# REPORT

## Pepper 5th anniversary symposium

## Endocrine Disruptors: Accelerating methods validation to improve our protection

**December 6th 2024, Paris**

*Crédit photos: Jean Hubert*

PLATEFORME PUBLIC-PRIVÉ POUR LA VALIDATION DES MÉTHODES DE CARACTÉRISATION DES PERTURBATEURS ENDOCRINIENS

Pepper

**January 2025**

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*Pepper thanks its founding members, supporting members and other supports*

*Pepper thanks the sponsors of the event*

*Pepper thanks the members of the event organizing committee : E. Poivet, E. Blaton, C. Boudet, V. d''Enfert, G. Lemkine*

# Abbreviations

CLP : Classification Labelling Packaging
CRO : contract research laboratory
DG RTD : Directorate-General for Research and Innovation
EATS : Estrogen, Androgen, Thyroid, Steroidogenesis
ECHA : European Chemical Agency
ED: Endocrine Disruptors
ENKORE : Endocrine Disrupting Chemicals and Knowledge on Health-Related Effects
EURION : European Cluster to Improve Identification of Endocrine Disruptors
GHS : Global Harmonized System
GOLIATH : Generation Of Novel, Integrated and Internationally Harmonized Approaches for Testing Metabolism Disrupting Chemicals
ISO: International Organization for Standardization
MAD : Mutual Acceptance of Data
NAMs : New Alternative Methods
NAMWISE : NAMs Within Integrated Safety & Efficacy evaluation of chemicals and pharmaceuticals
OECD : Organization for Economic Cooperation and Development
PARC : Partnership for the Assessment of Risks from Chemicals
SOP : Standard Operated Procedures
UNEA : United Nations Environment Assembly
UNEP : United Nations Environment Program
WHO : World Health Organization

# INTRODUCTION

**Philippe Prudhon, president of Pepper**
**Philippe Bodenez, Board member of Pepper/French Ministry of Ecological Transition**

Pepper team is glad to host this symposium on validation of methods of EDs characterization, to celebrate its 5th anniversary. Pepper became a reality at the end of 2019, when France included the public-private platform project in its EDs National Strategy, at a time when the various stakeholders - European Commission, national authorities, manufacturers and consumers - had expressed the need to speed up the process of identifying EDs to preserve health and the environment. The need for a complete, effective, demonstrative package, including methods validated to be universally recognized, is critical. However, available methods are still few and far between, while the effects and mechanisms of action of endocrine disruption are numerous. In addition, animal studies, which are cumbersome, long and expensive, require significant resources and are subject to substitution.
The 5th anniversary of PEPPER is an opportunity to take stock of the work carried out, to discuss the validation process and to find funding for the coming years. We would like to thank all speakers, facilitators and panelists, as well as Pepper previous presidents, Anne Dux and Laurence Jacques. We would like as well to thank our founding and benefactor members, our members, and the sponsors of the event for their support. We hope that today's debates will lead to pragmatic and concrete actions to accelerate the validation of methods for characterizing the hazards of chemical substances and of course EDs.

# SESSION 1 - Validation of methods in Europe, a tool for endocrine disruptors policies : challenges and perspectives


***Picture 1*** *: keynote speaker Jordane Wodli, European Commisision,*
***Picture 2*** *: From left to right panelists Philippe Hubert (Pepper), Ofelia Bercaru (ECHA), Maurice Whelan (ECVAM/JRC), Bob Diderich (OECD), Cécile Lemaître (French Ministry of Health) and facilitator Cécile Michel-Caillet (Anses)*

