*"The single biggest problem in communication is the illusion that it has taken place."*
Attributed[1] to George Bernhard Shaw (Irish playwright, 1856-1950)

*"Communication leads to community, that is, to understanding, intimacy and mutual valuing."*
Rollo May (American existential psychologist, 1909-1994)

Food for thought ...

# Engagement of Scientists with the Public and Policymakers to Promote Alternative Methods

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**Abstract**

Scientists are usually good at teaching, sometimes even to lay audiences. But communicating with journalists, activists, or policymakers can be a different story – hesitancy to make mistakes as well as the temptation to disproportionally promote one's own case come into play. The multitude of social media and other web-based outlets has diversified and accelerated the communication of science. Real-time reactions, sharing of data, tools and results, increasing invitation of personal opinion, demand for transparency, political correctness, and loss of trust in experts are challenges to researchers in general. The field of alternatives to animal testing is more political and important to lay audiences than many others, so its scientists must be especially aware of these challenges. Public engagement offers the opportunity to form community and create wide support for non-animal research and its implementation. This requires scientists to step out of the ivory tower of higher education and engage with diverse interest groups by outreach activities, interviews, and press releases, etc. by employing tailored communication.

## 1 Introduction

Scientists in academia are generally intelligent people; they burn for their research and do not count the hours they work overtime. However, when it comes to dinnertime conversation with non-scientists, many academics cannot easily answer questions about their work in a way that keeps the conversation flowing, captures the interest of their listeners, and gives them the confidence to ask further questions. Instead, they will often either start a monologue that is complex and filled with jargon or may demur that the subject matter they study cannot be conveyed in a short space of time or without specialized knowledge. While scientists are trained to speak publicly, this is usually to an expert audience at team meetings, conferences, or workshops. There they are used to communicating in a specific way to be mindful not to overstate their findings, to consider all relevant limitations, and not to generalize. They are rarely trained in storytelling[2,3] (Avraamidou and Osborner, 2009; Bertele et al., 2019) or public outreach and may not always take the time to prepare for it. To quote Robert Frost (American poet, 1874-1963) "*Half the world*

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[1] https://quoteinvestigator.com/2014/08/31/illusion/

[2] https://www.gsb.stanford.edu/insights/jennifer-aaker-seven-deadly-sins-storytelling

[3] https://www.mckinsey.com/featured-insights/innovation-and-growth/telling-a-good-innovation-story



*Konstanzer Online-Publikations-System (KOPS)*
*URL: http://nbn-resolving.de/urn:nbn:de:bsz:352-2-xe513ebhz02p2*

*is composed of people who have something to say and can't, and the other half who have nothing to say and keep on saying it*."

This has become evident on a major scale during the COVID-19 pandemic, where many scientists were suddenly in the national spotlight, explaining epidemiology, prevention and treatment approaches, scientific research studies, and the research process on television and social media channels. They produced 240,000 scientific papers in one year (Hartung, 2021), but the public was left desperately waiting for definitive answers and scientific leadership which they, with few exceptions, could not provide. In response, the scientists earned both public recognition and growing fanbases as well as criticism and death threats. A *Nature* survey on scientists who had commented about COVID-19 to the media or on social media recorded that 15% of the 321 respondents had received death threats (Nogrady, 2021). While 85% said their experiences with the media during the pandemic had been mostly or always positive, 5% said they had been mostly or always negative. Further, those who had experienced high frequencies of trolling or personal attacks indicated that this had affected their willingness to give interviews to the media in the future.

The field of alternatives to animal testing (i.e., animal-free, human biology-based methods) is continually expanding into different related scientific areas and adopting or adapting their methodologies to solve its technical challenges. However, "preaching to the converted" at 3Rs (replacement, refinement and reduction of animal experiments) conferences and workshops will only have limited effects when one wants to change general mindsets. Scientists working in this field also need to present and defend their work in other related scientific fields to inspire and inform peers of the technological opportunities offered by these methods and approaches and of their level of readiness for use. Such communication with peers will be most effective when based on strong scientific arguments addressed to fellow scientists who still focus on animal experimentation and may not be aware of alternative methods or to scientists from unrelated fields, who may not yet realize that their work could find application in the replacement of animal use.

Although the field of alternative methods is relatively small, it receives a lot of public interest. As discussed here, this is both challenge and opportunity. Engagement of scientists with the public and with policymakers is needed to increase and uphold an awareness for the growing and exciting field and the demand for paradigm change, to motivate decisions to increase funding in the field, and to grow public support for legislative changes that are relevant to human individual health and safety, our treatment of animals, and protection of the environment. A recent UK report[4] noted that "*human relevant NAMs funding represents between 0.2% and 0.6% of total biomedical research funding in the UK and ~0.02% of the total public expenditure*"; the situation in other parts of Europe or the US is probably similar, leaving a lot of room for improvement to keep the promise of phasing out animal research where possible, e.g., "*the final goal of full replacement of procedures on live animals for scientific and educational purposes as soon as it is scientifically possible to do so*" according to Directive 2010/63/EU (EU, 2010).

Tailored communication should be directed at specific populations and stakeholders within the public such as politicians, regulators, animal protection organizations, students, and school children. It is possible to present objective information on alternative methods for different levels of scientific understanding, but scientists must learn to make the effort to address these different target groups, especially also lay audiences. This is not easy as Carl Sagan (American science communicator, 1934-1996) noted "*We live in a society exquisitely dependent on science and technology, in which hardly anyone knows anything about science and technology*" and entails acquiring an awareness of audience-appropriate language, especially avoiding abbreviation and jargon overload, tailoring to the specific value system and the relevant level of background knowledge, using allegories, choosing a suitable level of detail, structuring information from general concepts to detailed ones, being prepared for typical questions or challenges, and getting across key messages rather than getting lost in detail or less relevant sidelines.

The European Union project S4D4C[5] (2018-2021) explored the connections between science, politics, and the public. We can adapt their project outcomes to alternative methods (Fig. 1). Academic scientists in the field of alternative methods are funded mainly by taxpayer money earmarked for the field by politicians or by funding of research grants by philanthropic foundations or animal welfare non-governmental organizations (NGOs); industry scientists in the field are driven by the need to produce products that conform with consumer needs and meet regulatory requirements. Similarly, politicians are driven by public needs and can direct taxpayers' money to fund science to fulfill these needs. Therefore, effective and broad outreach of scientists to the public, directly or mediated by animal welfare NGOs via advocacy programs or in the role of honest brokers, can push subjects related to animal welfare and new approach methodologies (NAMs) up the political agenda and increase the speed at which such challenges are tackled on the political and regulatory level as politicians are in turn accountable to the public. Animal welfare NGOs can drive part of the communication between the public and politicians via their lobbying and policy programs. Scientists have further opportunities for public engagement when called on by politicians to provide scientific policy advice. Much of this three-way communication is mediated by news and social media channels rather than classic science journals (Busquet and Vinken, 2019).

A willingness to give interviews or provide expertise, offering information to the media, e.g., via press releases, explaining activities or new publications via newsletters, providing materials for different target groups, and an active presence on social media are some of the ways to engage in public outreach and de-

[4] ww.eutoxrhttps://www.humanrelevantscience.org/all-party-parliamentary-group/bringing-back-the-human-transitioning-from-animal-research-to-human-relevant-science-in-the-uk/

