G. J. M., Josephine G. Lemmen, Bo Carlsson, J. Christopher Corton, Stephen H. Safe, Paul T. van der Saag, Bart van der Burg, and Jan-Åke Gustafsson. 1998. 'Interaction of Estrogenic Chemicals and Phytoestrogens with Estrogen Receptor β'. *Endocrinology* 139 (10): 4252–63. https://doi.org/10.1210/endo.139.10.6216.

Lakerveld, Jeroen, Alfred Wagtendonk, Ilonca Vaartjes, Derek Karssenberg, Jeroen Lakerveld, Brenda Penninx, Joline Beulens, et al. 2020. 'Deep Phenotyping Meets Big Data: The Geoscience and HEalth Cohort COnsortium (GECCO) Data to Enable Exposome Studies in The Netherlands'. *International Journal of Health Geographics* 19 (1): 49. https://doi.org/10.1186/s12942-020-00235-z.

Lamkarkach, Farida, Eva Ougier, Robert Garnier, Claude Viau, Marike Kolossa-Gehring, Rosa Lange, and Petra Apel. 2021. 'Human Biomonitoring Initiative (HBM4EU): Human Biomonitoring Guidance Values (HBM-GVs) Derived for Cadmium and Its Compounds'. *Environment International* 147 (February): 106337. https://doi.org/10.1016/j.envint.2020.106337.

Lathers, Claire M. 2002. 'Endocrine Disruptors: A New Scientific Role for Clinical Pharmacologists? Impact on Human Health, Wildlife, and the Environment'. *The Journal of Clinical Pharmacology* 42 (1): 7–23. https://doi.org/10.1177/0091270002042001001.

Le Du-Carrée, Jessy, Rania Boukhari, Jérôme Cachot, Joëlle Cabon, Lénaïg Louboutin, Thierry Morin, and Morgane Danion. 2021. 'Generational Effects of a Chronic Exposure to a Low Environmentally Relevant Concentration of Glyphosate on Rainbow Trout, Oncorhynchus Mykiss'. *Science of The Total Environment* 801 (December): 149462. https://doi.org/10.1016/j.scitotenv.2021.149462.

Le Du-Carrée, Jessy, Joëlle Cabon, Lénaïg Louboutin, Thierry Morin, and Morgane Danion. 2022. 'Changes in Defense Capacity to Infectious Hematopoietic Necrosis Virus (IHNv) in Rainbow Trout Intergenerationally Exposed to Glyphosate'. *Fish & Shellfish Immunology* 122 (January): 67–70. https://doi.org/10.1016/j.fsi.2021.12.021.

Le Du-Carrée, Jessy, Florian Saliou, Jérôme Cachot, Thierry Morin, and Morgane Danion. 2021. 'Developmental Effect of Parental or Direct Chronic Exposure to Environmental Concentration of Glyphosate on the Larvae of Rainbow Trout, Oncorhynchus Mykiss'. *Aquatic Toxicology* 237 (August): 105894. https://doi.org/10.1016/j.aquatox.2021.105894.

Leblanc, Jean-Charles, Jean-Luc Volatier, Véronique Sirot, and Nawel Bemrah-Aouachria. 2006. 'CALIPSO Etude Des Consommations ALimentaires de Produits de La Mer et Imprégnation Aux Éléments Traces, PolluantS et Oméga 3'. https://www.anses.fr/fr/system/files/PASER-Ra-Calipso.pdf.

Lee, Pei-Chen, Ismaïl Ahmed, Marie-Anne Loriot, Claire Mulot, Kimberly C. Paul, Jeff M. Bronstein, Beate Ritz, and Alexis Elbaz. 2018. 'Smoking and Parkinson Disease: Evidence for Gene-by-Smoking Interactions'. *Neurology* 90 (7): e583–92. https://doi.org/10.1212/WNL.0000000000004953.

Lhuilier, Dominique. 2010. 'Abstract'. *Nouvelle revue de psychosociologie* 10 (2): 11–28.

Lieury, Alain, Sonia Lorant, and Françoise Champault. 2014. 'Loisirs numériques et performances cognitives et scolaires : une étude chez 27 000 élèves de la 3e des collèges'. *Bulletin de psychologie* Numéro 530 (2): 99–125. https://doi.org/10.3917/bupsy.530.0099.

Lignell, Sanna, Marie Aune, Per Ola Darnerud, Annika Hanberg, Susanna C Larsson, and Anders Glynn. 2013. 'Prenatal Exposure to Polychlorinated Biphenyls (PCBs) and Polybrominated Diphenyl Ethers (PBDEs) May Influence Birth Weight among Infants in a Swedish Cohort with Background Exposure: A Cross-Sectional Study'. *Environmental Health* 12 (1): 44. https://doi.org/10.1186/1476-069X-12-44.

Lioy, Paul J., and Stephen M. Rappaport. 2011. 'Exposure Science and the Exposome: An Opportunity for Coherence in the Environmental Health Sciences'. *Environmental Health Perspectives* 119 (11). https://doi.org/10.1289/ehp.1104387.

Liu, Xiaoqin, Kathrine Pape Madsen, Camilla Sandal Sejbaek, Henrik Albert Kolstad, Jens Peter E Bonde, Jørn Olsen, Karin Sørig Hougaard, et al. 2019. 'Risk of Childhood Asthma Following Prenatal Exposure to Negative Life Events and Job Stressors: A Nationwide Register-Based Study in Denmark'. *Scandinavian Journal of Work, Environment & Health* 45 (2): 174–82. https://doi.org/10.5271/sjweh.3785.

Loïs, Grégoire. 2014. 'La Contribution de l'observation Citoyenne à La Recherche Scientifique:' *Pour* N° 223 (3): 43–51. https://doi.org/10.3917/pour.223.0043.

Loriol, Marc. 2014. 'Les Sociologues et Le Stress: Quelques Enseignements Des Recherches Anglo-Saxonnes'. *La Nouvelle Revue Du Travail*, no. 4 (May). https://doi.org/10.4000/nrt.1498.

Lucas, Victoria S., and Graham J. Roberts. 2005. 'Oro-Dental Health in Children with Chronic Renal Failure and after Renal Transplantation: A Clinical Review'. *Pediatric Nephrology (Berlin, Germany)* 20 (10): 1388–94. https://doi.org/10.1007/s00467-005-1929-2.

Lunghi, Mathias, Nathalie Arnich, Franck Lehuédé, Carine Dubuisson, and Anne Thébault. 2022. 'Consumption of Bivalve Shellfish in French Coastal Populations in the CONSOMER Study: Data for Acute and Chronic Exposure and Determinants of Consumption'.

Luo, Dan, Yabing Pu, Haoyuan Tian, Weixiang Wu, Xin Sun, Tingting Zhou, Yun Tao, et al. 2017. 'Association of in Utero Exposure to Organochlorine Pesticides with Thyroid Hormone Levels in Cord Blood of Newborns'. *Environmental Pollution* 231 (December): 78–86. https://doi.org/10.1016/j.envpol.2017.07.091.

Lynch, Courtney D., Leila W. Jackson, Paul J. Kostyniak, Bridget M. McGuinness, and Germaine M. Buck Louis. 2012. 'The Effect of Prenatal and Postnatal Exposure to Polychlorinated Biphenyls and Child Neurodevelopment at Age Twenty Four Months'. *Reproductive Toxicology* 34 (3): 451–56. https://doi.org/10.1016/j.reprotox.2012.04.013.

Maervoet, Johan, Griet Vermeir, Adrian Covaci, Nicolas Van Larebeke, Gudrun Koppen, Greet Schoeters, Vera Nelen, Willy Baeyens, Paul Schepens, and Maria K. Viaene. 2007. 'Association of Thyroid Hormone Concentrations with Levels of Organochlorine Compounds in Cord Blood of Neonates'. *Environmental Health Perspectives* 115 (12): 1780–86. https://doi.org/10.1289/ehp.10486.

Malin, Ashley J., Corina Lesseur, Stefanie A. Busgang, Paul Curtin, Robert O. Wright, and Alison P. Sanders. 2019. 'Fluoride Exposure and Kidney and Liver Function among Adolescents in the United States: NHANES, 2013–2016'. *Environment International* 132 (November): 105012. https://doi.org/10.1016/j.envint.2019.105012.

Mancini, Francesca Romana, Pauline Frenoy, Thibault Fiolet, Guy Fagherazzi, and Amélie Crépet. 2021. 'Identification of Chemical Mixtures to Which Women Are Exposed through the Diet: Results from the French E3N Cohort'. *Environment International* 152 (July): 106467. https://doi.org/10.1016/j.envint.2021.106467.

Manolio, Teri A. 2010. 'Genomewide Association Studies and Assessment of the Risk of Disease'. Edited by W. Gregory Feero and Alan E. Guttmacher. *New England Journal of Medicine* 363 (2): 166–76. https://doi.org/10.1056/NEJMra0905980.

Martin, Deborah, Fiona Lobo, Gwenaëlle Lavison-Bompard, Thierry Guérin, and Julien Parinet. 2020. 'Effect of Home Cooking Processes on Chlordecone Content in Beef and Investigation of Its By-Products and Metabolites by HPLC-HRMS/MS'. *Environment International* 144 (November): 106077. https://doi.org/10.1016/j.envint.2020.106077.

Meijer, Jeroen, Marja Lamoree, Timo Hamers, Jean-Philippe Antignac, Sébastien Hutinet, Laurent Debrauwer, Adrian Covaci, et al. 2021. 'An Annotation Database for Chemicals of Emerging Concern in Exposome Research'. *Environment International* 152 (July): 106511. https://doi.org/10.1016/j.envint.2021.106511.

Miller, Gary W., and Dean P. Jones. 2014. 'The Nature of Nurture: Refining the Definition of the Exposome'. *Toxicological Sciences* 137 (1): 1–2. https://doi.org/10.1093/toxsci/kft251.

Miller, Thomas H., Keng Tiong Ng, Samuel T. Bury, Sophie E. Bury, Nicolas R. Bury, and Leon P. Barron. 2019. 'Biomonitoring of Pesticides, Pharmaceuticals and Illicit Drugs in a Freshwater Invertebrate to Estimate Toxic or Effect Pressure'. *Environment International* 129 (August): 595–606. https://doi.org/10.1016/j.envint.2019.04.038.

Ministère des Solidarités et de la Santé. 2022. 'Biosurveillance'. 19 January 2022. https://solidarites-sante.gouv.fr/sante-et-environnement/activites-humaines/article/biosurveillance.

Mokrzyński, Krystian, Olga Krzysztyńska-Kuleta, Marcin Zawrotniak, Michał Sarna, and Tadeusz Sarna. 2021. 'Fine Particulate Matter-Induced Oxidative Stress Mediated by UVA-Visible Light Leads to Keratinocyte Damage'. *International Journal of Molecular Sciences* 22 (19): 10645. https://doi.org/10.3390/ijms221910645.

Moore, SE, AM Prentice, Y Wagatsuma, AJC Fulford, AC Collinson, R Raqib, M Vahter, LÅ Persson, and SE Arifeen. 2009. 'Early-Life Nutritional and Environmental Determinants of Thymic Size in Infants Born in Rural Bangladesh'. *Acta Paediatrica (Oslo, Norway : 1992)* 98 (7): 1168–75. https://doi.org/10.1111/j.1651-2227.2009.01292.x.

Moura, Alexandra, Noémie Lefrancq, Thierry Wirth, Alexandre Leclercq, Vítor Borges, Brent Gilpin, Timothy J. Dallman, et al. 2021. 'Emergence and Global Spread of Listeria Monocytogenes Main Clinical Clonal Complex'. *Science Advances* 7 (49): eabj9805. https://doi.org/10.1126/sciadv.abj9805.

Murray, C J. 1994. 'Quantifying the Burden of Disease: The Technical Basis for Disability-Adjusted Life Years'. *Bulletin of the World Health Organization* 72 (3): 429–45.

Nagaoka, Hiromi, Shinichiro Hirai, Hirotaka Morinushi, Shiro Mizumoto, Kana Suzuki, Hiroaki Shigemura, Naoto Takahashi, et al. 2020. 'Coinfection with Human Norovirus and Escherichia Coli O25:H4 Harboring Two Chromosomal BlaCTX-M-14 Genes in a Foodborne Norovirus Outbreak in Shizuoka Prefecture, Japan'. *Journal of Food Protection* 83 (9): 1584–91. https://doi.org/10.4315/JFP-20-042.

National Academies of Sciences, Engineering, and Medicine, Committee on Endocrine-Related Low-Dose Toxicity, Board on Environmental Studies and Toxicology, and Division on Earth and Life Studies. 2017. 'Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals'. Washington, D.C.: National Academies Press. https://doi.org/10.17226/24758.

National Research Council. 2012. *Exposure Science in the 21st Century: A Vision and a Strategy*. Washington, DC: The National Academies Press. https://doi.org/10.17226/13507.

Nedellec, Vincent, Ari Rabl, and William Dab. 2016. 'Public Health and Chronic Low Chlordecone Exposures in Guadeloupe; Part 2: Health Impacts, and Benefits of Prevention'. *Environmental Health* 15 (1): 78. https://doi.org/10.1186/s12940-016-0159-3.