## Keynote speech

### Jordane Wodli, DG Environment, European Commission

Pepper was born during the negotiations of the first (French) ED National Strategy (SNPE 1), back in 2013, and I am very glad to be there today to celebrate 5 years of Pepper. The European Union and the Commission are currently developing several regulatory approaches related to EDs and validation. The future REACH revision will lead to a modification of REACH annexes, and new data requirements for ED properties. An important success of the Chemicals Strategy for Sustainability is the addition of recent addition of two new hazard classes in CLP regulation, namely ED for human health and ED for the environment, and paves the way for an horizontal approach of hazard assessment of ED. Secondly, the "one substance, one assessment" approach involves a reattribution of tasks between EU agencies, and an improvement of data sharing (reuse of data, etc.). When it comes to international level, current negotiations take place at GHS level, to harmonize ED criteria at a global level, and include ED criteria within the GHS. Another element is the update of UNEP/WHO 2012 State of the science report on EDs, which should be presented at the next UNEA. On the research part, as part of Horizon Europe, we can mention the EURION project, financed by DG RTD, to support a cluster of projects developing new test methods for EDs. ENKORE, a new cluster, has been launched in June 2024, to succeed EURION. Another complementary aspect, especially interesting for Pepper, is the current development of a Roadmap on NAMs for ED characterization and identification, following a request from a European citizen initiative. The roadmap aims to be an overarching document setting milestones, on how to use NAMs to analyze and describe steps to replace animal testings, and include NAMs in regulations, to use them. The Commission stresses the importance of stakeholders, like Pepper, which have experience in pre-validation, and can help fill existing gaps. Mutual acceptance of data is an important aspect, funding, and better spending funding is another critical point, together with the consideration of regulatory needs, and prioritization on development test methods. The organizational structure of validation is another point to be addressed, where Pepper can also bring an added value. Both expert level and policy level decisions are needed. An interesting point is which legislation has a need for which endpoint, which can vary depending on sectorial legislations (cosmetics, medicines, etc.). Pepper can also help in ensuring an objective decision-making process, in building a balanced governance.

## Discussion panel

**Ofelia Bercaru (ECHA), Bob Diderich (OECD), Maurice Whelan (ECVAM/JRC), Cecile Lemaître (French Ministry of Health and Prevention), Philippe Hubert (Pepper), Cécile Michel-Caillet (Anses)**

### Quotes : a few words from panelists

"We need validation for MAD: we cannot except the US to accept a test result produced in the EU with European methods that they are not been part of developing. The only way to reach MAD is to develop together and that we all ask for the same methods to cover our regulatory data needs."

"Test guidelines are very important for the implementation of REACH to give confidence to those that test that they are accepted by the regulators."

"My recommendation would be to make use of what we have, deal with the knowns rather than the unknowns, and understand how we can use existing tests in regulatory decision-making."

"We now have a framework at EU level to identify those substances, thanks to CLP revision and new hazard classes on EDs, which is a prerequisite to banning them. But testing methods are needed, and they need to be validated at international level to be used and recognized in European regulations. As said, some methods exist today, but this is difficult to use them at international level, because making a regulatory use of them requires operations to prove reproducibility, repeatability, robustness."

"When we started Pepper, we started with the observation that there was a huge gap between research people and regulatory science […] The second point was to decide to be pragmatic and to go forward instead of waiting for something perfect. We are doing three kinds of things: select and identify relevant methods that should undergo validation, "technical validation", and then showing that one can trust what Pepper is doing."

## Summary

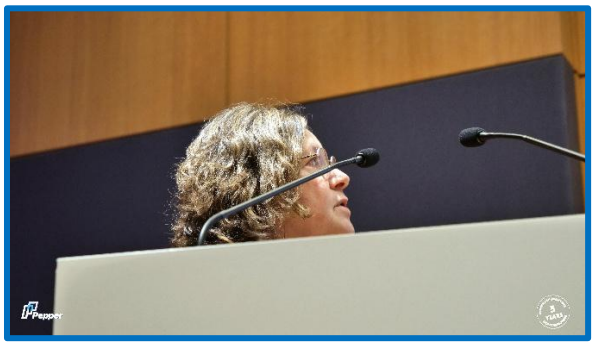
The first part of the discussion was to define the need for validated methods. This need was highlighted by some speakers to ensure the safe use of chemicals. However, the number of methods needed is still difficult to quantify. A number of 30 methods have been proposed as a reasonable set to ensure the characterization of PEs. At the same time, it was proposed to use the existing one because the participant identified the blockages more at the stage of acceptance by regulatory authorities and the industry rather than the existence of these validated methods. However, another speaker stressed that existing testing methods, or if non-animal methods were used, should have predictive capacity and provide legal certainty under CLP. CLP regulation has created a new hazard class for ED. To classify as an ED, a chemical needs to have endocrine activity, adverse effect and a plausible link between the two. The term 'validation' was then discussed by the panelists. The validation process is described in a dedicated OECD guidance and is defined by OECD members as "the process to assess reliability and relevance of a method intended for a particular purpose". It cannot define in advance the regulatory acceptance of the method and whether it will meet a specific need. However, validation acts as a means of building trust in the test result and represents a quality assurance system. Validation is only a step and the ultimate step is the inclusion into the regulatory requirements (or equivalent process). In the event that this process does not occur, one panelist wondered whether a simple technical validation would not be sufficient. The added-value of having TG tests methods was emphasized. It was concluded that validation embrace many different steps that could be distinguished. The role of each panelist affiliation in this process was described; Pepper has a real added value in terms of validation : the platform was launched at the same time as the 2nd (French) EDs Strategy, and is a successful initiative which has accelerated the process for 13 methods so far