[5] https://www.s4d4c.eu/

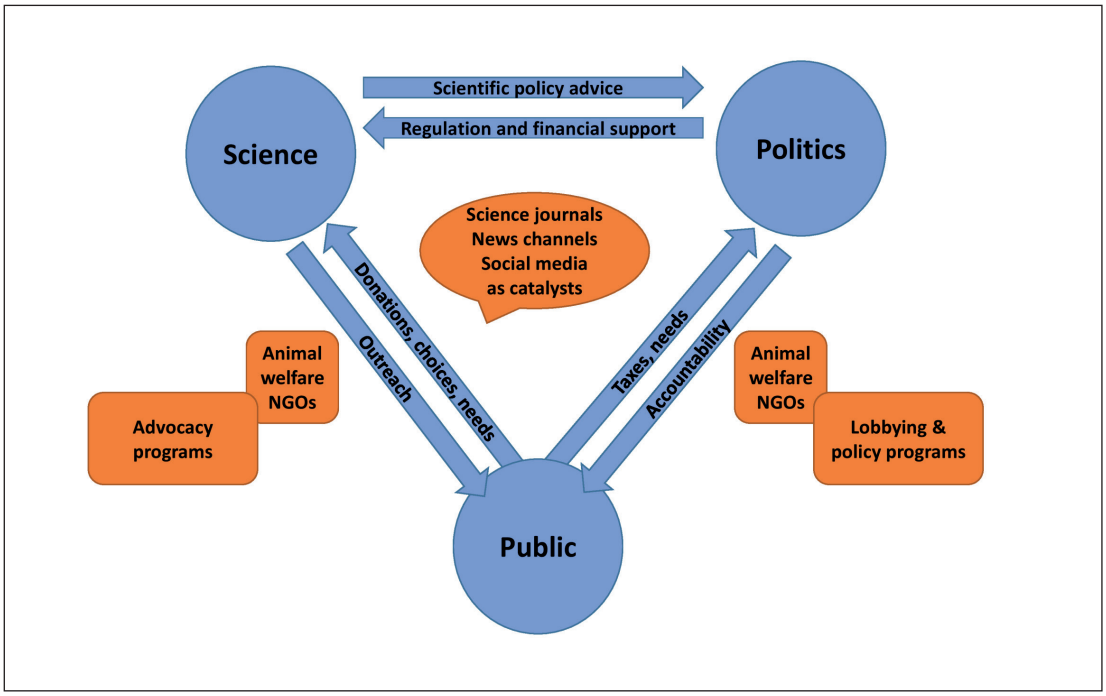



**Fig. 1: Interplay between science, politics and the public with regard to alternative methods**
Adapted from the European Union project S4D4C[5].

liver fact-based information. Media training for academics and employing science communication officers for organizations can improve the quality and uptake of such efforts.

## 2 Motivation for public outreach activities

Public opinion on the field of animal experimentation is typically collected and transported to scientists and to politicians by independent polls of public opinion. A Gallup poll, which has monitored acceptance of animal tests in the US since 2001, shows that while 65% of Americans found medical testing on animals morally acceptable in 2001, this had dropped to 51% by May 2019, and although the value increased to 56% during the COVID-19 pandemic, it had returned to 52% by May 2022[6].

However, this survey does not ask what consequences the people who answer would be prepared to accept in case animal experimentation or medical testing on animals were to be curtailed or halted. Would one be prepared to accept that under current regulations no new drugs, cosmetics (depending on country as animal testing of cosmetics ingredients is banned in multiple countries), pesticides, or food additives could be authorized? Or that the pace of scientific research and development would be slowed? Even if the regulations were adapted, would one be prepared to wait for all endpoints to be replaced with non-animal methods before such authorizations could take place? Or would one reevaluate the level of information one can already obtain from non-animal methods and the level of risk one would be prepared to accept before agreeing that a new drug can be tested in humans? There are no simple or straightforward answers to these questions, but asking them and discussing them engages all segments of society and gives us a collective sense of where we stand both emotionally and rationally in terms of what trade-offs people might be willing to accept.

The polls referenced above imply that there might be growing interest and openness for alternative methods among the public. This growing interest calls out for the need to inform the public on alternatives to animal experimentation. If the public is asked, for example, whether it approves or disapproves of the use of animals for research or of genetically engineering animals, it needs to be able to find objective information so it can formulate a response. In other words, individuals need to be able to come to an answer that is based on a certain level of evidence. One such approach is the open-access book initiated and co-edited by one of the authors (KH). Trying to protect animals used in research and education as a federal inspector for almost a decade, KH frequently witnessed the limitations of the animal protection laws she was charged with enforcing. She realized that the current regulatory system in the European Union does not sufficiently safeguard animals. The comprehensive book *Animal Experimentation: Working Towards a Paradigm Change* (Herrmann and Jayne, 2019) aims to inform the public about the shortcomings associated with animal use in science and to offer ways to work towards a paradigm change.

6 https://news.gallup.com/poll/1681/moral-issues.aspx

Providing evidence-based knowledge should be a high priority for scientists working in the field. As the speed at which alternative approaches arise increases, and this is communicated to the public, there will be increasing calls for additional societal investment and more pressure placed on policymakers to appropriate additional funding and make additional legislative changes. For example, it was the interest of laypersons in animal experiments and alternative approaches that led to the founding of both the Center for Alternative Testing (CAAT) in the US in 1981 (Goldberg, 2015) and to the creation of the journal *ALTEX* in 1984 to which the authors of this article are affiliated. Understanding the 3Rs and especially the "replacement" R can, for example, lead to consumers looking specifically for and selecting cosmetic brands with Leaping Bunny[7] certification and students preferring to choose science careers that avoid animal use, leading to generational change in academia. It can also help in drafting persuasive public petitions on alternatives.

A successful example of such a well-formulated petition is the 2012/13 European Citizen's Initiative (ECI) "Stop vivisection"[8], one of the first such initiatives to be registered after the petition tool was introduced and the third to reach the necessary signature thresholds, collecting more than 1.1 million signatures from EU citizens. The ECI argued that animal experimentation is ethically wrong and in contradiction with Article 13 of the Treaty on the functioning of the European Union but also that animal models are not suitable to predict human responses and may thus pose a danger to human health and the environment, hamper the development of new biomedical research methods, and hinder the use of more reliable and human-relevant but also more economical and efficient research methods. The ECI asked for the replacement of Directive 2010/63/EU with a proposal to phase out animal testing and make the use of human-relevant data compulsory. While in its answer to the ECI the European Commission[9] defended the Directive, as it already sets the full replacement of animals as an ultimate goal when scientifically possible and requires that non-animal alternatives replace animals as they become available, it also set out further actions including the organization of a conference with the scientific community and other stakeholders in 2016, to monitor compliance and enforcement of the legislation, to continue support for the development and validation of alternative approaches, and to continue dialogue with stakeholders, especially the scientific community, to advance the goals of phasing out animal testing. A second such conference also titled "Towards replacement of animals for scientific purposes" was held in 2021[10]. Several further 3Rs actions by the European Commission's Joint Research Centre (JRC), the EU science hub, followed the ECI (see Section 7.2 and 7.3).

A new ECI "Save cruelty free cosmetics – commit to a Europe without animal testing" (Box 1) was registered in 2021 and collected 1,414,327 signatures (not officially verified at the time of printing) by the time it closed in August 2022[11]. The extensive citizen participation shows how much the topic is of public interest and demonstrates that scientists and policymakers must pay attention to the public's view, even if their own views do not align with public sentiment.

**Box 1: European Citizen's Initiative: Save Cruelty Free Cosmetics**[11]

*Objectives*

With the EU ban on cosmetics tests on animals came the promise of a Europe in which animals no longer suffer and die for the sake of cosmetics. That promise has been broken. Authorities still demand animal tests on ingredients used in cosmetics, which goes against the expectations and wishes of the public and the intention of legislators.

Yet, never have we had such powerful non-animal tools for assuring safety or such a golden opportunity to revolutionise human and environmental protection. The European Commission must uphold and strengthen the ban and transition to animal-free safety assessment.

*We call on the European Commission to do the following:*

1. Protect and strengthen the cosmetics animal testing ban.
   Initiate legislative change to achieve consumer, worker, and environmental protection for all cosmetics ingredients without testing on animals for any purpose at any time.
2. Transform EU chemicals regulation.
   Ensure human health and the environment are protected by managing chemicals without the addition of new animal testing requirements.
3. Modernise science in the EU.
   Commit to a legislative proposal plotting a roadmap to phase-out all animal testing in the EU before the end of the current legislative term.

## 3 Challenges of public outreach activities

There is a variety of interest groups that support animal experimentation. These include among others Animal Research Tomorrow[12] (previously the Basel Declaration Society), the Concordat on Openness in Animal Research in the UK which hosts the website Understanding Animal Research (UK)[13], and the German

7 https://www.leapingbunny.org/

8 http://www.stopvivisection.eu/

9 https://ec.europa.eu/commission/presscorner/api/files/document/print/en/ip_15_5094/IP_15_5094_EN.pdf

10 https://ec.europa.eu/environment/events/scientific-conference-towards-replacement-animals-scientific-purposes-2021-02-02_en

11 https://europa.eu/citizens-initiative/initiatives/details/2021/000006 (accessed October 4, 2022)

12 https://animalresearchtomorrow.org

13 https://www.understandinganimalresearch.org.uk/

website *Tierversuche verstehen*[14], which are each supported by an alliance of scientific institutes. (For a critical appraisal of the Basel Declaration[15], not to be confused with the Brussels Declaration described in Section 5, see Gruber (2011)). They point out that many medical discoveries entailed animal experimentation and argue that animal use and laboratory animals remain essential for medical progress. This belief seems to be in so-called institutional "lock-in" in the culture of academic animal experimentation (Frank, 2005; Gluck, 2019). Those using animals in research rarely perceive a need for NAMs (Pound and Ram, 2020); besides the belief that animal research is indispensable, there is the widely held view that animal studies will translate better to the clinic once they are conducted and reported more rigorously (see e.g., Fitzpatrick et al., 2018). The groups that aggressively support using animals in research can be strident in their messaging, and scientists engaging in public outreach about NAMs must be prepared to deal with the challenges such groups present, especially on social media.