Nilsson, Eric E., Ingrid Sadler-Riggleman, and Michael K. Skinner. 2018. 'Environmentally Induced Epigenetic Transgenerational Inheritance of Disease'. *Environmental Epigenetics* 4 (2): dvy016. https://doi.org/10.1093/eep/dvy016.

NIOSH. 2022. 'Exposome and Exposomics'. 2022. https://www.cdc.gov/niosh/topics/exposome/default.html.

Nurminen, Noora, Damiano Cerrone, Jussi Lehtonen, Anirudra Parajuli, Marja Roslund, Maria Lönnrot, Jorma Ilonen, et al. 2021. 'Land Cover of Early-Life Environment Modulates the Risk of Type 1 Diabetes'. *Diabetes Care* 44 (7): 1506–14. https://doi.org/10.2337/dc20-1719.

Olivier Laurent, Yara Carrejo Gironza, Sophie Ancelet, Olivier Armant, Denis Bard, Katia Baumgartner, Sylvie Bortoli, et al. 2022. 'Le Projet LILAS : Analyse de l'application Des Approches Participatives Sur Les Multi-Expositions Environnementales et Les Risques Chroniques'. *Environnement, Risques & Santé* 21 (2): 129–36. https://doi.org/10.1684/ers.2022.1633.

OPERSEI. 2005. 'OPERSEI - Glossaire Relatif à l'évaluation Des Risques Sanitaires'. https://solidarites-sante.gouv.fr/IMG/pdf/Glossaire_relatif_a_l_evaluation_des_risques_sanitaires.pdf.

Orr, James A., Rolf D. Vinebrooke, Michelle C. Jackson, Kristy J. Kroeker, Rebecca L. Kordas, Chrystal Mantyka-Pringle, Paul J. Van den Brink, et al. 2020. 'Towards a Unified Study of Multiple Stressors: Divisions and Common Goals across Research Disciplines'. *Proceedings of the Royal Society B: Biological Sciences* 287 (1926): 20200421. https://doi.org/10.1098/rspb.2020.0421.

Ougier, Eva, Florence Zeman, Jean-Philippe Antignac, Christophe Rousselle, Rosa Lange, Marike Kolossa-Gehring, and Petra Apel. 2021. 'Human Biomonitoring Initiative (HBM4EU): Human Biomonitoring Guidance Values (HBM-GVs) Derived for Bisphenol A'. *Environment International* 154 (September): 106563. https://doi.org/10.1016/j.envint.2021.106563.

Pape, Kathrine, Xiaoqin Liu, Camilla Sandal Sejbæk, Niklas Worm Andersson, Ann Dyreborg Larsen, Hans Bay, Henrik Albert Kolstad, et al. 2021. 'Maternal Life and Work Stressors during Pregnancy and Asthma in Offspring'. *International Journal of Epidemiology* 49 (6): 1847–55. https://doi.org/10.1093/ije/dyaa133.

Parent-Thirion, Agnès, Isabella Biletta, Jorge Cabrita, Oscar Vargas Llave, Greet Vermeylen, Aleksandra Wilczyńska, Mathijn Wilkens, and Eurofound. 2016. 'Sixth European Working Conditions Survey – Overview Report', November. https://policycommons.net/artifacts/1840857/sixth-european-working-conditions-survey/2583901/.

Patel, Chirag J. 2017. 'Analytic Complexity and Challenges in Identifying Mixtures of Exposures Associated with Phenotypes in the Exposome Era'. *Current Epidemiology Reports* 4 (1): 22–30. https://doi.org/10.1007/s40471-017-0100-5.

Paustenbach, Dennis J. 2000. 'The Practice of Exposure Assessment: A State-of-the-Art Review'. *Journal of Toxicology and Environmental Health, Part B* 3 (3): 179–291. https://doi.org/10.1080/10937400050045264.

Perera, Thanusha, Shirani Ranasinghe, Neil Alles, and Roshitha Waduge. 2018. 'Effect of Fluoride on Major Organs with the Different Time of Exposure in Rats'. *Environmental Health and Preventive Medicine* 23 (1): 17. https://doi.org/10.1186/s12199-018-0707-2.

Perkins, Jordan T., Michael C. Petriello, Bradley J. Newsome, and Bernhard Hennig. 2016. 'Polychlorinated Biphenyls and Links to Cardiovascular Disease'. *Environmental Science and Pollution Research* 23 (3): 2160–72. https://doi.org/10.1007/s11356-015-4479-6.

Perrin, Frédérique, Fanny Tenenhaus-Aziza, Valérie Michel, Stéphane Miszczycha, Nadège Bel, and Moez Sanaa. 2015. 'Quantitative Risk Assessment of Haemolytic and Uremic Syndrome Linked to O157:H7 and Non-O157:H7 Shiga-Toxin Producing Escherichia Coli Strains in Raw Milk Soft Cheeses'. *Risk Analysis: An Official Publication of the Society for Risk Analysis* 35 (1): 109–28. https://doi.org/10.1111/risa.12267.

Perroud, Sandrine. 2018. 'La Géomédecine Pour Mieux Dépister Le Cancer Du Sein', October. https://actu.epfl.ch/news/la-geomedecine-pour-mieux-depister-le-cancer-du--2/.

Plaza-Rodríguez, Carolina, Leticia Ungaretti Haberbeck, Virginie Desvignes, Paw Dalgaard, Moez Sanaa, Maarten Nauta, Matthias Filter, and Laurent Guillier. 2018. 'Towards Transparent and Consistent Exchange of Knowledge for Improved Microbiological Food Safety'. *Current Opinion in Food Science*, Food Chemistry and Biochemistry * Food Bioprocessing, 19 (February): 129–37. https://doi.org/10.1016/j.cofs.2017.12.002.

Poissant, Julie. 2014. *Les conditions de succes des actions favorisant le developpement global des enfants: Etat des connaissances*. Institut national de santé publique du Québec. https://www.deslibris.ca/ID/241485.

Prado-Bert, Paula de, Carlos Ruiz-Arenas, Marta Vives-Usano, Sandra Andrusaityte, Solène Cadiou, Ángel Carracedo, Maribel Casas, et al. 2021. 'The Early-Life Exposome and Epigenetic Age Acceleration in Children'. *Environment International* 155 (October): 106683. https://doi.org/10.1016/j.envint.2021.106683.

Prata, Joana Correia, João P. da Costa, Isabel Lopes, Armando C. Duarte, and Teresa Rocha-Santos. 2020. 'Environmental Exposure to Microplastics: An Overview on Possible Human Health Effects'. *Science of The Total Environment* 702 (February): 134455. https://doi.org/10.1016/j.scitotenv.2019.134455.

Price, Elliott J., Chiara M. Vitale, Gary W. Miller, Arthur David, Robert Barouki, Karine Audouze, Douglas I. Walker, et al. 2022. 'Merging the Exposome into an Integrated Framework for "Omics" Sciences'. *IScience* 25 (3): 103976. https://doi.org/10.1016/j.isci.2022.103976.

Pruvost-Couvreur, Manon. 2020. 'Estimation de l'exposition Humaine Tout Au Long de La Vie Aux Contaminants Chimiques Par l'alimentation. Développement d'une Méthodologie et Évaluation Des Conséquences En Termes de Risques Sanitaires'. These de doctorat, Nantes, Ecole nationale vétérinaire. http://www.theses.fr/2020ONIR147F.

Purdom, C. E., P. A. Hardiman, V. V. J. Bye, N. C. Eno, C. R. Tyler, and J. P. Sumpter. 1994. 'Estrogenic Effects of Effluents from Sewage Treatment Works'. *Chemistry and Ecology* 8 (4): 275–85. https://doi.org/10.1080/02757549408038554.

Qiu, Xinghua, Tong Zhu, Bo Yao, Jianxin Hu, and Shaowen Hu. 2005. 'Contribution of Dicofol to the Current DDT Pollution in China'. *Environmental Science & Technology* 39 (12): 4385–90. https://doi.org/10.1021/es050342a.

Quévrain, Elodie, and Philippe Seksik. 2013. 'Microbiote intestinal : de la diarrhée post-antibiotiques aux maladies inflammatoires intestinales'. *La Presse Médicale*, Infections et parasitoses intestinales aiguës, 42 (1): 45–51. https://doi.org/10.1016/j.lpm.2012.09.017.

Rappaport, Stephen M. 2011. 'Implications of the Exposome for Exposure Science'. *Journal of Exposure Science & Environmental Epidemiology* 21 (1): 5–9. https://doi.org/10.1038/jes.2010.50.

Rappaport, Stephen M. 2020. 'Response to "the Role of the Exposome in Promoting Resilience or Susceptibility after SARS-CoV-2 Infection"'. *Journal of Exposure Science & Environmental Epidemiology* 30 (6): 905. https://doi.org/10.1038/s41370-020-00274-5.

Rappaport, Stephen M., and Martyn T. Smith. 2010. 'Epidemiology. Environment and Disease Risks'. *Science* 330 (6003): 460–61. https://doi.org/10.1126/science.1192603.

Ribas-Fitó, Núria, Maties Torrent, Daniel Carrizo, Laura Muñoz-Ortiz, Jordi Júlvez, Joan O. Grimalt, and Jordi Sunyer. 2006. 'In Utero Exposure to Background Concentrations of DDT and Cognitive Functioning among Preschoolers'. *American Journal of Epidemiology* 164 (10): 955–62. https://doi.org/10.1093/aje/kwj299.

Rider, Cynthia V., Kim Boekelheide, Natasha Catlin, Christopher J. Gordon, Thais Morata, MaryJane K. Selgrade, Kenneth Sexton, and Jane Ellen Simmons. 2014. 'Cumulative Risk: Toxicity and Interactions of Physical and Chemical Stressors'. *Toxicological Sciences* 137 (1): 3–11. https://doi.org/10.1093/toxsci/kft228.

Ritter, Roland, Martin Scheringer, Matthew MacLeod, Urs Schenker, and Konrad Hungerbühler. 2009. 'A Multi-Individual Pharmacokinetic Model Framework for Interpreting Time Trends of Persistent Chemicals in Human Populations: Application to a Postban Situation'. *Environmental Health Perspectives* 117 (8): 1280–86. https://doi.org/10.1289/ehp.0900648.

Roberts, Aaron P., Matthew M. Alloy, and James T. Oris. 2017. 'Review of the Photo-Induced Toxicity of Environmental Contaminants'. *Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology* 191 (January): 160–67. https://doi.org/10.1016/j.cbpc.2016.10.005.

Robinson, Oliver, Ibon Tamayo, Montserrat de Castro, Antonia Valentin, Lise Giorgis-Allemand, Norun Hjertager Krog, Gunn Marit Aasvang, et al. 2018. 'The Urban Exposome during Pregnancy and Its Socioeconomic Determinants'. *Environmental Health Perspectives* 126 (7): 077005. https://doi.org/10.1289/EHP2862.

Robinson, Oliver, and Martine Vrijheid. 2015. 'The Pregnancy Exposome'. *Current Environmental Health Reports* 2 (2): 204–13. https://doi.org/10.1007/s40572-015-0043-2.

Rock, Pauline de, Jean-Pierre Allenou, Emmamnuel Thouard, Nicolas Cimiterra, Jean-Louis Gonzalez, Charlotte Dromard, Claude Bouchon, et al. 2020. 'Recherche des voies de contamination des écosystèmes côtiers de Martinique par le chlordécone', 65p.

Rodríguez-Barranco, Miguel, Marina Lacasaña, Clemente Aguilar-Garduño, Juan Alguacil, Fernando Gil, Beatriz González-Alzaga, and Antonio Rojas-García. 2013. 'Association of Arsenic, Cadmium and Manganese Exposure with Neurodevelopment and Behavioural Disorders in Children: A Systematic Review and Meta-Analysis'. *Science of The Total Environment* 454–455 (June): 562–77. https://doi.org/10.1016/j.scitotenv.2013.03.047.

Rogan, W J, B C Gladen, J D McKinney, N Carreras, P Hardy, J Thullen, J Tingelstad, and M Tully. 1987. 'Polychlorinated Biphenyls (PCBs) and Dichlorodiphenyl Dichloroethene (DDE) in Human Milk: Effects on Growth, Morbidity, and Duration of Lactation.' *American Journal of Public Health* 77 (10): 1294–97. https://doi.org/10.2105/AJPH.77.10.1294.

Rogan, W J, Beth C. Gladen, James D. McKinney, Nancy Carreras, Pam Hardy, James Thullen, Jon Tinglestad, and Mary Tully. 1986. 'Neonatal Effects of Transplacental Exposure to PCBs and DDE'. *The Journal of Pediatrics* 109 (2): 335–41. https://doi.org/10.1016/S0022-3476(86)80397-3.

Román, Enriqueta, Isabel Wilhelmi, Javier Colomina, Joaquín Villar, María Luz Cilleruelo, Verónica Nebreda, Manuel Del Alamo, and Alicia Sánchez-Fauquier. 2003. 'Acute Viral Gastroenteritis: Proportion and Clinical Relevance of Multiple Infections in Spanish Children'. *Journal of Medical Microbiology* 52 (Pt 5): 435–40. https://doi.org/10.1099/jmm.0.05079-0.

Roquelaure, Yves. 2018. 'Troubles Musculo-Squelettiques et Facteurs Psychosociaux Au Travail'. 142. Bruxelles, Belgique: European Trade Union Institute. https://www.etui.org/sites/default/files/FR-Rapport-142-roquelaure-WEB.pdf.

