EUROPEAN COMMISSION
JOINT RESEARCH CENTRE
Health and Food
Systems Toxicology Unit
EU Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM)

Summary Record

PARERE Meeting 30 March 2023, Ispra, Italy

The 12th meeting of the Preliminary Assessment of Regulatory Relevance network (PARERE) was held on 30 March 2023 (morning) at the European Commission's Joint Research Centre, Ispra, Italy (the list of participants and the agenda are included in Annex 1 and 2, respectively). The PARERE meeting was followed up by a PARERE-ASPIS Workshop on how best to achieve regulatory relevant research on 30 March (afternoon) and 31 March (morning). Part 1 of the workshop presented and discussed regulatory relevant research undertaken within the ASPIS cluster and its three projects ONTOX, PrecisionTox and RISK-HUNT*3R* (EU H2020 funded project), whereas Part 2 was dedicated to the JRC recommendations for more regulatory relevant research. This summary record covers only the 12th PARERE meeting.

Welcome and Updates

The meeting was chaired by Valérie Zuang, EC/JRC/EURL ECVAM. She welcomed all members and invited new members to introduce themselves. New members included Laure Geoffroy (INERIS, Institut National de l'Environnement Industriel et des Risques, Paris, France); Marketa Dvorakova (Czech Republic, substituting for Kristina Kejlová at this meeting); Tomasz Sobanski (ECHA, substituting for Laura Rossi at this meeting) and Emma Persson (Swedish 3R Centre, substituting for Kaisa Askevik at this meeting).

The chair highlighted the different agenda points, which were up for discussion, and approved the draft agenda. She then invited the PARERE members who volunteered to provide updates on activities within the PARERE network in the respective Member States and in the respective Commission DGs and EU Agencies. Additional information on these updates can be found in the respective presentations on CIRCABC. Updates were provided by Belgium, Italy, Finland, Czech Republic, Slovak Republic, Spain, the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER), EFSA and the European Commission's Directorate Generals Environment (DG ENV); Research and Innovation (DG RTD) and Joint Research Centre (JRC/EURL ECVAM). Updates from EURL ECVAM included new test (pre)submissions, the revision of the chapter on skin sensitisation of the Globally Harmonized System of Classification and Labelling of Chemicals (GHS); follow-up activities to the OECD project in the area of developmental neurotoxicity (DNT), innovating chemical

safety assessment ("Chemicals 2.0") and the related EPAA project; follow-up to the ECVAM thyroid hormone validation study and activities at the OECD thyroid hormone expert group; test readiness criteria applied within the EU Horizon 2020 project EURION; updates on the ECVAM Scientific Advisory Committee (ESAC) and updates on the revision of OECD GD 34 on the validation and international acceptance of new or updated test methods for hazard assessment.

Birgit Mertens (Belgium) provided a brief update on some of the activities conducted in Belgium within the context of the Three Rs (Replacement, Reduction, and Refinement of animal use in science). As they do every year, they organised two meetings with their Belgium PARERE network, each centred on a specific topic. In July 2022, they held a meeting focused on EU Horizon 2020 and Horizon Europe projects in the field of new approach methodologies (NAMs) for toxicology. The ONTOX project, as well as the ALTERNATIVE project related to the development of a platform for cardiotoxicity assessments were presented, and a third presentation was on the PARC project, in which Belgium is involved. In December 2022, they had another meeting of their Belgium PARERE network, this time focused on the topic of PBPK modelling. They provided a general introduction to the concept of PBPK and discussed how it is currently used for regulatory applications in the field of drugs. The Flemish Government in Belgium has initiated roundtable conversations with the sector. They conducted an exploratory survey with scientists in the fields of neurosciences, immunology, and oncology to discuss potential replacements of animal models. They then conducted a broader survey and discussion with different organizations in Flanders to develop concrete action plans to reduce or replace animal testing. Seventeen organizations have committed to actions within the domain of the Three Rs, specifically on replacement and reduction. Twenty-five diverse actions have been defined, ranging from activities related to organoids to proposals for animal sharing in research. An official communication on these action plans is forthcoming, and an event is planned for October or November 2023 to present the different actions. In collaboration with the Brussels Government, they organized a study day on laboratory animals and alternatives in March 2023. The event was successful, with over 250 attendees. They continue to work on the Replace project, extending their database on new approach methodologies. They have specific events planned for this year, including a study day in collaboration with the Brussels region, an event with the Flemish region, educational webinars, and a joint symposium with Twinalt and IC 3Rs at the VUB. Currently, their Replace database contains about 230 methods. They also submitted a proposal for the validation of the GENOMARK assay, a transcriptomic-based biomarker for genotoxicity, to ECVAM. ECVAM required some clarifications on the pre-submission over the summer to which Belgium recently responded.