This is illustrated by a tweet from the European Animal Research Association (EARA)[17], London, tagging one of the co-authors of this article (TH) (Box 2). The tweet responds to a more nuanced statement about the development of the COVID-19 vaccines. While the average development time for vaccines is 10.71 years (Pronker et al., 2013), we witnessed the extremely fast and unusually successful development of at least nine vaccines for COVID-19 – a substantial benefit to public health. After a careful analysis of the scientific literature, one of the co-authors pointed out that this seems to be linked to skipping many of the traditional vaccine development steps in animal models, e.g., in Kang et al. (2021): "*When the pandemic began, no 'good' animal model of COVID-19 could be established, and such a model is still lacking today. This lack of animal models apparently did not impede the remarkably fast development of COVID-19 vaccines and therapeutics. Indeed, the absence of animal models compelled clinicians to accelerate the preparation and the undertaking of human clinical trials, apparently with enormous success rates well above the average 6% market entry probability for vaccines after entering clinical trials (Pronker et al., 2013). ... In response to the COVID-19 pandemic, we have witnessed nine medical miracles, as nine vaccines have been developed, tested, and accepted within a year. The extraordinary speed of vaccine development was possible because typical development phases were accelerated or skipped, and vaccine candidates were moved into clinical trials with minimal animal testing. Safety tests, including a small number of nonhuman primate studies, were part of this development, but the traditional larger studies with animal models could not take place within these time constraints. Based on this experience, strategies for vaccine and therapeutic development should be revisited, at least for some viruses*." Notably, these statements were coauthored by two NIH researchers and were reviewed and cleared by their institutes before publication. The European Federation of Pharmaceutical Industries and Associations (EFPIA), which represents the biopharmaceutical industry operating in Europe, stated "*While usually regulators require that the industry shows a product is safe in animals before it goes to clinical trials, for COVID-19 vaccines, regulators accepted that preclinical studies could be conducted in some cases in parallel to the first clinical studies to save time considering the urgent need for COVID-19 vaccines. ... It is not required to demonstrate the efficacy of the SARS-CoV-2 vaccine candidate in animal challenge models prior to proceeding to FIH [first-in-human] clinical trials (doing animal testing in parallel with human testing)*."[16]

A team led by Merel Ritskes-Hoitinga (2022) interviewed regulators, industry scientists and other experts, and examined more than 150 regulatory filings concerning human testing and emergency approval for COVID-19 vaccines "*to see how regulatory scientists considered ways to maintain human safety while breaking with tradition*." They found "*another innovation was allowing human studies to begin before all standard animal tests had been concluded*". Schwedhelm and coworkers (2021) analyzed animal use for COVID-19 research in Germany in more detail. "*However, the overall number of approved animals for research on SARS-CoV-2 continues to rise, despite the success of various vaccine development programs. ... The surprisingly low numbers of animals approved for SARS-CoV-2 research might be related to the extreme pace of research. The 'race' towards a vaccine in combination with the lockdown of non-essential research led to a focus on essential studies; in this sense, the pandemic created a pressure to reduce animal numbers to the absolute minimum. At the same time, animal experiments may have been replaced with alternative methods whenever they provided faster results*." Figure 2 is reproduced from their paper. It shows clearly the delay of animal experimentation (NB, here the licensing, not the execution) relative to the successful development of vaccines and treatments. Noteworthy, 90% of experiments were done in mice, which are not susceptible to SARS-CoV-2 unless genetically altered (Bao et al., 2020); it is unlikely that a large portion of these were huACE-2 transfected – the only sensitive mice. A very exact timeline is available for the Moderna vaccine (Corbett et al., 2020): "*Remarkably, this led to the start of a first in human Phase 1 clinical trial on March 16, 2020, 66 days after the viral sequence was released, and a Phase 2 began 74 days later on May 29, 2020 .... Prior to vaccination of the first human subject, expression and antigenicity of the S-2P antigen delivered by mRNA was confirmed* in vitro *..., and immunogenicity of mRNA-1273 was documented in several mouse strains*." So, clearly, neither efficacy studies in an infection model were carried out, nor optimizations of formulations; the extent of safety studies is

14 https://www.tierversuche-verstehen.de/

15 https://www.basel-declaration.org/basel-declaration-en/assets/File/Declaration/Declaration_en_Z%C3%BCrich.pdf

16 Fitting vaccine research into one year – Were animals used? A blog by EFPIA and Vaccines Europe; https://www.efpia.eu/news-events/the-efpia-view/blog-articles/fitting-vaccine-research-into-one-year-were-animals-used/

17 https://www.eara.eu/about-eara

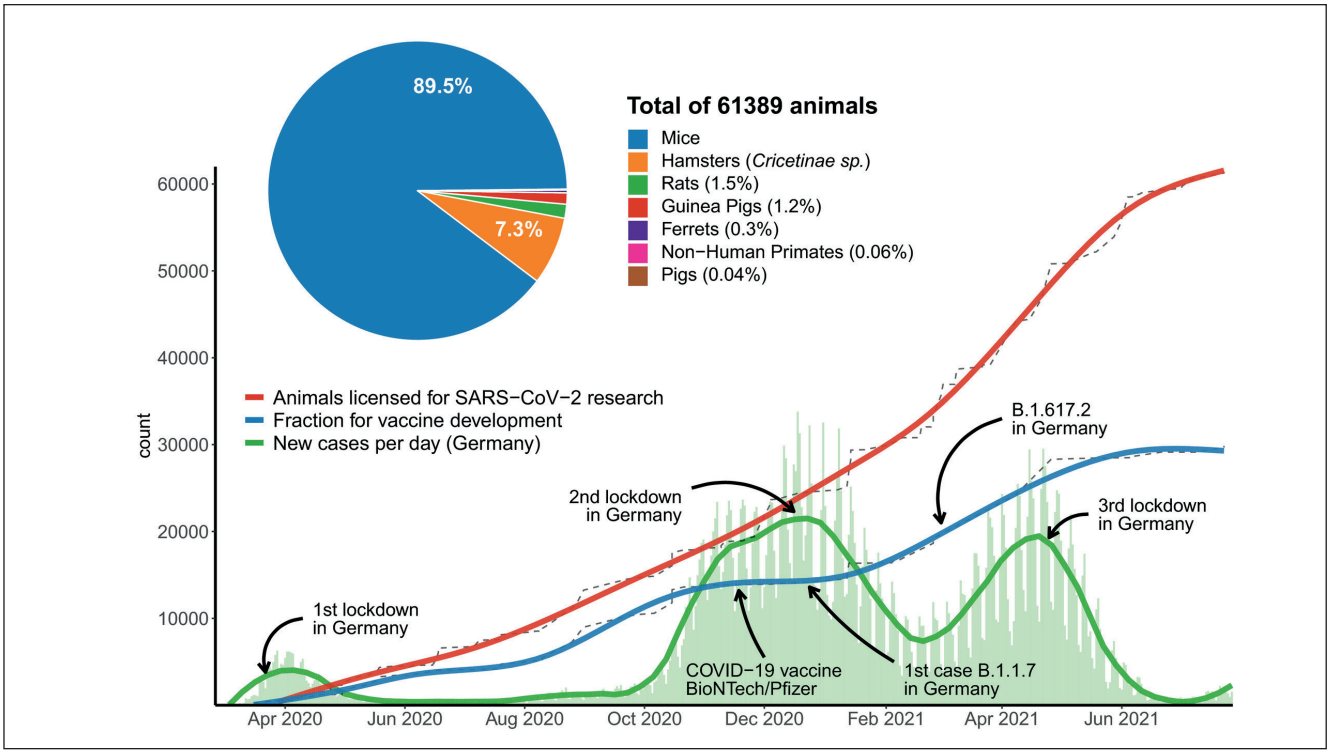



**Fig. 2: Animals used for SARS-CoV-2 research in Germany**
Reproduced from Schwedhelm et al. (2021). Between February 1, 2020 and July 27, 2021, 61,389 animals were approved for research projects related to SARS-CoV-2. The authors of the study identified these projects by first searching for relevant keywords (SARS, COVID, CORONA) in the database www.AnimalTestInfo.de. They then manually sorted and analyzed matching NTS. The number of reported human infections in Germany started rising in early March 2020 (green curve; data from German registry for confirmed SARS-CoV-2 infections (Robert-Koch-Institute, Berlin)). The red curve represents all animals belonging to projects approved by German authorities that make a reference to SARS-CoV-2 research. The blue line represents all animals in projects that mentioned research or development of vaccines against SARS-CoV-2. Corresponding raw data are visible as grey lines. The pie chart illustrates the proportions of animal models used for SARS-CoV-2 research.

not clear but must have been rather limited before going first-in-human given this timeline.

