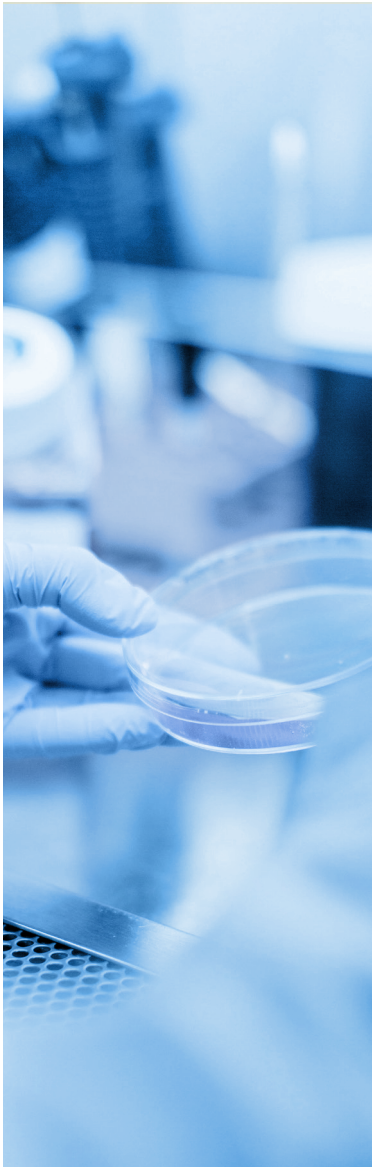
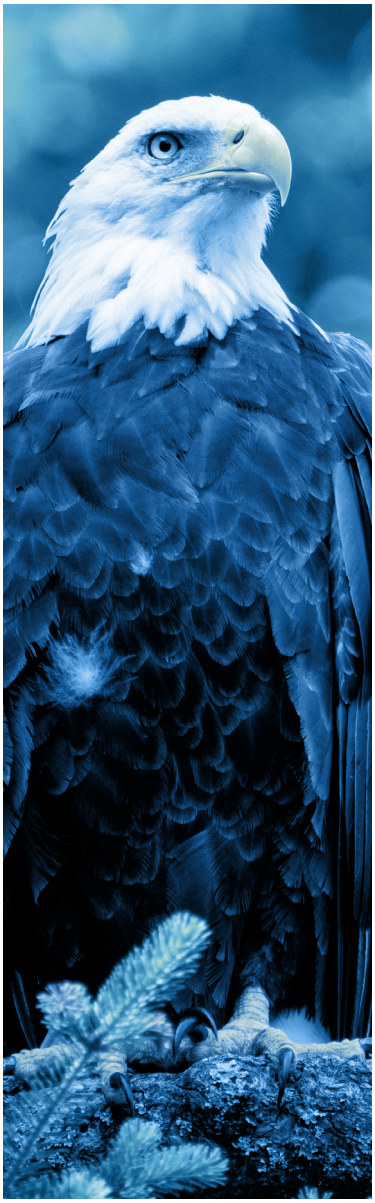
PUBLIC-PRIVATE PLATFORM
FOR THE PRE-VALIDATION
OF ENDOCRINE DISRUPTORS
CHARACTERIZATION METHODS

Pepper





“We are certain of the following: a large number of man made chemicals that have been released into the environment, as well as a few natural ones, have the potential to disrupt the endocrine system of animals, including humans.”

This statement, made by scientists at a conference in Wingspread, Wisconsin, in 1991, is at the origin of the concept of endocrine disruptor (ED). It unified observations on humans and wild animals, through identifying a new mode of action that led to a reassessment of the toxicity of certain substances. Thus, in December 2021, following the consideration of its ED effect, the European Food Safety Authority (EFSA) recommended dividing by 100,000 the tolerable daily intake of bisphenol A (BPA), a chemical widely used in many sectors.