Roszkowska, Anna, Miao Yu, Vincent Bessonneau, Jennifer Ings, Mark McMaster, Richard Smith, Leslie Bragg, Mark Servos, and Janusz Pawliszyn. 2019. 'In Vivo Solid-Phase Microextraction Sampling Combined with Metabolomics and Toxicological Studies for the Non-Lethal Monitoring of the Exposome in Fish Tissue'. *Environmental Pollution* 249 (June): 109–15. https://doi.org/10.1016/j.envpol.2019.03.024.

Runge, Jakob, Peer Nowack, Marlene Kretschmer, Seth Flaxman, and Dino Sejdinovic. 2019. 'Detecting and Quantifying Causal Associations in Large Nonlinear Time Series Datasets'. *Science Advances*, November. https://doi.org/10.1126/sciadv.aau4996.

Sabatier, Pierre, Charles Mottes, Nathalie Cottin, Olivier Evrard, Irina Comte, Christine Piot, Bastien Gay, et al. 2021. 'Evidence of Chlordecone Resurrection by Glyphosate in French West Indies'. *Environmental Science & Technology* 55 (4): 2296–2306. https://doi.org/10.1021/acs.est.0c05207.

Safford, B., A. M. Api, C. Barratt, D. Comiskey, E. J. Daly, G. Ellis, C. McNamara, et al. 2015. 'Use of an Aggregate Exposure Model to Estimate Consumer Exposure to Fragrance Ingredients in Personal Care and Cosmetic Products'. *Regulatory Toxicology and Pharmacology* 72 (3): 673–82. https://doi.org/10.1016/j.yrtph.2015.05.017.

Saïbi-Yedjer, Lynda, Ariane Dufour, Marie Baudoin, Sonia Poisson, Jean-Cédric Reninger, Anne Thebault, and Chris Roth. 2018. 'Évaluation Du Descripteur 9 « Questions Sanitaires » En France Métropolitaine. Rapport Scientifique Pour l'évaluation 2018 Au Titre de La DCSMM'. Saisine 2015-SA-0238-DCSMM. https://dcsmm.milieumarinfrance.fr/Le-Plan-d-Action-pour-le-Milieu-Marin/Cycle-2-2018-2024/Consultation-des-documents-de-l-evaluation-du-Cycle-2/Questions-sanitaires-France-metropolitaine.

Sánchez, Cecilia A., Sonia Altizer, and Richard J. Hall. 2020. 'Landscape-Level Toxicant Exposure Mediates Infection Impacts on Wildlife Populations'. *Biology Letters* 16 (11): 20200559. https://doi.org/10.1098/rsbl.2020.0559.

Sandoval, José Luis, Rebecca Himsl, Jean-Marc Theler, Jean-Michel Gaspoz, Stéphane Joost, and Idris Guessous. 2018. 'Spatial Distribution of Mammography Adherence in a Swiss Urban Population and Its Association with Socioeconomic Status'. *Cancer Medicine* 7 (12): 6299–6307. https://doi.org/10.1002/cam4.1829.

Santé Canada. 2019. 'Recommandations Pour La Qualité de l'eau Potable Au Canada. Le Manganèse'. Document technique H144-39/2017F-PDF. Ottawa, Ontario: Bureau de la qualité de l'eau et de l'air, Direction générale de la santé environnementale et de la sécurité des consommateurs, Santé Canada. http://www.canada.ca/fr/sante-canada/services/sante-environnement-milieu-travail/rapports-publications/qualite-eau.html.

Sarigiannis, D. A. 2017. 'Assessing the Impact of Hazardous Waste on Children's Health: The Exposome Paradigm'. *Environmental Research* 158 (October): 531–41. https://doi.org/10.1016/j.envres.2017.06.031.

Sarigiannis, Dimosthenis A, Spyros P. Karakitsios, Evangelos Handakas, and Alberto Gotti. 2020. 'Development of a Generic Lifelong Physiologically Based Biokinetic Model for Exposome Studies'. *Environmental Research* 185 (June): 109307. https://doi.org/10.1016/j.envres.2020.109307.

Sari-Minodier, Irène, Philippe Sotty, Karamoko Coulibaly, Luc Decosse, and Alain Botta. 2008. 'L'expologie ou la nécessité d'articuler les données relatives aux dangers, à l'homme et à son activité'. *Sante Publique* 20 (hs): 77–85.

Sarkis, Noëlle, Olivier Geffard, Yves Souchon, André Chandesris, Martial Férréol, Laurent Valette, Benjamin Alric, et al. 2020. 'How to Quantify the Links between Bioavailable Contamination in Watercourses and Pressures of Anthropogenic Land Cover, Contamination Sources and Hydromorphology at Multiple Scales?' *Science of The Total Environment* 735 (September): 139492. https://doi.org/10.1016/j.scitotenv.2020.139492.

Schlüter-Vorberg, Lisa, and Anja Coors. 2019. 'Impact of an Immunosuppressive Human Pharmaceutical on the Interaction of a Bacterial Parasite and Its Invertebrate Host'. *Aquatic Toxicology* 206 (January): 91–101. https://doi.org/10.1016/j.aquatox.2018.11.007.

Scholz, Stefan, John W. Nichols, Beate I. Escher, Gerald T. Ankley, Rolf Altenburger, Brett Blackwell, Werner Brack, et al. 2022. 'The Eco-Exposome Concept: Supporting an Integrated Assessment of Mixtures of Environmental Chemicals'. *Environmental Toxicology and Chemistry* 41 (1): 30–45. https://doi.org/10.1002/etc.5242.

Schreier, Hannah MC, Hsiao-Hsien Hsu, Chitra Amarasiriwardena, Brent A Coull, Lourdes Schnaas, Martha María Téllez-Rojo, Marcela Tamayo y Ortiz, Rosalind J Wright, and Robert O Wright. 2015. 'Mercury and Psychosocial Stress Exposure Interact to Predict Maternal Diurnal Cortisol during Pregnancy'. *Environmental Health* 14 (1): 28. https://doi.org/10.1186/s12940-015-0016-9.

Sejbaek, Camilla Sandal, Hans Bay, Ann Dyreborg Larsen, Petter Kristensen, Vivi Schlünssen, Anne-Marie Nybo Andersen, Jens Peter Bonde, Mette Juhl, and Karin Sørig Hougaard. 2018. 'Combined Exposure to Lifting and Psychosocial Strain at Work and Adverse Pregnancy Outcomes—A Study in the Danish National Birth Cohort'. Edited by Umberto Simeoni. *PLOS ONE* 13 (9): e0201842. https://doi.org/10.1371/journal.pone.0201842.

Senier, Laura, Phil Brown, Sara Shostak, and Bridget Hanna. 2017. 'The Socio-Exposome: Advancing Exposure Science and Environmental Justice in a Postgenomic Era'. *Environmental Sociology* 3 (2): 107–21. https://doi.org/10.1080/23251042.2016.1220848.

Sharifinia, Moslem, Zahra Afshari Bahmanbeigloo, Mehrzad Keshavarzifard, Mohammad Hossein Khanjani, and Brett P. Lyons. 2020. 'Microplastic Pollution as a Grand Challenge in Marine Research: A Closer Look at Their Adverse Impacts on the Immune and Reproductive Systems'. *Ecotoxicology and Environmental Safety* 204 (November): 111109. https://doi.org/10.1016/j.ecoenv.2020.111109.

Shirai, Jeffry H., and John C. Kissel. 1996. 'Uncertainty in Estimated Half-Lives of PCBS in Humans: Impact on Exposure Assessment'. *Science of The Total Environment* 187 (3): 199–210. https://doi.org/10.1016/0048-9697(96)05142-X.

Sillé, Fenna C. M., Spyros Karakitsios, Andre Kleensang, Kirsten Koehler, Alexandra Maertens, Gary W. Miller, Carsten Prasse, et al. 2020. 'The Exposome - a New Approach for Risk Assessment'. *ALTEX* 37 (1): 3–23. https://doi.org/10.14573/altex.2001051.

Sirot, V., C. Dumas, J. C. Leblanc, and I. Margaritis. 2011. 'Food and Nutrient Intakes of French Frequent Seafood Consumers with Regard to Fish Consumption Recommendations: Results from the CALIPSO Study'. *Br J Nutr* 105 (9): 1369–80. https://doi.org/10.1017/S0007114510005027.

Sirot, Véronique, Gilles Rivière, Stéphane Leconte, Jean-Charles Leblanc, Martine Kolf-Clauw, Paule Vasseur, Jean-Pierre Cravedi, and Marion Hulin. 2021. 'Infant Total Diet Study in France: Exposure to Substances Migrating from Food Contact Materials'. *Environment International* 149 (April): 106393. https://doi.org/10.1016/j.envint.2021.106393.

Sisto, Renata, Arturo Moleti, Ľubica Palkovičová Murínová, Soňa Wimmerová, Kinga Lancz, Juraj Tihányi, Kamil Čonka, et al. 2015. 'Environmental Exposure to Organochlorine Pesticides and Deficits in Cochlear Status in Children'. *Environmental Science and Pollution Research* 22 (19): 14570–78. https://doi.org/10.1007/s11356-015-4690-5.

Slaby, Sylvain, François Le Cor, Vincent Dufour, Lucile Auger, Laure Pasquini, Olivier Cardoso, Laurence Curtet, et al. 2022. 'Distribution of Pesticides and Some of Their Transformation Products in a Small Lentic Waterbody: Fish, Water, and Sediment Contamination in an Agricultural Watershed'. *Environmental Pollution* 292 (January): 118403. https://doi.org/10.1016/j.envpol.2021.118403.

Solovieva, Svetlana, Tiina Pensola, Johanna Kausto, Rahman Shiri, Markku Heliövaara, Alex Burdorf, Kirsti Husgafvel-Pursiainen, and Eira Viikari-Juntura. 2014. 'Evaluation of the Validity of Job Exposure Matrix for Psychosocial Factors at Work'. Edited by James Coyne. *PLoS ONE* 9 (9): e108987. https://doi.org/10.1371/journal.pone.0108987.

Soto, A M, C Sonnenschein, K L Chung, M F Fernandez, N Olea, and F O Serrano. 1995. 'The E-SCREEN Assay as a Tool to Identify Estrogens: An Update on Estrogenic Environmental Pollutants.' *Environmental Health Perspectives* 103 (suppl 7): 113–22. https://doi.org/10.1289/ehp.95103s7113.

Sprong, Corinne, Amélie Crépet, Francesca Metruccio, Urska Blaznik, Chris Anagnostopoulos, Despo Louca Christodoulou, Bodil Hamborg Jensen, et al. 2020. 'Cumulative Dietary Risk Assessment Overarching Different Regulatory Silos Using a Margin of Exposure Approach: A Case Study with Three Chemical Silos'. *Food and Chemical Toxicology* 142 (August): 111416. https://doi.org/10.1016/j.fct.2020.111416.

Stingone, Jeanette A., Germaine M. Buck Louis, Shoji F. Nakayama, Roel C.H. Vermeulen, Richard K. Kwok, Yuxia Cui, David M. Balshaw, and Susan L. Teitelbaum. 2017. 'Toward Greater Implementation of the Exposome Research Paradigm within Environmental Epidemiology'. *Annual Review of Public Health* 38 (1): 315–27. https://doi.org/10.1146/annurev-publhealth-082516-012750.

Suzuki, Takafumi, Takanori Hidaka, Yoshito Kumagai, and Masayuki Yamamoto. 2020. 'Environmental Pollutants and the Immune Response'. *Nature Immunology* 21 (12): 1486–95. https://doi.org/10.1038/s41590-020-0802-6.

Tamayo y Ortiz, Marcela, Martha María Téllez-Rojo, Belem Trejo-Valdivia, Lourdes Schnaas, Erika Osorio-Valencia, Brent Coull, David Bellinger, Rosalind J. Wright, and Robert O. Wright. 2017. 'Maternal Stress Modifies the Effect of Exposure to Lead during Pregnancy and 24-Month Old Children's Neurodevelopment'. *Environment International* 98 (January): 191–97. https://doi.org/10.1016/j.envint.2016.11.005.

Tang-Péronard, Jeanett L, Berit L Heitmann, Helle R Andersen, Ulrike Steuerwald, Philippe Grandjean, Pál Weihe, and Tina K Jensen. 2014. 'Association between Prenatal Polychlorinated Biphenyl Exposure and Obesity Development at Ages 5 and 7 y: A Prospective Cohort Study of 656 Children from the Faroe Islands'. *The American Journal of Clinical Nutrition* 99 (1): 5–13. https://doi.org/10.3945/ajcn.113.066720.

Testai, Emanuela, Camille Bechaux, Franca M. Buratti, Keyvin Darney, Emma Di Consiglio, Emma E.J. Kasteel, Nynke I. Kramer, et al. 2021. 'Modelling Human Variability in Toxicokinetic and Toxicodynamic Processes Using Bayesian Meta-analysis, Physiologically-based Modelling and in Vitro Systems'. *EFSA Supporting Publications* 18 (4). https://doi.org/10.2903/sp.efsa.2021.EN-6504.

Thébault, Anne, Pauline Kooh, Vasco Cadavez, Ursula Gonzales-Barron, and Isabelle Villena. 2021. 'Risk Factors for Sporadic Toxoplasmosis: A Systematic Review and Meta-Analysis'. *Microbial Risk Analysis* 17 (April): 100133. https://doi.org/10.1016/j.mran.2020.100133.