A thorough reading of the literature leaves little room for doubt that a drastically trimmed development process enabled fast clinical testing with unusually high success rates, and this message is an important lesson that scientists who support NAMs seek to bring to the public's attention. Nevertheless, the pro-animal testing community is seeking to dampen this information by directing attention away from COVID-19 vaccine development lessons.

Taken together, scientists engaging in public outreach are well advised to undergo communication training, consider the unique characteristics of the stakeholder groups they are addressing, ensure they place the key messages they want to get across, and are well prepared for challenges to their statements from different and not necessarily scientifically based perspectives.

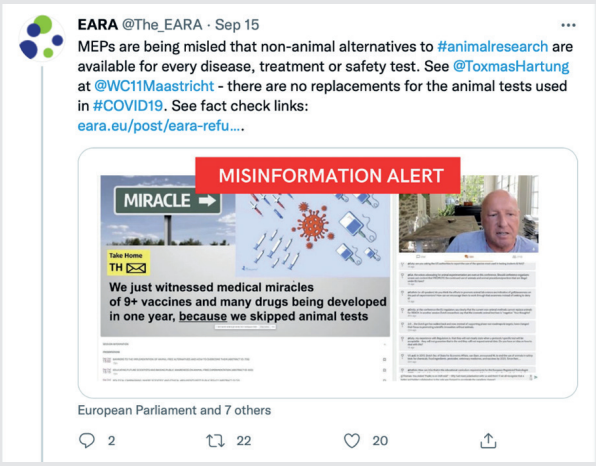
### Box 2: Example of strident communication by a pro-animal experimentation lobby group

The European Animal Research Association (EARA)[17], London, is a pro-animal testing organization, supported by a large number of organizations[18], some of whom are also engaged in alternative methods promotion. On September 15, 2021, they tweeted the photo and message below while the European Parliament was debating animal testing.

The defamatory character of the tweet prompted an email from the author (TH) to EARA on September 22, 2021:

> *"I would like to see how you can claim that I do not adequately inform about this topic. BTW, I have never stated that no animal tests were used to register*

[18] Board members:
Public organizations: EPV (European Primate Veterinarians), FENS (Federation of European Neurosciences Societies); GIRCOR; Max Delbrück Center / Tierversuche Verstehen; Max Planck Society; NOVA Medical School; Research4Life; SGV (Swiss Laboratory Animal Science Association);
Private organizations: AAALAC; AnimalhealthEurope; Labcorp; GSK; Ellegaard Göttingen Minipigs; Envigo Marshall Bioresources; Sanofi




*COVID-19 drugs and vaccines because I know better. However, if you claim that traditional animal-based development took place before human trials you do not understand the nature and time needs of these development processes, which take on average more than a decade. Furthermore, the screenshot you are using represents copyrighted material. First, it is taken from a conference available only behind a paywall. Second, the two graphics shown are copyrighted. I am willing to accept a public apology using the same means of distribution and including your membership."*

In a response, Executive Director Kirk Leech refused such apology and cited a number of studies carried out after the first human trials. He stated, "*we will continue to challenge any continued public claims that animal tests were skipped in the production of Covid-19 vaccines, using EARA's social media platforms, including our 18 Twitter channels across Europe*." The author (TH) refrained from pursuing a defamation case after noticing that the tweet had been retweeted just 22 times and liked 20 times. Probably it will find more readers here…

## 4 Public opinion on animal use can drive legislation – the example of European cosmetics regulation

After decades of lobbying by animal protection organizations, the 7th amendment to the cosmetics legislation (Directive 2003/15/EC of 27 February 2003, now replaced by Regulation (EC) No 1223/2009) introduced a ban on animal testing for cosmetic products after 2004 and cosmetic ingredients after 2009. The amendment also prohibited the marketing of cosmetic products containing ingredients that have been tested on animals after March 11, 2013. The amendment does not prohibit companies from using animal testing to fulfill regulatory requirements in other countries, though the advocate general Leendert Geelhoed at the European Court of Justice in the case of France against the 7th amendment in May 2005 had a different view[19]: "*…it seems clear that the ban on animal tests applies equally to tests performed for the purposes of complying with other legislation, in so far as substances that have been the subject of such tests may not be used as or in cosmetic products. This interpretation seems necessary for the effet utile of the Directive and is consistent with the intention expressed in the preparatory documents leading up to its adoption*". This became critical in the 2020 ECHA Board of Appeal case on dual use[20], where a cosmetic supplier protested unsuccessfully against a decision to require new *in vivo* tests for two cosmetic ingredients for REACH.

Following this, Knight et al. (2021) examined REACH dossiers for chemicals for which the only reported use is cosmetics to determine the extent of new *in vivo* testing caused by REACH. We found the REACH database has 3,206 chemical dossiers with cosmetics as a reported use. Of these, 419 report cosmetics as the only use, and 63 of these have *in vivo* tests that were completed after the Cosmetic Regulation ban on *in vivo* testing. Registrants largely used alternative, non-animal methods to evaluate ingredients for REACH, but some still conducted new *in vivo* tests to comply with REACH requirements for toxicity data and worker safety assessments. The study was covered in the *Guardian*[21] and several other journals and prompted the ongoing creation of the Alternative Cosmetic Policy Action Conference to support ECHA in the upcoming revision of the Cosmetics Product Regulation by translating NAMs into regulatory applications and by enforcing testing bans for cosmetics ingredients. Notably, EFSA has committed to NAM development and implementation in their EFSA Strategy 2027[22].

## 5 Guidance on formulating scientific policy advice

A large number of legislative proposals have a scientific component, requiring advice from competent authorities and stakeholders. This is obviously an opportunity for lobbying with considerable ethical implications. Edler et al. (2022) discuss "*the continuing dissatisfaction with the quality and effects of science-policy interactions in both theory and practice*". In 2017, the Brussels Declaration[23] (Box 3) was launched to address these ethical issues. One of the authors (TH) had the privilege to co-organize parts of its generation. "*It is a 20-point blueprint for a set of ethics and principles to inform work at the boundaries of science, society and policy. It makes the case for a multidisciplinary ap-*

19 http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:62003C0244:EN:HTML
20 https://echa.europa.eu/documents/10162/5edc86c5-4397-54c6-831c-e53bcf90643d; https://echa.europa.eu/documents/10162/d18040f0-231b-a73a-9cea-c540276d8b3d
21 https://www.theguardian.com/environment/2021/aug/19/hundreds-of-uk-and-eu-cosmetics-products-contain-ingredients-tested-on-animals
22 https://www.efsa.europa.eu/sites/default/files/2021-07/efsa-strategy-2027.pdf
23 https://www.sci-com.eu/main/docs/Brussels-Declaration.pdf

*proach that will encourage greater integrity and accountability among stakeholders*" (Kazatchkine et al., 2017).

**Box 3: The Brussels Declaration**
**Science, Society & Policy-Making: A New Blueprint of Ethics & Principles – key messages**

Extracted from the text[23] adopted on 17 February 2017 during an announcement symposium at the American Association for the Advancement of Science's Annual Meeting held in Boston, USA. It is based on 5 consultation meetings between 2012 and 2017 with more than 300 individuals from 35 countries.