EDs, because they interact with hormones, can sometimes be very active at low doses. They can have critical harmful effects at certain stages of life and be inactive at others. And they can cause harm to health and environment. It is therefore important to identify and characterise them.

However, we are still lacking validated tests to evaluate the ED character of a substance and its mode of action, and to study all the effects of EDs.

On the other hand, many laboratories develop test methods. When they are not validated, the repeatability, the reproducibility and the relevance of the test are not secured. These methods can then both lead people to believe, wrongly, in the nontoxicity of certain substances and disqualify others without any scientific ground.

Established in 2019, Pepper is the culmination of 10 years of efforts. It combines public and private resources and ambitions to bring a solution to this problem by developing and funding the pre-validation of characterisation methods in order to provide mankind with the ED toolbox that it is critically lacking.

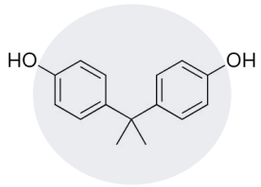
Work has started. The team is in place. Several methods are in pre-validation. In Europe, more and more laboratories are aware of the opportunity offered to them to validate their methods. But to continue, accelerate and sustain Pepper’s action, we need your support. We need to raise around 26 million euros to allow us, over the next 10 years, to pre-validate the 25 to 30 methods capable of reliably identifying chemicals’ ED properties.

With your help, we can meet the challenge!

Laurence Jacques, *President, Pepper*

WHAT IS AN **ENDOCRINE DISRUPTOR** (ED)?

An ED is "an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations" (WHO, 2012). It is a natural or synthetic chemical which can block, mimic or disrupt a hormonal function. This disruption may lead to diseases, disorders or ill health. Above all, because the level of hormones involved in so many vital functions is actually low, even very low level exposure to EDs can have a strong and sometimes permanent impact on health. And EDs can have the same damaging effects on animal species and affect biodiversity.