Thébault, Anne, Peter F. M. Teunis, Jacques Le Pendu, Françoise S. Le Guyader, and Jean-Baptiste Denis. 2013. 'Infectivity of GI and GII Noroviruses Established from Oyster Related Outbreaks'. *Epidemics* 5 (2): 98–110. https://doi.org/10.1016/j.epidem.2012.12.004.

Tilson, Hugh A., Joseph L. Jacobson, and Walter J. Rogan. 1990. 'Polychlorinated Biphenyls and the Developing Nervous System: Cross-Species Comparisons'. *Neurotoxicology and Teratology* 12 (3): 239–48. https://doi.org/10.1016/0892-0362(90)90095-T.

Torres-Sánchez, Luisa, Stephen J. Rothenberg, Lourdes Schnaas, Mariano E. Cebrián, Erika Osorio, Maria del Carmen Hernández, Rosa M. García-Hernández, Constanza del Rio-Garcia, Mary S. Wolff, and Lizbeth López-Carrillo. 2007. '*In Utero p* , *p* '-DDE Exposure and Infant Neurodevelopment: A Perinatal Cohort in Mexico'. *Environmental Health Perspectives* 115 (3): 435–39. https://doi.org/10.1289/ehp.9566.

Toselli, Francesca, Isabelle de Waziers, Mary Dutheil, Marc Vincent, Peter A. Wilce, Peter R. Dodd, Philippe Beaune, Marie-Anne Loriot, and Elizabeth M. J. Gillam. 2015. 'Gene Expression Profiling of Cytochromes P450, ABC Transporters and Their Principal Transcription Factors in the Amygdala and Prefrontal Cortex of Alcoholics, Smokers and Drug-Free Controls by QRT-PCR'. *Xenobiotica; the Fate of Foreign Compounds in Biological Systems* 45 (12): 1129–37. https://doi.org/10.3109/00498254.2015.1040102.

Traoré, Thiéma, Camille Béchaux, Véronique Sirot, and Amélie Crépet. 2016. 'To Which Chemical Mixtures Is the French Population Exposed? Mixture Identification from the Second French Total Diet Study'. *Food and Chemical Toxicology* 98 (December): 179–88. http://dx.doi.org/10.1016/j.fct.2016.10.028.

Traoré, Thiéma, Anne Forhan, Véronique Sirot, Manik Kadawathagedara, Barbara Heude, Marion Hulin, Blandine de Lauzon-Guillain, Jérémie Botton, Marie Aline Charles, and Amélie Crépet. 2018. 'To Which Mixtures Are French Pregnant Women Mainly Exposed? A Combination of the Second French Total Diet Study with the EDEN and ELFE Cohort Studies'. *Food and Chemical Toxicology* 111 (Supplement C): 310–28. https://doi.org/10.1016/j.fct.2017.11.016.

Trnovec, Tomáš, Eva Šovčíková, Milan Husťák, Sona Wimmerová, Anton Kočan, Dana Jurečková, Pavel Langer, L'ubica Palkovičová, and Beata Drobná. 2008. 'Exposure to Polychlorinated Biphenyls and Hearing Impairment in Children'. *Environmental Toxicology and Pharmacology* 25 (2): 183–87. https://doi.org/10.1016/j.etap.2007.10.030.

Trudeau, Vance L, Paisley Thomson, Wo Su Zhang, Stéphane Reynaud, Laia Navarro-Martin, and Valérie S. Langlois. 2020. 'Agrochemicals Disrupt Multiple Endocrine Axes in Amphibians'. *Molecular and Cellular Endocrinology* 513 (August): 110861. https://doi.org/10.1016/j.mce.2020.110861.

Turyk, Mary, Henry A. Anderson, Lynda Knobeloch, Pamela Imm, and Victoria W. Persky. 2009. 'Prevalence of Diabetes and Body Burdens of Polychlorinated Biphenyls, Polybrominated Diphenyl Ethers, and p,P′-Diphenyldichloroethene in Great Lakes Sport Fish Consumers'. *Chemosphere* 75 (5): 674–79. https://doi.org/10.1016/j.chemosphere.2008.12.035.

UNICEF France. 2021. 'De l'injustice sociale dans l'air. Pauvreté des enfants et pollution de l'air'. https://reseauactionclimat.org/wp-content/uploads/2021/10/injusticesocialedanslair_rapport_final_webpages.pdf.

US Agency for Toxic Substances and Disease Registry. 1994. 'Toxicological Profile for Hexachlorocyclohexanes'. Atlanta, Georgia: Agency for Toxic Substances and Disease Registry. https://www.atsdr.cdc.gov/toxprofiles/tp43.pdf.

———. 2000. 'Toxicological Profile for Polychlorinated Biphenyls (PCBs)'. Atlanta, Georgia: Agency for Toxic Substances and Disease Registry. https://www.atsdr.cdc.gov/toxprofiles/tp17.pdf.

———. 2005. 'Toxicological Profile for α-, β-, γ-, and δ-Hexachlorocyclohexane'. Atlanta, Georgia: Agency for Toxic Substances and Disease Registry. https://www.atsdr.cdc.gov/toxprofiles/tp43.pdf.

———. 2012a. 'Toxicological Profile for Cadmium'. Atlanta, Georgia: Agency for Toxic Substances and Disease Registry. https://www.atsdr.cdc.gov/toxprofiles/tp5.pdf.

———. 2012b. 'Toxicological Profile for Manganese'. Atlanta, Georgia: Agency for Toxic Substances and Disease Registry. https://www.atsdr.cdc.gov/ToxProfiles/tp151.pdf.

———. 2015. 'Toxicological Profile for Hexachlorobenzene'. Atlanta, Georgia: Agency for Toxic Substances and Disease Registry. https://www.atsdr.cdc.gov/ToxProfiles/tp90.pdf.

———. 2016. 'Addendum to the Toxicological Profile for Arsenic'. Technical Report. Atlanta, Georgia: Agency for Toxic Substances and Disease Registry. https://www.atsdr.cdc.gov/toxprofiles/tp5.pdf.

———. 2017. 'Toxicological Profile for Polybrominated Diphenyl Ethers (PBDEs)'. Atlanta, Georgia: Agency for Toxic Substances and Disease Registry. https://www.atsdr.cdc.gov/toxprofiles/tp207.pdf.

———. 2018. 'Glossary of Terms'. 13 November 2018. https://www.atsdr.cdc.gov/glossary.html.

———. 2019. 'Toxicological Profile for DDT, DDE, DDD (Draft for Public Comment)'. Atlanta, Georgia: Agency for Toxic Substances and Disease Registry. https://stacks.cdc.gov/view/cdc/83602.

———. 2020. 'Toxicity Profile for Mirex and Chlordecone'. Atlanta, Georgia: Agency for Toxic Substances and Disease Registry. https://www.atsdr.cdc.gov/toxprofiles/tp66.pdf.

U.S. Environmental Protection Agency (EPA). 2011. 'Exposure Factors Handbook: 2011 Edition'. EPA/600/R-09/052F. Washington, DC: National Center for Environmental Assessment. http://www.epa.gov/ncea/efh.

US EPA. 2014. 'Integrated Science Assessment (ISA) for Lead'. EPA/600/R-10/075F. Washington, DC: U.S. Environmental Protection Agency.

———. 2015. 'Literature Review on Neurodevelopment Effects & FQPA Safety Factor Determination for the Organophosphate Pesticides'. U.S. Environmental Protection Agency. https://www.regulations.gov/document/EPA-HQ-OPP-2009-0317-0083.

———. 2017. 'Toxicological Review of Benzo[a]Pyrene'. EPA/635/R-17/003Fa. Washington, DC: U.S. Environmental Protection Agency. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0136tr.pdf.

U.S. Food and Drug Administration. 2016. 'Arsenic in Rice and Rice Products Risk Assessment Report'. http://www.fda.gov/Food/FoodScienceResearch/RiskSafetyAssessment/default.htm.

Vafeiadi, Marina, Theano Roumeliotaki, Georgia Chalkiadaki, Panu Rantakokko, Hannu Kiviranta, Eleni Fthenou, Soterios A. Kyrtopoulos, Manolis Kogevinas, and Leda Chatzi. 2017. 'Persistent Organic Pollutants in Early Pregnancy and Risk of Gestational Diabetes Mellitus'. *Environment International* 98 (January): 89–95. https://doi.org/10.1016/j.envint.2016.10.005.

Vanacker, Marie, Paul Quindroit, Karine Angeli, Corinne Mandin, Philippe Glorennec, Céline Brochot, and Amélie Crépet. 2020. 'Aggregate and Cumulative Chronic Risk Assessment for Pyrethroids in the French Adult Population'. *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association* 143 (September): 111519. https://doi.org/10.1016/j.fct.2020.111519.

Vanacker, Marie, Jessica Tressou, Guillaume Perouel, Philippe Glorennec, and Amélie Crépet. 2020. 'Combining Data from Heterogeneous Surveys for Aggregate Exposure: Application to Children Exposure to Lead in France'. *Environmental Research* 182: 109069. https://doi.org/10.1016/j.envres.2019.109069.

Vangay, Pajau, Tonya Ward, Jeffrey S. Gerber, and Dan Knights. 2015. 'Antibiotics, Pediatric Dysbiosis, and Disease'. *Cell Host & Microbe* 17 (5): 553–64. https://doi.org/10.1016/j.chom.2015.04.006.

Verger, P., J. Tressou, and S. Clémençon. 2007. 'Integration of Time as a Description Parameter in Risk Characterisation: Application to Methyl Mercury.' *Regul. Toxicol. Pharmacol.* 49 (1): 25–30.

Vermeulen, Roel, Emma L. Schymanski, Albert-László Barabási, and Gary W. Miller. 2020. 'The Exposome and Health: Where Chemistry Meets Biology'. *Science* 367 (6476): 392–96. https://doi.org/10.1126/science.aay3164.

Viant, Mark R., Timothy M. D. Ebbels, Richard D. Beger, Drew R. Ekman, David J. T. Epps, Hennicke Kamp, Pim E. G. Leonards, et al. 2019. 'Use Cases, Best Practice and Reporting Standards for Metabolomics in Regulatory Toxicology'. *Nature Communications* 10 (1): 3041. https://doi.org/10.1038/s41467-019-10900-y.

Vineis, P., M. Chadeau-Hyam, H. Gmuender, J. Gulliver, Z. Herceg, J. Kleinjans, M. Kogevinas, et al. 2017. 'The Exposome in Practice: Design of the EXPOsOMICS Project'. *International Journal of Hygiene and Environmental Health* 220 (2): 142–51. https://doi.org/10.1016/j.ijheh.2016.08.001.

Vineis, Paolo. 2015. 'Exposomics: Mathematics Meets Biology'. *Mutagenesis*, September, gev068. https://doi.org/10.1093/mutage/gev068.

Vineis, Paolo, Mauricio Avendano-Pabon, Henrique Barros, Mel Bartley, Cristian Carmeli, Luca Carra, Marc Chadeau-Hyam, et al. 2020. 'Special Report: The Biology of Inequalities in Health: The Lifepath Consortium'. *Frontiers in Public Health* 8. https://www.frontiersin.org/article/10.3389/fpubh.2020.00118.

Voet, Hilko van der, Waldo J. de Boer, Johannes W. Kruisselbrink, Paul W. Goedhart, Gerie W. A. M. van der Heijden, Marc C. Kennedy, Polly E. Boon, and Jacob D. van Klaveren. 2015. 'The MCRA Model for Probabilistic Single-Compound and Cumulative Risk Assessment of Pesticides'. *Food and Chemical Toxicology*, Toxicity testing and model development for estimating cumulative and aggregate exposure to pesticide residues in Europe, 79 (May): 5–12. https://doi.org/10.1016/j.fct.2014.10.014.

Vrijheid, Martine. 2014. 'The Exposome: A New Paradigm to Study the Impact of Environment on Health'. *Thorax* 69 (9): 876–78. https://doi.org/10.1136/thoraxjnl-2013-204949.

Vrijheid, Martine, Xavier Basagaña, Juan R. Gonzalez, Vincent W. V. Jaddoe, Genon Jensen, Hector C. Keun, Rosemary R. C. McEachan, et al. 2021. 'Advancing Tools for Human Early Lifecourse Exposome Research and Translation (ATHLETE): Project Overview'.

Environmental Epidemiology 5 (5): e166. https://doi.org/10.1097/EE9.0000000000000166.

Vrijheid, Martine, Maribel Casas, Mireia Gascon, Damaskini Valvi, and Mark Nieuwenhuijsen. 2016. 'Environmental Pollutants and Child Health—A Review of Recent Concerns'. *International Journal of Hygiene and Environmental Health* 219 (4–5): 331–42. https://doi.org/10.1016/j.ijheh.2016.05.001.

Vrijheid, Martine, Rémy Slama, Oliver Robinson, Leda Chatzi, Muireann Coen, Peter van den Hazel, Cathrine Thomsen, et al. 2014. 'The Human Early-Life Exposome (HELIX): Project Rationale and Design'. *Environmental Health Perspectives* 122 (6): 535–44. https://doi.org/10.1289/ehp.1307204.