## Conclusion

**Dr Cécile Michel-Caillet, Anses, session's facilitator**

"The effort to be made in terms of regulatory needs is enormous and it would be more bearable if it were shared by the actors of all regulations with hazard identification needs. In addition, many scientific fields are likely to develop methods that need to be explored. Validation is a complex process, in which different phases can probably be distinguished. The concept and its definition must be harmonized, and ongoing work such as that conducted by Pepper and the OECD aims to improve the system. Also, when a method has been validated and proves to be robust, i.e., it guarantees the necessary legal certainty in its interpretation, the path leading to its guideline, and ultimately the inclusion and acceptance among all stakeholders, will be guaranteed. "

# SESSION 2 - Validation, the missing link to move from research to tools and methods: experience and expectations from the field



***Picture 1:*** *Keynote speaker Dr Ella Atlas, Health Canada, chair of Pepper scientific council*
***Picture 2:*** *From left to right panelists Michael Oelgeschlaeger (German Federal Risk Assessment Agency), Joëlle Rüegg (Uppsala University), Gregory Lemkine (Watchfrog laboratory), Majorie van Duursen (Vrije Universiteit Amsterdam), Sjoerd Verkaart (CRL), Patrick Balaguer (IRCM/Inserm), and facilitator Sebastian Hoffmann (seh consulting + services)*

## Keynote speech

**Dr Ella Atlas, Health Canada, president of Pepper scientific Council**

Under OECD Council decision of 1981, which is legally binding, guidelines generated in any member country in accordance with OECD test guidelines and GLP principles should be accepted for regulatory purposes in all member countries. What is validation in an OECD context? A developer, generally an academic lab, proposes an assay, with the objective of making it a guideline. Are regulatory authorities in need of the test, and are they going to accept it? This is one of the major gaps. What data need to be provided? Is the test reproducible, sensitive, specific? OECD GD 34, provides some guidance. A test is developed by scientists, academics, then they optimize the assay and develop a methodology or SOP to be followed. There are several stages: independent review of the SOP and the results to be provided to the OECD, pre-validation stage, inter and intra-laboratory transferability, assessment of the test performance, evaluation of its relevance and reliability and finally, development of a test guideline for use under mutually accepted data (MAD). There are many stages, and the process is very slow and can take years. As a result, very few standardized tests do exist. The challenge is that there are thousands of chemicals with potential ED properties, and using animal models as the only tests can be