**Section 1: Science and policy – A crucial relationship**

1. Science is a fundamental pillar of knowledge-based societies
2. Science can help provide the evidence base for public policy
3. Sound public policy is crucial for the direction and priorities of science
4. The dialogue between science and policy is never straight-forward

**Section 2: What we expect from the scientific community**

5. The integrity of science needs to be clear and the integrity of scientists providing advice must be unimpeachable
6. The full range of scientific disciplines should be included; notably, the social sciences can play a key role in improving how the public may react or adapt
7. Scientists must learn to use established communication channels for providing policy advice more effectively and be less aloof and perhaps less arrogant
8. Scientists must listen and respond to criticism

**Section 3: What we expect from the policy-making community**

9. Policy-makers must listen, consult and be held accountable
10. Ethical consideration of the impact of policy decisions is crucial
11. Policy-makers have to challenge science to deliver on public investment
12. Policy-makers should be willing to justify decisions, particularly where they deviate from independent scientific advice
13. Policy-makers should acknowledge the potential for bias and vested interests contrary to the scientific consensus

**Section 4: What we expect from the public, media, industry and interest groups**

14. The public plays a critical role in influencing policy and must be included in the decision-making process
15. Industry is an investor in knowledge generation and science and has every right to have its voice heard
16. Interest groups similarly have every right to have their voice heard as guardians of the common good or legitimate sectoral interests
17. Advice from any source to policy-making must acknowledge possible bias

**Section 5: Scientific advice & greater inclusivity need to be integrated more effectively**

18. Scientific advice must be more involved in all stages of the policy-making process
19. Policy-making must learn to cope with the speed of scientific development and include greater foresight and policy anticipation
20. Societal investment in science will always require priority-setting, nevertheless, advances in public health deserve special attention

The contribution of one of the authors (TH) to co-organize (by chairing the working group *What do we expect from the scientific community?*) was prompted by personal experiences in the context of scientific policy support: The European REACH regulation for industrial chemicals was a major piece of legislation agreed in 2006. It had to find a balance between public health and worker safety goals on the one hand and costs and animal use on the other – opposing policy goals. Then Vice-President of the European Commission, Guenter Verheugen, said on November 7, 2005[24] that "*in the worst-case scenario*" 3.9 million more animals could be used for testing, which he said was "*not ethically defensible*". He added that the Commission had ideas that would enable it to reduce this extra testing by 70%. This statement was based on assessments by the European Commission's own JRC, and it was a key communication to make this legislation pass the political decision-taking process.

One author (TH), who joined the JRC in 2002, was part of shaping and implementing REACH, e.g., by heading the development of test guidance for industry with about 200 experts and many aspects of the animal welfare provisions of the legislation. He challenged these estimates early on in numerous internal communications. He was ultimately allowed to lead an inter-unit taskforce to reassess the burden of the legislation, the report of which was peer-reviewed by sixteen external reviewers. The best-case scenario suggested the need of 8 million and the worst case of 23.3 million animals, the latter corresponding to testing costs of €3.6 billion. JRC leadership took the decision not to communicate or publish these numbers, and the policy process was finalized half a year later. During a leave of absence on personal grounds from the European Commission, the author took the opportunity to redo this analysis based on exclusively public data and published the results in *Nature* (without reference

[24] http://news.bbc.co.uk/2/hi/europe/4437304.stm

to the non-published report discussed above) with the details in *ALTEX* (Hartung and Rovida, 2009; Rovida and Hartung, 2009): The new analysis suggested about 54 million animals to be used and costs of almost €10 billion, taking also into account the offspring produced during reproductive toxicology tests over two generations of animals, as required by Directive 2010/63/EU, and the projected growth of the EU and the chemical industry. This led not only to a press release by the European Chemicals Agency refuting the analysis but also a hearing by the European Commission on whether TH broke EC rules. In this context, the earlier study became public and led to press coverage (Gilbert, 2010). While this process ultimately found no wrongdoing and had no disciplinary consequences, the respective *Nature* article gained much interest. In several subsequent studies, the estimates set out in *Nature* and *ALTEX* proved largely correct, the latest with the 2020 publication of EU animal use statistics on the year 2017 showing that reproductive toxicity testing alone accounted for 7.8 million animals in that single year (Hartung and Tsatsakis, 2021). It is important to note that this high number of animals is not immediately visible in the respective EU statistics (Busquet et al., 2020) as the unborn pups (though protected by the EU legislation) are not included in the statistics, as stated only in a footnote.

Clearly, both courage and persistence are required to challenge the status quo. Unfortunately, the institutional response of failing to make important reports public, and later denial and political gamesmanship hindered the possible improvement of REACH processes. It is tempting to see this linked to the fact that Europe's share of global chemical sales has declined from 32% to 15% in this time.

## 6 Experience from the CAAT policy programs

With the chair for evidence-based toxicology instated in 2009 and the creation of the Evidence-based Toxicology Collaboration (EBTC)[25] in 2010, we are promoting transparent, objective approaches based on factual evidence and avoiding biases. Evidence-based toxicology is the development and use of transparent, consistent, and objective methods for assessing scientific evidence to answer questions about adverse effects of chemical substances on living organisms. This follows the vision to make evidence-based methodologies the standard that is used to ensure public health, a healthy environment, and a sustainable future. EBTC is fulfilling this vision by bringing together the international toxicology community to work on adapting and developing evidence-based methods and frameworks that facilitate the use of evidence-based toxicology and systematic reviews to inform regulatory, environmental, and public health decisions.

### 6.1 CAAT's US policy program

In 2007, CAAT received a grant to develop a new program in public policy, education, and outreach[26]. The ongoing program is aimed at educating policymakers and legislators about the need for alternatives to the use of animals in toxicity and safety testing and in biomedical research. Implemented by one of the coauthors (PL) and now run independently but in collaboration with CAAT, the program works closely with members of the US Congress, aiming to give new and alternative approaches their rightful place and encourage the development, use, and expansion of non-animal alternatives in the private sector and federal agencies. The toxicology policy program has three major parts: an educational component, an advocacy component, and an outreach component.

The education component is founded on pedagogical training. A key achievement was the creation of a Humane Sciences and Toxicology Policy Certificate Program as part of the Hopkins curricular offerings[27]. This certificate program is open to all Hopkins students and can also be completed by anyone who applies directly to the certificate program and meets the entry criteria. Certificate programs offer focused academic training in specific areas of public health, with topics ranging from human rights to health informatics, from vaccine science to public health economics. The certificate program introduces and explains the application of the 3Rs as guiding principles of humane science and demonstrates how the use of humane science principles in biomedical research can lead to more robust scientific methodology and knowledge. The program's course of study covers the scientific principles needed to appreciate humane science and identify and evaluate its implications in biomedical research and public health policy. Two co-authors of this article (PL and KH) are the co-directors of this certificate program. Persons completing the certificate program will be well equipped to translate new toxicological knowledge into scientifically credible product safety evaluations and hazard assessments and apply these concepts to environmental health decision-making. Certificate programs typically require less time and coursework than a degree, making them appealing both to current Bloomberg degree students desiring specialization in particular topic areas and to individuals seeking to learn more about specific areas of public health. Individual programs may be geared toward current students, non-degree-seeking students, or to a broad audience. This certificate includes the course *Animals in Research: Law, Policy, and Humane Sciences*[28], which was initially taught by co-author PL and since 2018 is instructed by KH, who fully revamped and expanded the course. Besides discussing how to fully apply the 3R principle, and how to properly conduct experiments, the course explores the main shortcomings of animal use in science and prepares students to critically appraise the validity of animal and non-animal models and methods. KH also teaches *Animal Ethics*[29] that is part of the certificate program, addressing eth-

[25] http://www.ebtox.org

[26] https://publichealth.jhu.edu/2007/caat-program

[27] https://e-catalogue.jhu.edu/public-health/certificates/humane-sciences-and-tox-policy/#courserequirementstext

[28] https://www.jhsph.edu/courses/course/36166/2022/187.625.81/animals-in-research-law-policy-and-humane-sciences

[29] https://www.jhsph.edu/courses/course/36523/2022/180.638.81/animals-in-research-ethics

ical issues arising from the use of animals in biomedical research and emphasizing the role the 3Rs of animal experimentation play when choosing the model best suited for a research study. An additional aspect of the educational program is a post-doctoral training program for attorneys interested in laboratory animal law supervised by co-author PL. These attorneys work closely with Hopkins scientists and other students to gain a sophisticated understanding of non-animal alternatives and animal models.

The Hopkins toxicology program's advocacy work is focused on US federal laws, regulations, and policies. The program regularly visits members of the US House of Representatives and the Senate, sponsors and participates in briefings on Capitol Hill, and writes editorials[30,31] highlighting important issues. The program seeks to effect laws and the support to 3Rs aspects and programs and has been successful in adding such provisions to laws. Examples are the work on the 2016 Toxic Substances Control Act (TSCA) reauthorization (Locke and Myers, 2011) or the current discussion of a Humane Research and Testing Act (Locke et al., 2021). A strong focus is on laboratory animal law (Griffin and Locke, 2016; Locke, 2016).

Another ongoing focus of the program is to work with US regulatory agencies. A set of challenges here is that (1) regulators often see these alternative methods as one-to-one replacements of animal tests instead of recognizing that these methods might replace only a portion of a toxicologic phenomenon (i.e., animal tests are in many ways like black boxes); (2) that validation and regulatory acceptance should not be based on the animal test being replaced but rather on the human toxicological pathway in question (see below); and (3) that validation and regulatory acceptance are two different political/policy processes, so that validation under one law/regulation/directive does not mean validation under another.