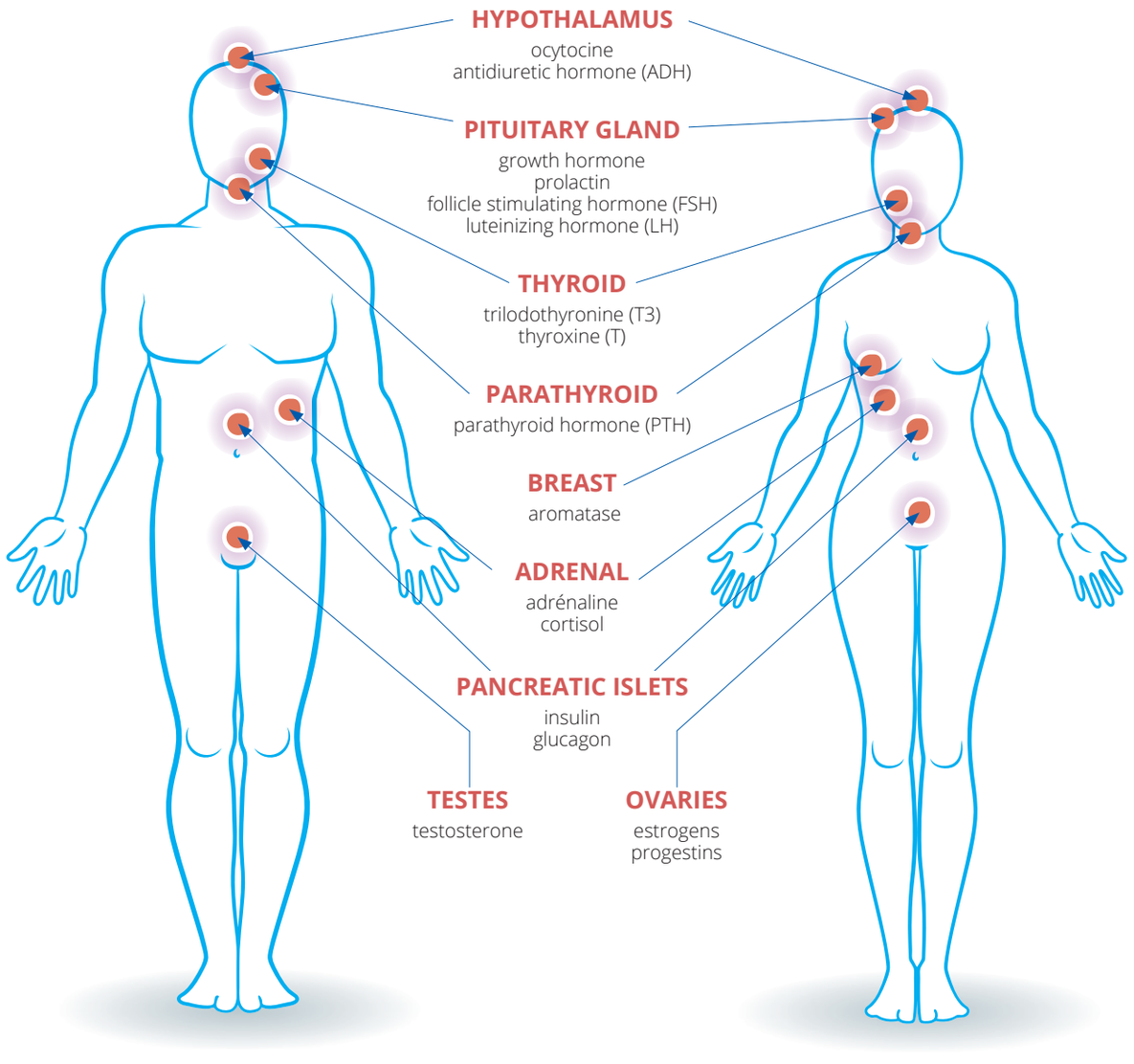


EDs interact with the endocrine chemical messaging system involved at every stage of life, from conception to old age. This "hormone signalling" system orchestrates the body's main essential functions: metabolism, immunity, reproduction, cognition etc.

> ***The ED notion was conceptualised in 1991 by 21 scientists meeting in Wingspread*** *(Wisconsin, USA)* ***at the initiative of Theo Colborn****. At that time, the main issues at stake were the alteration of sexual development from exposure to chemicals and human/wildlife interaction. Since then, the pressure against EDs has gradually intensified: a growing number of potential damages have been identified, risk management tools have started to include the new potential issues; more recently, EDs have been integrated into the "****EU Chemicals Strategy for Sustainability****" (2020) and the EU is creating in 2022 an "ED" class in the classification, labelling and packaging of chemicals ("CLP" Regulation).*

Endocrine disruption: the issues at stake

- **Numerous organs and hormones**
- **Responsible for the regulation of numerous physiological functions (reproduction, development, metabolism, heart rate, fertility ...)**
- **Long term and potentially irreversible effects**
- **Effects even at low dose**



HOW ARE WE EXPOSED TO ENDOCRINE DISRUPTORS IN OUR DAILY LIVES?

We may breathe, eat, drink and come into contact with endocrine disruptors every day. They may be present inside our homes, our schools and workplaces as well as in consumer products - clothing, toys, cosmetics, electronics, furniture, household products, cars, building materials, bathing and drinking waters, food, packaging etc. Research revealed the presence of many EDs in most people who were tested, including newborns.

THE CASE OF BISPHENOL A, banned from food containers

Bisphenol A (BPA) is a synthetic chemical substance mainly used in the manufacture of resins and plastics. In France, this substance was potentially used by about sixty industries. Since 1 January 2015 in France, BPA has been banned from use in the composition of food containers (baby bottles, bottles, cans etc.). In June 2017, the European Union classified BPA as a "substance of very high concern" under the REACH regulation, as an endocrine disruptor. REACH also banned its use in cash register receipts and thermal paper from 2 January 2020 and, on 15 December 2021, EFSA proposed to reduce the tolerable daily intake for humans by a factor of 100,000 in an opinion submitted for consultation. It should be noted that consumers have often been a step ahead of regulation, for example by ceasing to buy baby bottles containing BPA before their ban.