Emma Di Consiglio (Italy) mentioned that Italy is involved in several work packages in the PARC project. Their main activity is related to work package 5 on hazard assessment, and work package 6 for innovation in regulatory risk assessment. They aim to evaluate the human relevance of NAMs and are involved in three projects within task 6.4.2. Another important work package is WP7, which focuses on the analysis and use of big data. Within the national network of PARERE, they are developing *in silico* models. One project is related to the OECD WNT project on "Development of an Assessment Framework (QAF) for (Q)SAR model predictions", led by ISS, and another is for the implementation of risk governance in nanotechnology, Gov4Nano, led by RIVM. They are also developing a platform of *in silico* models with the Pharmacological Institute Mario Negri. This software is used by EFSA, ECHA, and UBA. They are currently awaiting the grant signature and kick-off meeting for a new project funded by EFSA. This project relates to the implementation of the NAMs roadmap advancing toxicokinetic knowledge in chemical risk assessment. The key aspect is the evaluation of ADME processes and the application of kinetic parameters *in silico* models. The final objective is the integration of these models and parameters in the quantitative *in vitro* to *in vivo* extrapolation. Italy's national PARERE network has a link with the Italian agency for Medicine AIFA who reported some news from EMA, including a different approach for the evaluation of impurities in medicinal products and the introduction of the concept of virtual control groups. EMA also

launched a call for experts, within the framework of the re-organisation of the EMA Working Parties and the set-up of the new CHMP/CVMP Joint 3Rs Working Party within the Non-Clinical Domain, for the Non-Clinical NAMs European Specialised Expert Community. The National Centre of Alternative Methods in Brescia is involved in the validation of two tests within that call. Another important activity led by Italy, in collaboration with the OECD, is the evaluation and development of new guidelines for the integrated approach for intestinal fate of nanomaterials. Italy continues their mission in education, dissemination, and training in collaboration with the Italian Three Rs Center. They have participated in several congresses and lessons organised by the Three Rs Center. They are also involved in the evaluation of a global assessment of one health based on the Three Rs and a new network course for European cooperation in science and technology. They have numerous activities in education in various Italian universities, including Naples, Milan, and Messina. They recently published a paper in their journal on the activity of the PARERE network. They also collaborate with the Italian platform for alternative methods and the animal welfare body. There is a high demand for training courses on the subject of the Three Rs. They received requests for consultation from FRESCI teams seeking opinions on the use of experimental models in research and the Three Rs principle.