The final focus area of the toxicology program is outreach to key stakeholders, such as attorneys. One of the co-authors (PL) offers a course as part of a law LLM program focused on laboratory animal law. The course explains the US federal legal system governing laboratory animal law and alternatives as well as environmental laws such as TSCA and the Interagency Center for the Validation of Alternative Methods (ICCVAM) Act of 2000. Members of the program are also active in professional organizations, such as the American Bar Association, which houses an animal law committee[32].

### 6.2 CAAT's EU policy program

The CAAT-EU policy program was started in 2011 by co-authors FB, TH, and PL and since 2013 has been run by FB, now through Altertox[33]. Looking back at a decade of the CAAT Europe policy program at the heart of EU institutions and experience in providing training to European Commission JRC scientists from 2019 to 2022 in a course towards "informed evidence for policy making" conceptualized by Topp et al. (2018), a few theoretical concepts and lessons learned can be shared in terms of engagement of scientists with policymakers to promote alternative methods.

Science can bring evidence to the political discussion by suggesting amendments to proposed legislative texts. The EU policy program has accompanied many relevant legal initiatives (Leist et al., 2014; Busquet et al., 2014, 2020; Busquet and Hartung, 2017), and a further important contribution was the interpretation of the EU animal use statistics (Daneshian et al., 2015). Nevertheless, science is only one element taken into consideration in the legislative text. Members of the European Parliament (MEPs) are not always receptive to appointment requests when they are linked with an ongoing legislative file, and while some have a more technical approach (i.e., they want to understand and master the technicalities of the issues), others follow a more political approach (i.e., they address the topic based on the political values represented in their political group). This is also discussed in "*The Honest Broker – making sense of science in policy and politics*" by Roger Pielke Jr. (2007), who identifies the two key components of policymaking as being "facts" and "values".

Science should also be communicated and disseminated to policymakers independently of the political and legislative agenda. The science of alternative methods is a complex topic with its own dilemmas, e.g., cell culture techniques commonly require the use of animal-derived materials that may be associated with animal suffering such as fetal bovine/calf serum, basement membrane extracts (e.g., Matrigel), antibodies obtained from ascites fluid, primary cells from animals, and other animal-derived products obtained by invasive sampling (van der Valk et al., 2018; Murphy et al., 2022; Gruber and Hartung, 2004; Cassotta et al., 2022). Communication activities build trust in the topic, make policymakers familiar with technical terms used by the scientific community, and build a relationship, but are challenged by recurring emergencies as policymakers (elected or non-elected) are increasingly crisis-driven.

Probably the hardest task of science advice is to translate a scientific issue into a policy activity and generate the critical mass to move it forward. A successful example was an initiative 5-6 years ago on data access and data harmonization of toxicological dossiers. It started with a scientific article (Luechtefeld et al., 2016) and became an informal working group at the European Parliament covering the whole spectrum of political groups. It was followed by a pilot project introduced by the MEPs – with the blessing of the EU Agencies (ECHA, EFSA, and EMA) and industry stakeholders (CEFIC, EFPIA, and CropLife Europe) – to assess the feasibility of a unique EU chemicals database covering the entries of toxicological data from the dossiers but also integrating non-GLP data from academia. This is of critical importance for computational toxicology leveraging such data. Looking back, it is challenging to understand why some initiatives work. Some of the successful ingredients are possibly being

30 https://thehill.com/opinion/energy-environment/462269-epas-bold-step-forward-good-for-animals-and-science-better-for/

31 https://thehill.com/blogs/congress-blog/healthcare/594605-a-new-agency-to-accelerate-biomedical-science-can-succeed/

32 https://www.americanbar.org/groups/tort_trial_insurance_practice/committees/animal-law/?login

33 https://academy.altertox.be

at the right place at the right time with the right topic and presenting them in the right way. It seems like a miracle when everyone suddenly agrees, but our experience is that it is possible.

Some general tips for providing advice to policymakers are: be visible, be available, be creative, be useful, be patient. In an approach to a policymaker, it is useful to consider what role one wants to take. *The Honest Broker* describes four idealized roles scientists can choose to play in relation to policy and politics: In brief, the pure scientist generates a corpus of knowledge that is distantly related to societal benefits. The science arbiter provides broad factual information without giving advice and sits on an expert committee. The issue advocate cherry picks information to influence a decision. Finally, the honest broker provides a set of policy options based on the corpus of knowledge and the societal needs they could benefit. How and what information is presented requires careful planning. It is crucial to learn to explain important scientific concepts using simple terms (see the Feynman Technique[34]). Information should be presented by starting with the conclusion and explaining issues in more detail according to the interest of the policymaker; this is called the "inverted pyramid approach"[35]. While scientists believe in data, p-values, peer-reviewed publications, and meta-analysis, politicians are often more interested in polls, demonstrations, footage, and headlines. It is also helpful to be aware that the scientific advice provided may be shared with and challenged by other stakeholders (industry, peers, NGOs, etc.) and therefore networking and stakeholder mapping, i.e., determining potential actors involved in the topic, can help to consider and include their concerns (e.g., affordability and availability of NAMs).

Uncertainty can be understood as a lack of knowledge regarding a question for which a definitive answer is desired. Science is seen as the solution to reduce the uncertainty level, but generating new knowledge requires time and money. Postponing a political decision based on the argument that all the science is not yet available can be dangerous and destructive. If the uncertainties cannot be reduced at the time science input is requested, it can be helpful to rank (from known, partially known, not known to unknowable) and frame (Where does the uncertainty come from? The methodology, the technology, etc.) them as nicely explained in the report "Scientific advice to European policy in a complex world" (EC, 2019). The European Commission often relies on impact assessments to inform policy decisions. This process is useful but can be an open door to postpone controversial issues. As stated earlier in this article series (Hartung, 2009): "*…we will need to find the right balance between scientific proof of causation and the need to take protective measures also in the absence of final evidence … especially those questions not yet addressed are not 'non evidence-based' but 'not yet evaluated'*."

Finally, actors involved in policymaking must learn that "when no one is happy with the result, this probably means it was a good compromise".

## 7 Public engagement activities

### 7.1 Approaches to and motivation for public engagement

The message in the field of alternatives has changed from one asking for compassion and arguing with ethics (both still universally valid arguments) to one that focuses on scientific progress and innovation, promoting human-relevant research, high-end technology, and higher cost-efficiency. This may have been the reason for the introduction of the term "new approach methodology (NAM)" to replace "alternatives to animal experiments" or "3Rs methods", although one might argue that the term NAM may not be the optimal solution, especially for communication with the public. The Center for Contemporary Sciences[36] promotes the use of the terms "human-biology based methods" and "human-specific medical research", which are more informative and less at risk of becoming outdated if we consider that what is a new approach methodology today may be out of date tomorrow. Other options are "non-animal methods", "animal-free methods" or "methods based on human cells and artificial intelligence".

The goal of demonstrating that alternative methods are at least as good as animal experiments in predicting toxicity sounds like an obvious one that will preserve the level of human health safety. However, studies investigating the reproducibility of animal experiments have found them not well reproducible themselves (Luechtefeld et al., 2016). And high drug attrition rates show that they are not predictive of human effects (Hartung, 2013). NAMs are designed with controls, consider and measure uncertainty, and define applicability domains. The highest form of validation of alternative methods is the OECD Test Guideline. Such guidelines are mutually accepted by regulatory agencies of OECD countries for testing purposes. However, other levels of qualification of methods for specific contexts of use can be acceptable and informative also for regulatory purposes, and relevance of models can be sufficient for their use in biomedical research.

When talking about alternatives to animal experiments, typical questions one may be asked include "Are there alternatives to animal experiments?" or "Are animal experiments useful?" A mini-series of recent BenchMarks articles in *ALTEX* explores the latter question, starting with how complicated this seemingly simple question really is (Pallocca et al., 2022a,b).

In the current discussion on alternatives to animal testing, which revolves around the terms ethics, safety, science and regulation, taking an economic viewpoint (Bottini and Hartung, 2009, 2010; Meigs et al., 2018) adds different aspects to these terms that are all important considerations for companies that may have a choice between testing substances using animals or using validated alternative methodology for a variety of applications. Ethics is an important aspect both of corporate culture and for brand marketing. Being able to document involvement in the research and development of replacement methods (scientific

34 https://fs.blog/feynman-technique/

35 https://www.nngroup.com/articles/inverted-pyramid/

36 https://contemporarysciences.org/

publications, support of 3Rs organizations, sponsorship of conferences and congresses) or the reduction in the use of animals in a company (Marty et al., 2022) or marketing non-animal contract research or products increases pride and loyalty of workers to their company. Such activity can be used for marketing of products, e.g., Leaping Bunny[7]. The economic promise of the science of alternative methods lies in product development, e.g., in being able to develop and market new cosmetics with innovative ingredients developed without animal experimentation, but also in developing and marketing test methods, test kits, contract research and software and machines needed to perform these. And improvement of the human relevance of testing promises to reduce liability issues arising from toxicities in drugs, chemicals, agricultural products including pesticides, food additives, cosmetics, etc. that must be withdrawn from the market owing to safety concerns not picked up in animal experiments and the consequences this can have to a brand or company name.