Waltisperger, Dominique. 2007. 'Pénibilité : Les Ouvriers Sont Stressés Eux Aussi'. *Santé & Travail*, no. 057 (January): p.42-45.

Warner, Marcella, Amelia Wesselink, Kim G. Harley, Asa Bradman, Katherine Kogut, and Brenda Eskenazi. 2014. 'Prenatal Exposure to Dichlorodiphenyltrichloroethane and Obesity at 9 Years of Age in the CHAMACOS Study Cohort'. *American Journal of Epidemiology* 179 (11): 1312–22. https://doi.org/10.1093/aje/kwu046.

Weitekamp, Chelsea A., Linda J. Phillips, Laura M. Carlson, Nicole M. DeLuca, Elaine A. Cohen Hubal, and Geniece M. Lehmann. 2021. 'A State-of-the-Science Review of Polychlorinated Biphenyl Exposures at Background Levels: Relative Contributions of Exposure Routes'. *Science of The Total Environment* 776 (July): 145912. https://doi.org/10.1016/j.scitotenv.2021.145912.

WHO/IPCS. 1984. 'Chlordecone'. 43. Environmental Health Criteria. https://inchem.org/documents/ehc/ehc/ehc43.htm.

———. 1991. 'Alpha- and Beta-Hexachlorocyclohexanes'. 123. Environmental Health Criteria. www.inchem.org/documents/ehc/ehc/ehc123.htm.

———. 1997. 'Hexachlorobenzene'. 195. Environmental Health Criteria. https://inchem.org/documents/ehc/ehc/ehc195.htm.

Wild, Christopher. 2005. 'Complementing the Genome with an "Exposome": The Outstanding Challenge of Environmental Exposure Measurement in Molecular Epidemiology'. *Cancer Epidemiology Biomarkers & Prevention* 14 (8): 1847–50. https://doi.org/10.1158/1055-9965.EPI-05-0456.

———. 2009. 'Environmental Exposure Measurement in Cancer Epidemiology'. *Mutagenesis* 24 (2): 117–25. https://doi.org/10.1093/mutage/gen061.

———. 2012. 'The Exposome: From Concept to Utility'. *International Journal of Epidemiology* 41 (1): 24–32. https://doi.org/10.1093/ije/dyr236.

Windsor, Fredric M., M. Glória Pereira, Christy A. Morrissey, Charles R. Tyler, and Steve J. Ormerod. 2020. 'Environment and Food Web Structure Interact to Alter the Trophic Magnification of Persistent Chemicals across River Ecosystems'. *Science of The Total Environment* 717 (May): 137271. https://doi.org/10.1016/j.scitotenv.2020.137271.

Woodruff, Tracey J., Lauren Zeise, Daniel A. Axelrad, Kathryn Z. Guyton, Sarah Janssen, Mark Miller, Gregory G. Miller, et al. 2008. 'Meeting Report: Moving Upstream—Evaluating Adverse Upstream End Points for Improved Risk Assessment and Decision-Making'. *Environmental Health Perspectives* 116 (11): 1568–75. https://doi.org/10.1289/ehp.11516.

World Health Organization. 1985. 'Constitution de l'OMS', 18p.

———. 2011. 'DDT in Indoor Residual Spraying : Human Health Aspects', Environmental health criteria, 241, . https://apps.who.int/iris/handle/10665/44560.

———. 2012. 'Les Risques Pour La Santé Mentale : Aperçu Des Vulnérabilités et Des Facteurs de Risque. Document de Base Établi Par Le Secrétariat Général de l'OMS En Vue de l'élaboration d'un Plan d'action Global Sur La Santé Mentale'.

———. 2014. *Social Determinants of Mental Health*. Geneva: World Health Organization. https://apps.who.int/iris/handle/10665/112828.

———. 2019. 'FAO/WHO Expert Consultation on Dietary Risk Assessment of Chemical Mixtures (Risk Assessment of Combined Exposure to Multiple Chemicals)'. Summary Report. Geneva: World Health Organization. https://www.who.int/foodsafety/areas_work/chemical-risks/Euromix_Report.pdf.

World Health Organization Europe. 2009. 'Mental Health, Resilience and Inequalities'. https://www.euro.who.int/__data/assets/pdf_file/0012/100821/E92227.pdf.

———. 2010. *Guidelines for Indoor Air Quality: Selected Pollutants*. Copenhagen, Denmark. https://www.euro.who.int/__data/assets/pdf_file/0009/128169/e94535.pdf.

Wright, E. C., S. A. Johnson, R. Hao, A. S. Kowalczyk, G. D. Greenberg, E. Ordoñes Sanchez, A. Laman-Maharg, B. C. Trainor, and C. S. Rosenfeld. 2017. 'Exposure to Extrinsic Stressors, Social Defeat or Bisphenol A, Eliminates Sex Differences in DNA Methyltransferase Expression in the Amygdala'. *Journal of Neuroendocrinology* 29 (6). https://doi.org/10.1111/jne.12475.

Wu, Qier, Xavier Coumoul, Philippe Grandjean, Robert Barouki, and Karine Audouze. 2021. 'Endocrine Disrupting Chemicals and COVID-19 Relationships: A Computational Systems Biology Approach'. *Environment International* 157 (December): 106232. https://doi.org/10.1016/j.envint.2020.106232.

Zartarian, Valerie, Jianping Xue, -Velez Rogelio Tornero, and James Brown. 2017. 'Children's Lead Exposure: A Multimedia Modeling Analysis to Guide Public Health Decision-Making'. *Environmental Health Perspectives* 125 (9): 097009. https://doi.org/10.1289/EHP1605.

Zhao, Jinshun, Kui Liu, and Xialu Lin. 2013. 'Toxic Effects of the Interaction of Titanium Dioxide Nanoparticles with Chemicals or Physical Factors'. *International Journal of Nanomedicine*, July, 2509. https://doi.org/10.2147/IJN.S46919.

ANNEXES

Annexe 1 Context, issues and terms of reference for the task that ANSES decided to entrust to a WG reporting to its Scientific Board

anses
agence nationale de sécurité sanitaire
alimentation, environnement, travail
Connaître, évaluer, protéger

CSET 18/02.03
Exposome WG project

ANSES and the exposome

Context, issues and terms of reference for the task that ANSES decided to entrust to a WG reporting to its Scientific Board

Since it was developed by C Wild in 2005, the concept of the exposome has given rise to numerous research projects that form part of a continuum of questions to science about the role of environmental factors in the development of chronic diseases, which have become the leading cause of death in developed countries in recent decades. The interest shown in this concept has extended beyond research teams to convince public decision-makers. Its adoption in the French Act of 28 January 2016 on the modernisation of the health system thus introduced provisions in the Public Health Code referring to the concept of the exposome:

- Under the provisions relating to general health administration, and more specifically those on health policy, Article L.1411-1, Subparagraph 1: *The monitoring and observation of the health status of the population and the identification of its main determinants, particularly those related to education and living and working conditions. Identification of these determinants is based on the concept of the exposome, understood as the integration over an entire lifetime of all the exposures that can influence human health.*
- Under the provisions relating to the protection and promotion of maternal and child health, and more specifically on the general organisation and missions, Article L. 2111-1: *The State, local authorities and social security bodies shall participate, under the conditions laid down in this Book, in the protection and promotion of maternal and child health, which shall include in particular [...] 5° Prevention and information measures on health risks associated with environmental factors, based on the exposome concept.*

However, it has yet to be largely implemented by ANSES, whether scientifically or methodologically.

I. Context and progressive establishment of the exposome concept

The inclusion of the exposome concept in the Act was preceded by various steps in public action: it was the subject of methodological work in the 2015-2019 National Environmental Health Action Plan (Action no. 34), and a major theme of strategic thinking for action in environmental health in the construction of the National Public Health Plan, which was just adopted in 2018 (see the opinion of the High Council for Public Health (HCSP, 2017)).

This concept previously emerged and was refined by environmental health researchers within the international scientific community, while leading researchers such as C. Wild, Rappaport and Smith, Buck Louis and Miller have helped formulate and enhance it since the beginning of the decade. Players from the French community and ANSES have also contributed to this emergence.

This concept leads to all exposures (from all sources – such as the environment and food – and due to all types of pathogens – whether chemical, physical, biological, or even psychosocial factors) resulting from working and living conditions or individual behaviour, being considered in the assessment and identification of biological responses and then of the health effects in terms of chronic diseases. It takes account of the extremely close ties between human health and interactions with ecosystems in all living and working environments. Going beyond the classical approaches in toxicology and infectiology (hazard/exposure/dose-effect relationship/risk qualification) followed individually for each stress factor, the exposome concept calls for five important/key factors of health and chronic disease development to be taken into account more explicitly and concomitantly:

- The role of the accumulation of exposure over time, and the delayed nature of the emergence of certain health effects (particularly following chronic exposure);
- Consideration of the "exposure window", based on the observation that the same exposure does not produce the same effects depending on the life period during which the human being is exposed;
- The accumulation of external exposure, both in terms of stressors (physical, chemical, microbiological) and routes of exposure (ingestion, breathing, contact, etc.) leading to internal exposure of different organs and biological systems;
- The interaction between these stressors in the activation of adverse response pathways at cellular level, then in organs, leading to the expression of disease;
- The influence of psychosocial factors as determinants of exposure causes and trajectories.

Although it is an easily accepted assumption that each of these factors weighs in the construction of the response of living beings to their exposure history, their respective weights in this overall response have not yet been determined. This constitutes a source of uncertainty found in public debates on sensitive topics, where the transition from assessment to decision forces a less balanced response. The relevance of experimental models in determining dose-response relationships, confounding factors in epidemiological studies, the consideration of adjustments related to extrapolations (safety factors) in conventional toxicological approaches, etc. are all sources of uncertainty to which this concept ultimately aims to provide a response.

II. The issues and tasks for the Agency

It is important for the Agency to systemically assess the practical consequences of including the exposome concept in legislation by considering the prospects opened up by the scientific work already published and in progress, for its own work and strategic orientations. Based on the formulation of ANSES's corporate purpose, "Investigate, Evaluate, Protect", this would involve outlining points of discussion and then action for the Agency to enable this concept to be developed and integrated in the deployment of its core activities.

ANSES therefore proposes setting up a working group under the Scientific Board, whose primary objective will be to identify these opportunities and build a roadmap with milestones and priorities.

This may include, as appropriate:

- identifying the opportunities, avenues and means for its implementation in the various Agency components: research and reference, monitoring and vigilance, risk assessment, authorisation and marketing of regulated products;
- identifying partnerships and joint work at different levels (regional, national, European, international);
- identifying the need for development/certification of new skills to meet these needs.

Under the key word "Investigate", the activities of the research (implementation) and reference laboratories, as well as those relating to research funding (Research Funding & Scientific Watch Department) or the Agency's monitoring and vigilance missions could be considered.

This could include an examination of how to involve the laboratories and assessment departments in the relevant projects, at national level, or in European (H2020 or FP9 to come) and international initiatives, in order to clarify the concept's scientific developments. Some work towards this goal has already been undertaken (e.g. HBM4EU for overall monitoring, Euromix on the consideration of mixtures, etc.).

In addition to the Agency's own activities, the contribution of the research funding (PNR EST) and scientific watch functions should also be considered, in order to promote and identify the progress being made by the communities on these topics.

As highlighted by the explanation of the exposome concept, the acquisition of data (at different time and space scales) is a major challenge in building its foundations. It would also be useful to reflect on how the Agency's core activity components work on the acquisition/exploration/processing/dissemination of data associated with exposure and its consequences. This could also include the monitoring and vigilance missions which, through the signals they gather, constitute cases of investigation that enable the concept to be tested.

Under the key word "Evaluate", which refers to our risk assessment activities, the concept of the exposome constitutes both a methodological challenge and an analytical key to progress in the assessment of complex situations. As a methodological challenge, it requires the assessment tools inherited from classical toxicology and infectiology to be strengthened, to enable exposures of different types (biological, physical and chemical factors, or even stressors passing through different exposure routes) to be combined with great care, in order to provide a response and recommendations that are tailored to the situations encountered, while identifying the experimental elements needed to validate them.

This also requires progress in terms of knowledge, measurement ("omics" technologies) and recording of exposure (particularly over time and in the various matrices). In terms of analytical keys, the concept will undoubtedly become more operational thanks to the development of advanced methods for assessing complex exposure situations (e.g. contaminated sites and soil, areas with cumulative exposure, etc.).

As the "combinatory" nature of the avenues of exploration in this field is particularly vast, the Scientific Board's working group will be expected to help prioritise the topics to be undertaken.

The ambition "Protect", constitutes the integration of the risk assessment and monitoring actions already mentioned above, in addition to the management of risks related to the fields of biocidal products, plant protection products and veterinary medicines. The exposome concept therefore adds further challenges to the previous ones. It should also be noted that at this stage this same concept has not appeared in the Environmental Code or in other legislative codes dealing with registration or authorisation mechanisms for risk activities.

Risk management paradigms may need to be substantially revised in light of the (scientifically logical) linkages highlighted when cumulative exposures by type and throughout life are taken into account. And this integration also has an impact on all the components (assessment/monitoring/management) of risk governance.