Tuula Heinonen presented the activities in Finland. Numerous education and dissemination events have been conducted regarding NAMs and *in vitro* models. However, the most significant effort has been the establishment of the Finnish Three Rs Centre, a joint initiative by the Ministry of Agriculture and Forestry and FICAM (previously led by the speaker). The Ministry, responsible for the implementation of Directive 2010/63 and for maintaining the PARERE network, conducted a survey in 2016 revealing the need for more education, especially in the areas of cell and *in vitro* models. Based on this survey, the Ministry proposed the creation of the Three Rs Centre in Finland, which was launched in May 2022. The Centre's vision is to actively collect and distribute up-to-date information about methods, technologies, practices, and strategies to replace, reduce, and refine animal studies in research and education, thereby limiting the use of animals to projects where no other scientifically reliable methods or testing strategies are available. The Centre's activities include informing researchers and operators about the Three Rs, delivering up-to-date information about methods and technologies that replace animal experiments, communicating research activities of different research groups, and managing information on national and international training events, legislation, and official guidelines. The Centre also organizes training and education courses, including an annual advanced training course at the University of Tampere. More information, can be found on the Finnish Three Rs Centre's website.

Marketa Dvorakova (Czech Republic) presented the activities of the National Institute of Public Health in the Czech Republic, a 100-year-old institution with 500 employees housed in 25 buildings. The institute's primary tasks are related to hygiene, environmental protection, and consumer protection. The speaker belongs to the Centre of Toxicology and Health Safety, which has a unit dedicated to alternative toxicological methods. They focus on the implementation and validation of new approach methodologies. The centre serves as the contact point for alternatives, is part of the EU NETVAL network, and has established the Three Rs Centre in the Czech Republic. They provide methodological guidance and harmonize legislation in the Czech Republic. They have state-of-the-art cell culture laboratories where they have implemented various methodologies, including flow cytometry, microscopy techniques, molecular biology techniques, and chemical analysis. The centre also works with human volunteers for clinical studies, particularly for testing cosmetics which cannot be tested on animals. They offer commercial services for NGOs or companies that want their products tested using a range of new approach methodologies. They are planning to implement additional methodologies, particularly in the areas of genotoxicity, skin sensitization, respiratory sensitization, and endocrine disruption. They serve as OECD experts and voluntarily comment on OECD test guidelines and other documents. Marketa and her colleague, Kristina, are involved in various committees and organizations related to animal welfare and toxicology. They also

collaborate with universities, proposing doctoral programs and projects, and participate in international collaborations, including two COST actions. For more information or details about their activities, the speaker invites contact via email.

Guillermo Repetto (Spain) discussed the actions taken in Spain in the past year, particularly those focusing on the internal use of animals. In the previous year, there was a 69% increase in the use of animals, mainly due to the inclusion of independently feeding larvae as animals, as mandated by the directive for the protection of animals used for scientific purposes. This dramatic increase is significant, especially in aquaculture where a single project can use a large number of larvae. They also discussed continuous education initiatives, with the deadline for renewal of applications for continuing education for persons involved in animal experiments in Spain. For the first time in Spain, research projects on alternatives to animals, were prioritized with other 17 thematic priorities in 2022 by the Ministry of Science and Innovation. In addition, the Ministry of Science and Innovation stated that the design of a strategy for the promotion of alternatives should be proposed by the Spanish Committee for the Protection of Animals Used for Scientific Purposes. The Ministry of Social Rights has introduced an award for groups working on the implementation of alternatives. The speaker also mentioned various dissemination activities coordinated by the Spanish Network for Alternative Methods to Animal Experimentation (REMA) to promote alternatives to laboratory animals, including social media campaigns, book chapters, and journal articles. Several meetings and workshops were held last year for training scientists and promoting the use of alternatives. All this information is available on their website.

Renate Kraetke (SCHEER) provided an overview of the activities of the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) and the Scientific Committee on Consumer Safety (SCCS) at the European Commission. Both committees provide broad-based opinions on health and environmental risks, consumer safety, public health, and emerging issues not covered by other European Union risk assessment bodies. SCHEER often relies on external experts due to the diverse range of topics they handle. Currently, SCHEER has 16 members. For the opinions, SCHEER frequently uses data from *in vitro* or *in vivo* studies, epidemiology, reports from other organizations, and occasionally, confidential information from calls for information. SCHEER's current mandates focus on the safety of titanium dioxide in toys, the potential health effects of exposure to electromagnetic fields, and animal welfare related to the revision of Annex 3 and 4 of Directive 2010/63 on the protection of animals used for scientific purposes. Specific tasks within this mandate include examining key accommodation parameters for the welfare of zebrafish, best methodologies for humanely killing zebrafish, and housing requirements for passerine birds kept in captivity for scientific purposes. In 2022 and early 2023, SCHEER published several opinions, e.g. on draft environmental quality standards for priority substances under the Water Framework Directive, on the presence of cobalt in toys and on the evidence on radio frequency, as well as a statement on emerging health and environmental issues. All mandates and opinions are published on their website for public access.