problematic, because we cannot possibly assess tens thousands of chemicals using standardized tests as accepted today by the regulations. Historically, EDs were limited to EATS, but many other tissues can be the target for ED and there is a gap in the testing for EDs, including metabolic diseases, immunotoxicity, etc. There is a need to speed up, as there are so many chemicals being produced and already on the market, which need to be tested. We need to evaluate new methods based on reproducibility, biological relevance, regulatory usefulness – this is a big one. Incorporating methods, as an integrated approach, like standardized by the OECD, is probably the way to go. Today, health outcomes related to metabolic disorders are a huge burden for morbidity and mortality of population in developed societies. However, studies can have a blind spot for the tissues affected by many of the metabolic disrupting chemicals: adipose, pancreas, liver, muscles. Another issue is: can you actually rely on the information in the literature to make regulatory decisions? To be accepted by regulators, you need to prove reproducibility, which is the exact same experiment repeated multiple times in separate laboratories. Academic labs are not going to do it, except if there are incentives, because of no interest in reproducing exactly someone else's results, no benefit for career progression, required funding or attracting students. Another problem is to gather a sufficient number of chemicals to prove the specificity and sensitivity of the assay, in the chemical space. Several examples [such as the glucocorticoid transactivation study, adipogenesis, estrogen receptor activation] highlight the importance of using standardized methods to address an endpoint. Coming to NAMs, they are being developed at a very high rate, like for instance by the US EPA. There is a lot of data out there, however if not accepted by the regulatory community, how is it going to move the regulation speed? Some of these NAMS require a lot of expertise, and standardized protocols should be developed for every lab to be able to replicate those results. There is a need for organizations like Pepper to take some of those methodologies and move them forward to make them become standardized tests. To conclude, test developers, generally academics, are from Mars, and regulators from Venus, or *vice versa*, and we need a practical guide for improving communication, and to get assays that can be used by everybody. To move forward, more labs need to participate in the validation exercises. Methodologies to investigate ED effects are advancing constantly in academic labs. Collaboration between academia, regulatory agencies and industry is imperative to arrive at MAD.

## Discussion panel

**Patrick Balaguer (Inserm/IRCM), Majorie van Duursen (Vrije Universiteit Amsterdam), Gregory Lemkine (Watchfrog Laboratory SA), Michael Oelgeschlaeger (German Federal Institute for Risk Assessment), Joëlle Rüegg (Uppsala University), Sjoerd Verkaart (Charles River Laboratory), Sebastian Hoffmann (she consulting + services)**

### Quotes : a few words from panelists

"As CROs, if there is a guideline, industry would like to perform the test, and this is something we do for them. Most important to them is to show our clients that we do our regular core business, it does not matter so much if we need to test a number of chemicals/compounds."

"I think we can also reduce the budgets […] in the whole validation process, we can also be a little more pragmatic on what's really needed to validate a test method, and what's nice to know and what needs to be known."

"If we don't have criteria on adversity, we cannot develop alternative methods on these criteria, so we really need a strong academic research to work on fundamental research, and, sorry, to work with animals, because that is what will give us the possibility to develop non-animal methods. […]. There is a need of mutual agreement of the need to develop methods."

"You can improve the impact of validation papers if we try to solve some controversial problems in validation, by introducing some controversial chemicals I the process, for which you know there are false positives or false negatives."

"Everyone in academic research should once be in this respect [of doing validation], because then you would have more respect in how you write materials and methods. […] Pepper in this validation process, they take you by the hand and guide you through every single step."

"In my experience, validation never goes the way you plan it, so project planning is made relatively difficult. [..]. People often underestimate the difficulty of developing a functional SOP. This is a lot of work, and it is crucial to involve a naive lab in [that phase]. The blinding [stage] really shows if there is unbiased evaluation of the data."