- How is it possible to apply the principle of responsibility of the socio-economic player generating the risk when it requests an authorisation from the public authorities?
    - On what hazard basis should it establish its demonstration of risk control?
    - Which limit(s) should it use to demonstrate the acceptable level of exposure generated?
    - How could ALARA-type principles be implemented...
- How can the "polluter pays" principle be applied?
- How can the existence of different modes of exposure (work and personal life), at different periods of life and involving exposure to anthropogenic or natural hazards via monitored vectors (air, water, food, materials) of sources be taken into account in management mechanisms?
- What role should be played by individual behaviours and situations that can modulate exposure?

It should first be emphasised that these questions have a broad scope and extend into fields (ethical, scientific, legal, etc.) that may go beyond the remit of ANSES's mission, and that the work on these topics undertaken by the Agency with its Scientific Board will also endeavour to define what falls strictly within the Agency's sphere of competence and what should be addressed in other frameworks and contexts.

III. A WG reporting to ANSES's Scientific Board

In order to respond to the issues presented in the previous section, the Agency proposes setting up a WG under its Scientific Board, which could bring together at least a few members of the Scientific Board interested in the issue and experts from different ANSES entities.

The prior discussion with the Scientific Board could in principle define the scope of the missions to be considered (research/assessment/vigilance/monitoring/management).

The work could be based on different steps:

- Bibliographical (and monitoring) work to assess the latest developments and the concept's consolidation from a scientific perspective;
- Hearings by the WG with various figures representing the different stakeholders (scientists, managers, parliamentarians, NGOs), mainly to determine the maturity and political expectations regarding the concept;
- Identification of national, European and international initiatives that contribute to its consolidation;
- Identification of milestones in the mission areas investigated.

The timetable remains to be defined according to the mandate (scope) and objectives.

The findings will be reported to the Scientific Board and then to the Agency's thematic steering committees and Board of Administrators.

Annexe 2 List of selected PNR EST projects dealing with the exposome

List of projects funded by the PNR EST selected for analysis and dealing with one or more components of the exposome.

[1] GEOCAP-PAST (EST-2013-228)

[2] GEOCAP-BIRTH (EST-2016-161)

[3] ZIP (EST-2017-009)

[4] NeuroBiomecaTMS (EST-2014-77)

[5] VITEXPENTE (EST-2021-251)

[6] EPICAP (EST-2012-129)

[7] Icare-Antilles (EST-2013-114)

[8] MULTIASTHMANET (EST-2018-55)

[9] ICARE-VADS (EST-2018-207)

[10] HyPAxE (EST-2019-39)

[11] EXPOSOMFPI (EST-2019-241)

[12] PrémaBQuA (EST-2012-157)

[13] HeLME-UV (EST-2013-205)

[14] EMBRYORAD (RF-2018-25)

[15] ModExPro (EST-2013-177)

[16] TeM(i)S–ESP (EST-2011-107)

[17] SCORISK-PRO (EST-2012-18)

[18] EXPO-ENFANTS (RF-2019-04)

[19] BrumiSaTerre (EST-2016-15)

[20] SESAP (EST-2012-166)

[21] PoDéMos (EST-2019-116)

[22] INFLAREF (RF-2012-21)

[23] silimmun (EST-2015-32)

[24] BarBaPAhR (EST-2015-113)

[25] NanOCo (EST-2019-184)

[26] TOXI-LED (EST-2017-23)

[27] AMeCE (EST-2015-91)

[28] ETNA2 (EST-2015-99)

[29] CARBATOX (EST-2017-102)

[30] TROPHIPLAST (EST-2018-17)

[31] POMELO (EST-2020-102)

[32] TrEMIT (EST-2017-93)

Annexe 3 Further research for the formal request on waste workers

Sumex2 job-exposure matrices were produced by the occupational health department of *Santé Publique France* (Table 7 and Table 8), in collaboration with Inserm. Based on data from the Sumer 2003 survey, they were used to identify occupational exposure in 2003 (71 chemical agents, 18 classes of chemical hazards and 3 physical hazards), according to the industry sector (coded with the French NAF 2003 nomenclature of activities) and/or occupation (coded with the 2003 PCS nomenclature of occupations and socio-professional categories).

Table 9 shows the results obtained for classes of chemical hazards for which the average intensity of exposure of household waste management workers was neither low nor very low.

Table 7: Occupation codes used in connection with household waste management (2003 PCS nomenclature of occupations and socio-professional categories)

2003 PCS nomenclature
387f ENVIRONMENTAL ENGINEERS AND TECHNICAL MANAGERS
477d ENVIRONMENTAL AND POLLUTION TREATMENT TECHNICIANS
628e SKILLED SANITATION AND WASTE TREATMENT WORKERS
684b UNSKILLED SANITATION AND WASTE TREATMENT WORKERS
644a DRIVERS OF HOUSEHOLD WASTE COLLECTION VEHICLES

Table 8: Activity code chosen in connection with household waste management (2003 French NAF activity nomenclature)

NAF nomenclature Rev1 (2003)
90.0B Collection and treatment of household waste ✓ collection and transport of household waste, urban waste and non-hazardous industrial waste ✓ sorting and disposal of non-hazardous waste by all means: incineration, composting, controlled landfill, burial, underwater immersion ✓ management of landfill sites, storage sites, non-hazardous waste transfer stations ✓ management of incineration facilities

Table 9: Agents or classes of chemical hazards for which the average intensity of exposure of household waste management workers was neither low nor very low (Sumex2 extraction)

NAF 2003 description	**COLLECTION AND TREATMENT OF HOUSEHOLD WASTE (90.0B)**				
2003 PCS nomenclature	**Unskilled sanitation and waste treatment workers (684b)**	**Drivers (64)**			
Hazard	Surfactants	Surfactants	Ammonia and aqueous solutions	Ketones other than n-methyl-pyrrolidone	Wood dust
Percentage of exposed workers	16%	9%	2%	2%	3%
Mean exposure intensity	0.31	0.21	0.23	0.26	High (~50%

NAF 2003 description	COLLECTION AND TREATMENT OF HOUSEHOLD WASTE (90.0B)				
					exposure limit)
Mean exposure period	9.3 hours	2.6 hours	From 2 to less than 10 hours		

Annexe 4 Value of taking co-exposure to other contaminants into account when assessing the risk of chlordecone exposure in the French Caribbean – the example of organochlorines

Current management measures for chlordecone focus on this compound and target the production and consumption of foods with low levels of chlordecone, or aim to ensure better targeting of individuals whose exposure must be reduced, or investigate the possible risks induced by such overexposure (formal request to the HAS currently being examined). However, exposure to chlordecone is only one component of the chemical exposome of French Caribbean populations, whose other facets are still poorly understood, especially with regard to concomitant exposure to other contaminants that may have similar biological targets and therefore combined effects.

The proposed example here focuses on organochlorine compounds that have common effects with chlordecone and whose persistence in the environment constitutes a source of exposure for living organisms, even if their levels have been decreasing since the ban on their production and use several decades ago.

A- Co-exposure of the French Caribbean population to organochlorines

The French Caribbean population over 60 years of age has high *p,p'*-DDE concentration levels compared with other populations.

Studies measuring PCB 153, PCB 180 and *p,p'*-DDE concentration levels in the French Caribbean adult population compared with other populations are shown in Table 10.

The study by Emeville et al. (2015) reported plasma concentrations of PCBs, *p,p'*-DDE and chlordecone (CLD) in the male population of Guadeloupe (between 48 and 77 years of age). The authors distinguished between cancer patients and unaffected individuals (controls) in terms of their levels of contamination by these substances (Emeville et al. 2015).

A campaign to analyse organochlorine contamination in the French Caribbean population (Guadeloupe and Martinique) was carried out by the InVS in 2013-2014 on the entire male-female population (Kannari study (Dereumeaux and Saoudi 2018)):

- In Guadeloupe, the average age of the sample (n=292, 187 women + 105 men) was 48 years, 63% of the male population recruited was over 49 years of age. Comparison with the data of Emeville et al. (2015) is difficult due to the different characteristics (age and gender) of the two populations (Emeville et al. 2015).
- For Martinique, only data from the Kannari study are available (Dereumeaux and Saoudi 2018).

This French Caribbean contamination was compared to the serum concentrations in samples collected by the ENNS from the population in Mainland France in 2006-2007 (Fréry et al. 2013, 13) (Table 10). As the ENNS presented its results (geometric means) by age group without differentiating by sex, the comparison could only be made by considering the male population.

A comparison was also made with values from campaigns conducted at similar times in the USA and Canada. However, the demographic characteristics also differ, with the data reported by NHANES relating to the adult population (age ≥ 20 years), both male and female combined.

Table 10: Summary of the main studies measuring concentration levels (ng/g lipids) of PCB 153, PCB 180 and *p,p'*-DDE in the French Caribbean adult population compared with other populations

	Periods	Geometric mean ng/g lipids		
		PCB153	**PCB180**	**p,p'-DDE**
INTERNATIONAL				
NHANES US n=1298-1378 m+w ≥ 20 years	2003-2004	**23.7** (22.3-25.1)	**19.0** (17.9-20.1)	**268** (217-288)
CHMS Canada n=281 men 40-59 years n=280 men 60-79 years	2007-2009	 **23** (20-27) **47** (41-54)	 **22** (19-26) **47** (41-53)	 **145** (117-179) **258** (212-313)
MAINLAND FRANCE				
ENNS (Fréry et al. 2013) n=386 m+w 18-74 years *n=267 m+w 40-74 years* *n=254 women* *n=132 men* n=119 m+w 18-39 years n=190 m+w 40-59 years n=77 m+w 60-74 years	2006-2007	 **113** *164* *121* *105* 64 149 202	 **94** *140* *91* *97* 51 129 168	 **118** *154* *152* *89* 78 143 182
GUADELOUPE				
Karuprostate (Emeville et al. 2015) n=655 men 48-77 years	2004-2007	***134*** [c] *(750 ng/L)*	***115*** [c] *(640 ng/L)*	**320** [c] *(1770 ng/L)*
Kannari (Dereumeaux and Saoudi 2018) n=292 m+w 19-88 years n=187 women n=105 men n=60 m+w 19-39 years n=142 m+w 40-59 years n=90 m+w 60-88 years	2013-2014	 **31** 19 28 10 36 99	 **22** 31 33 5 28 85	 **121** 141 97 46 135 304
MARTINIQUE				
Kannari (Dereumeaux and Saoudi 2018) n=450 m+w 19-88 years n=272 women n=178 men n=73 m+w 19-39 years n=215 m+w 40-59 years n=162 m+w 60-88 years	2013-2014	 **44** 42 46 14 51 107	 **31** 28 35 7 41 91	 **81** 102 60 27 83 217

m: men; w: women; c: calculated from concentrations in µg/L using data from Emeville et al. 2015

Regardless of the compounds (all bioaccumulative) or populations studied, a tendency for concentrations to increase with age is constantly observed.

With regard to PCBs (153 and 180):

- The contamination measured in men over 48 years of age in Guadeloupe between 2004 and 2007 (134 ng/g lipids for PCB 153 and 115 ng/g lipids for PCB 180) was higher than that measured at a similar period (2007-2009) on a similar population (men over 40 years of age: between 23 and 37 ng/g lipids for PCB 153 and between 22 and 47 ng/g lipids for PCB 180) in Canada. On the other hand, these levels appear to be equivalent to or slightly lower than those measured in a mixed population over 40 years of age in mainland France during the same period (between 149 and 202 ng/g lipids for PCB 153 and between 129 and 168 ng/g lipids for PCB 180).
- More recent contamination measurements observed in Guadeloupe (2013-2014) in men and women over 40 years of age (between 36 and 99 ng/g lipids for PCB 153 and between 28 and 85 ng/g lipids for PCB 180) showed a decrease in this contamination between 2004 and 2014.
- The comparison of concentration levels measured in Guadeloupe or Martinique in 2013-2014 with levels reported in mainland France (2006-2007), which is more complicated because it relates to different study periods, nevertheless showed a downward trend in mainland France as well as in the French Caribbean (Figure 34 and Figure 35).