Georges Kass (EFSA) discussed their strategy and efforts to move towards next-generation risk assessment using new approach methodologies. He highlighted some key areas of focus, such as the development of guidance documents and the outsourcing of projects to develop NAMs. EFSA is currently working on guidelines to use NAMs in 'read across' approaches for food safety assessment, aiming to increase confidence in chemical read across by incorporating biological and toxicological evidence from NAMs. He also mentioned several outsourced projects, including one focusing on developmental neurotoxicity, another on human variability in toxicodynamics, and a third on the applicability domain for using read across in pesticide risk assessment. Other projects include studying the immunotoxicity of PFAS *in vitro* and the applicability of NAMs for assessing the risk of pesticide metabolites. EFSA has launched another project, "NAMs for Nano," and is calling for submissions for an Adverse Outcome Pathway (AOP) for developmental neurotoxicity and a project

on *in vitro* transcriptomics to predict target organ toxicity. A tender specification has also been launched for a project on multi-omics workflow to derive human reference points and health-based guidance values from quantitative *in vitro* data. Georges concluded by encouraging listeners to reach out for more information and thanking them for their time.

Katrin Schutte (EC/DG ENV) provided updates on implementing Directive 2010/63/EU and the REACH Regulation. The first point related to the Test Method Regulation, which details the methods to be used under the REACH Regulation. A major update was published recently that implements the decision to no longer translate each method into all European languages, a process that was complicated and delayed the introduction of methods into the regulation. Instead, approved OECD methods will be listed in a table with reference to the respective international method. The second point is a successful European Citizens initiative on cruelty free cosmetics, which gathered more than 1.2 million validated signatures. This initiative calls for the protection and strengthening of the cosmetics animal testing ban and for the transformation of the EU Chemicals Regulation so that chemicals could be managed without any new animal testing requirements. Katrin also mentioned an upcoming workshop on transitioning to a chemical safety assessment process without animal testing hosted by ECHA and co-organised by COM, ECHA, CEFIC, EPAA, PETA on 31 May to 1 June 2023. This workshop will focus on identifying critical areas that still require animal testing to steer the development of non-animal testing methods. The overall goal is to transition to a system that does not rely on animal testing. Katrin then informed about an EDQM - EPAA pyrogenicity conference to move away from the rabbit model and introduce an *in vitro* alternative test, the Monocyte Activation Test (MAT). A recent development in the European Medical Agency was also highlighted. The agency has revamped their Three Rs working party whose focus is to apply the principles of the Three Rs in medicine testing. Finally, Katrin promoted two open access modules of the ALURES database. The first module provides statistical data on animal testing in the EU, while the second provides non-technical project summaries of authorised projects (https://environment.ec.europa.eu/topics/chemicals/animals-science/statistics-and-non-technical-project-summaries_en). These tools will help improve transparency and understanding of animal use in science and provide the required evidence base to prioritise efforts for the development of non-animal alternatives. DG ENV encourages feedback to further improve these resources.