Finally, the economic benefit of the development and use of alternative methods can lie in having the edge when under an economic area's trade policy. In the European Union, Directive 2010/63 states that animal experiments should not be performed when alternative methods are available. ECHA has released an initiative[37] seeking feedback on the update of approved methods for the testing of chemicals. The initiative states that a number of animal tests "*are no longer considered appropriate to generate new information under Regulation (EC) No 1907/2006*" and should therefore be deleted.

### 7.2 Higher education outreach activities

Science outreach, also called education and public outreach (EPO or E/PO) or simply public outreach, is defined by Wikipedia[38] as an umbrella term for a variety of activities by research institutes, universities, and institutions such as science museums aimed at promoting public awareness (and understanding) of science and making informal contributions to science education. Typical examples include public talks, lectures, and discussions, visiting primary and secondary schools, workshops or schools for teachers and/or students, supporting science fairs and similar events, as well as the online aggregation of science activities, resources, and programs. CAAT's outreach activities now increasingly include these and have replaced the traditional mono-directional education style. A current strategic reorganization aims to embrace these more engaging formats. This is in part owed to the COVID-19 pandemic, which has drastically increased our digitalization. Online educational courses have flourished with students from all over the world being able to take part without the prohibitive expense of travel and accommodation, visa problems, and time away from family and other obligations.

In 2020, CAAT and the Physicians Committee for Responsible Medicine (PCRM) co-organized and co-hosted the first US Summer School on innovative approaches in science. The Summer School was originally planned as an in-person event but, due to the COVID-19 pandemic, it was transitioned to a virtual event, which opened it to a wider audience (McCarthy et al., 2021). Over 600 international students and early-career researchers attended a comprehensive program that also included a session on how to communicate science to journalists with Denise-Marie Ordway from Harvard Kennedy School Shorenstein Center on Media, Politics and Public Policy. Presentation slides and recordings are available online[39]. PCRM hosted the 2nd US Summer School on innovative approaches in science in June 2021, this time as a hybrid event with both in-person and online attendance. Presentations and recordings are available online.[40]

PCRM provides two training programs: The Early-Career Researchers Advancing 21st Century Science (ERA21) program[41] helps students and early career scientists to appreciate human-relevant science, and the NAMs Use for Regulatory Application (NURA) continuing education program[42] provides NAMs training to industry, government, and academic scientists.

The European Union Reference Laboratory for alternatives to animal testing (EURL ECVAM) at the JRC is committed to providing 3Rs education and training resources. They have been hosting a biannual summer school that focuses on animal-free approaches in science in Ispra, Italy, for several years, and they provide traineeship positions for early-career scientists. One action that followed the ECI "Stop vivisection" has been the introduction of the 3Rs into secondary school, university, and continuing education programs. The JRC's 2021 report on the topic speaks especially to decision-makers and influencers within education and training systems who contribute to policymaking and help to implement new educational resources into curricula (EC et al., 2021). Additionally, the EURL ECVAM commissioned a literature review series on advanced non-animal models for respiratory diseases (Gribaldo and Dura, 2022; Hynes et al., 2020), breast cancer (Folgiero et al., 2020; Gribaldo and Dura, 2022), neurodegenerative diseases (Gribaldo and Dura, 2022; Witters et al., 2021), cardiovascular diseases (Celi et al., 2022), autoimmune diseases (publication in progress), immune oncology models (Gribaldo et al., 2021; Romania et al., 2021), and immunogenicity testing for advanced therapy medicinal products (Canals et al., 2022).

The open-access NAT (Non-Animal Technologies) database[43] by the NGO Doctors Against Animal Experimentation (*Ärzte gegen Tierversuche*) contains all information on modern non-animal methods of the above-mentioned disease areas as well as from other areas of biomedicine and life sciences and is a great resource for scientists and the interested public.

37 https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12100-Chemicals-regulation-update-of-EU-rules-for-test-methods_en

38 https://en.wikipedia.org/wiki/Science_outreach

39 https://pcrm.widencollective.com/portals/tgkpbij2/SummerSchool2020

40 https://pcrm.widencollective.com/portals/kovr2gjw/SummerSchool2022

41 https://www.pcrm.org/ethical-science/ethical-education-and-training/ERA21

42 https://www.pcrm.org/ethical-science/animal-testing-and-alternatives/nura

43 https://nat-database.org

Since free online offerings make science education and training more equitable, CAAT has made two of its substantial courses freely available for anyone to enroll; the massive open online courses (MOOCs) are accessible through Coursera (Box 4).

**Box 4: CAAT's COURSERA classes**

*The Courses*
Toxicology 21: Scientific Applications and Evidence-based Toxicology courses were designed as online courses and were launched on COURSERA in 2018. Both courses have more than 7000 learners each (September 25, 2022).

**Toxicology 21: Scientific Applications (4.7 stars, 98% likes on COURSERA)**[44] familiarizes students with the novel concepts being used to revamp regulatory toxicology in response to a breakthrough National Research Council Report "Toxicity Testing in the 21st Century: A Vision and a Strategy". It presents the latest developments in the field of toxicology: moving away from animal testing toward human-relevant, high-content, high-throughput integrative testing strategies. Active programs from EPA, NIH and the scientific community world-wide illustrate the dynamics of safety sciences. Some of the lectures in the course are given by guest speakers from NIH, EPA, Humane Society and ScitoVation.

*Learning objectives:*
Upon successfully completing this course, students will be able to:
- Debate and criticize the shortcomings of the current approach to hazard assessment
- Evaluate the technologies entering the regulatory arena
- Explain the challenges of toxicology 21st century to change the paradigm in toxicology
- Explain mechanisms of toxicity and toxicokinetics as the basis for testing strategies
- Describe novel types of data and bioinformatics entering regulatory evaluations
- Implement Tox21 (PubChem, Data Visualization and integration suites) and EPA CompTox web application[45] interactive web applications to mine and assess Tox21 and ToxCast high-throughput chemical screening data

*Topics covered in the lectures:*
- *In vitro* toxicology: NRC report review, paradigm shift
- High-throughput screening strategies
- High-content test strategies
- 3D organotypic human-relevant models for toxicity testing: organ-on-chip
- Human-on-chip approaches
- Epigenetics in interplay between genetics and environment
- Pathway of Toxicity (PoT) and Adverse Outcome Pathways (AOP)
- Biokinetic modeling and computational toxicology
- Bioinformatics for information-rich data analysis
- IATAs and integrated testing strategies
- NTP/NIH Tox21 program: results and implementation
- EPA ToxCast program and EDSP program, results and implementation

**Evidence-based Toxicology (4.7 stars, 98% likes on COURSERA)**[46] familiarizes with the concepts of evidence-based medicine, and its translation to toxicology. Concepts of systematic reviews, meta-analysis, risk-of-bias, and various quality assurance schemes are introduced in the course. The National Toxicology Program, the Environmental Protection Agency (EPA) and authorities worldwide are increasingly embracing these concepts. Evidence-based toxicology (EBT) is a rapidly evolving discipline that represents a way to transparently and consistently evaluate scientific evidence, which can then be applied to address critical questions in toxicology. EBT is especially useful in the fields of regulatory toxicology and risk assessment, where numerous studies must be considered, weighed, and integrated to support decision-making.

The course provides students with fundamental knowledge about EBT approaches currently in use (or in development) that integrate and utilize diverse sources of data. These approaches include meta-analysis and systematic reviews, as used in evidence-based medicine. Introduces, explains, and expands upon techniques such as the risk of bias, QA/QC, good laboratory practice and validation, and the role that these tools and techniques play in assuring maximum confidence in evidence-based approaches.

