Paving the way for a Future without Animal Testing

EPAA 20th Anniversary

epaa20

The European Partnership
for Alternative Approaches to Animal Testing

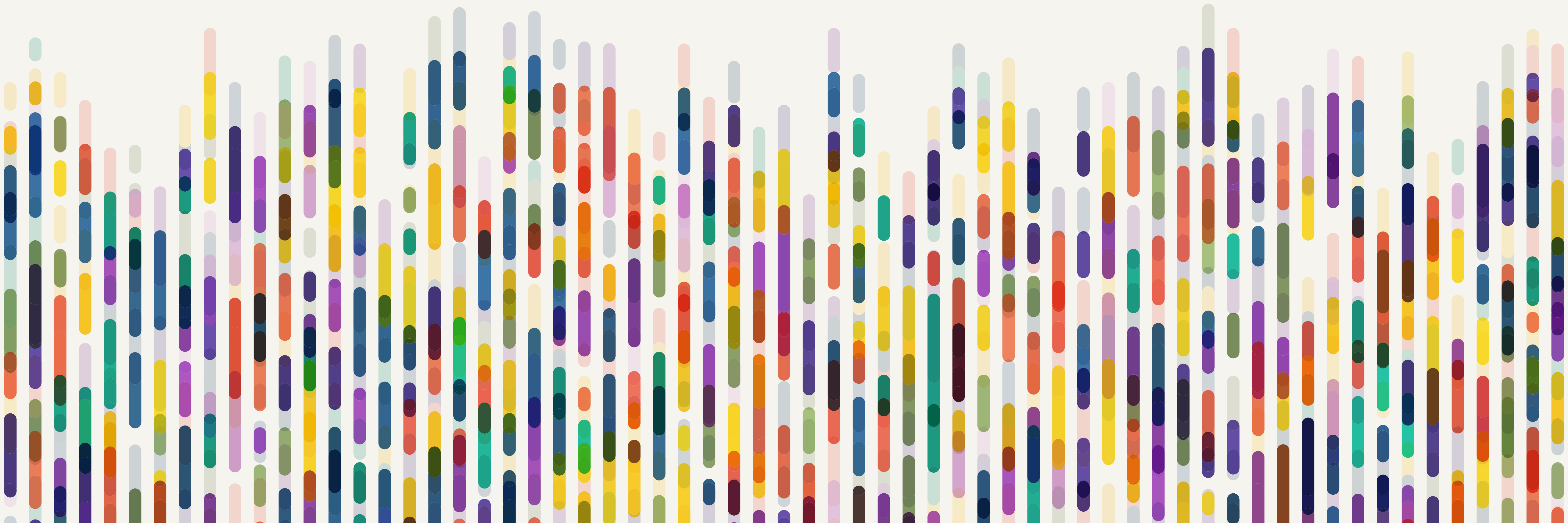


TABLE OF CONTENTS

FOREWORD

Europe leads the way to end animal testing. First and foremost, it is a question of ethical responsibility. A step forward in the natural, logical course of history. But it is more than that. It is also a step forward to position Europe as a center of excellence for innovative research.

Twenty years ago, the European Partnership for Alternative Approaches to Animal Testing (EPAA) began as a bold experiment—a public-private partnership committed to replacing animal testing with innovative, science-based alternatives. Today, it became a European success story: proof that we can align innovation, industrial competitiveness, and ethical responsibility.

EPAA has shown that regulatory ambition and industrial innovation can be complementary. They reinforce each other. By building trust across sectors, fostering scientific dialogue, and championing the 3Rs - the principles of Replacement, Reduction, and Refinement of animal use in testing - EPAA has helped bring animal-free methods into the regulatory mainstream.

This is evident in chemicals safety assessments and in one of Europe's proudest achievements: the ban on animal testing for cosmetics, which has inspired action worldwide.

As we implement the European Commission's roadmap to phase out animal testing, the EPAA's experience will be indispensable. It has created not only a knowledge base but a community—one capable of delivering smarter, safer, and more sustainable solutions for Europe.

The transition to animal-free methods opens doors to faster innovation, more targeted safety assessments, and access to new markets. EPAA has laid the foundation. Our task now is to scale this vision—together.

So that animal testing becomes, once and for all, a thing of the past.

STÉPHANE SÉJOURNÉ

EUROPEAN COMMISSIONER, DG GROW

A Reflection from the EPAA Co-Chairs

Twenty years ago, the European Commission and industry came together with a bold and shared ambition: to advance innovative approaches to safety assessment that reduce, refine, and ultimately replace the use of animals in testing. That partnership became the European Partnership for Alternative Approaches to Animal Testing—EPAA.

What started as a forward-looking initiative has grown into a trusted platform for scientific collaboration, regulatory dialogue, and ethical progress. Together, our members have achieved tangible milestones: from validated test guidelines and international regulatory acceptance to cross-sector innovation challenges and support for the next generation of 3Rs scientists.

As Co-Chairs, we are proud to reflect on EPAA's journey—a journey marked by openness, perseverance, and a deep sense of shared responsibility. The commitment of our partners across sectors has been the driving force behind the EPAA's success and its growing impact in Europe and beyond.

Now, as we look to the future, the momentum continues. With the Commission's roadmap as our guide, we enter a new phase: transforming proven science into updated regulatory practice. The shift toward animal-free safety assessment is no longer a distant aspiration—it is becoming a reality.

Thank you to all who have shaped EPAA's legacy. The next chapter is ours to write—together.

GIULIA DEL BRENNA

EPAA EUROPEAN COMMISSION CO-CHAIR

GAVIN MAXWELL

EPAA INDUSTRY CO-CHAIR

MEMBERSHIP

41 Companies (including 1 SME)

ADAMA
AstraZeneca
BASF We create chemistry
BAYER
Beiersdorf
Boehringer Ingelheim
CHANEL
CLARIANT
COLGATE-PALMOLIVE
CORTEVA agriscience
DOW
dsm-firmenich
essity
ESTĒE LAUDER
EVONIK Leading Beyond Chemistry
Gowan
GSK
Henkel
HUNTSMAN Enriching lives through innovation
Johnson&Johnson
Kanebo
L'ORÉAL GROUPE
LVMH
MERCK
MANE
NOVARTIS
novonesis
novo nordisk
P&G
reckitt
REVLON
sanofi
SHISEIDO
SOLVAY
straticell
SYENSQO
symrise
syngenta
Unilever
zoetis

5 DG's of the EC

DG GROW
DG ENV
DG SANTE
DG JRC
DG RTD

European Commission

10 Sectoral Associations

A·I·S·E since 1952
animalhealth europe
cefic
Cosmetics Europe the personal care association
CropLife Europe
efpia
FOODDRINK EUROPE
ifra
IOFI
sme united CRAFTS & SMEs IN EUROPE

Including Partner Agencies

ECHA EUROPEAN CHEMICALS AGENCY
efsa
EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH

HISTORY CHAPTER

20 years of efforts to change the mindset to increase use of non-animal methodologies for safety assessment

When it comes to safety assessment of chemicals, we had to find a balance between ethics and science. We need to make sure that the pace of development, acceptance of new methodologies by regulators and promotion of education all go hand-in-hand to make most of the momentum started in Europe that is being embraced worldwide.

Europe has pioneered the promotion of alternative approaches to testing on animals. European regulations were the first to require fewer animal tests for assessing safety and no in vivo tests at all if alternatives were available. In fact, the EU has invested massively in developing, validating and accepting new alternative approaches. I am very proud to have been one of the founders of the European Partnership for Alternative Approaches to Animal Testing in 2005, a public private partnership between companies and the European Commission.

CHARLES LAROCHE

EPAA INDUSTRY CO-FOUNDER

I confess that launching such initiative as not been easy at all, some sectors considering this approach as too much driven by the regulatory requirements imposed to the cosmetics industry. Without the personal support of Dagmar Roth Behrendt, Member of the European Parliament, the Commissioner for Industry, Günther Verheugen, the Commissioner for Research, Janez Potočnik, the launch of EPAA would not have been possible.

The goal of the EPAA is to share information on alternatives to accelerate their validation and acceptance. One of the largest projects has been the skin sensitisation project that focused on comparing new *in vitro* skin sensitisation models based on 3D-epidermis with a set of difficult to test reference chemicals. This work has resulted in validated non-animal tests that are accepted as OECD Test Guidelines.

These European regulations and developments have inspired many similar initiatives overseas, which is a great achievement. Meanwhile, the EPAA partners have further worked to strengthen the European lead in more effective assessment for safer products while bringing benefits for animal welfare.

