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Proceedings of a workshop to address animal methods bias in scientific publishing

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Meeting Report

Proceedings of a Workshop to Address Animal Methods Bias in Scientific Publishing

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Summary

Animal methods bias in scientific publishing is a newly defined type of publishing bias describing a preference for animal-based methods where they may not be necessary or where nonanimal-based methods may already be suitable, which impacts the likelihood or timeliness of a manuscript being accepted for publication. This article covers the output from a workshop between stakeholders in publishing, academia, industry, government, and non-governmental organizations. The intent of the workshop was to exchange perspectives on the prevalence, causes, and impact of animal methods bias in scientific publishing, as well as to explore mitigation strategies. Output from the workshop includes summaries of presentations, breakout group discussions, participant polling results, and a synthesis of recommendations for mitigation. Overall, participants felt that animal methods bias has a meaningful impact on scientific publishing, though more evidence is needed to demonstrate its prevalence. Significant consequences of this bias that were identified include the unnecessary use of animals in scientific procedures, the continued reliance on animals in research—even where suitable nonanimal methods exist, poor rates of clinical translation, delays in publication, and negative impacts on career trajectories in science. Workshop participants offered recommendations for journals, publishers, funders, governments, and other policy makers, as well as the scientific community at large, to reduce the prevalence and impacts of animal methods bias. The workshop resulted in the creation of working groups committed to addressing animal methods bias and activities are ongoing.

1 Introduction

Publishing plays a crucial role in the advancement of science, the implementation of medical interventions, and the progress of researchers' careers. In practical terms, scientific publishing is one of the most important tools for a scientist to share novel work with their field, get feedback, and apply for funding to further their research. However, the publishing process can be influenced by biases introduced by journal editors and reviewers (Lee et al., 2013). Thus, there is a need to identify and address biases that occur within the publishing process. One such bias was recently identified as “animal methods bias in publishing:” a preference for animal-based methods where they may not be necessary or where nonanimal-based methods may already be suitable, which affects the likelihood of a manuscript being accepted for publication or introduces a significant delay to manuscript acceptance (Krebs et al., 2022).

On April 20 and 21, 2022, diverse stakeholders gathered virtually for a Workshop to Address Animal Methods Bias in Scientific Publishing to carry out the following charge: 1) Explore a range of stakeholder perspectives, including from academic and industry researchers, journal editors, and government representatives; 2) Describe the current state of animal- and nonanimal-based experimental systems; 3) Describe animal methods bias in publishing and related biases in publishing and peer review; 4) Identify potential causes, consequences, and mitigation strategies for animal methods bias in publishing. The workshop consisted of presentations from subject matter experts, large and small group discussions, and anonymous polling. A summary of these activities as well as a set of recommendations for addressing animal methods bias in publishing is provided in this report.

Workshop Speakers

Christopher Cederroth, Ph.D.
Principal Researcher
Department of Physiology and Pharmacology
Karolinska Institute

Pierre Deceuninck
Data Scientist
European Commission Joint Research Centre

Alexandra Freeman, Ph.D.
Founder, Octopus
Executive Director, Winston Centre for Risk & Evidence Communication

Donald E. Ingber, M.D., Ph.D.
Founding Director and Core Faculty

Wyss Institute for Biologically Inspired Engineering
Harvard University

Catharine E. Krebs, Ph.D.
Medical Research Specialist
Physicians Committee for Responsible Medicine

Judith Madden, Ph.D.
Editor-in-Chief, *Alternatives to Laboratory Animals*, Sage Publishing
Professor of *in Silico* Chemical Assessment, Liverpool John Moores University

Alicia Pains, Ph.D.
Principal Scientists, Lead Systems Toxicology
esqLABS GmbH

Merel Ritskes-Hoitinga, D.V.M., Ph.D., Animal Welfare Officer, Dipl. ECLAM
Professor in Evidence-Based Transition to Animal-Free Innovations
Faculty of Veterinary Medicine
Utrecht University

Clare Stanford, D. Phil.
Editor; *British Journal of Pharmacology*, *Journal of Psychopharmacology*, *Neuronal Signaling*, *European Journal of Neuroscience*
Emeritus Professor of Translational Neuropharmacology, University College London

2 Workshop introduction: “Animal Methods Bias in Publishing” by Catharine E. Krebs

In the Workshop Introduction, Krebs introduced the concept of animal methods bias in publishing and provided preliminary evidence ascertained via a survey (Krebs et al., 2022). As opposed to “publication bias,” which is defined by the Catalogue of Bias as when the likelihood of a study being published is affected by the *findings* of the study (DeVito and Goldacre, 2019), “animal methods bias” is when the likelihood of a study being published is affected by the *methods* of the study, namely animal versus nonanimal methods. Animal methods bias is therefore defined as a preference for animal-based methods where they may not be necessary or where nonanimal-based methods may be suitable, which, in the context of publishing, affects the likelihood or timeliness of a study being published.