Christian Desaintes (EC/DG RTD) presented two open calls. The first aims to gain confidence in new approach methodologies for regulatory safety and efficacy testing of both chemicals and pharmaceuticals. The call opens on 26 October 2023 with a deadline of 11 April 2024, and has a budget of 2 million. The objective is to bring together NAM developers, end users, and regulators to inform the regulators on NAM solutions available and identify how these could be most effectively used. The second call is for research on non-animal human-based tools for biomedical research. It is a two-stage call, with the opening on 30 March 2023 and the first stage deadline on 19 September 2023. The second stage deadline is 11 April 2024. The aim is to develop non-animal tools for biomedical research where animal models are currently used but are of limited translational value. Finally, Christian mentioned the idea of a European Research Area (ERA) action to bring together a critical mass of Member States in the field of alternatives to animal testing. This idea was brought up in response to a remark made by representatives of the Citizen initiatives, who stated that there was not sufficient commitment from Member States to phase out animal testing. Christian invited feedback on this idea.

General update from EURL ECVAM

Raffaella provided an update on the status of method submissions received on alternative test methods. Two full submissions were received in the area of genotoxicity, specifically on *in vitro* micronucleus and comet assays in 3D reconstructed skin models, both of which have been validated. The ESAC peer review process for these methods has started. Several pre-submissions were also

received. These include the Light up cell system (LUCS) for measuring general and basal cytotoxicity and to inform on acute oral toxicity starting dose. However, the method was not prioritized for further evaluation. The ProtReact, an *in chemico* method for skin sensitization, was not prioritized either due to it not having significant advantages over existing methods and need for additional work on within-laboratory and between-laboratory reproducibility as well as predictive capacity. The BioDEpi skin irritation test, a similar method to already validated reference methods, was not prioritized either. The GENOMARK, a transcriptomic-based biomarker methodology for identifying genotoxic agents in HepaRG, is still undergoing further development. Based on the feedback recently received from the submitter, EURL ECVAM is finalising its evaluation.

Silvia discussed the work done over the past two years to incorporate non-animal methods into the revision of Chapter 3.4 on skin and respiratory sensitization of the Globally Harmonized System for the Classification and Labelling of chemicals. The new approach allows for the classification of substances using defined approaches and stand-alone *in vitro* methods, with further tiers for additional *in vitro* data and overall weight of evidence, if results are inconclusive or inconsistent. Silvia also mentioned the work on developmental neurotoxicity (DNT), collaborating with EFSA to increase confidence in non-animal methods for risk assessment. EFSA is in the process of publishing a call for tender for DNT methods, specifically assessing the transferability of these methods. Additional EURL ECVAM in-house activities include standardizing the needs for imaging-based methods used in DNT and potentially establishing a chemical library to facilitate the development and optimization of DNT methods.

Andrew presented the work done towards incorporating non-animal methods into the revision of REACH. He noted that there is a common perception that these new approach methodologies are not sufficiently validated or standardized and may lead to less safety and more uncertainty. However, Andrew asserted that NAMs can be used to make the same risk management decisions as current animal-based methods, providing an equivalent level of protection. A future vision is proposed where all chemicals are considered and evaluated according to concern, aiming to minimize animal testing and eventually completely replace it. It is suggested that this future regulatory system would be applicable to all substances on the market, provide a high degree of regulatory certainty, and still encourage innovation. Andrew then discussed the current approach to chemical regulation, where a small percentage of chemicals of high concern are banned, a larger proportion of hazardous chemicals undergo risk assessment, and the largest group of chemicals are either deemed non-hazardous or have not been assessed. He concluded by proposing a new NAM-based classification system. This system would be calibrated using the large evidence base on currently classified chemicals, ensuring that chemicals of similar hazard levels end up in the same categories. This would both mimic the current system and provide a higher level of protection by applying it to a wider range of chemicals. This new system would rely on NAMs for toxicodynamics and toxicokinetics, and could guide future risk assessments.