Today, with the creation of the Roadmap, EPAA is on the brink of a new paradigm. Moving from the development of New Methodologies through the adoption and implementation of updated regulatory requirements.

It has taken 20 years to build a wonderful and expected 'piano'. It's trust all stakeholder to play with that 'piano' in the next coming years to make sure that animal testing for regulatory requirements will be an approach from the past and replaced by better science in safety assessment.

JANEZ POTOČNIK

EPAA EUROPEAN COMMISSION CO-FOUNDER

20 years from the time when with my good colleague Commissioner Gunther Verheugen we launched the European Partnership for Alternative Approaches to Animal Testing (EPAA) ... who would believe. It was a good moment, proving again that cooperation across different fields and interests is a way to success. And EPAA is a success.

Over the past 20 years, it has helped transform cutting-edge research into practical New Approach Methodologies that reduce reliance on animal testing. It stands as a model of how scientific innovation, guided by ethics, can reshape the future of safety assessment. EPAA's work to advance and validate New Approach Methodologies exemplifies the bridge between EU research and real-world regulatory change. Its contribution to the Roadmap reflects how science and policy can come together to deliver humane, high-quality safety assessment. And remaining humane is most important task for us humans, isn't it?

EPAA Conference "Europe goes Alternative" on 7 November 2005

On 7 November 2005, the European Commission hosted the landmark conference 'Alternative Approaches to Animal Testing' in Brussels, marking the first Annual Conference of the European Partnership for Alternative Approaches to Animal Testing (EPAA). The event brought together stakeholders from industry, academia, animal welfare organizations, and regulatory bodies to discuss policy and scientific advancements in the 3Rs: Replacement, Reduction, and Refinement of animal testing.

Vice President Günter Verheugen and Commissioner Janez Potočnik opened the conference, emphasizing the EU's leadership in animal welfare and the importance of robust scientific validation of alternative methods. The conference complemented the 5th World Congress on Alternatives held earlier that year in Berlin. Key sessions addressed European action on animal welfare, risk assessment, and regulatory acceptance of alternatives. Industry leaders from BASF, Bayer, Procter & Gamble, L'Oréal, and Unilever showcased their commitment to the 3Rs, while regulatory bodies like ECVAM and ICCVAM highlighted the need for faster validation and acceptance processes.

The conference culminated in the adoption of the 3Rs Declaration, establishing a voluntary European Partnership to promote alternative approaches. The declaration outlined a collaborative action programme to map research, foster innovation, and facilitate regulatory acceptance of alternative methods. NGOs welcomed the initiative, calling for active participation.

The event was widely regarded as a breakthrough, setting the foundation for EPAA's mission to advance humane science through cross-sector collaboration and innovation.

TESTIMONIALS

Quotes from policymakers

TILLY METZ

EUROPEAN PARLIAMENT

“20 years of EPAA marks two decades of building bridges between regulators, scientists, industry, and NGOs—advancing a more humane Europe. As a key partner in driving change and innovation, EPAA plays a vital role in making the world a less cruel place. I deeply value our longstanding collaboration and look forward to continuing our joint efforts toward phasing out animal testing.”

NIELS FUGLSANG

EUROPEAN PARLIAMENT

“Animal testing is a crucial matter when it comes to combatting poor animal welfare in the EU. The 20th anniversary of EPAA marks two decades of advancing new approaches to testing where animals are not suffering, driving the transition towards more ethical, safe and effective testing methods, through collaboration, research, legislation and outreach.”

SIRPA PIETIKÄINEN

EUROPEAN PARLIAMENT

“We need visionaries and forerunners - those who lead the way for progress and the future. EPAA has certainly fulfilled its task during its 20 years of existence by creating and catering information, supporting politicians and civil servants in scientific understanding and gathering the constituency together to move the world forward to better protect human beings with more precise and reliable *in vitro* testing, and to better avoid futile animal suffering. In this, I will rely on EPAA in the future as well.”

SHARON MCGUINNESS

EUROPEAN CHEMICALS AGENCY (ECHA)

“The promotion and use of alternative methods for chemical safety assessments is a strategic priority for ECHA. To achieve the objective to replace animal tests, we need to have sound science, strong collaboration and robust knowledge. Working and partnering with EPAA is important for ECHA as it brings different stakeholders and experts together who share a common goal, namely, to replace or reduce animal testing by innovative, non-animal testing methods/New Approach Methodologies (NAMs). We congratulate EPAA on their 20th anniversary and we look forward to continuing to work with them”

Testimonials from industry

KRISTIN SCHREIBER

DG GROW, EUROPEAN COMMISSION

"EPAA is more than a partnership—it is a catalyst. Launched in 2005 under the leadership of then-Commissioner Günter Verheugen, EPAA has spent two decades uniting regulators, industry, academia, and civil society in a shared pursuit: advancing animal-free testing methods grounded in science, trust, and cooperation.

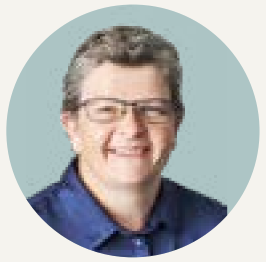
As we move forward with the European Commission's roadmap to phase out animal testing, EPAA's 20-year track record offers the expertise and momentum needed to drive regulatory progress. Its cross-sector experience with animal-free methods will be essential to making this transition a success.

The roadmap sets a clear strategic direction for Europe's future in safety assessment—one that is innovative, humane, and sustainable. EPAA's role in supporting its implementation, through practical collaboration and scientific excellence, is more vital than ever.

EPAA has shown what is possible when innovation meets collaboration. In the years ahead, it will remain a cornerstone of Europe's transition toward humane and future-ready safety assessment."

JULIA FENTEM

UNILEVER



"Congratulations to EPAA on its 20th anniversary and thank you to all those who have played an active part in its numerous successes. In recent years, we have secured the necessary commitment and collaboration from all EU stakeholders to truly accelerate the transition to non-animal approaches, a vision conceived in 2003 during our early discussions on establishing a cross-sector industry partnership with the European Commission. With the incredible progress made by the scientific community, I believe it is now incumbent on us all to maintain momentum in delivering an EU roadmap and ongoing EPAA leadership to eliminate animal testing."

STEVEN VAN DEN BROEK

CEFIC

"EPAA continues to impress with its unique ability to bring together five European Commission Directorates-General, key agencies, 40 companies, and 9 European industry federations in a truly collaborative platform. Cefic particularly values its transparency and determination to phase out animal testing in chemical safety. Looking ahead, we hope EPAA will keep fostering open dialogue and real-world implementation of the commission's roadmap for phasing out animal testing through shared case studies and practical experiences. Congratulations!"

NATHALIE MOLL

EFPIA

"EFPIA is proud to have been part of the EPAA journey from the very beginning. The EPAA's 20-year legacy is one of collaboration and innovation. Contributing to this collective effort to accelerate the shift towards alternative approaches that protect human health while upholding animal welfare is a responsibility we embrace. As the European Commission prepares a roadmap to phase out animal testing for chemical safety assessment, the EPAA's work has never been more relevant. EFPIA values this unique partnership, laying the scientific and regulatory groundwork for a sustainable, animal-free future in safety testing."

DIRK JACOBS

FOODDRINK EUROPE

"At FoodDrinkEurope, we believe that advancing NAMs is essential to ensuring the future of safe, sustainable, and innovative food systems. Through our long-standing collaboration with EPAA, we have actively contributed to creating constructive, science-based dialogue between regulators and industry, and to building the trust and frameworks needed to accelerate the uptake of non-animal testing approaches in food safety."

JOHN CHAVE

COSMETICS EUROPE

"Cosmetics Europe values its long-standing collaboration with EPAA, and shares EPAA's commitment to innovative, animal-free approaches to safety assessment. We believe that promoting alternatives to animal testing is not only a scientific imperative but also a shared ethical responsibility. EPAA's two decades as a pillar of this common commitment has been an important factor in the significant progress we have made."

BORIS MÜLLER

SYMRISE/IFRA

"Symrise [and the fragrance industry] congratulate EPAA on its 20th anniversary. Together, we are celebrating two decades of shared progress in promoting scientifically robust alternatives to animal testing and their regulatory acceptance in European legislation. EPAA's unique cross-sectoral platform brings together authorities, industry, NGOs and academia. It has thus helped increase collaboration and enhance knowledge sharing, with the aim to reduce reliance on animal studies and supporting broader adoption of innovative safety approaches. In parallel, the fragrance sector, notably through IFRA, RIFM, and the IDEA project, continues to advance and apply New Approach Methodologies. These efforts are part of a science-based and responsible approach to safety."