ALL SECTORS ARE CONCERNED

WE MUST ACT NOW TO ENSURE A HEALTHIER ENVIRONMENT FOR FUTURE GENERATIONS

Numerous studies have confirmed that EDs can have a wide range of effects on humans and fauna: reduced reproductive capacity, sexual malformations, early puberty, certain cancers (breast, ovaries, prostate, testicles), delayed cognitive development, altered response to stress, obesity, diabetes etc. However, we have very limited knowledge on many substances. The effects may also vary according to the period of life during which exposure occurs. In utero development, early childhood and puberty are critical periods in this respect, as early exposure can have consequences arising later in life.

A group of experts has estimated in 2015 the cost of damages linked to EDs in the European union at €157 BILLION per year, not including environmental costs.

> *"We must act now to reduce our exposure to EDs and that of our children, to ensure a healthier environment for future generations."*

IMPROVING IDENTIFICATION TO PROTECT HEALTH AND THE ENVIRONMENT

At the end of 2021, 15 substances and families of substances were identified as EDs by the European Chemicals Agency. In addition, ANSES has identified 906 "substances of interest" with regard to ED characterisation. The high number of suspected but not yet characterised substances attests to the scale of the problem. We have to identify the mechanisms of action, the range of effects and the causal link between endocrine activity and harmful effect, which requires to carry out several tests for each substance. There are still only few methods available and they generally focus on only one of the three above-mentioned dimensions of endocrine disruption. Moreover, they require heavy and expensive studies (a reference test for mammals, the "OECD 443" guideline, can involve the sacrifice of more than 1,000 rats, two years of work and a budget of €1.3 million).

We are sorely lacking a comprehensive, efficient, accredited framework, involving minimal animal testing and including methods which are validated to be universally recognised.

A BLATANT LACK OF VALIDATED TEST METHODS

The lack of validated test methods (i.e. methods whose quality has been proven and acknowledged by international authorities), combined with concerns around EDs, creates a level of uncertainty detrimental to society and businesses. Aware of these limitations, the European Commission called, in 2018, to progress in the development of international test guidelines with the development of methods free of unnecessary animal suffering.

This situation also generates a proliferation of experiments led by public and private laboratories, but which often do not meet the quality criteria (repeatability, reproducibility, relevance of the measurement) to draw a reliable conclusion.

These problems lead to both the under-detection of EDs and the exclusion of certain substances which may be too quickly qualified as EDs. Progress is therefore needed. This is why the European Union has defined a **framework for action and research on endocrine disruptors** and France, for instance, has established its **second National Strategy on Endocrine Disruptors (SNPE).** The Commission worked on the definition of hazard categories for an "Endocrine Disruptors" class in the CLP regulation (Classification Labelling and Packaging).

Pepper is therefore a "validation accelerator"

providing this missing and essential link between researchers and regulators. To this end, the project pools public and private resources in order to optimise the connection between research and the needs expressed by the society and the industry. At the end of the road, the OECD develops guidelines for chemicals testing and validates methods, awarding them multilateral recognition by member countries and enforceability in chemical regulations. This expertise gives Pepper a unique know-how in the technical implementation and validation of ED tests, with the support of an international network of qualified partners and laboratories. Established by France, the Pepper project is thus part of the European logic.