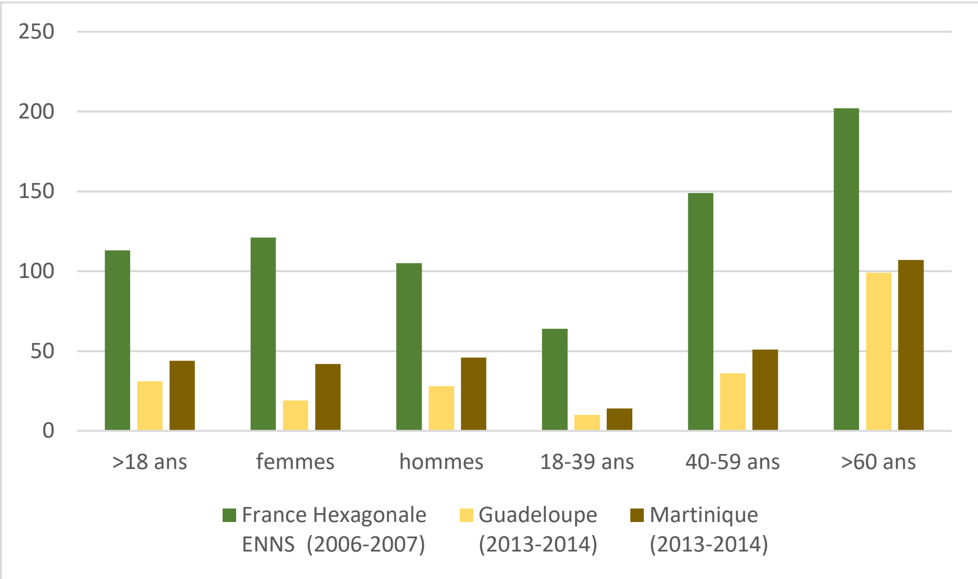


Figure 34: PCB 153 concentration levels in the French Caribbean and in mainland France of adults over 18 years of age (in ng/g of lipids)

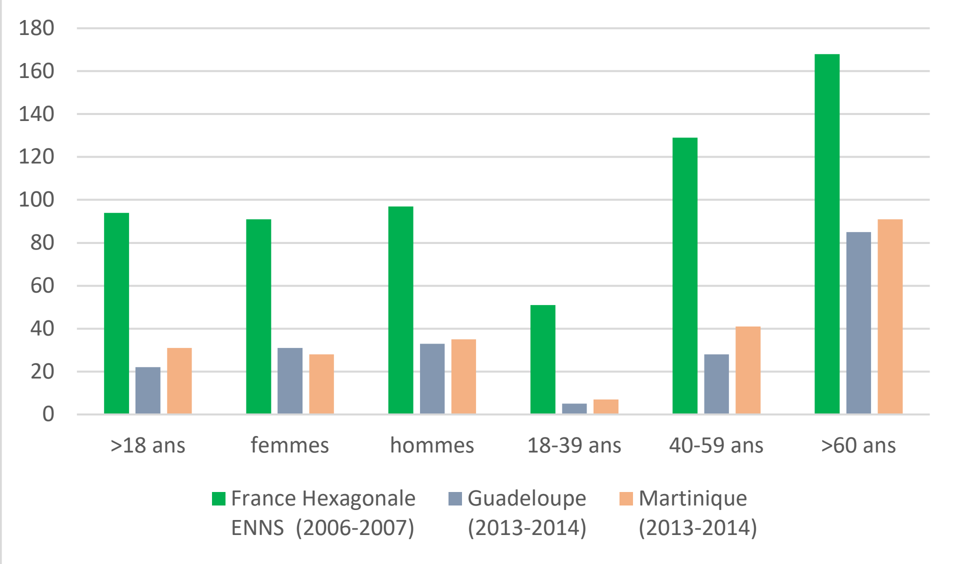


Figure 35: PCB 180 concentration levels in the French Caribbean and in mainland France of adults over 18 years of age (in ng/g of lipids)

With regard to *p,p'*-DDE:

- The average levels measured in 2004-2007 in Guadeloupe in a male population over 48 years of age (320 ng/g lipids) were higher than those reported for an equivalent and contemporary population in Canada (between 145 and 258 ng/g lipids). Similarly, they were higher than those reported in mainland France for the same period (men and women over 40 years of age: between 143 and 182 ng/g lipids).
- Recent contamination measured in 2013-2014 showed a high level for adults over 60 years of age (304 ng/g lipids in Guadeloupe and 217 ng/g lipids in Martinique) (Figure 36). A more detailed analysis of the distribution of this contamination (Table 11 and Figure 37) reveals a marked difference in the higher percentiles, especially in Guadeloupe. Thus the levels observed in Guadeloupe (2013-2014) and expressed in ng/g lipids[77] were between 1.85 (at P50) and 3 (at P95) times higher than those observed in mainland France (2006-2007).
- *p,p'*-DDE contamination was systematically higher in women than in men (Figure 36).

[77] Expressed in ng/l, the levels were between 1.6 (at P50) and 2.3 (at P95) times higher than those observed in mainland France (2006-2007).

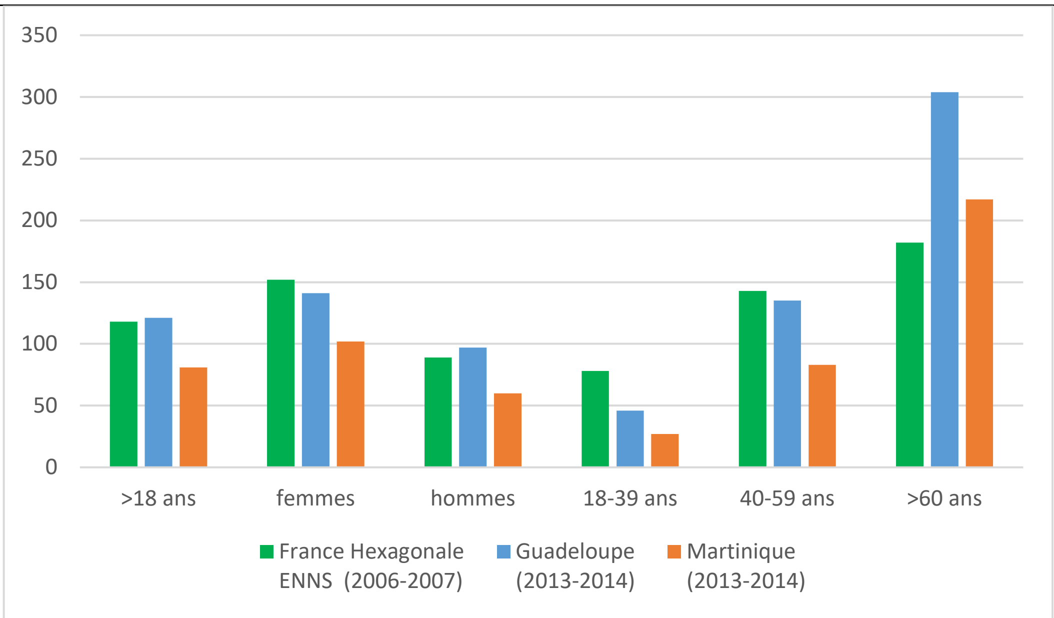


Figure 36: *p,p'*-DDE concentration levels in the French Caribbean and in mainland France of adults over 18 years of age (in ng/g of lipids)

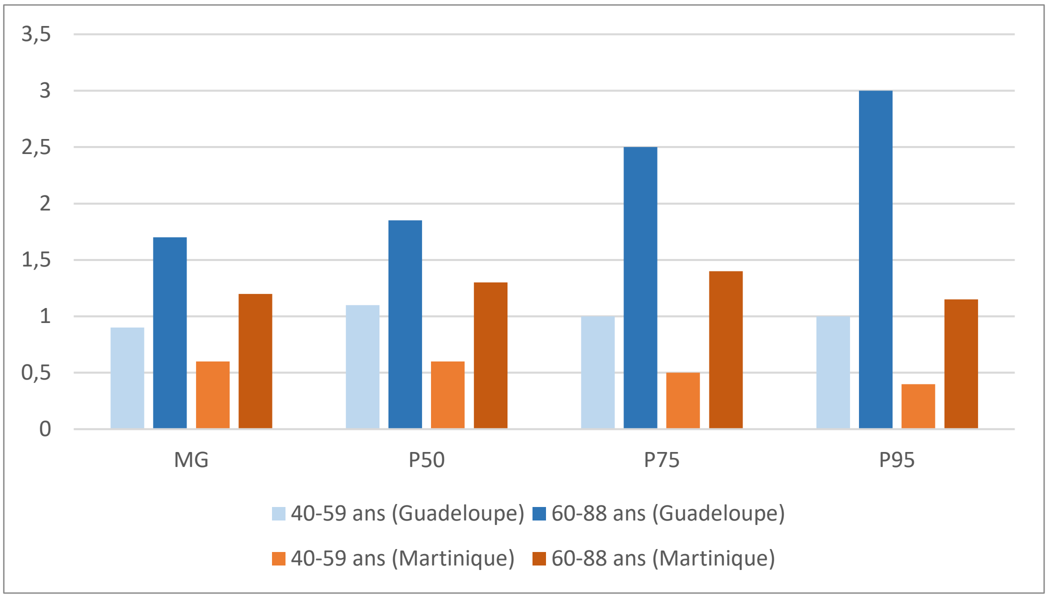


Figure 37: Ratio of *p,p'*-DDE contamination in individuals over 40 years of age between Guadeloupe and Martinique and mainland France (ng/g lipids)

Table 11: Distribution of *p,p'*-DDE contamination in Guadeloupe/KANNARI study 2013-2014 and in Metropolitan France/ENNS 2006-2007. Ratio of contamination for the age groups 40-59 and >60 years

***p,p'*-DDE**	**Geometric mean**		**P50**		**P75**		**P95**	
	ng/g lipids	ng/L	ng/g lipids	ng/L	ng/g lipids	ng/L	ng/g lipids	ng/L
Guadeloupe 2013-2014 KANNARI								
N=292 m+w	121	646	104	570	336	1935	1533	7205
40-59 years	**135**	**750**	**133**	**699**	**268**	**1594**	**986**	**4902**
60-88 years	**304**	**1712**	**336**	**1879**	**696**	**3910**	**2369**	**12309**
∑ women	141	761	148	772	442	2437	1626	8278
∑ men	97	516	77	445	248	1339	1106	5298
Martinique 2013-2014 KANNARI								
N=450 m+w	81	440	83	427	203	1121	596	3312
40-59 years	**83**	**451**	**80**	**466**	**138**	**744**	**344**	**1866**
60-88 years	**217**	**1268**	**236**	**1438**	**400**	**2322**	**919**	**5609**
∑ women	102	556	100	546	229	1390	761	4203
∑ men	60	328	63	320	154	819	397	2259
Metropolitan France 2006-2007 ENNS								
N=386 m+w	118	760	104	699	214	1411	729	4932
40-59 years	**143**	**985**	**125**	**888**	**270**	**1791**	**922**	**5676**
60-88 years	**182**	**1254**	**181**	**1177**	**280**	**1987**	**790**	**5318**
∑ women	152	1003	146	899	281	2066	790	5564
∑ men	89	560	86	558	144	924	657	3825
Ratio [Guadeloupe]/[Metropolitan France]								
40-59 years	0.9	0.8	1.1	0.8	1	0.9	1	0.86
60-88 years	**1.7**	**1.4**	**1.85**	**1.6**	**2.5**	**2**	**3**	**2.3**
Ratio [Martinique]/[Metropolitan France]								
40-59 years	0.6	0.5	0.6	0.5	0.5	0.4	0.4	0.3
60-88 years	**1.2**	**1.0**	**1.3**	**1.2**	**1.4**	**1.2**	**1.15**	**1.0**

These data support a possible French Caribbean specificity with regard to high *p,p'*-DDE concentration levels in individuals over 60 years of age, particularly in Guadeloupe. Indeed, the concentration levels reported in 2006-2007 and then in 2013-2014 were still higher than for the other age groups and were higher than those reported in mainland France in 2006-2007 (not counting the possible decrease in concentration levels in metropolitan France since 2006-2007).

B- What are the sources of organochlorines (DDE and PCBs)?

Although we have no precise data on the sources of exposure to PCBs and DDT in the French Caribbean, several reports (Anses 2011a; Fréry et al. 2013; Weitekamp et al. 2021) have shown that since these substances were banned, food has been the main source of exposure for the general population in all the territories studied. According to the InVS (Fréry et al. 2013), in metropolitan France, more than 90% of total exposure to PCBs comes from food, and in adults, more than 50% of dietary exposure to PCBs comes from fishery products (freshwater and sea fish, seafood). The same report indicates that the main route of exposure to DDT and its transformation products in the environment (DDE and DDD) is currently via food. The highest estimated average levels of DDT residues are found in milk, ultra-fresh dairy products, eggs and egg products, and seafood (Anses 2011a). Apart from food, a possible source of exposure to DDT could be the relatively recent use of dicofol in agriculture. Indeed, dicofol was used in combination with tetradifon in Martinique and Guadeloupe until 2008 as a mite-control treatment for the aerial parts of banana trees (Gentil et al. 2018). Depending on the production site, the dicofol could contain up to 25% DDT (Qiu et al. 2005).

C- Effects of organochlorines observed on populations living in the French Caribbean

Epidemiological studies conducted in recent years on the French Caribbean population have revealed a number of health effects in individuals exposed to organochlorine compounds.

1- *p,p'*-DDE, PCBs and prostate cancer

Emeville et al. (2015) identified a significant association between plasma *p,p'*-DDE concentrations and prostate cancer (PCa) in Guadeloupe, in the same male population as Multigner et al. (2010), in terms of age – over 45 years – and numbers. The association was significant for plasma levels of *p,p'*-DDE ≥ 5.19 µg/L (5^{th} quintile versus 1^{st} quintile <0.79 µg/L) with an odds ratio (OR) of the same order of magnitude as that for chlordecone (Table 12).