SYBILLE MILLET

COSMED/SMEUNITED

"As a representative of cosmetic SMEs within the EPAA, Cosmed is pleased to contribute to the collective effort to develop and gain regulatory acceptance of NAMs. The cosmetics sector, where animal testing has been fully banned since 2013, remains particularly committed to this cause. Significant challenges remain in comprehensively assessing all hazard properties of substances and safeguarding the innovation capacity of SMEs, and EPAA continues to be the most effective platform to support these discussions."

JAN ROBINSON

A.I.S.E

"As a founding member of EPAA, A.I.S.E. is proud and delighted to reflect on all it has accomplished in the past twenty years. The human and environmental safety of detergent products and their ingredients is of paramount important to A.I.S.E. and its members, and we are committed to achieving this without the use of animal testing. We look forward to supporting and contributing to further advances in the establishment and uptake of New Approach Methodologies through EPAA."

STEPHANIE NADZIALEK

CROPLIFE EUROPE

"CropLife Europe is proud to support the European Partnership for Alternative Approaches to Animal Testing (EPAA), reinforcing our commitment to science-based innovation and the advancement of non-animal methods in regulatory safety assessment, particularly their uptake in regulation, and guidance by synergizing effectively with regulators, NGOs and other industry sectors. Being a data-rich platform, CropLife Europe has played a pivotal role in advancing key initiatives such as derivation of case studies to support Weight of Evidence (WoE) approaches for acute systemic toxicity, carcinogenicity assessment and contributed the User Forum approach to facilitate the implementation of new approach methodologies (NAMs) for skin sensitization. The organization has also contributed significantly, providing leadership roles, to the development of the NAMs Designathon challenge, identified opportunities to waive the dog as a second species across different regulated sectors, and driven significant progress in carcinogenicity assessment through the integration of NAMs, aligned with the 3Rs principles. Finally, CropLife Europe has provided valuable input across multiple Partner Forums, including those focused on toxicokinetics, exposure considerations, endocrine disruption, etc. This work has been instrumental toward the EU COM Road Map Initiative, supporting its elevation to a broader, cross-sectoral, and globally aligned platform."

ROXANE FELLER

ANIMALHEALTHEUROPE

"AnimalhealthEurope member companies are committed to the 3Rs approach and actively work to Replace, Reduce, and Refine the use of animals in medicines development and production where possible. We have been an active member of the EPAA since its inception and have participated in several successful projects to harmonise global batch testing requirements for vaccines, and to reduce the use of animals in skin sensitisation potency assessments and establish 3Rs synergies so that there is no need to generate new research data. We look forward to continued collaboration with the EPAA to find alternatives and further reduce the need to use animals."

Mirror group:

EMILY MCIVOR

"The EPAA has fostered vital dialogue across industry sectors, and between the European Commission, industry, agencies, and animal protection groups. Identifying achievable opportunities for change has allowed the EPAA to accelerate progress in several areas, while strategic input concerning the Commission's roadmap to phase out animal testing has created new avenues for impact. It has been a privilege to collaborate with so many dedicated individuals, to advance animal welfare as well as protection of human health and the environment."

EMMA GRANGE

"The Mirror Group provides an invaluable connection between stakeholders and the EPAA; it's a privilege to sit as the chair of the group and I'm excited to see the advances which will be brought. The transition to animal-free approaches for regulatory testing is an important goal we all strive for, and which will bring benefits to all, but will only be delivered through effective partnerships such as the EPAA."

VERA ROGIERS

"EPAA's collaborative efforts have successfully united industry, academia, and regulators in a shared vision for humane, predictive, and sustainable safety assessment. It is inspiring to see how this partnership continues to shape a future where scientific excellence and the principles of the 3Rs go hand in hand. I am proud to be a member of its Mirror Group."

Twenty Years of EPAA: Achievements in Advancing Alternatives to Animal Testing (2005–2025)

Introduction and Background

The **European Partnership for Alternative Approaches to Animal Testing (EPAA)** was launched in 2005 as a unique public-private partnership between the European Commission and multiple industry sectors. Its mission is to accelerate the replacement, reduction, and refinement (3Rs) of animal use in regulatory testing through collaborative science and innovation. Over the past 20 years, EPAA has pooled knowledge and resources from pharmaceutical, chemical, cosmetic, agrochemical, food, fragrance, animal health, detergents and other industries to develop **New Approach Methodologies (NAMs)** – innovative non-animal tests and strategies – and to facilitate their validation and regulatory acceptance in Europe and beyond.

From its inception, EPAA's vision has been to ensure that safety testing for drugs, chemicals and consumer products can rely on **better, more predictive non-animal methods** without compromising human and environmental safety.

It began formal operations in 2006 under an initial 5-year mandate, which has been successfully renewed through 2025 due to encouraging results and continued stakeholder commitment. Today, EPAA encompasses collaboration across **eight major industry sectors** – including human pharmaceuticals (EFPIA), veterinary medicines (AnimalhealthEurope), chemicals (CEFIC), cosmetics & personal care (Cosmetics Europe), crop protection (CropLife Europe), fragrances (IFRA), food & drink (FoodDrinkEurope), detergents & maintenance products (AISE), as well as SMEs – working together with the **European Commission**, including the EU Reference Laboratory for alternatives (EURL ECVAM), ECHA, EFSA, and EMA. This broad alliance places EPAA in an ideal position to promote the development and acceptance of alternative approaches to animal testing for meeting regulatory requirements in a holistic, cross-sector and science-based manner.

Key Achievements Across Industry Sectors

EPAA's influence spans a wide array of industry sectors, each with different regulatory testing needs. The following sections summarize **major achievements over 2005–2025 by sector/domain**, highlighting how EPAA initiatives led to new alternative methods, supported their validation, and eventual regulatory acceptance (in the EU and internationally). These achievements range from scientific breakthroughs (new *in vitro* tests and computer models) to encouraging and facilitating concrete changes in guidelines, regulations, and industry practices. On this journey, the EPAA has joined forces and collaborated with relevant external stakeholders and scientific organisations, such as the UK NC3Rs, EDQM, MEB, ECETOC, IIVS, Humane World for animals, and others.

Human Pharmaceuticals

In the human pharmaceutical sector, EPAA has been instrumental in rethinking traditional animal-heavy safety testing paradigms and supporting the adoption of more predictive, human-relevant methods. Notable accomplishments include:

- **Carcinogenicity Testing Reform:** Human pharmaceuticals historically required long-term carcinogenicity studies in two species (rat and mouse) for most new drugs. An EPAA-supported data-sharing initiative pooled results from **289 pharmaceutical compounds** to assess the true value of the second long-term rodent bioassay. The analysis published in 2016[1] showed that in many cases a **2-year carcinogenicity study in rats could be waived** without compromising human safety, if other data (e.g. from 3–6-month toxicity studies, genotoxicity tests, and pharmacological mechanism knowledge) showed no cancer risk. The dataset demonstrated high concordance – 92% predictive for non-carcinogens and 98% for carcinogens – using the shorter-term and *in vitro* information. These findings, presented to regulators, **questioned the relevance** of routine 2-year rodent tests. EPAA's cross-company project provided a scientific foundation that informed international guideline discussions (e.g. at ICH, the International Council for Harmonisation) about waiving redundant studies. Indeed, experts concluded that a weight-of-evidence approach could maintain safety while sparing many animals. Building on this, EPAA extended the approach to other sectors (see agrochemicals below) and supported its consideration in global forums. This work has contributed to regulators granting waivers for some carcinogenicity studies, thereby **reducing the use of hundreds of rodents per drug** without impacting human health decisions.

- **Biopharmaceuticals (Monoclonal Antibodies):** Advanced biotech therapies such as monoclonal antibodies often undergo extensive animal testing, including long-duration toxicity studies in primates or transgenic models. The **Monoclonal Antibody Safety project (2020–2023)** examined if certain *chronic toxicity tests* and the use of "recovery" animals (animals kept alive for a period after dosing to check for delayed effects)

1 dx.doi.org/10.3389/fmed.2016.00045

could be reduced. By gathering real-world data from past drug programs in collaboration with the Netherlands Medicines Evaluation Board (MEB), the project developed **criteria for waiving or shortening chronic studies** on a case-by-case basis. An EPAA workshop in April 2021 with regulators and companies discussed these results, and in 2023 the team published two peer-reviewed papers with concrete recommendations. One paper proposed a **Weight-of-Evidence decision model** to determine when a 6-month toxicity study (in one species) is sufficient for antibody drug[2]. **The second paper (led by the NC3Rs) analysed the use of recovery groups, suggesting that in many cases these extra animals add little new information**[3]. These publications in *Regulatory Toxicology and Pharmacology* have been disseminated widely – including a joint EPAA/NC3Rs webinar for regulators in April 2023 – and are expected to influence global regulatory guidance on biotech medicines. The impact is a potential cut in the number of non-human primates or other large animals used per drug tested, while still ensuring safety This reflects an ongoing commitment by both industry and agencies to seek *humane science* without compromising risk assessment.