## Summary

For academic labs who develop methods, validation of methods is very challenging because they are not organized or equipped to do that, and not used to testing chemicals repeatedly, writing the SOPs, etc. One challenge is that method validation doesn't allow neither publications in so-called high impact journals, nor to students to learn different methods. On timing, validation processes take very long, and funding from EU projects, [such as EURION] stops after some time, not allowing to complete validation, and new funding has to be found. No consensus exists on funding. Some consider research projects should not fund validation, because validation is not research, and scientists' core business is to lecture and research, while others consider academic research should be involved in validation, as sometimes unexpected adverse effects would be observed, which will feed research. The methods developed by private laboratories have to fill various data gaps and regulatory needs. SMEs have this way of working : adapting to needs, etc. and have an important role to play. Not all labs validating tests are working the same way : universities have been described as being very flexible, and not used to working with SOPs, while CROs are said to be generally not flexible and only working with SOPs. Coming to validation stages : the "blinding" is essential to allow unbiased evaluation of the data, because completely different results are not something uncommon, and the method is intended to be used to unknow test chemicals. Besides money, tools are needed as well. Interactive and independent support with validation expert managers was mentioned as crucial, for CROs for instance. An entity which takes the lead in the process, establishes and keeps timelines, and provides constructive feedback is essential. Pepper does a critical job in validation. Because it is an independent institution, Pepper has more flexibility than some national public authorities. It proves also to be more sustainable. On governance: Pepper's relevance committee was mentioned as a unique space of discussion where different stakeholders - NGOs, science, industry – share their points of view on the needs and relevance to develop a method. It is transparent and has a very democratic way of selecting assays and could be further improved in acting more upstream. One option discussed for the future was a "validation institute", so a more institutional approach [than Pepper]. Among technical aspects, an important one mentioned was the continuous availability of cells. If the validation is successful, cells have to become commercially viable, if not, only the developer labs can perform the tests. On the number of methods/assays to be validated, a discussion on what is really necessary, and what assays are going to be validated is necessary. Some consider a handful rather than a hundred new assays are needed. They would have to be relevant in terms of social need, to pay back to society. "Validation" is not a terminology only valid only for the field of methods validation. Any kind of validation would have similar challenges, like the selection of criteria, etc. and synergies would make sense, in the biomarker medical field, also in more commercial interest fields, etc. Communication between medical and chemical/biocidal fields needs to improve. Industry support was mentioned as essential for a method to be used, as part of a tripartite agreement between science, authorities and industry. Methods, once validated, should be tools to reach MAD, and be performed in three different continents: that's a huge work.

## Conclusion

**Sebastian Hoffmann, seh consulting + services, session's facilitator**

"From what we have heard, a lot is going on on validation. Based on the discussions, I see several needs. Firstly, a need for collaboration - between academia, SMEs and those that help in validation. Secondly, a need from regulators to bring regulatory needs into the process, to ensure that the final products are fit for purpose. And finally, a cross-sectoral collaboration. What I heard about Pepper, is that it is unique, provides a gathering platform where stakeholders can exchange, and builds trust. Shortly, it is a "doing body", that makes validation happen."

# SESSION 3 - Validation, a common good: mutualizing resources and organization to accelerate and secure validation in the long term


***Picture 1:*** *Keynote speaker Hans Meijer, Dutch Ministry of Infrastructure and Water Management*
***Picture 2:*** *From left to right panelists Robert Landsiedel (BASF), Tony Musu (ETUI), Pascal Sanders (PARC/Anses), Juliette Legler (EURION/Utrecht University), Katherine Santizo (Cefic), Alain Chabrolle (FNE), Laure Geoffroy (NAMWISE/Ineris), and facilitator Nathalie Homobono (French Ministry of Economy)*

## Keynote speech

### Hans Meijer, Dutch Ministry of Infrastructure and Water Management

The topic of this session is how to use and organize our resources better in validation. In previous sessions, we answered the question: do we need to validate all tests ? No, we need to make a selection, and have governments accelerate the validation of the test methods which we really need, to increase the safety of chemicals as soon as possible. Within the EU, we have comprehensive regulations of chemicals, but test methods are still lacking when it comes to assessing whether chemicals or pesticides can contribute to illnesses disrupting the immune or endocrine systems. For some complex issues, and despite large public resistance, we still rely heavily on animal testing which is not only expensive but also inhumane especially when not necessary. So, the problem is clear, and there's large support to solving the issue, but there seems to be a lack of recognition of the need for validation. It takes money and time to validate. But when you work on chemical safety, you want to be safe today, and certainly not in five to ten years from now. Moreover, starting a validation process offers no guarantee of a positive outcome. Today, the part of EU and national funds spent on validation is very limited, whereas it is necessary to spend appropriate amounts to all steps in the chain. So we need to identify gaps, put money where they are, make sure we include all relevant stakeholders, that methods will be useful and available for all relevant parties. One important message is that we need money, but mostly, we need to use available funds more effectively. Involving industry is important, not only for funding, but also because they can contribute with a lot of science, and at the end, clear

