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ALTERNATIVES TO ANIMAL TESTING

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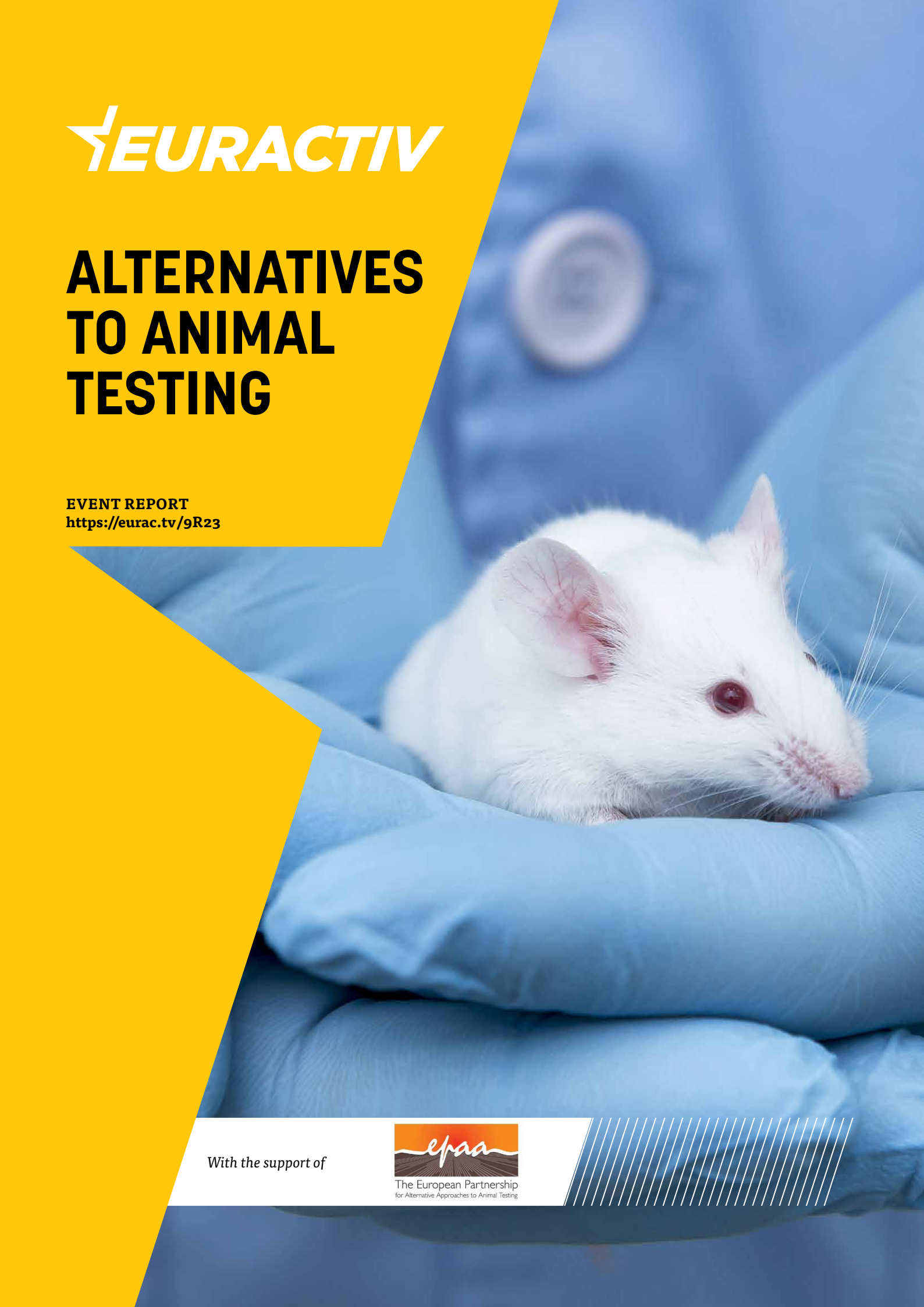

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The EU legislation provides that principles of Replacement, Reduction and Refinement (3Rs) should be "considered systematically" when animals are used for scientific purposes in the EU

These alternatives are basically scientific guiding principles for the more ethical use of animals in testing, avoiding or replacing the use of animals.