- **Batch Testing of Biologicals:** EPAA has achieved major strides in eliminating obsolete animal-based quality control tests for human and veterinary biological products (vaccines, antibodies, etc.). A flagship effort is the **Vaccines Consistency Approach (VCA)**, which advocates using advanced *in vitro* assays and product analytical data to ensure each vaccine batch is produced consistently, rather than repeating animal tests for every lot. Starting in 2010, EPAA's Vaccine Consistency initiative brought together human and veterinary vaccine manufacturers, the European Medicines Agency (EMA), and the European Directorate for Quality of Medicines (EDQM). EPAA co-organised *proof-of-concept* studies and workshops to demonstrate that for certain vaccines

For **human vaccines**, EPAA's work with EDQM and regulators bore fruit with the **rabies vaccine ELISA**. The traditional NIH rabies potency test involves injecting mice with vaccine and live virus, causing lethal rabies in control animals. EPAA facilitated collaborative studies evaluating ELISA methods that measure rabies glycoprotein content as a proxy for potency. By 2017, an international study coordinated by EDQM (BSP148) was underway with EPAA support, and by 2023 phase 2 was completed successfully, demonstrating the ELISA's **transferability and reliability across labs and virus strains**. This is a **major milestone**: results show the *in vitro* assay works for most vaccine strains worldwide. The next step – already in progress – is to use this data to **revise the European Pharmacopoeia monograph for human rabies vaccine**, so that the ELISA becomes the accepted method and the mouse test can be phased out. Importantly, EPAA ensured global outreach for this effort: data were presented to regulators in emerging economies (e.g. DCVMN in India) and to the U.S. NICEATM/ICCVAM community, generating international buy-in.[4]

This work **raised awareness among global regulators** and prepared the ground for a larger Innovative Medicines Initiative (IMI) project, which was launched in 2016 with €8 million funding, aiming at fully validating the consistency approach for multiple vaccines (VAC2VAC[5]). *Outcome:* By 2018, tangible regulatory changes occurred: the EPAA Harmonisation of 3Rs in Biologicals project team formally requested deletion of the general **Abnormal Toxicity Test (ATT)** and other archaic tests from international pharmacopoeias. In response, the **European Pharmacopoeia in 2018/2019 eliminated the ATT** from dozens of product monographs, and the World Health Organization (WHO) followed by discontinuing the ATT in its guidance in late 2018. Likewise, for veterinary vaccines, EPAA's push led to the development of global VICH guidelines in 2018–2020 that **waive the Target Animal Batch Safety Test** (TABST) for certain inactivated and live veterinary vaccines meeting certain consistency criteria. In practical terms, these changes mean that manufacturers no longer have to inject mice/guinea pigs (for ATT) or target species (for TABST) to release each batch of vaccines, provided modern *in vitro* tests and production controls assure the quality. This has spared significant animal use worldwide.

- **Removal of Redundant Acute Toxicity Tests:** another success in pharma is simply the *abolition* of certain tests: Through science and advocacy, acute lethality testing (LD50 type studies) was **phased out in the pharmaceutical sector** earlier on. By the late 2000s, regulators accepted that acute toxicity in drug development can be assessed by other means (e.g. using dose-ranging data from repeated-dose studies), and EPAA reinforced this paradigm across sectors. In an EPAA review of acute systemic toxicity requirements, it was noted that **acute toxicity studies are no longer required for pharmaceuticals**, reflecting regulatory 3R progress[6]

  EPAA has leveraged this experience to advocate similar waivers in chemicals testing.

Overall, the pharmaceutical domain has seen **faster integration of 3Rs approaches** in its regulations in part due to EPAA's initiatives: e.g. *ICH guidelines* now allow more flexible testing strategies, the EMA has eliminated certain animal tests from its guidance, and industry's use of new methods has grown. EPAA's role as a convener of industry scientists, toxicologists, and regulators has been key to aligning on science-based reductions in animal use while **maintaining a high level of patient safety.**

2 doi.org/10.1016/j.yrtph.2022.105329
3 doi.org/10.1016/j.yrtph.2023.105339
4 doi.org/10.1016/j.vaccine.2016.12.039
5 www.vac2vac.eu
6 doi.org/10.1093/toxsci/kfq143

Veterinary Medicines and (veterinary) vaccines

The animal health industry (veterinary pharmaceuticals and vaccines) is another important sector under EPAA's umbrella. Vaccines, in particular, historically rely on animal tests for batch release (potency and safety) and posed a significant 3Rs challenge. EPAA made vaccines a priority early on, knowing that **hundreds of thousands of animals** (mice, guinea pigs, rabbits, etc.) are used annually in Europe for routine vaccine quality control. Key achievements include:

- **Vaccine Consistency Approach** (for Veterinary Vaccines)**:** As mentioned above under pharmaceuticals, EPAA championed the Consistency Approach – ensuring each vaccine lot is produced to the same quality as a thoroughly characterised reference lot, using primarily *in vitro* and analytical data.
  For veterinary vaccines, EPAA focused on Clostridial vaccines (e.g. for farm animals) which require particularly heavy animal testing. Many clostridial toxoid vaccines still used a **Minimum Lethal Dose (MLD)** test in guinea pigs or mice as an in-process control. EPAA co-organized workshops in 2013 with EDQM to address this, and supported a collaborative study (BSP130) on a cell-based assay alternative. By 2015, that study succeeded in demonstrating concordance between the cell assay and in vivo results for one vaccine, prompting further validation steps [7 8 9]

  EPAA's vaccine project technical committee also served as a **cross-learning platform between human and veterinary vaccine experts**, enabling techniques developed for human vaccines to be tried for animal vaccines and vice versa. Thanks to EPAA's efforts, the concept of the vaccines consistency approach gained traction: manufacturers saw the benefit of improved product characterization, and regulators saw improved safety assurance plus animal welfare gains. A direct outcome was the influence on **WHO and OIE** policy – EPAA's submissions in 2016–2018 encouraged these bodies to formally call for elimination of redundant batch safety tests. By 2019, the **OIE (World Organisation for Animal Health) had revised its guidance** to drop the general safety test from veterinary vaccine requirements, aligning with what Europe had done. Additionally, a **VICH guideline (GL55/59)** now provides a framework for waiving lab animal batch safety tests for veterinary vaccines internationally. This means that if a manufacturer has a consistent production process and performs other *in vitro* checks, they no longer need to sacrifice groups of mice or guinea pigs for each batch – a practice that had continued in some regions. The impact on animal use is enormous: for example, clostridial vaccine testing was estimated to use around 50% of all animals for EU veterinary vaccine quality control, so replacing those tests could halve the animal numbers in this area.

- **Deleting Obsolete Tests in Veterinary Medicines:** Beyond vaccines, EPAA also looked at tests like the **target animal safety test** for veterinary pharmaceuticals (where a high dose is given to the target species to look for adverse effects, often causing distress). Through its *Advancing 3Rs in Regulatory Toxicology* project (completed in the 2010s), EPAA reviewed such requirements across sectors and regions. They found considerable variation and many tests driven by tradition rather than true need. The project chose **carcinogenicity and batch safety tests** as areas with greatest potential, as discussed. As a result, Europe and others have dropped the routine **target animal batch safety test** (TABST) for veterinary vaccines that meet waiver criteria. Similarly, **acute toxicity tests** for veterinary drugs were aligned with human pharma (i.e. not required separately if other data suffice). EPAA's multi-sector surveys helped regulators realize that safety margins built into veterinary dose setting made some animal tests superfluous.

- **3Rs Training and Culture Change:** The animal health sector also benefited from EPAA's educational initiatives. For example, EPAA's Refinement Prize (awarded to technicians and researchers improving animal welfare) has had winners from veterinary schools and vaccine companies for innovations like training pigs to cooperate with procedures or refining horse antibody production. By publicizing these through EPAA conferences, the partnership spreads a culture of care and refinement in areas where complete replacement is not yet possible. Furthermore, EPAA has extended its outreach internationally; it has coordinated **training in non-animal methods in China** (an important emerging market for both human and vet products) aiming to promote 3Rs awareness and acceptance in countries where animal testing had been the norm. Such efforts help ensure that as Europe eliminates a test, other countries will accept the alternative data for imports, etc., thereby **magnifying the global impact**.