Pilar presented an ongoing project under the European Partnership for Alternative Approaches to Animal Testing (EPAA). The project explores how non-animal science can be used in regulatory decisions for chemical safety. In a workshop held in 2021, several key challenges in applying new approach methodologies in a regulatory context were identified. They discussed the need for changes in regulatory frameworks, the exploration of tiered schemes that include exposure and NAMs, and the need for increased opportunities for using NAMs that are fit for regulatory purposes. A follow-up group has been looking at a framework developed by ECETOC, which proposes tiered approaches using *in silico, in vitro*, and *in vivo* methods for hazard and exposure. The group has also been exploring a long-term vision for the use of NAMs for chemical classification. Pilar mentioned that the current priority is to focus on using NAMs for hazard classification, and a small group has been exploring this concept further. The group aims to categorize chemicals into low, medium, and high concern groups based on their intrinsic properties, kinetics, and dynamics. They plan to trial the

concept in the area of repeated dose toxicity. Pilar concluded by mentioning upcoming plans, including a hackathon-type event aimed at developing a classification scheme and a meeting to finalize the details of the challenge they want to put forward. The specifics of the project are still being discussed.

Ingrid presented the EURL ECVAM validation study that aims to assess methods relevant to the thyroid hormone system. Ingrid explained that there are currently no established *in vitro* test guidelines for thyroid disruption within the framework of the Organisation for Economic Co-operation and Development (OECD). This gap led the OECD to compile all relevant modes of action for thyroid hormone disruption in 2014 and list all possible methods that could be used to address these mechanisms. In 2017, EURL ECVAM began an in-depth evaluation of 18 such methods, each of which addresses one or more molecular initiating events. These are the key biochemical interactions that, when disrupted, can lead to changes in thyroid hormone levels within the bloodstream and tissues. This is significant as it can lead to a variety of health effects. Fourteen of those methods progressed. Ingrid also touched on the AOP network as a tool for understanding thyroid hormone system disruption. She mentioned the upcoming plans within the OECD expert group on thyroid hormone methods, which include assessing the methods using a set of standardized operating procedures and study reports. They will also be comparing their data with data from other existing sources and potentially developing some methods into test guidelines. Ingrid also mentioned their ongoing close cooperation with the PARC project, which aims to better understand how these methods can be integrated to assess the thyroid hormone disrupting potential of chemicals. Ingrid thanked all who are involved in the project, including the method developers and in particular the EU-NETVAL labs carrying out the work, many on a voluntary basis, as no funding was provided by some Member States, which was considered a problem.

Fenia provided an update on the H2020 project EURION, the European cluster to improve identification of endocrine disruptors. This work utilizes test readiness criteria initially developed by a group of scientists including former ECVAM colleagues. The criteria were initially proposed in 2018 to assess new approach methods related to developmental neurotoxicity for regulatory use. The criteria, divided into three phases, were later amended for utilization in the EURION cluster, a group of eight research projects that focus on four main themes: thyroid disruption, developmental neurotoxicity, metabolic disorders, and female reproduction. The test method developers have been using these amended criteria to assess the readiness of their methods for validation. These criteria have been used to score the readiness of methods on a scale from A to D, where A indicates that the method is ready or nearly ready, and D indicates that it is not ready at all. They have also been used to guide project work, including a project with the Public-Private Platform for the Pre-Validation of Endocrine Disruptors Characterization Methods (PEPPER). Fenia noted that they have further revised the criteria to harmonize terminology with the Good *In Vitro* Method Practices (GIVIMP) document from 2018. This revision also added new sub-items for data evaluation. The updated criteria were then tested in a workshop with partners from the EURION cluster, who found the criteria to be useful for identifying gaps in their methods and increasing awareness of what is required for their method to be as complete as possible for validation. Fenia concluded by noting that while the template was originally developed to assess the readiness of endocrine-disruption-related *in vitro* methods, it could be used for any *in vitro* method, whether cell-based or cell-free. She also noted that the template has a dynamic nature and could be changed in the future as needed.