According to the European Commission, these alternatives aim to:

- *obtain the required information without the use of live animals;*
- *reduce the numbers of animals whilst obtaining the same level of information;*
- *refine the use of live animals so as to cause less pain, distress or suffering, or improve the welfare of the animals.*

But these alternatives, according to the EU executive, should also have as the objective to develop "better and more predictive scientific tools" to protect human and animal health.

This event report looks into what is needed to build further confidence in these alternatives.

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EU citizens and industry expect 'big reduction' in mandatory animal testing

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Dr Julia Fentem: "The scientific knowledge and non-animal models and tools we now have available enable us to take those decisions responsibly in most cases without any new animal testing." [Jonny Thompson]

The European Chemicals Agency (ECHA) and the Joint Research Centre scientists have a key role to play in meeting the demand of EU citizens and industry, who want to see a big reduction in mandatory animal testing via new methodologies, Dr Julia Fentem told EURACTIV in an interview.

"The scientific knowledge and non-animal models and tools we now have available enable us to take those

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decisions responsibly in most cases without any new animal testing," she said.

Dr Julia Fentem is the head of Unilever's Safety and Environmental Assurance Centre (SEAC). She spoke to EURACTIV.com ahead of the 2019 conference of the European partnership for alternative approaches (EPAA) "Building confidence for the use of 3Rs" on 29 October.

How many animals die annually from testing worldwide? Do you have data regarding the EU?

Statistics for most countries are not available. The EU leads the way in promoting data transparency on animals used for scientific purposes, and in ensuring implementation of the Three Rs principles, i.e. to replace, reduce and/or refine the use of laboratory animals wherever possible. The Directive 2010/63/EU introduced new requirements for data reporting by the EU member states, and the Commission is required to publish the collated EU data in the new format for the first time in November. Since the scope and criteria have been broadened from reports issued in the past, it is difficult to predict actual numbers.

Could you explain what the 3Rs (Replacement, Reduction and Refinement) approach is? Do you have a practical example?

The concept of the Three Rs, and the underpinning philosophy and principles, was first articulated 60 years ago (in 1959) by Russell & Burch in their book "The Principles of Humane Experimental Technique". The approach is designed to avoid any unnecessary animal use or suffering in scientific experiments and testing.

These principles are the underpinning of the EU animal protection legislation first introduced in 1986 (Directive 86/609/EEC) and updated in 2010 (Directive 2010/63/EU). Whilst many steps have been taken to reduce the numbers of animals use for product safety assessment purposes since the 1980s, and to refine any studies that were absolutely essential so that the animals involved experienced the minimum suffering possible, the animal testing ban implemented under the EU Cosmetics Regulation was the driver for full replacement of animals by non-animal approaches.

How are you planning to build confidence in the 3Rs as a way to avoid or replace the use of animals?

We must continue to build the confidence to use both existing and new 3Rs approaches for decision-making by all stakeholders, particularly by government regulators and scientists in industry. This is particularly critical when those decisions have consequences for public health, consumer safety and our planet (environmental sustainability). We must be confident that decisions which are made based on applying new 3Rs, non-animal science and novel tools are fully protective of human health and our environment.

We are looking to build confidence by helping to develop the capability and capacity needed with new and much wider groups of industrial and government safety assessors across the world, and also by training our next generation of safety assessors very differently (e.g. in non-animal safety science and exposure-based human health and environmental safety assessment) from how toxicologists and eco-toxicologists were educated in the past. To be confident in our decisions as safety assessors, it is critical we develop skills and experience in how non-animal data are applied in an integrated way to make decisions.

The European Partnership for Alternative Approaches to Animal Testing (EPAA) has a key role to play in continuing to help build the knowledge and expertise needed, e.g. through establishing user forums and holding working sessions where case studies and real-life complex product safety assessments can be discussed by multi-disciplinary groups of regulatory and industrial scientists to increase use and acceptance of new approach methodologies (NAMs).

There are good training programmes run by trade associations, and some university courses where the 3Rs approaches are included. There are also now a few new global partnership initiatives – such as the Animal-Free Safety Assessment (AFSA) collaboration being coordinated by Humane Society International – which will increase our global reach with new non-animal safety assessment training materials and approaches targeted for industrial and regulatory safety assessor communities.

What are the main regulatory challenges to push the 3Rs forward, especially in the EU?

As a safety scientist having worked in the area of non-animal approaches for almost 30 years, for an NGO, in government and in industry, I believe that the scientific knowledge and non-animal models and tools we now have available enable us to take those decisions responsibly in most cases without any new animal testing. For example, computational modelling of human biology responses to relevant chemical exposures, and generating relevant data with human cells and tissues, are often more scientific ways to ensure we protect consumers and ensure that our products are safe for

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them.