In summary, EPAA's work in the human as well as veterinary vaccine domain has

7 www.researchgate.net/publication/299524992_Validation_of_alternative3Rs_methods_for_the_in-process_quality_control_of_Clostridium_septicum_vaccines_BSP130_participants_workshop_report_15-16_September_2015
8 pharmeuropa.edqm.eu/app/BioSN/content/BioSN-0/2021-5-Clostridium-septicum-vaccine-antigens-Part-2.pdf
9 freepub.edqm.eu/publications/PUBSD-168/detail

directly reduced animal suffering by targeting high-impact batch tests, while also modernizing quality control to be more scientific. Vaccines are safer and more consistent as a result of better *in vitro* assays, and the animals (from rodents to large animals) have been spared painful procedures. It is a prime example of how pursuing the 3Rs can be a *win-win* for both ethics and quality of science.

Chemicals and Industrial Products (REACH and CLP Sectors)

The chemicals sector – covering industrial chemicals (under REACH), consumer products (cleaning agents, detergents, food additives, etc.), and specialty chemicals – historically used large numbers of animals for toxicology tests due to regulatory requirements. EPAA's cross-industry platform (including chemical manufacturers, downstream users like detergents/fragrances/food and agencies like ECHA, EFSA) has driven several advancements in non-animal safety assessment for chemicals:

- **Acute Toxicity and Dose-Level Refinement:** Acute systemic toxicity tests (to determine lethal dose or hazard classification) are a significant area where EPAA has sought full replacement. Recognizing that for **industrial chemicals and agrochemicals, acute toxicity tests are still a legal requirement** (unlike in pharma/cosmetics), EPAA formed a project team in 2008 to promote alternative strategies. The team's efforts yielded a major change in **2016**, when the EU *REACH* regulation's standard requirements were amended to allow companies to **waive the second route acute toxicity test (dermal route)** under certain conditions. Specifically, if sufficient oral toxicity data and weight-of-evidence suggest that dermal exposure would not add new information, the rabbit skin LD50 test can be omitted. EPAA had provided the scientific justification for this policy shift, compiling data that dermal tests rarely alter classifications when a robust oral test exists.[10 11] This regulatory acceptance was a concrete 3Rs win, preventing unnecessary poisoning of animals for duplicative tests. In parallel, EPAA has worked on **refining acute toxicity** determinations – for instance by identifying earlier humane endpoints (clinical signs) that predict lethality, so that fewer animals die during required tests. An EPAA consortium including industry toxicologists, EURL ECVAM, and the UK NC3Rs published recommendations and a *peer-reviewed paper* on using *clinical signs instead of death* as the endpoint, enabling investigators to stop tests once severe signs occur[12]. These recommendations have been presented at international forums to spread best practices.

Next step: EPAA's ultimate goal is an "animal-free decision framework" for acute toxicity. Work is underway on integrating *in vitro cell assays* and computational models to replace *in vivo* acute tests entirely, a challenging but crucial area for the future.

- **Skin Sensitisation (Allergy) Testing:** A standout success story in alternatives has been skin sensitisation – determining whether a substance can cause allergic contact dermatitis. Thanks to concerted efforts by regulators, industry (including EPAA members Cosmetics Europe, Cefic, IFRA), and EURL ECVAM, a suite of **non-animal tests for skin sensitisation** was validated in the 2010s. These include the Direct Peptide Reactivity Assay, KeratinoSens, and h-CLAT assays, which cover key steps of the immune reaction. By 2015–2018, the OECD had adopted these as Test Guidelines, and by 2019 it even approved integrated *Defined Approaches* that combine multiple NAMs to fully replace the traditional mouse test (LLNA). EPAA significantly contributed to the **implementation and regulatory uptake** of these methods. It organized a series of training workshops (in 2013, 2015, and 2019), hosted by ECHA in Helsinki, specifically to educate industry and regulators on how to use the new non-animal sensitisation methods in practice. These "hands-on" sessions, co-sponsored with partners like Cefic's Long-Range Research Initiative (LRI) and Cosmetics Europe, improved the peer-to-peer knowledge sharing among experts from companies and government. As a result, confidence in these methods grew, facilitating their acceptance under EU regulations. For example, under **REACH**, companies began routinely submitting *in vitro skin sensitisation data* instead of animal test results, and ECHA's guidance recognized these methods as valid. EPAA also helped establish a **"Skin Sensitisation User Forum"** in 2019 – a network of practitioners who regularly exchange case studies and troubleshooting tips on NAM usage. This is important because regulators often require robust justification when novel methods are used; having a body of shared experience and positive case examples helps *harmonize interpretations*. By building this community of practice, EPAA ensured that the scientific validation done at OECD translates into real-world regulatory acceptance.[13]

Today, the EU Cosmetics Regulation explicitly requires non-animal methods for sensitisation (animal tests are banned), and REACH

10 doi.org/10.1093/toxsci/kfq143
11 dx.doi.org/10.1016/j.yrtph.2013.02.005.
12 linkinghub.elsevier.com/retrieve/pii/S027323002300185X

13 doi.org/10.1016/j.yrtph.2019.104477; https://doi.org/10.1016/j.yrtph.2020.104767

registrations have largely moved to NAM-based dossiers for this endpoint – a clear replacement is about to be achieved. Furthermore, EPAA's model has been influential globally: defined approaches for skin sensitisation are now being adopted by authorities in e.g. the US and Canada, following the OECD's lead, demonstrating the international ripple effect of these efforts.

- **Systemic Toxicity and Next-Generation Risk Assessment:** Despite progress in acute and local toxicity endpoints, evaluating **systemic toxicity (repeated-dose effects, organ toxicity)** remains heavily reliant on animal studies. EPAA has a long history of exploring how new science (-omics, cell culture, computational modelling) can tackle systemic toxicity. Starting with its 2008 *"Blue Sky"* workshop and a 2010 seminar on *"Harnessing the Chemistry of Life – Revolutionising Toxicology"*[14], EPAA anticipated what is now called *Next Generation Risk Assessment (NGRA)*[15]. In recent years, EPAA's *NAMs for Chemical Safety* working groups (WG1 & WG2) have tackled this challenge. The **2021 deep-dive workshop** identified concrete needs to increase regulatory confidence in NAMs for systemic endpoints. Three key areas emerged: (1) establishing clear **quality criteria** for NAM data (so regulators know the data is robust and reproducible); (2) updating regulatory frameworks to **move away from seeing the animal test as the default "gold standard"**, by creating tiered testing schemes where exposure info and NAM results can suffice if they are informative; and (3) adjusting REACH annexes and guidance texts to explicitly **facilitate the use of NAMs** (for example, clarifying when an *in vitro* result can replace an *in vivo* study requirement). Following the workshop, EPAA partners published a full report in *Regulatory Toxicology and Pharmacology* to disseminate these insights[16]. One outcome has been the proposal of an EPAA **"Designathon" challenge** (launched in 2023) to spur innovative solutions for predicting systemic toxicity using combinations of NAMs[17]. This challenge, run with the scientific community, targets human *systemic toxicology* – one of the last and most complex frontiers for animal replacement. It underscores EPAA's strategy of *collaborative innovation*: bringing regulators, industry, and scientists together to co-design new methodologies that, if successful, can be fed into OECD test guideline development or EU regulatory acceptance pathways. While full replacement of chronic toxicity testing is still aspirational, EPAA's work has laid critical groundwork (such as identifying predictive biomarkers and developing organ-on-chip models through its 3Rs Science prize program) for future breakthroughs.

- **Chemicals Strategy and Policy Input:** EPAA's achievements in the chemical domain are not only technical but also policy-oriented. The partnership has become a key stakeholder in EU chemical safety initiatives. For instance, as the European Commission formulated its **Chemical Strategy for Sustainability (CSS)** in 2020–2021 – which calls for increased use of NAMs to ensure "sustainable" chemicals – EPAA provided expert input on how alternative methods can be integrated to both protect health and reduce animal use. The cross-sector representation in EPAA allows it to present a unified industry voice in favour of modern, non-animal approaches (whereas in the past, different industries might have had divergent views on alternatives). EPAA members also informed the development of EU research priorities, leading to useful EU-funded research programmes, such as the €60 million **ASPIS cluster** of Horizon projects (ONTOX, PrecisionTox, RiskHunter) dedicated to animal-free safety assessment of chemicals. Although EPAA is not a funding body, its existence and advocacy helped motivate these large-scale projects by demonstrating industry's commitment to implement the outcomes. Additionally, EPAA regularly liaises with ECHA sharing knowledge on the applicability of NAMs and has representation in forums like EURL ECVAM's **PARERE network**, which reviews the regulatory relevance of proposed new alternative methods. All these activities have ensured that the **3Rs are central to chemical safety regulation** in the EU – exemplified by REACH's clause that animal testing is "a last resort", backed up by robust alternative methods development.