indication of risks is in their interest as well. For instance, Alzheimer's disease has been recognized as linked to basically all pesticides. However it is not clear which pesticide(s), so industry would benefit to know and link an effect to a chemical, to turn to another less problematic chemical. And, also the availability of animal-free test methods might reduce time and costs and create more safety of chemicals. So, Pepper's work is important on validation of tests for EDs. A similar approach should be used as well for other endpoints like the harm to the immune system or neurodegenerative effects. In the EU, I would like to refer to the role of the European Commission, and to the Council decision asking the Commission to make a Strategy on Tests and Validation. This should help in achieving an harmonized approach towards testing and validation, and increase efficiency. Such a strategy should give further guidance and clarity and increase efficiency.

## Discussion panel

**Alain Chabrolle (FNE), Laure Geoffroy (NAMWISE), Robert Landsiedel (BASF SE), Juliette Legler (Utrecht University), Tony Musu (ETUI), Pascal Sanders (Anses), Katherine Santizo (Cefic), Nathalie Homobono (French Ministry of Economy)**

### Quotes : a few words from panelists

"From my experience on what LRI (Long-range Research Initiative) does: it really utilizes the industry experience, and the way of work for industry to better improve how we assess chemicals.[…]. On validation, the global piece is quite important: for industry, as global companies, I would agree that we should be European […] this has to be further discussed before implemented, because it becomes a little bit complicated."

"We should find a way for a better communication between developers and regulators. Basically, regulators have to make decisions/opinions based on available data. Having one place to encourage dialogue, and have a more regulatory vision when developing tools than looking purely to answer a scientific challenge."

"Within GOLIATH, the (EURION) project that I coordinated, we pre-validated four different methods for identifying metabolic disorders and worked with experts in validation who acted as an independent advisory group. We learned as scientists the important steps involved in validation, which I would recommend to every scientist. I would recommend including validation in scientific projects."

"We would need somebody to set priorities, run the trials [….] really to organize it, all that is missing. I think it [validation] is totally an under-professionalized area. If you want to do a validation, you're all on yourself, and everybody has to have all the experience you need from the start. Coming to the proposal: let's have an organization which is collecting this experience, giving it and giving the frame for validation, and it already exists."

"Coming to the definition of a common good : when a shared objective for the whole community, and for instance public service/safety and risk assessment agencies contribute to the common good. To build trust in those processes, they must be based on science, evidence-based science, to get an evaluation process which is robust, recognized and shared by all."

"We are glad of the evolution of the CLP legislation, its new hazard classes. Another example is the CMR directive, which protects workers: Belgium is the first country to have extended the scope of the CMR directive to EDs. We think this is a good evolution. On the question "who should pay?" it is clear that the industry should be the main contributor to methods validation, since those who are putting the chemicals on the market are responsible to make sure that they can be safely used."

"Becoming a member of Pepper relevance committee seemed natural to us, because elsewhere in Europe, people working on ED are used to working with similar platforms with funding, governance, objectives. Several options are open for the future : a European Economic Interest Grouping? A participation of research programs? A tax on widespread pollution? etc?"

## Summary

Scientific knowledge has been questioned for several years, and science faces a crisis of reproducibility, not only on NAMs but in general. From a research perspective, the fact that