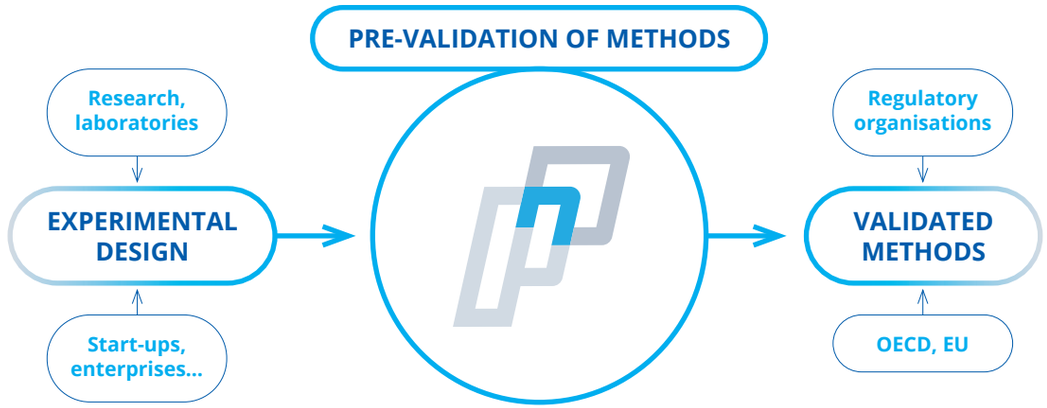
AN INNOVATIVE FRAMEWORK FOR THE FUNDING OF PRE-VALIDATION

The international Pepper project addresses the following four issues: long lists of substances to be evaluated; a blatant lack of validated test methods; costly and time-consuming laboratory work needed to validate the robustness of test methods; lack of dedicated financial resources at European and national levels. Launched on 2 December 2019, Pepper offers an innovative framework for the funding of pre-validation, i.e. the essential step consisting in making laboratory methods reliable so that international authorities can incorporate them into a regulatory framework. The work consists in identifying new methods and having them verified by "naive" laboratories in order to complete the toolbox critical to EDs identification.

In this context, Pepper manages and funds the following three activities:

- identifying and documenting test methods for the identification of EDs;
- organising inter-laboratory tests (reproducibility of results etc.);
- proposing successfully pre-validated methods to international authorities.

Pepper, the missing link



PEPPER PROVIDES THIS MISSING AND ESSENTIAL LINK BETWEEN RESEARCHERS AND REGULATORY ORGANISATIONS

Pepper, AN ACCELERATOR FOR THE VALIDATION OF TEST METHODS

Pepper's governance (an association under the French law of 1901) is made of several entities guaranteeing efficiency, ethics and transparency: the Board of Directors, the Scientific Council, the Ethics Committee and the Relevance Committee - whose role is to prioritise the methods likely to enter the pre-validation phase. The selection of methods is therefore made by a committee involving environmental associations, health and biodiversity stakeholders, industry and public bodies representatives. This committee includes French, European and international organisations. It brings together researchers from the academic and industrial sectors.

The Pepper team coordinates the daily running of the project, thanks to a large network of partners (some of which are part of the Relevance Committee and the Scientific Council). In total, more than 70 experts contribute to the work.
Pepper's annual budget (operations, laboratory tests, scientific monitoring etc.) is currently around €3 million (half public, half private).