Cosmetics and Consumer Products

The cosmetics, personal care, and consumer products sector has arguably seen the most dramatic regulatory shift, thanks to the EU's proactive stance on animal testing bans. EPAA has helped to **support industry's transition to 100% non-animal testing strategies** and to help resolve scientific gaps that the bans created:

- **Cosmetics Animal Testing Ban Implementation:** The EU Cosmetics Directive and Regulation phased in a strict ban on animal testing: since 2009 for most endpoints, and fully by **March 2013** for all human health effects (including complex endpoints like repeated-dose and reproductive toxicity). This bold policy meant that cosmetic companies could no longer rely on any new animal data for safety substantiation. EPAA, which includes Cosmetics Europe and major cosmetics manufacturers (L'Oréal, Unilever, P&G, etc.) as partners, was a crucial forum for **ensuring alternative methods were in place** to meet this challenge.

  Through EPAA, cosmetic companies shared breakthroughs with other sectors – for example, *reconstructed human skin* models for skin irritation were developed and validated by cosmetic companies and then actively promoted via EPAA to be accepted for

14 analyticalsciencejournals.onlinelibrary.wiley.com/doi/10.1002/jat.1666
15 doi.org/10.1016/j.yrtph.2020.104668
16 doi.org/10.1016/j.yrtph.2022.105261
17 single-market-economy.ec.europa.eu/calls-expression-interest/epaa-designathon-human-systemic-toxicity_en

chemicals testing as well DOI[18][19][20]

EPAA also worked to **fill remaining gaps** in the early 2010s: it identified that for endpoints like repeated-dose toxicity and reproductive toxicity (which by 2013 still had no full replacements), a temporary solution was needed. EPAA members contributed to a European Commission *technical report* in 2013 on the state of alternative methods for these "complex endpoints".[21]

The report acknowledged that while complete replacements were not yet available in 2013, the ban would proceed — thereby intensifying efforts such as the SEURAT-1 research program (a €50 million public-private partnership on systemic toxicity alternatives, co-funded by the cosmetics industry and EU). EPAA served as a stakeholder platform to disseminate results from these research programs. By fostering a united front between regulators and industry on the importance of non-animal approaches, EPAA helped **maintain confidence in the ban** and avoid derailment. Notably, as alternative methods for systemic toxicity began to emerge (e.g. organ-on-chip for liver toxicity, combined *in vitro* assays for endocrine effects), EPAA's cross-sector nature allowed lessons from pharmaceuticals and chemicals to be translated into the cosmetics context and vice versa[22].

- **Integrated Testing Strategies for Consumer Products:** Consumer product companies (soap, detergent, and fragrance manufacturers in EPAA) also faced safety testing demands,

for example for detergents under the Detergents Regulation and for fragrances under REACH and cosmetic allergens rules. EPAA helped provide these companies access to the latest NAMs. One example is in **eye irritation testing** – important for products like soaps or cleaners. Non-animal eye irritation tests (such as the *Bovine Corneal Opacity and Permeability test* and reconstructed human cornea models) became OECD-approved around 2009–2015, and EPAA partners from the detergent sector worked with chemical sector partners to implement these broadly, so that testing of cleaning products no longer involves the traditional rabbit Draize test.[23]

The European detergents & maintenance products industry association *(AISE)*, an EPAA member, reported that by adopting these alternatives and promoting them via EPAA, the household products industry was able to comply with EU requirements **without new animal tests**. Similarly, in the **fragrance sector**, many substances require toxicological evaluation for safe use. Fragrance companies under IFRA (EPAA partner) benefitted from EPAA-coordinated research into *local toxicity* endpoints – e.g. skin sensitisation as discussed, and phototoxicity – leading to validated assays that they could use for IFRA standards instead of animal tests[24] By **sharing the cost and knowledge** of alternatives development across sectors, EPAA made it economically and scientifically feasible for smaller consumer product companies (including SMEs) to transition to non-animal testing.

In summary, through EPAA's collaborative activities, the cosmetics and consumer products industries successfully navigated one of the most stringent animal testing bans in the world. **No new cosmetic product has been tested on animals in the EU for over a decade**, a fact made possible also thanks to EPAA's actions supporting the validation and acceptance of alternative methods. This accomplishment not only improved *animal welfare* but also drove *scientific innovation* in human biology-based test methods that are now cross-pollinating into chemical and pharmaceutical safety science.

Agriculture and Crop Protection (Agrochemicals)

Agrochemicals (pesticides such as insecticides, herbicides, fungicides) have traditionally required very extensive animal testing under regulations like the EU Plant Protection Products law and similar regimes worldwide. EPAA's crop protection industry members (now under CropLife Europe) have collaborated with other sectors to find synergies in reducing animal tests for these substances:

- **Carcinogenicity Waivers for Pesticides:** Building on the success with pharmaceuticals, EPAA initiated a project in 2017 focused on **carcinogenicity assessment of agrochemicals**. Two-year rodent carcinogenicity studies are usually mandated for pesticides, consuming a large number of animals. The EPAA project, led by scientists at the Dutch RIVM, collected data on **over 400 agrochemical active substances**. Of these, about 170 were identified as *non-genotoxic* (not DNA-damaging) and were analyzed to understand their mechanisms of causing tumors (if any). In 2019, EPAA convened an expert workshop with regulators (including EU Member State authorities, EFSA, and US EPA observers) to discuss a **Mode-of-Action (MOA) driven approach** for pesticide carcinogenicity.[25]

  The workshop strongly supported moving away from blanket 2-year

18 linkinghub.elsevier.com/retrieve/pii/S088723330900246X
19 dx.doi.org/10.1177/026119290703500614
20 pubmed.ncbi.nlm.nih.gov/22943518/
21 op.europa.eu/en/publication-detail/-/publication/1acff55b-fff9-4c14-9e2f-013c68ceae74
22 doi.org/10.1016/j.yrtph.2015.07.007
23 youtu.be/TiZbp5KDHI8?si=WNGeHj6ZIobJ5rx6

24 doi.org/10.1016/j.yrtph.2019.104473.
25 doi.org/10.1016/j.yrtph.2014.04.009

testing toward a strategy that uses knowledge of a chemical's MOA, combined with shorter-term tests, to decide if a long-term study is truly needed. The analysis suggested that if certain conditions are met (e.g. no genotoxicity, predictable toxicological modes of action, etc.), **40–60% of pesticide long-term studies could potentially be waived** without loss of safety. This represents a huge 3Rs impact, as each such study uses at least 400 rats over two years. The EPAA project identified 10 key MOA "profiles" for non-genotoxic carcinogens among pesticides, and also highlighted data gaps (cases of tumors with unknown mechanism). Two scientific papers were published in 2020 detailing these findings. DOI[26]

A second phase of the project (2020–2023) then worked on addressing the "known unknowns" by filtering out tumors that only occurred at excessive doses, thereby focusing on relevant cancer findings, and started developing a **weight-of-evidence (WoE) decision scheme** for predicting carcinogenic potential **without a 2-year bioassay**. As of 2023, criteria for defining these "known unknowns" have been established (e.g. distinguishing high-dose effects) and a WoE approach is being formulated. *Impact:* This EPAA initiative has enabled the agrochemical industry to engage with regulators (EFSA and international bodies) discussing concrete proposals on when a rodent cancer test can be scientifically waived. It complements parallel efforts by the OECD (which is developing an *Integrated Approach*

to Testing and Assessment for carcinogenicity) and by US EPA (which in recent years began granting waivers for some pesticide rodent cancer studies). EPAA's facilitation of data-sharing and collective analysis has been crucial – individual companies would not have had access to the broad dataset needed to draw these conclusions. Going forward, if regulatory guidelines change to allow MOA-based waivers for pesticides, it will be in large part due to the groundwork laid by the EPAA projects demonstrating evidence that **safety can be assured with fewer animals**.

- **3Rs in Ecotoxicology and Other Tests:** While human health testing has been a major focus, EPAA's agrochemical members have also considered animal use in environmental safety testing (ecotoxicology). Tests like fish acute toxicity and avian toxicity involve many animals. EPAA has provided support to EU and OECD efforts aimed at alternatives here – for example, promoting the **fish embryo test** as a replacement for adult fish acute tests (recognized as an alternative in some jurisdictions), or encouraging the development of *in vitro* assays for endocrine disruption screening (to reduce specialized animal tests). In the EPAA "Designathon" launched in 2023, one of the challenges is systemic toxicity which covers ecotoxic endpoints as well. Moreover, EPAA's collaboration with the chemicals sector on acute toxicity is equally beneficial to pesticides (since pesticide regulations often mirror REACH requirements). Indeed, the **dermal acute toxicity waiver** that EPAA supported under REACH in 2016 was later mirrored in the pesticide domain, with authorities accepting just one-route acute tests for certain formulations, thereby reducing animal numbers[27] These cross-cutting gains show how EPAA leverages progress in one regulatory domain to influence another.