Whilst that is my view of the current status of our safety science (and the future also looks positive as we start to leverage new cutting-edge technologies), many of the current regulatory approaches are still based mainly on traditional animal toxicology testing. Here, we also have to openly acknowledge that animal test data are not always fully predictive of human responses, and we often apply various so-called 'safety factors' when extrapolating those data to humans.

A big challenge is one of mindset – it does require a different way of thinking, and for us all to embrace the new science and technology opportunities, to lead for both scientific and regulatory change. This is increasingly the challenge for today's regulators: how do they best keep up with the latest scientific developments, and how do regulations and guidelines keep up with the safety science and assessment approaches we are now experienced in and confident to use to make decisions within some of our companies.

In the chemicals' safety assessment area, an excellent international governmental collaboration initiative has been taken in the past few years to accelerate the application of new approach methodologies: APCR- 'accelerating the pace of chemical risk assessment'.

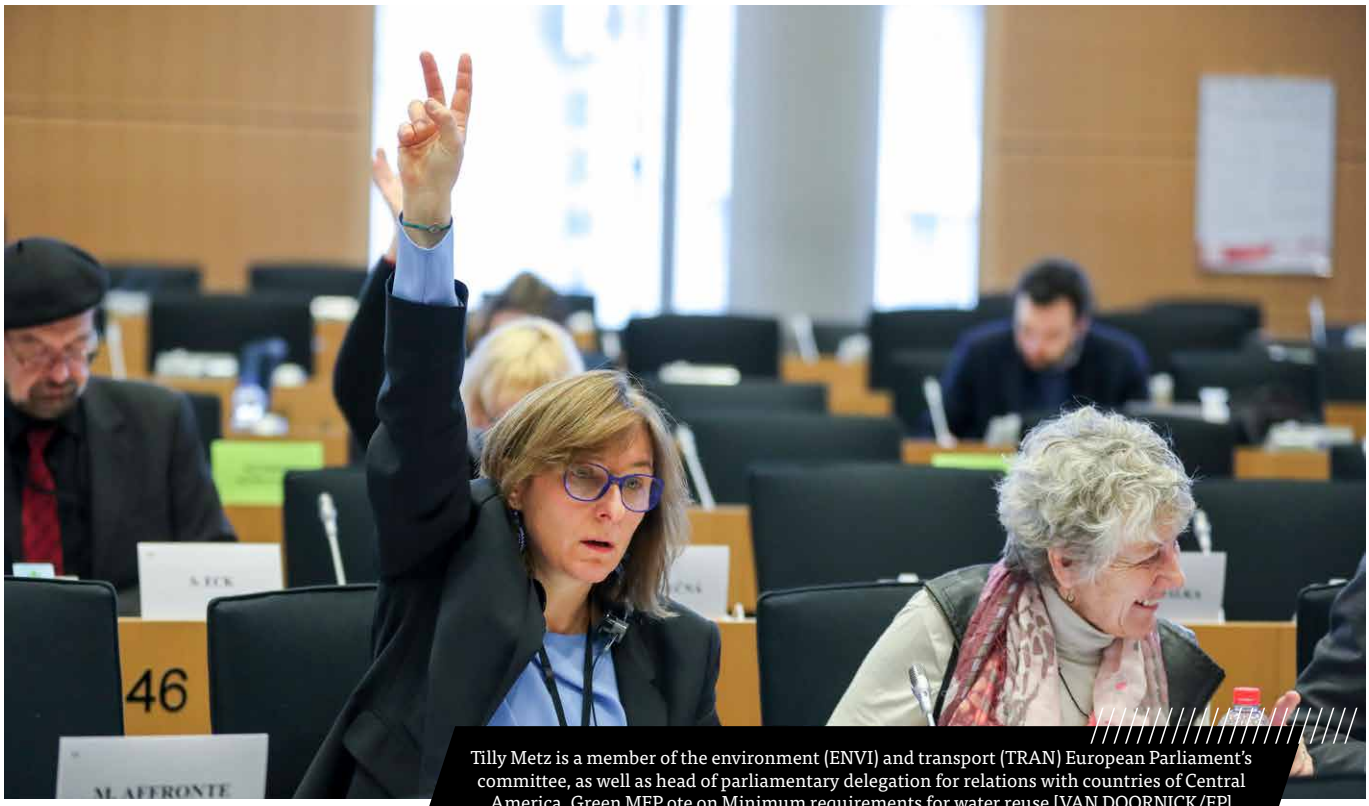
This could change progress in the implementation of 3Rs, non-animal approaches for chemicals registration and evaluation purposes. This is a priority need in the EU, where consumers, NGOs and industry want to see a big reduction in mandatory animal testing, and where there is a clear leadership role for the European Chemicals Agency (ECHA) regulators and the Joint Research Centre scientists to play in driving the changes needed, working in collaboration with other key stakeholders and leading scientists.