João provided updates on the EURL ECVAM Scientific Advisory Committee (ESAC), including the establishment of a new committee of nine members and the creation of a continuously open call for applications to create a pool of experts for different peer reviews. João encouraged the sharing of the link to experts in regulatory areas to send in their applications. Currently, the ESAC is conducting a peer review on genotoxicity without the need for external experts. João also mentioned a new project proposal by the Commission, through the Joint Research Centre, the United States and the

Netherlands to the OECD for revision of Guidance Document 34. The document, published in 2005, has been useful in facilitating validation and acceptance of methods, but due to the evolution of toxicological science, the document needs revision. The proposal will be discussed at the next WNT meeting in April 2023.

The chair thanked the speakers and added that more information and details on all these topics can be found in the EURL ECVAM Status Report 2022 on non-animal methods in science and regulation, which had just been published. She then opened the floor for discussions and questions.

Discussion with the PARERE members

Knud Peterson (Denmark) raised the recurring issue of a lack of funding for the validation of new approach methodologies. He mentioned a recent workshop where it was suggested that the OECD system is too slow and should be changed to expedite the adoption of NAMs. He noted that some parties suggested replacing the term "validation" with "confidence building." However, he asserted that validation is a critical part of building confidence in these methods. Knud pointed out that while significant funding has been allocated to projects aimed at gaining experience and confidence in NAMs, there is little to no funding specifically allocated to validating NAM methods that are ready for use. An EU project with a budget of 2 million euros and a Horizon 2020 project with a budget of 50 million euros had been mentioned, but only one project, the EURION project, has some money allocated for pre-validation. Knud concluded by expressing frustration that many scientific projects end up with "bits and pieces left all over the place" that are not put into use due to the lack of funding for validation. He emphasized the need for better financing for validation as it is critical for confidence building and the adoption of NAMs.

Related to this, the chair added that the WNT had recently issued a call for financial support for the validation of new test methods for regulatory use.

Betty Hakkert (NL) apologized for not presenting the NL's work but assured that it is similar to the rest of the group's projects. She highlighted the need for funding for validation purposes. She suggested that the Commission should consider this, as labs often lack proper funding which hinders their progress. Betty also emphasized the importance of having regulators involved from the early stages of projects, not for a few minutes but for several hours, to help identify and address important issues. She advocated for funding for regulators to provide their input and expertise, to help developers and to ensure the end result is robust and practical. She believed this approach would be very beneficial for addressing issues such as those presented by Andrew. She emphasized that this is a collective effort and needs to be addressed together.

The chair reminded that this aligns precisely with the role of PARERE. PARERE has e.g. been consulted on the Horizon 2020 ASPIS project where it can contribute insights early in the process.

Betty endorsed the shared opinions and highlighted the importance of validation work in her institute. She suggested that endorsing projects which can cover costs for small research groups, not just large consortia, could be very beneficial. She acknowledged the need for impactful, large-scale work, but also emphasized the significance of smaller, repeated tasks carried out by many individuals in generating essential data to evaluate the effectiveness of a method.

Maurice Whelan (EURL ECVAM) agreed with the previous statements but added that they are in a challenging position because Directive 2010/63 requires Member States to contribute to validation of methods, which is why it is not funded by the Commission. He believes it is unrealistic to expect the Commission to fund all validation activities. He agreed with Knud's point about needing to better utilize the significant funding in ASPIS and PARC to aid translation or validation. Maurice mentioned the costly EURL ECVAM thyroid study the Commission has funded through general purpose funds, as EURL ECVAM does not have a validation budget. He emphasized the need to understand the real costs of studies to better lobby for necessary funding and pointed out that out of the billion euros spent on funding alternatives over 20 years, only a fraction was associated with validation, which the Commission considers a poor investment. He suggested that there was a need to present a stronger case with figures and start focusing more attention on this issue. He concluded by expressing gratitude to the OECD for initiating a process to address this issue.