- **Global Harmonization for Agrochemicals:** Like in pharma, differing requirements across the world can lead to redundant testing for pesticides. EPAA's harmonization agenda (through workshops and discussions with bodies like OECD) also covered agrochemical data requirements. By presenting the case that some long-standing animal tests (e.g. separate dog studies or mouse carcinogenicity tests) may not be scientifically necessary, EPAA gave European regulators evidence to push for changes in international test guidelines. This is aligned with the OECD's vision of avoiding duplicative testing – a principle strongly endorsed in OECD's Animal Welfare Resolution of 2016. EPAA, via industry participants who also sit on OECD working groups, has funnelled its project results (like the MOA-based Carcinogenicity approach) into those discussions. In one instance, an EPAA-coordinated workshop in 2019 on cross-sector carcinogenicity (pharma and pesticides) explicitly included OECD observers and was cited as

26 https://linkinghub.elsevier.com/retrieve/pii/S0273230020302154

27 dx.doi.org/10.1016/j.yrtph.2013.02.005

complementing "other international activities by OECD and US EPA"[28]

This underscores EPAA's role as a **bridge between EU innovation and global regulatory evolution**.

Overall, while the regulatory frameworks for crop protection still mandate many animal studies, EPAA's work in the last 20 years has paved the way for a more science-driven, risk-based testing paradigm. As authorities begin to allow waivers for certain studies (e.g. EPA's 2019 policy to reduce animal testing for pesticides), the scientific rationales often trace back to collective analyses like those initiated by EPAA. This will continue to be a critical area where further investment is needed (see *Future Directions* below).

Informing the European Union Policy and Funding

One of EPAA's notable strengths is its ability to translate scientific progress on alternatives into opportunities for **policy and regulatory change**. Over 20 years, EPAA has substantially informed EU policies related to animal testing and humane science, as well as on the allocation of funding for 3Rs research:

- **Embedding 3Rs in EU Legislation:** The EU has been at the forefront of legislating the 3Rs principle, and EPAA played a supporting role in this leadership. The **EU Directive 2010/63/EU**, which came into force in 2013, is a cornerstone law that governs the protection of animals used for scientific purposes. It explicitly sets the *final goal of the full replacement* of animal use and makes the 3Rs mandatory in all research and testing in the EU. While the Directive was proposed by the European Commission, EPAA provided a platform for industry to constructively input into the process, ensuring broad support for its ambitious aims. The Directive also established EURL ECVAM as the reference laboratory for alternatives and called for enhanced validation and regulatory acceptance of new methods. EPAA, being a Commission-industry partnership, has since acted as an implementation partner: many of the **specific measures** in the Directive (e.g. encouraging sharing of best practices, avoiding duplicate testing via data sharing, and promoting alternative methods R&D) are directly advanced by EPAA projects and workshops. By demonstrating that industry was willing and able to adopt alternative methods, EPAA helped policymakers be confident in setting strict provisions like *"no animal test if an alternative exists"*. This clause from Directive 2010/63/EU – now law in all Member States – has real teeth: as noted earlier, the Pharmacopoeia cannot require an animal test if an alternative is recognized, forcing regulators to keep methods updated and sparing animals from outdated tests.
- In 2024 and 2025 the EPAA has re-oriented several of its projects towards the development of action plans in different areas of toxicology to directly contribute to the EC Roadmap for phasing out animal testing in chemical safety assessments.
- The **Animal-Free Chemical Safety Assessment (AF-CSA) Conference** was organised by EPAA in March 2025 as a truly cross-sectoral event, involving more than 250 experts.[29]

Participants worked in breakout groups to develop animal-free safety assessment strategies capable of addressing European chemical regulatory information requirements without animal testing. Each breakout group proposed short, medium and long-term actions for potential inclusion in the European Commission Roadmap. These recommendations and discussions on the so-called "regulatory sandboxes" helped define EPAA's role in supporting the implementation of the Roadmap as an efficient collaborative organisational structure.

- **Strategic Funding and Programs:** EPAA's public-private nature means it does not directly fund large research. However, it has been **highly influential in guiding EU research funding** priorities. EPAA frequently partners with the European Commission's research arms and industry sectors in setting up frameworks for 3Rs R&D:
  - The earlier mentioned **SEURAT-1** initiative (2011–2016), a cluster of research projects focused on "Safety Evaluation Ultimately Replacing Animal Testing", was a joint venture of the EU (FP7 program) and Cosmetics Europe, totalling €50 million. Many EPAA member companies and Commission officials were involved in SEURAT. The knowledge gained (e.g. on integrated liver toxicity testing) was shared through EPAA events to ensure cross-sector uptake. EPAA essentially helped **transfer SEURAT outcomes** beyond cosmetics into chemicals and pharma.
  - Under Horizon 2020, the formation of the **ASPIS cluster** (2020–2025, combining ONTOX, Risk-Hunt3R, PrecisionTox projects for animal-free chemical safety) was influenced by the recognized need from DG RTD, EPAA and EURL ECVAM to tackle systemic toxicity. ECVAM's 2021 status report notes heavy involvement in ASPIS and references EPAA as a partner in spreading those results. EPAA has hosted ASPIS scientists at its conferences and integrated their progress (e.g. new computational models for toxicity) into discussions with industry regulators. In this way, EPAA ensures that EU funding in NAMs yields practical regulatory outcomes by **connecting researchers with regulatory end-users** early on.
- **European Parliament and Council Engagement:** By providing a neutral ground for dialogue, EPAA has indirectly affected political positions on animal testing. MEPs (Members of European Parliament) have attended EPAA annual conferences – the 10th anniversary conference in 2015 was even hosted by an EP Parliament committee chair. The visibility of EPAA's work helped build confidence among policymakers that an eventual "animal-free testing" goal is credible.

28 doi.org/10.1016/j.yrtph.2020.104789

29 single-market-economy.ec.europa.eu/document/download/987d11b2-46ea-450b-b7ca-3c36017e7c67_en?filename=AF-CSA%20Conference%202025%20-%20flash%20report.pdf

This contributed to the European Parliament's **2021 resolution** calling on the Commission to develop an Action Plan for ending all animal testing. In the resolution's debate, references were made to successes in alternatives (like cosmetics) and the need for cross-sector collaboration – essentially echoing the EPAA model. The Commission's response to the Parliament has been to highlight existing initiatives, with EPAA cited as a key example of public-private partnership delivering results in this area.

- **EU Directives and Regulations on Specific Methods:** In some cases, EPAA's technical work has directly fed into regulatory documents. For instance, after EPAA and partners demonstrated the success of the Monocyte Activation Test (MAT) as an alternative pyrogen test, the European Pharmacopoeia introduced a chapter encouraging its use. EPAA's continuing collaborative efforts with EDQM toward phasing out of the rabbit pyrogen tests led to a roadmap (to 2026) to replace them with *in vitro* methods. EDQM in 2022 published draft chapters on MAT: a clear instance of scientific to regulatory translation. Another example: EPAA's workshop findings on skin sensitisation were included in an OECD Guidance Document that accompanied the Defined Approach TG, illustrating how EPAA's on-the-ground training and feedback informed the international guidance.

In summary, EPAA has had a **multifaceted contribution to EU policy** – by advocating for 3R principles in law, by informing the technical details of regulations, and by shaping the research that underpins future policy shifts. The partnership's success has even been recognized as a model in other domains (for example, a similar public-private partnership for *alternatives in biomedical research*, inspired by EPAA is being discussed). The EU's progressive stance – from banning cosmetics animal testing to requiring alternatives via legislation – has been strengthened and enabled by the scientific confidence that EPAA helped build.