Table 12: Risk of prostate cancer in Guadeloupe related to exposure to chlordecone and/or DDE: odds ratio (OR) and 95% confidence interval (95% CI) in Multigner et al. (2010) and Emeville et al. (2015)

OR (95% CI)						
	Multigner et al. 2010 DDE and PCBs not taken into account	**Emeville et al. 2015** Model not adjusted for other organochlorines	Model adjusted to: DDE	PCB153	DDE + PCB153	PCB153 + chlordecone
Chlordecone						
≥ 0.96 µg/L[a]	1.77 (1.21–2.58)					
≥ 1.03 µg/L[b]		1.65 (1.09–2.48)[d]	1.64 (1.09–2.47)[d]	1.70 (1.12–2.56)[d]	not calculated	
***p,p'*-DDE**						
≥ 5.19 µg/L[c]				1.53 (1.02–2.30)[f] 1.73 (1.08–2.78)[e]		1.51 (1.01–2.27)[f]

[a] 3[rd] tertile (LOD 0.25 µg/L); [b] 5[th] quintile (LOD 0.06 µg/L); [c] 5[th] quintile

[d] adjusted for age, waist-to-hip-ratio, PSA screening history, and total plasma lipid concentrations. Missing values were imputed using a multiple imputation by chained equation (MICE) approach in five data sets;

[e] adjusted for age, waist-to-hip ratio, type 2 diabetes, alcohol, total plasma lipid concentration and PCB153. Missing values were imputed using a multiple imputation by chained equation (MICE) approach in five data sets.

[f] adjusted for age, waist-to-hip ratio, type 2 diabetes, alcohol, total plasma lipid concentration, PCB153 and restricted to control and cases with complete datasets

The PCa-PCB 153 association was not significant (PCB 153 was the PCB indicator used in the analysis).

The Emeville et al. (2015) study was reported by the IARC (2018) in Monograph No. 113 on the evaluation of the carcinogenic potential of DDT[78] and its metabolites (Emeville et al. 2015; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2018); the IARC stressed that this epidemiological study was the largest case-control study to date on DDE and prostate cancer based on biological measurements of exposure.

***p,p'*-DDE contamination is a risk factor for prostate cancer in Guadeloupe.**

2- ***p,p'*-DDE, PCBs and neurodevelopmental toxicity**

The studies carried out by the teams of L. Multigner and S. Cordier, as part of the TIMOUN mother-child cohort in Guadeloupe, measured the concentrations of *p,p'*-DDE and PCB 153 in parallel with those of chlordecone in the umbilical cord, in the studies on child health (cognitive, motor and behavioural effects, infant growth and thyroid function in the infant population). Other elements known to be risk factors (mercury, lead) or beneficial factors (selenium, docosahexaenoic acid [DHA]) for neurodevelopment were also taken into account. Measurements were taken in umbilical cord blood (plasma or whole blood), to reflect prenatal contamination. Postnatal contamination was only measured for chlordecone, in breast milk collected three months after delivery. The significant sex-dependent decrease in thyroxine associated with prenatal exposure to *p,p'*-DDE is evidence of its impact on thyroid function. Given the role of thyroid function in neurodevelopment, *p,p'*-DDE contamination is liable to affect the child population in the same way as chlordecone.

Along with immunotoxicity, the neurodevelopmental toxicity of PCBs was one of the two criteria used to establish guideline values for PCBs, by the WHO (Faroon et al. 2003) and by AFSSA in 2007 (Anses 2007a). In the case of PCBs, numerous epidemiological studies report reduced cognitive performance and motor and psychomotor deficits, associated with pre- and postnatal exposure (Tilson, Jacobson, and Rogan 1990; Jacobson and Jacobson 1996; Trnovec et al. 2008; Lynch et al. 2012), but not all are convergent.

p,p'-DDE has a similar toxicological profile to that of chlordecone. Indeed, the most significant effects of DDT and DDE have been observed on neurocognitive and behavioural development, which may persist in childhood (Eskenazi et al. 2006; Ribas-Fitó et al. 2006; Torres-Sánchez et al. 2007; van den Berg et al. 2017).

DDT, DDE and PCBs appear almost systematically in the cocktail of organochlorines in contaminated environments and have been incriminated simultaneously as aetiological factors in neurological disorders (Rogan et al. 1986; 1987). This requires them to be treated as confounding factors in the analysis of associations, but this is not always done. Neglecting the

[78] DDT has been classified in Group 2A as probably carcinogenic to humans; with sufficient evidence in animals for the carcinogenicity of both DDT and *p,p'*-DDE.

effect of any of these contaminants could bias the results and interpretations[79], and **lead to inappropriate management measures being taken**.

Contamination by *p,p'*-DDE and PCBs is likely to affect the child population in the same way as chlordecone.

D- Other effects of organochlorines reported more generally in animals and humans

Organochlorines often encountered in contamination studies include *p,p'*-DDE (active metabolite of DDT), PCBs, hexachlorobenzene (HCB), β-HCH (degradation or contamination product of lindane or γ-HCH). Their toxicity in animals and humans has been summarised by the ATSDR (US Agency for Toxic Substances and Disease Registry 2019; 2000; 2015; 2005; 2020), the WHO (WHO/IPCS 1984; 1991; 1997; Faroon et al. 2003; World Health Organization 2011) and the IARC, the latter of which re-assessed the carcinogenicity of PCBs in 2016, and that of DDT/DDE/DDD and lindane in 2018 (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2016; 2018).

Due to their lipophilicity, these organochlorines cross the placental barrier and pass into breast milk; their half-life of several years in humans, except for chlordecone, favours their bioaccumulation and long-term toxicity.

The qualitative analysis of their toxicity shows a common toxicological profile: hepatotoxicity, neurotoxicity and neurodevelopmental toxicity, reprotoxicity and endocrine disruption (Table 13).

[79] A typical example is hearing impairment in children and adolescents following exposure to neurotoxic substances during development; these disorders were for a long time attributed to PCBs alone (Crofton et al. 2000; Trnovec et al. 2008), until Sisto et al. 2015 demonstrated that other organochlorines were also involved, especially *p,p*'-DDE, *p,p'*-DDT, the β-isomer of hexachlorocyclohexane (β-HCH) and hexachlorobenzene, all of which are correlated with PCB153 (Sisto et al. 2015).

Table 13: Toxicological properties common to the organochlorines chlordecone, *p,p'*-DDE, PCB, HCB and lindane

Toxicity	CLD	***p,p'*-DDE** ATSDR 2004	**PCB** ATSDR 2004	**HCB** ATSDR 2004	**Lindane (γ-HCH)** ATSDR 2005
Half-life	63-165 d	6.9 years[a]	3-9 years (7-14)[b] 3-10 years (work)[c]		1-25 d[d] 7 years β-HCH
Nephrotoxicity	x				x
Hepatotoxicity	x	x	x	x	x
Immunosuppression		x	x	x	x
Thyroid hormone alterations		x	x	x	
Reprotoxicity	x	x	x	x	x
Neurotoxicity	x	x	x	x	x
Neurodevelopment	x Timoun	x EPA 2004, Timoun	x		
Foetotoxicity Malformations		x	x	x	x (animal)
IARC classification	2B 1987	2A (DDT) 2018	1 2016	2B 2001	1 2018
Endocrine disruptor	Binds to ERα, ERβ	Antiandrogenic	Oestrogenic or Antioestrogenic depending on the congeners*		Antiandrogenic Antioestrogenic
Other					Haematoxicity

[a](Ritter et al. 2009); [b](Grandjean et al. 2008); [c](Shirai and Kissel 1996); [d](US Agency for Toxic Substances and Disease Registry 1994); * in addition to alterations of thyroid activities by some PCB metabolites

The mechanisms of endocrine disruption by substances found alongside chlordecone differ according to the compounds.

- DDT and its metabolites induce oestrogen-dependent cell proliferation (Soto et al. 1995); while *o,p*'-DDT is a weak agonist of the ERα and ERβ oestrogen receptors (Kuiper et al. 1998), *o,p*'-DDT, *p,p'*-DDT and especially *p,p'*-DDE are androgen receptor antagonists, with *p,p'*-DDE being the most potent antiandrogen among them (Kelce et al. 1995; 1997).

At the thyroid level, a significant inverse relationship has been noted between DDE concentrations and thyroid hormone levels in umbilical cord blood in several mother-child cohort studies in China (Luo et al. 2017) and Europe (Maervoet et al. 2007; Krönke et al. 2022).

p,p'-DDE contamination was significantly associated with an increased incidence of *diabetes* (T2D) (Turyk et al. 2009; Cox et al. 2007; Everett et al. 2007). Prenatal exposure was associated with childhood obesity in twelve prospective studies (Vrijheid et al. 2016), with significant sex-dependent effects in boys, compared with girls (Warner et al. 2014).

- **The endocrine activity of PCBs** on steroidal sex hormones is more complex, as their antioestrogenic or antiandrogenic activity depends on the degree of chlorination of the congeners, the position of the chlorines in the structure, and the activity of their metabolites (Bonefeld-Jørgensen et al. 2001): highly chlorinated congeners are antioestrogens and their hydroxylated metabolites are more active than the parent compound. On the other hand, low-chlorinated PCBs and their hydroxylated metabolites are generally oestrogenic. It is therefore difficult to predict the activity of a PCB contamination cocktail given the variety and diversity of these contaminants. Note that Goncharov et al. (2009) found a decrease in testosterone levels in the Native American (Mohawk) male population, significantly associated with four congeners (PCB 74, 99, 153 and 206) and four congener groups (mono-ortho-substituted, di-ortho-substituted, tri- and tetra-ortho-substituted, and dioxin-like TEQs), which supports the previous assertions.

The thyroid is the main target organ for PCBs after the liver. They interfere at different levels of thyroid function: binding to the thyroid receptor (agonists), competing with thyroid hormones for transporter proteins to the target tissues, decreasing thyroid hormone levels (Krönke et al. 2022). These effects on thyroid function may have been responsible for the cognitive, motor or psychomotor deficits recorded during *in utero* and/or postnatal exposure mentioned in section 2 on "*p,p'*-DDE, PCBs and neurodevelopmental toxicity" (Tilson, Jacobson, and Rogan 1990; Jacobson and Jacobson 1996; Trnovec et al. 2008; Lynch et al. 2012).

Cardiovascular disorders in the form of an increased incidence in *hypertension* were demonstrated in the population of Anniston (Alabama, US), which had suffered from longstanding exposure to industrial PCB pollution (Goncharov et al. 2010). Epidemiological studies are now able to identify exposure to persistent organic pollutants, especially PCBs, as a risk factor for hypertension, diabetes and obesity, all of which result from the genesis and progression of cardiovascular disorders (Perkins et al. 2016).

Many cases of gestational diabetes (Vafeiadi et al. 2017) and childhood obesity (Tang-Péronard et al. 2014; Lignell et al. 2013; Dallaire et al. 2014) have been attributed to PCB exposure.

The neurodevelopmental, cognitive and behavioural effects of ***p,p'*-DDE and PCBs**, which may persist in childhood, explain why the female population of childbearing age and the infant population are considered targets of their toxicity (Eskenazi et al. 2009; World Health Organization 2011). Furthermore, the involvement of prenatal exposure to DDE and PCBs in childhood obesity needs to be explored in the French Caribbean.

More broadly, the involvement of these organochlorines as factors in hypertension, type 2 diabetes and obesity in the general adult population should be studied.

E- Combined effects of chlordecone and other organochlorines

There are currently no data on possible interactions between CLD and other OCs in terms of health risk, even though, as presented in Table 13, CLD and other OCs share common toxicological effects and targets.

F – Conclusions on co-exposure to organochlorines in the French Caribbean and their health effects

Although the available data, in particular those on food contamination, are currently insufficient to carry out a quantitative assessment of the risks associated with exposure to other OCs, they converge in showing the advantage of considering these substances in the same way as CLD. Indeed, the evidence from the literature presented above illustrates the fact that the co-exposure of French Caribbean populations to persistent organic pollutants – in particular PCBs and DDE – raises health questions about the combined risk of metabolic syndrome with multiple consequences, neurodevelopmental risks in the infant population, and prostate cancer in the male population, associated with exposure to chlordecone.

G- Conclusion on the need to consider other contaminants when assessing the risks of chlordecone exposure

The example of organochlorines in the context of persistent chlordecone contamination in the French Caribbean shows the need to extend the risk assessment of CLD to other environmental contaminants.

Like organochlorines, other contaminants found in the French Caribbean environment such as PAHs, dioxins and furans, hexachlorobenzene, pentachlorobenzene and DDE could potentially interact with chlordecone on several health outcomes, or cumulate their effects. Their identification is necessary for a more comprehensive assessment of the risks and to better adapt management measures.

The Exposome WG believes that there is a need to broaden the scope of investigation of exposure to chemical contaminants of interest in the French Caribbean, beyond chlordecone alone. In the area of food, this requires a total diet study in the French Caribbean, coupled with a biomonitoring study. The next biomonitoring study (Kannari 2) will be an opportunity to conduct such an integrated study in order to update and collect contamination data on other contaminants of interest and better document their dietary sources.

Monitoring of organochlorine contamination should cover the whole population and not be limited to adults heavily contaminated by chlordecone, which would risk neglecting long-term and multi-generational metabolic diseases, which may affect the child population, women of childbearing age, and the population in general (Gore et al. 2015)**.**

The biomonitoring of human populations (e.g. HBM4EU) developed in Europe has indisputable value (Ganzleben et al. 2017)**, as has its application to the French overseas *départements* (DROM) and the outermost regions of the European Union. It is even a necessary condition to strengthen the policy of prevention and health management related to chlordecone.**

FRENCH AGENCY FOR FOOD, ENVIRONMENT AND
OCCUPATIONAL HEALTH & SAFETY

14 rue Pierre et Marie Curie F-94701 Maisons-Alfort Cedex
www.anses.fr — @Anses_fr

979-10-286-0461-5 - Legal deposite: march 2024 - Anses Editions - CC BY-NC-ND