*Learning objectives:*
Upon successfully completing this course, students will be able to:
- Discuss the advantages of evidence-based and bioinformatics approaches
- Describe the principles of systematic review and meta-analysis
- Explain quality assurance schemes in scientific work
- Explain the basis of validation processes
- Identify reasons for bias in scientific work
- Apply quality scoring to published studies

[44] https://www.coursera.org/learn/toxicology-21
[45] https://comptox.epa.gov/index.html#/
[46] https://www.coursera.org/learn/evidence-based-toxicology

In April 2021, one of the co-authors (KH) started a bimonthly, free of charge 3Rs webinar series[47] with national and international expert speakers to train scientists, competent authority members in charge of licensing projects in the EU, members of animal experimentation committees, and IACUCs and animal welfare officers. The series, which is also open to the interested public, covers best practice approaches and latest advancements in the 3Rs as well as insights into the history of animal use in research, transition science, and psychology to accelerate the much-needed paradigm change towards human-relevant, animal-free methods. Veterinarians and scientists receive educational credits, and slides and recordings are made available afterwards. The series has attracted hundreds of learners from all over the world. In November 2021, KH initiated a biannual early-career scientists' workshop on NAMs in biomedical research. The goals are to provide the newest information on human biology-based methods and to connect early career scientist so that they can support one another in this comparatively niche area of science with animals still being the default models.[48]

### 7.3 Outreach to primary and secondary schools

Animal use and alternatives are not usually part of school curricula. Doctors Against Animal Experimentation developed a Germany-wide school project[49] in 2018 together with scientists and teachers. It is addressed to school children of different ages composed of study material that is available for download free of charge on biological differences between humans and animals, ethics, animal free research and law. The materials include work sheets for individual or group work, suggestions for discussions, project work and theater productions, movies, and brochures. Schools may also invite qualified animal protection teachers. The European Schoolnet Academy was asked by the JRC to build learning activities for secondary schools to give an introduction to the 3Rs of animal experimentation. The classes help students to develop critical thinking and science literacy skills by exploring a variety of topics, including ethics in science, laboratory animal welfare, and availability of innovative human-relevant technologies. The learning activities developed for teachers were made accessible via MOOCs[50].

The journal *Frontiers for Young Minds* publishes science articles directed at children in six broad sections including human health. Scientists are invited to describe and explain their discoveries in a language that is targeted at young readers. Reviewers aged between 8 and 15 then provide feedback to the authors on how to improve the articles before publication and are credited alongside the article. Articles on alternatives are "The 3Rs: What are medical scientists doing about animal experiments"[51] and "Organ-on-Chip: Playing LEGO® With Mini-Organs to Reduce Animal Testing and Make Medicines Safer"[52]. In a recent collaboration, headed by David Pamies (University of Lausanne, formerly CAAT), the Swiss 3R Competence Centre, Altertox, the Swiss Federal Institute of Technology in Lausanne (EPFL), and CAAT, supported by the European Commission, a set of three articles, one each on replacement[53], refinement[54] and reduction[55], was generated for *Frontiers for Young Minds* and presented in a live event to kids from the International School of Lausanne, who served as reviewers. Coauthor TH contributed one of these articles and presented it. A video[56] was released concomitantly with the publications, and all partners will support the dissemination of these materials to make them available for middle and high school education.

### 7.4 Public outreach activities

As described above, many outreach activities are targeted at other scientists or master students. To move things to a larger scope, we need to make more use of tailored communication to different target groups. Numerous activities are already underway, see for example the open-access book *Animal Experimentation: Working Towards a Paradigm Change* (Herrmann and Jayne, 2019) described above, but there is still much untapped potential, e.g., in the form of different (social) media channels by which interest and support can be raised for such activities on every scale.

The NC3Rs offers Public Engagement Awards[57] of up to £1,500 for NC3Rs-funded researchers to engage with the public about approaches taken to replace, reduce and refine animal use. These can be online engagement activities, including videos, laboratory open days, hands-on workshops, informal discussions with public groups, school visits, exhibitions, or talks as part of a local science event or partnership events with a local community group or scientific society. CAAT's 3Rs webinar series mentioned earlier is also open to the interested public. Most webinars are recorded and can be watched on YouTube[58]. Next to the well-known TED talks[59], Pint of Science[60] is a grass-root community of thousands of scientists in many countries, who share and

47 https://www.berlin.de/lb/tierschutz/fortbildung/
48 https://www.berlin.de/lb/tierschutz/alternativen-zu-tierversuchen/artikel.1129019.php
49 http://www.tierschutz-in-der-schule.de/
50 https://www.europeanschoolnetacademy.eu/courses/course-v1:3Rs+AnimalsInScience+2020/about
51 doi:10.3389/frym.2018.00044
52 doi:10.3389/frym.2020.544390
53 doi:10.3389/frym.2022.959496
54 doi:10.3389/frym.2022.954413
55 doi:10.3389/frym.2022.953662
56 https://www.youtube.com/watch?v=j-w76Vy8sLA&t=697s
57 https://nc3rs.org.uk/our-funding-schemes/public-engagement-awards
58 https://www.youtube.com/playlist?list=PL3NHpHL7bAZc-7WgMraXuAMw27KBWAQ7p
59 https://www.ted.com/talks
60 https://pintofscience.com/

discuss their findings with people in their local pub, bar, café, or public space. Such activities can be an opportunity for engaged scientists to communicate with the public about NAMs.

When the Lush Cosmetics and Ethical Consumer Research Association created the Lush Prize in 2012, the largest prize within the non-animal testing area, with an initially annual, now biannual prize fund totaling £250,000, this created a new level of recognition of the field of alternatives to animal experiments. The Lush Prize fund is either awarded in full for one major scientific breakthrough in the field (Black Box Prize), which has occurred once to date (2015 for mapping the first adverse outcome pathway), or split equally between five categories, i.e., science, training, public awareness, lobbying and young researchers.

The Phoenix Zones Initiative's (PZI)[61] that has the mission to further the rights, health, and wellbeing of people, animals, and the planet through education, research, and advocacy, recently offered a free four-week virtual Transforming Medical Research Training and Mentorship Program that covered the following topics: history of human and animal research policies and practices, and the ethical principles of research; predictive value and limitations of using animal research to guide human medical advancements; the current state of technological advancements; ways to transform medical research in academic institutions and industry, and explored opportunities to advance evidence-based interprofessional and cross-sectoral interventions[62]. The program was open to medical professionals, who received medical education credit (CME) for participation, and also to the interested public. The Phoenix Zones Initiative continues to offer webinars on how to transition to ethical, innovative research that benefits both people and animals.

Citizen science (also known as community science, crowd science, crowd-sourced science, civic science, or volunteer monitoring) is scientific research conducted, in whole or in part, by amateur (or nonprofessional) scientists[63]. While this has not yet been extended to new approach methods, it could be an interesting outreach opportunity.

General public outreach activities contribute to raising interest and awareness of issues around the replacement of animal experiments and reach members of all stakeholder groups on a different level to targeted communication with these groups.

## 8 Conclusions

The relationship between science, policy, and the public is a highly dynamic process that can be visualized as a triangle with each of these concepts as vertices (Fig. 1). The interactive nature of this relationship determines the pace of change toward alternative methods that are human biology-based and animal-free. The pace of change is set by those who understand and utilize effective communication and outreach techniques. Certain pressure groups serve as accelerants, especially journalists, influencers on social media, NGOs, lobbyists, and activists. The attitudes, needs, and approaches to communication of these stakeholders are very different. Understanding the diverse roles and expectations as well as their respective toolboxes is key to fostering joint progress. Tony Robbins formulated this "*To effectively communicate, we must realize that we are all different in the way we perceive the world and use this understanding as a guide to our communication with others*". The political sovereignty of the public, the advantage in knowledge of the scientific community, and the power privilege of the political establishment make these unbalanced relationships. Thankfully, the transition to innovative animal-free approaches is a win-win-win situation for the triangle partners.

Moving effectively toward this triple-win scenario requires that the scientific community develop and deliver clear, evidence-based messages about the 3Rs and NAMs. In an academic setting, university chairholders for animal-free methods, as installed first by the Doerenkamp-Zbinden Foundation[64] and followed with chairs for Evidence-Based Transition to Animal-Free Innovations in Utrecht held by Merel Ritskes-Hoitinga and for 3Rs and New Approach Methodologies in Krems held by Winfried Neuhaus in 2022, and collaborations of 3Rs centers (Neuhaus, 2021) with a clear focus on innovative human biology-based science will play important roles in changing the paradigm.

Scientists supporting human-centric methods should recognize that an essential part of their training and job responsibilities includes education in public outreach. It is of critical importance to learn how to engage proactively with the public, journalists, and policymakers by their chosen channels. Championing new approach techniques – and explaining to the public why such science is necessary for the future – will help to change the paradigm in which animals are the "gold standard" and hasten our progress towards human biology-based methodologies.

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