Global Impact and International Harmonization

EPAA's initiatives have not been confined to Europe; they have also had **measurable impact on international policy frameworks and harmonization efforts**. By collaborating with global counterparts and sharing its successes, EPAA has helped raise standards for animal welfare and alternative methods worldwide:

- **OECD Test Guidelines and Global Acceptance of NAMs:** The Organisation for Economic Co-operation and Development (OECD) develops harmonized test guidelines that member countries (including EU nations, the US, Japan, etc.) adhere to for chemical safety. Many alternative methods need OECD endorsement to be broadly accepted. EPAA, through its industry experts and collaboration with EURL ECVAM, has been instrumental in getting new methods into the OECD system. As described earlier, assays for skin irritation, corrosion, eye irritation, and skin sensitisation all became OECD guidelines in the late 2000s/2010s. EPAA members often contributed data and co-authored validation studies that OECD working groups used. For example, when OECD adopted **Test Guidelines 442C, 442D, 442E** for skin sensitisation NAMs (DPRA, ARE-Nrf2 luciferase, and h-CLAT assays), EPAA had already been running workshops and trials on those methods. This meant European industry was ready to use them immediately, setting a precedent that influenced uptake in other OECD countries. Moreover, EPAA's emphasis on *Defined Approaches* helped the OECD move into that new territory (**Test Guideline 497** in 2021 was the first non-animal **Defined Approach** guideline). An EPAA/Cefic/LRI workshop in 2019 in Helsinki was explicitly referenced in the OECD's guidance as an example of how industry and regulators can build confidence in integrated NAM use. By fostering agreement among EU stakeholders first, EPAA smoothed the path for OECD consensus. In effect, **Europe acted as a test-bed** for NAMs under EPAA cross-sector coordination that facilitated the OECD process.

- **International Cooperation on Alternative Test Methods (ICATM):** ICATM is a collaboration of governmental bodies from the EU, US (ICCVAM/NICEATM), Canada, Japan (JaCVAM), South Korea, etc., aimed at aligning validation and evaluation of alternative methods. While EPAA is not a government entity, it has strong ties with ICATM through the European Commission. EURL ECVAM, part of DG JRC and a core ICATM member, often brings EPAA project results to the ICATM table. For example, EPAA's vaccine consistency work was presented to the **U.S. ICCVAM** committee: the 2018 NICEATM meeting saw EPAA experts share the rabies ELISA progress. Similarly, EPAA and Health Canada experts jointly led the 2015 workshop on eliminating the Abnormal Toxicity Test, resulting in a publication in *Biologicals* https://doi.org/10.1016/j.biologicals.2017.05.006. This publication laid out an action plan for global deletion of ATT, which dovetailed with ICATM's objectives.

Indeed, after Europe axed ATT, countries like India and the US followed – India abolished the ATT for human vaccines in 2018, citing the changes in European/Ph. Eur. Standards. The **ICATM framework** ensures that such changes are communicated and encouraged internationally, and EPAA provides much of the success stories and data that fuel these discussions. The result is a *globally coordinated shift*: for instance, by 2020, **WHO published guidelines** recommending phasing out animal batch tests when consistency approaches are in place, which is directly aligned with EPAA's work.

- **Influence on ICCVAM and US Policies:** The United States in recent years has stepped up efforts to reduce animal testing, with agencies like EPA and FDA launching NAM programs. EPAA's achievements have provided a proof-of-concept that ambitious reductions are possible. For example, the **US EPA's 2019 announcement** to eliminate all mammalian chemical testing by 2035 (an unprecedented goal) was partly enabled by the availability of alternative methods for many endpoints – several of which (skin sensitisation, eye irritation, acute toxicity waiver policies) were pioneered or first implemented in the EU via EPAA partners. Communication channels exist: EPAA often invites ICCVAM representatives to its conferences, and vice versa, to exchange updates. When EPAA's deep-dive workshop in 2021 identified barriers to NAM use, those findings were shared with the US FDA-led initiatives on regulatory science. A concrete example is **skin sensitisation**: EPAA's User forum concept was discussed with ICCVAM, contributing to the US considering how to train regulators on defined approaches. Another example is the **2-year carcinogenicity waivers** – the US FDA participated in discussions about the pharma data EPAA generated, which influenced the ICH process. In 2022, ICH adopted a revised S1B Guideline allowing a weight-of-evidence approach to possibly skip the 2nd rodent species for carcinogenicity.

- **Collaboration with Other Regions (China, Brazil, etc.):** As mentioned, EPAA hasn't limited itself to OECD countries. Notably, EPAA engaged with **China's FDA (NMPA)** by providing training on OECD alternative methods. This was significant, as China historically required animal tests for cosmetics and some pharma products. Partly due to international advocacy including from EU stakeholders, China in 2021 relaxed requirements to accept certain non-animal safety data for cosmetics. EPAA can claim some credit in that *the knowledge transfer and confidence building* – such as training Chinese labs in how to perform alternatives – was done under its auspices in collaboration with entities like the Institute for *In Vitro* Sciences (IIVS). Similarly, EPAA's engagement in global 3Rs conferences (like World Congress on Alternatives) and with Latin American regulators (Brazil's ANVISA, etc.) has helped propagate EU's high standards. By showing evidence of success in a regulatory context, EPAA's message to international counterparts is compelling: *these methods are not just theoretical, they work and are accepted by Europe's stringent regulators*. This has accelerated harmonization, with more countries adopting OECD alternative methods and, in some cases, enacting their own bans on testing cosmetics on animals (as seen in several countries following the EU lead).

- **Global 3Rs Awards and Initiatives:** EPAA's model of prizes for 3Rs science has been mirrored by others. ICCVAM now gives a travel award for young scientists, and there's an international 3Rs prize by Lush Cosmetics. These may seem small, but they foster a new generation of researchers worldwide focusing on NAMs. EPAA's emphasis on **recognizing 3Rs excellence** (since 2010) adds prestige to the field globally, encouraging talent to enter.

In essence, EPAA has functioned as a **global catalyst**. European policy and innovation often lead the way, and through EPAA's outreach and collaborations, those advancements quickly traverse borders. International bodies like OECD, WHO, VICH, and ICCVAM have been receptive to input backed by EPAA because it represents a consensus of major industries plus regulators – a powerful combination. The outcome is greater worldwide alignment: for example, when OECD deletes a redundant test guideline or accepts a new alternative, it applies across all member countries, multiplying the impact far beyond Europe. By linking EU progress with international acceptance, EPAA ensures that the drive toward animal-free testing is truly global in scope.

3Rs Science prize

The purpose of the EPAA 3Rs Science prize is to promote positive contributions from industry or academia and to encourage more scientists in the future to focus their research on the 3Rs objectives. Young scientists working on 3Rs alternative methods for safety and/or quality testing are eligible for this prize.

Refinement Award

The refinement prize targets those who develop and implement refinement approaches to animal testing. The aim is to support innovative approaches and raise awareness on the benefits for animal welfare and science alike, as well as on their usefulness for the day-to-day application.

Student grants

Every year, a number of international conferences bring together world-class scientists working on 3Rs alternatives to animal testing (Replacement, Reduction or Refinement). Costs linked to participation often prevent students with promising work from attending. For this reason, the EPAA partners decided to launch the 3Rs Student Grants with the aim to sponsor and facilitate the participation of students and young scientists in important scientific events.

9 3Rs Science Prize

6 Refinement Prize

31 3Rs Student Grants

61 Publications since 2006

4 Communication / best poster

LOOKING AHEAD

EPA A's vision for the next 20 years

As the European Partnership for Alternative Approaches to Animal Testing (EPAA) marks two decades of progress, its commitment to advancing humane, science-based safety assessment remains stronger than ever. With the European Commission's roadmap providing strategic direction, EPAA is poised to play a pivotal role in accelerating the transition away from animal testing in regulatory frameworks.

Over the next five years, EPAA's vision is structured around three strategic priorities:

1. Bridging the Gap Between Research and Regulation

Scientific innovation in non-animal methods is advancing rapidly, yet the translation of these breakthroughs into regulatory practice remains a challenge. EPAA will focus on strengthening this critical bridge—supporting initiatives that convert promising research into validated tools and frameworks that meet regulatory standards.

2. Building Confidence in Non-Animal Methods

Widespread adoption of alternatives depends on trust. EPAA will work to demonstrate the reliability of non-animal approaches through transparent validation, evidence-based success stories, and active engagement with regulators and stakeholders. By fostering collaboration and sharing knowledge, EPAA aims to ensure that these methods are not only developed—but also accepted and implemented.

3. Supporting a Global Regulatory Transition

Given the global nature of industry, harmonization is essential. EPAA will collaborate with international partners to align safety frameworks, reduce redundant testing, and promote mutual recognition of non-animal methods. This global perspective is vital for maintaining Europe's leadership in ethical and sustainable science.

This forward-looking agenda reflects both ambition and necessity. The coming years will be critical in shaping a regulatory environment that embraces innovation while upholding the highest standards of safety. EPAA stands ready to lead this transformation—through partnership, purpose, and a shared belief that better science means better safety, without animals.

GROW-EPAA@ec.europa.eu