What could the next European Commission and Parliament do in this respect?

Mandatory animal testing for new chemicals is an area to put more focus on, building on the international governmental collaboration that is now in place (APCRA above). The US EPA announced a policy change in September 2019 to eliminate funding for all mammalian studies by 2035 and committed funding to advance research on new approach methodologies (NAMs). A similar commitment from the EU Commission and Parliament would be a significant step in also demonstrating that its world-leading 3Rs legislation, now in place for over 30 years, continues to drive the reduction and replacement of animal testing that EU citizens increasingly expect.

Green MEP calls for EU action plan on alternatives to animal testing

By Gerardo Fortuna | EURACTIV.com



Tilly Metz is a member of the environment (ENVI) and transport (TRAN) European Parliament's committee, as well as head of parliamentary delegation for relations with countries of Central America. Green MEP ote on Minimum requirements for water reuse [VAN DOORNICK/EP]

All initiatives to promote alternatives to animal testing are welcome, but lawmakers should be bolder and impose some mandatory measures as well, Luxembourgish MEP Tilly Metz has said.

According to the Green MEP, policymakers must not give up their ambition of making the "3 Rs" approach to animal testing mandatory.

The "3 Rs" concept – on Replacement, Reduction and Refinement of animal testing – was introduced 60 years ago by scientists W.M.S. Russel and R.L. Burch in their seminal work on "The Principles of Human Experimental Technique".

Since then, the scientific community, NGOs, politicians, and even the general public have espoused the concept and developed it further.

"It's not a luxury, it should be an obligation," said Metz, who spoke last month at the annual conference of the European Partnership for Alternative Approaches to Animal Testing (EPAA) in Brussels.

In order to encourage alternative approaches to animal testing, Metz suggested a strategic action plan, including new product labelling rules and changing the mission of the European Chemicals Agency (ECHA) as part of a broader review of EU legislation on the matter.

"We've been working on such a shift for a long time and it is not going to happen if we don't propose a package of actions that we can really do," Metz argued.

Society's reliance on animal testing

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is no longer a cultural issue, she continued, but more about mentality and habits.

"We do a lot of animal testing because we are used to. We should assess how really efficient animal testing is," she said, citing figures showing that 80% of animal testing is currently not efficient.

In this sense, education plays a central role in spreading the message of the 3R's, Metz said. But programmes should not be limited to researchers or university students, she added, saying primary schools should be included as well.

EU ROLE

Asked what the European Commission could do, the Luxembourgish MEP listed products labelling rules, EU research programs and financial aid to SMEs developing alternative techniques to animal testing.

Alternatives should also be promoted abroad, Metz pointed out. In this respect, the EPAA supports training for Chinese scientists, helping the Asian giant develop alternative tests for its booming cosmetics industry.

But promoting the 3 Rs approach beyond Europe also poses challenges. In China for instance, regulatory authorities and policymakers are reluctant to change legislation until the scientific infrastructure is ready.

"Compared to other countries like Brasil, the Chinese don't do the shift to alternatives if they're not prepared or if their laboratories aren't ready," a speaker from the private sector pointed out.

An official from the Commission's environment directorate (DG ENV) mentioned a pilot project providing e-learning modules aimed at helping researchers become more knowledgeable on alternative methods. Efforts are also supported in the context of implementing Directive 2010/63/EU on the protection of animals used for scientific purposes, the official pointed out.

Dr Julia Fentem, head of Unilever's Safety and Environmental Assurance Centre (SEAC), said that leadership in this field comes from different places and different sectors also thanks to passionate individuals who have committed themselves to search for alternative methods.

AND THIS YEARS' REFINEMENT PRIZE GOES TO...