Helena Kandarova (Slovak Republic) mentioned that validation does not necessarily need to be too expensive. She argued that only methods that are at a certain level of readiness/maturity should undergo validation, which would not necessarily cost 2 million euros. She believed it was important to assess what is ready for validation to avoid premature and costly validations. Helena, who is also involved in the ONTOX project, highlighted their communication with regulators and their efforts to implement aspects of work into the project to ensure methods are ready to be validated. She also suggested that all research programs funded by the European Union and the European Commission should require a certain level of readiness of methods for validation. Helena revealed that they do not receive any funding for running their NETVAL laboratory, but they were able to secure funding through national and international research projects. She suggested that research consortia should involve national NETVAL laboratories for their expertise. She expressed the difficulty in convincing ministries to fund them because they have other priorities and lack funds. She also mentioned how the responsibility for alternative methods is shared among different ministries, making it challenging to secure funding.

Martin Paparella (Austria) acknowledged that while everyone agreed validation is important, there was not a clear consensus on what validation entails. He stressed that the OECD project on updating guidance document 34 will be crucial in clarifying this. Martin also emphasized that validation should ideally be aimed at a specific goal or use and that a significant change in regulatory approaches is needed. He suggested the introduction of new GHS classes that incorporate new, NAM-based mechanisms as risk or hazard indicators, similar to genotoxicity. He believed that these discussions need to evolve to better understand the purpose for which methods will be validated. He expressed his optimism about the initiative "Chemicals 2.0" and looked forward to contributing to the ongoing discussion.

João Barroso (EURL ECVAM) agreed that excessive spending on validation should be avoided, noting that the validation of the EpiOcular and SkinEthic test methods for eye irritation costed over 2 million euro. João informed that he analysed past validation studies and found that the difference between within- and between- laboratory reproducibility was less than 10%, with between-lab reproducibility always above 80%. He questioned the value gained from the most expensive part of validation studies, namely ring trials involving three labs and testing many chemicals. He agreed with Martin's point that it is necessary to redefine what validation and confidence building means, as the

ultimate goal is to ensure that protocols are robust and transferable, which does not necessarily require extensive ring trials.

Tuula Heinonen (Finland) mentioned that Finland allocates 200,000 euros per year from the state budget for validation, emphasizing that the strongest argument for this allocation was the obligation set by Directive 2010/63. She indicated that Finland only has one ministry to negotiate with, which was supportive of the validation. However, she expressed concern about potential changes with the incoming new government. She encouraged the Commission to emphasize the obligation of Member States to support the validation of alternative methods during meetings with the National Contact Points. She also agreed on the importance of high-quality validation, suggesting that there should be eligibility criteria for labs to ensure the quality of work performed by the labs.

The chair thanked for the engaging and lively discussion on these important points and closed the meeting.

Annex 1 - Participants

Austria
Belgium
Czech Republic
Denmark
Finland
France
Germany
Ireland
Italy
Latvia
Poland
Slovak Republic
Spain
Sweden
The Netherlands

European Commission:
DG ENV
DG RTD
JRC

EU Agencies:

ECHA
EFSA

Scientific Committees:

SCHEER

Annex 2 – Agenda

List of participants

PARERE single points of contact
Commission services
EU agencies

12th meeting of the Preliminary Assessment of Regulatory Relevance (PARERE) network
JRC Ispra, 30 March 2023

Building 55, JRC Conference Centre, Room B

09:30-09:35	**Welcome** (Chair: Valérie Zuang)
09:35-09:40	**Adoption of the agenda**
09:40-11:00	**Round-table of brief updates from PARERE members** (on a voluntary basis)
11:00-11:15	Break
11:15-12:00	**Updates from EURL ECVAM** Including topics such as: revising UN GHS classification criteria; updating REACH information requirements and future directions; test submissions; upcoming ESAC peer reviews; OECD activities
12:00-12:30	Discussion
12:30-13:30	*Lunch Break*
13:30-18:00	PARERE-ASPIS workshop (see specific workshop agenda)