ENKORE, the next cluster of EDCs projects at EU level – successor of EURION - is not focusing on test methods development was called a "missed opportunity" by some panelists. In the field of toxicology for example, the need for fundamental research to always go hand in hand with the implication of methods for the greater good, for public health and the environment was stressed as well. One panelist pointed out that animal methods and NAMs should not be opposed but rather considered complementary, while underpinned by prioritization. At international level, in addition to OECD, there are other existing systems developing methods, like ISO, the standardization system, for which, contrary to OECD, you have to pay to access guidelines/protocols. At EU level, political will was deemed necessary to improve validation. From an NGO perspective, one motivation to participate in Pepper has been the fact that today scientific knowledge is challenged. This has two types of negative consequences: an insecurity in decision-making which happens to block regulation, and a loss of trust from the general public. And validation is at the heart of these issues. Pepper plays a role in unifying, by starting from each stakeholder's experience. A laboratory without professional experience in validation, loses a lot of time and money, and needs to be guided – as does Pepper. Pepper can be called a "common good" as it shares the experience of its team on validation applied to ED tests. In today's society, discussions on decision-making are complex, many contexts of uses exist, and validations can therefore have different levels, different targets… which may be an obstacle to move from research to use. OECD is clearly the highest level, with MAD at the international level. From a trade union perspective, validation of methods is needed to protect efficiently workers who manufacture chemicals, and those exposed to them in different sectors of the economy. The evolution of EU legislation (CLP regulation for instance) is seen as positive for workers' protection. On the trust issue, a public-private approach is considered as contributing to trust. Regarding funding, the model of Massachusetts and its Toxic Use Reduction Act was mentioned. Some panelists considered that labs should fund themselves to participate in validation, since to offer the method to customers later on, they have to establish, run and test it anyway. Pepper for instance, with its public-private funding, provides a space where two different worlds can meet, which is certainly key for developing new tools. In terms of organization, there is a need for both national and EU networks of private and public laboratories, to allow risk assessment agencies and regulators to access shared competence and more trust in developed methods. If better organization and control of validation are reached, including quality insurance in the development process, the rest of funding should be covered by those who want the tests in the end. Since validation benefits both industry and regulators, a public-private partnership approach seems a right option to many. Furthermore, validation could include a more market-based approach, and incur costs on participating labs, to allow a kind of "natural" selection of relevant methods.

## Conclusion

**Nathalie Homobono, French Ministry of Economy, session's facilitator**

"Validation is clearly considered as a kind of common good, which should be at the same time robust, valid and efficient on the long-term. Pepper plays a role in it today, and this should be continued or consolidated, but under which form? The issue is still pending. All of you expressed strong support for involving a diversity of stakeholders to build and ensure trust in validation results. In terms of funding, a diversity of funding, including public and private contribution, is seen as a guarantee for robustness, whether at the stage of research programs – although diverging views do exist – or later in the process. Finally, on governance, the diversity of stakeholders involved is certainly an important aspect to take into account."

# CONCLUSION

**Philippe Prudhon, president of Pepper**

All speakers and panelists recognize validation is essential to improve EDs characterization, and that is true for all assays whatever the goal. Secondly, validation appears as the natural continuation of research to feed the regulatory process. Just as a standard meter is key to measure, a series of methods validated and recognized by all is key to identifying ED. Thirdly, we should avoid wasting money and time to validate certain methods which would duplicate existing ones or produce information we already know or produce data that are felt useless. To avoid this, an inventory of existing methods should be conducted, which Pepper did 5 years ago, when we started, but would need to be updated to reflect new scientific data. The diversity of panelists shows the need to have a debate with all stakeholders. This includes of course research laboratories, Contract Research Organizations, national and European public authorities, scientists, industry, but also NGOs and workers. Indeed, EDs characterization is a societal concern, and a real educational effort is needed to make debates understandable to non-experts, or more often between experts in different domains. Pepper Relevance Committee reflects this approach. As we have seen, we already have regulatory instruments, such as REACH and CLP regulations, in which ED became a new hazard class. Time is now to act. Since we absolutely need a panel of methods to characterize ED, first because industry has the obligation to answer public authorities on the properties of their substances, in particular ED properties. Secondly because all interested parties need a pragmatic and rapid response. Any future (European) Strategy on method development and their validation should consider evolution of knowledge, science, experience, and new expectations but in the short term we should act. If a clear institutional framework for guidance and maybe operations is a highly desirable long-term objective, a pragmatic approach to encourage efficient and rapid action, and entities to collaborate, seems adequate in the meantime. Coming to funding, dedicating funds to validation, whether through research programs or other kinds of processes, is required for success and to improve our ED knowledge. Today's discussions have opened the door to finding solutions for validation, and confirmed strong commitment, as embodied by 5 years of existence: accelerating methods validation to improve our protection!

**All resources on the event are available at:**

https://livee.io/minisite-pepper

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