The EPAA platform, which brings together the EU executive and the private sector in promoting the development of alternative approaches to animal testing, is now entering the final year of its action programme (2015-2020).

In order to spread the use of alternatives to animal testing, EPAA also awards grants and prizes for researchers and students, such as the Refinement Prize.

Probably not the most intuitive or obvious of the 3Rs, Refinement nevertheless plays an equally important role.

Simply put, the refinement method is the modification of procedures, husbandry or care practices aimed at minimising animal pain and distress, enhancing their well-being.

A jury made up of 6 members, 2 each from the Commission, the industry and the mirror groups, is tasked to award a scientific project implementing refinement approaches in a day-to-day application.

Jury members give a score assessing the project's creativity and innovation, but also whether the new method proposed has a potential for wider applications.

This year, the prize was assigned to Dr. Yvonne Armbrecht from the University of Veterinary Medicine of Hannover, who presented an effective approach to train animals to cooperate in routine procedures like weighing and blood sampling.

Her case study focuses on the effect of positive conditioning that can reduce stress in sheep during routine handling situations by "communicating" with them through a clicker or a target bar.

Target bar is used to direct sheep into a certain direction and distance, while each "click" of the clicker means something that the animal is trained to understand. For instance, the sound of one click means "you performed well" or "I want you to show this behaviour more often," the researcher explained.

OPINION / PROMOTED CONTENT

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It is time to think differently on animal alternative approaches

By Rob Roggeband | EPAA

Rob Roggeband. [EPAA]

The European Partnership for Alternative Approaches to Animal Testing (EPAA) is a unique partnership between industry and European Commission in the EU with an overall goal to increase confidence in the use of the so-called 3Rs – Replacement, Reduction, Refinement of animal testing – a concept introduced 60 years ago by Russel and Burch.

Rob Roggeband is the Industry co-chair of EPAA.

In almost 15 years, EPAA has contributed significantly to the advancement of 3Rs in toxicology. From the industry side, we have brought together the pharmaceutical, cosmetic, agrochemical, fragrance and detergent sectors and over the years we have learnt a lot from each other when it comes to regulatory toxicology. After all, whether one does toxicology for medicine, a cosmetic or detergent, the basic principles of toxicology are applicable universally. The advances in mechanistic understanding of the disease and biological processes leading to adverse outcomes have enabled us to make more informed

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safety decisions with the appropriate and right degree of conservatism built-in.

In 2019, EPAA organized three workshops, one on skin sensitization, one on carcinogenicity and one on repeated dose toxicity. In these workshops, we bring leading scientists from academia, industry and regulators together to discuss and agree on how to make safety decisions in a risk assessment and a regulatory toxicology context.

These user fora have generated rich discussions that were integrated into peer-reviewed publications in the scientific literature. After all, we are all interested in one thing, that is to make safety decisions for human safety using the best and state-of-the-art science, and the most relevant data on ingredients increasingly including data from non-animal alternatives.

We are in a world where "fear of chemistry" seems to be on the rise. The right experts in academia, industry and in the Competent Authorities must continue to work together to ensure confidence in human safety assessments including new generation risk assessments, or NGRA, those that are built on non-animal approaches to toxicology.

As EPAA looks ahead at its next 5-year Action Program for 2021-2025 we see an increasingly important role for NGOs in contributing to building consumer confidence in the safety of ingredients and safety assessments using non-animal approaches in toxicology based on mechanistic understanding of biological pathways in man.

Through the EPAA partnership and the so-called user fora of industry, regulators and academia we need to get increasingly comfortable to make safety decisions based on a weight of evidence of all available data, ideally without the generation of new animal data. We need to move away from a default "checkbox" approach where we dose animals with unrealistically high levels of ingredients to only find ourselves having to explain why the effects observed at these very high doses are irrelevant in a human safety assessment context.

The alternative methods should not be validated against e.g. subchronic animal studies, as we risk losing many valuable and perfectly safe ingredients. Instead, these alternative methods should drive better and more effective safety decisions. New generation risk assessment approaches need to reflect, even more than in the past, the concept of exposure-based approaches, in contrast to establishing only the hazard potential of a chemical, in order to drive most relevant risk assessment decisions across sectors.

Indeed, the continued dialogue between academia, regulators and industry is the way forward and this is where the partnership in EPAA can play a unique role, in Europe but also globally, working towards the common goal: Better toxicology science with less and ultimately no new animal testing. It is time to think differently on animal alternative approaches.

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