THE FIRST RESULTS

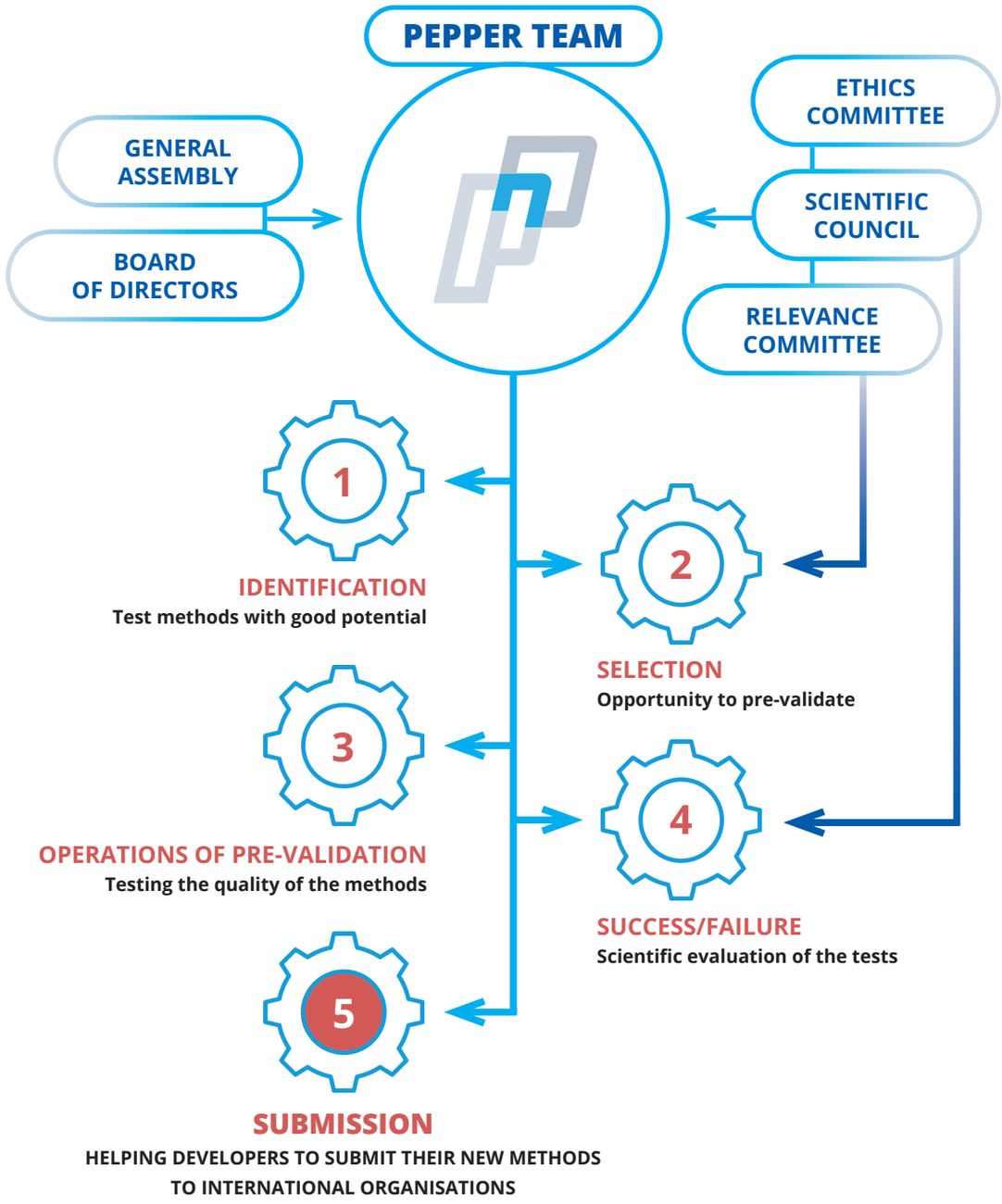
IN 2020, following a call for tenders, 17 methods were identified and submitted to Pepper's Relevance Committee, three of which were selected on 11 September 2020 to enter the pre-validation phase. These three methods aim at assessing the effect of substances respectively on:

- placental function in pregnant women, using human cells;
- hormone synthesis, using effects observed on human adrenal cells;
- activation of the glucocorticoid receptor, using human cancer cells (cervical adenocarcinoma).

IN OCTOBER 2021, three new methods were selected to assess the effects of substances on:

- the retinoic system (involved in multiple functions such as reproduction and development, eyesight etc.), by measuring the transactivation of the retinoic acid receptor on human cells;
- avian sexual development, by exposure inside the hen's egg;
- cognitive function, by measuring the proliferation of human neural progenitor cells.

Involving stakeholders in Pepper's gorernance



TESTIMONIALS

The issue of EDs concerns most industries. Wishing to assert their social responsibility, participate in the global research effort and protect consumers, several dozen partners have joined Pepper (companies, laboratories, government departments, international organisations and NGOs), thus contributing, through their know-how and specific knowledge, to providing solutions in the field of endocrine disruption.

Barbara Pompili,

French Minister of Ecological Transition and Solidarity

To identify EDs and withdraw them quickly from the market, we need internationally validated tests and methods. These tests must be developed in order to better characterise the harmful effects of EDs on ecosystems and human health, by identifying the modes of action of these substances. In this respect, I support the development of the Pepper public-private platform, a French initiative already including some European partners, and I invite European stakeholders, both public authorities and European industries, to join this platform, so as to accelerate the rolling-out of characterisation methods, which is really at the core of the ED issue.

GOUVERNEMENT
Liberté
Égalité
Fraternité

Bob Diderich,

Head of Division at the OECD

The OECD has been working on these issues for many years and agrees with the observation made by several stakeholders that there is still a real need for the development and, in our case, the validation, of test methods. We see the [Pepper] platform as a complementary tool to the work of the OECD, which will allow our Organisation to be more rapid and efficient in its work on the guidelines. We therefore welcome again this initiative which will accelerate the research and development of such methods.

OECD
BETTER POLICIES FOR BETTER LIVES

Bernard Bigot,

President Fondation de la Maison de la Chimie

The Fondation de la Maison de la Chimie, given the importance of EDs in terms of public health, wished to financially support the launch of the Pepper platform. By developing new ED characterisation methods that are currently lacking, this initiative will allow both improve consumer protection and provide the industry with a more secure working environment.

Fondation de la Maison de la Chimie

HOW TO TAKE PART?

In order to secure and consolidate its resources on the long term and to increase its outreach and the number of validated test methods, Pepper is particularly looking to recruit new Founding and Supporting members at European and international level.

You are invited to support Pepper to accelerate the development and pre-validation of test methods and contribute to the common good.

CONTRIBUTIONS FROM LEGAL ENTITIES *(institutions and companies)*

CONTRIBUTION AMOUNT	COMMITMENT	OBJECTIVE	COMMUNICATION	CATEGORY OF MEMBERS
500,000 €/year	3 years	To fund the pre-validation of 3 full tests	Associated to the institutional communication of Pepper	Founding platinum
500,000 €/year	One-off	To fund the pre-validation of one full test	Associated to the institutional communication of Pepper	Sponsor
151,000 €/year	One-off	To contribute to the work of Pepper over 3 years	Associated to the institutional communication of Pepper	Founding gold
31,000 €/year	One-off	To support the work of Pepper over 3 years	Associated to the institutional communication of Pepper	Supporting
1,000 €/year	Annual	To support the work of Pepper during 1 year		Ordinary

Other types of contributions are possible: please contact us for any question.

CONTRIBUTIONS FROM INDIVIDUALS

CONTRIBUTION AMOUNT	COMMITMENT	OBJECTIVE	COMMUNICATION	CATEGORY OF MEMBERS
100 €/year	Annual	To support the work of Pepper during 1 year		Individual

THANK YOU TO ALL OUR FOUNDING MEMBERS

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RÉPUBLIQUE FRANÇAISE

MINISTÈRE DE LA TRANSITION ÉCOLOGIQUE ET SOLIDAIRE

Fondation de la Maison de la Chimie

FRANCE CHIMIE
CRÉER
RÉVÉLER
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THANK YOU TO ALL OUR SUPPORTING MEMBERS

MINISTÈRE DU TRAVAIL, DE L'EMPLOI ET DE L'INSERTION
Liberté Égalité Fraternité

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Liberté Égalité Fraternité

BAYER

LVMH / RECHERCHE
Parfums & Cosmétiques

Afise
Fédérer & promouvoir

BASF
We create chemistry

PEPPER TEAM

From left to right

Director
Philippe HUBERT

Management, public relations
LOUISETTE KAISERMANN

Senior toxicologist
Elise GRIGNARD

Ecotoxicologist
Andrea RIVERO ARZE

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