To ground the discussion, definitions of animal-based and nonanimal-based experiments were provided as follows. An animal-based experiment was defined as: “An experiment performed in a living non-human animal or in a non-human animal-derived organ, tissue, or other biological product, e.g., an animal *in vivo* model or animal cell-derived *in vitro* model.” A nonanimal-based experiment was defined as: “An experiment performed in a living human or in a human-derived organ, tissue, or other biological product, or in a nonanimal specimen, or *in silico*, e.g., human cell-derived *in vitro* model, even if it uses animal-based materials such as buffers or antibodies, or a purely computational model.”

To gather evidence of this newly defined type of bias in publishing, a survey was conducted to assess the experiences and perceptions of authors and reviewers related to animal- and nonanimal-based experiments during peer review. The survey contained 33 questions and was completed by 90 respondents working in a variety of biological and biomedical fields. Highlights of the survey findings included that 21 survey respondents performed animal-based experiments for the sole purpose of anticipating reviewer requests for them; 30 respondents have been asked by reviewers to add animal-based data to a study that otherwise had no animal-based experiments; and 11 of those 30 respondents did not feel the request was justified, 14 sometimes did, and three did.

The survey identified potential sources of animal methods bias in publishing as a preference for animal methods and lack of awareness of appropriate nonanimal methods for a given hypothesis. Finally, the survey identified potential consequences of animal methods bias in publishing as delayed time to publication, rejection or withdrawal, publishing in lower impact journals, and performing additional animal experiments which would not have otherwise been performed. Although this survey provided preliminary evidence of animal methods bias in publishing, the sample size was too small to be sufficiently representative, and additional investigations are needed to further describe and understand animal methods bias in publishing and identify its sources, impacts, and potential solutions. The workshop described herein served as a venue to further explore this issue.

3 “Is it Time for Reviewer 3 to Request Human Organ Chip Experiments Instead of Animal Validation Studies?” by Donald E. Ingber

In a presentation based on his paper by the same title (Ingber, 2020), Ingber made the case that animal experiments in both clinical drug development and toxicity testing are often not reproducible, are subject to high variability, do not reliably predict clinical

response, and are ethically problematic. Thus, he argued, that peer reviewers' requests that animal studies be added to validate *in vitro* experiments are misguided (Hamm et al., 2017; Bailey, 2021).

Ingber provided a plethora of examples from his team's work using organs-on-chips—engineered microchips containing living human cells that reconstitute organ-level functions—to demonstrate that human organs-on-chips may be the most relevant validation tool. The Wyss Institute has developed a large variety of human organ chip models for parts of the lung (Huh et al., 2010; Si et al., 2021), intestine (Kasendra et al., 2018; Sontheimer-Phelps et al., 2020), bone marrow (Chou et al., 2020), and other tissues and organs, as well as for vaccine testing (Goyal et al., 2022) and drug toxicology (Jang et al., 2019), where they are identifying drug toxicities to humans that had not been detected in animals (Ewart et al., 2021). Organs-on-chips can be used individually, linked together a few at a time (Herland et al., 2020), or in a group of as many as 15 to form a human body-on-a-chip (Novak et al., 2020; Ingber, 2022).

Organs-on-chips provide a window to molecular and cellular scale activities in and between living human cells within a relevant tissue and organ context. Because of the three-dimensional design of organs-on-chips, scientists who use them can mimic not only the chemical and structural aspects of the *in vivo* environment, but also the physical cues, such as flow and pressure. With this capability, Ingber's group was able to study the effects of breathing motions on viral infection (Bai et al., 2022) and cancer growth (Hassell et al., 2017). Ingber described his experience submitting this manuscript to a journal for publication and having it rejected unless he agreed to conduct animal experiments. Ingber explained to the editor that conducting a multi-week breathing versus non-breathing tumor growth study in an animal would be impossible, because a non-breathing animal would not survive. After this explanation, the editor agreed to publish the article. Ingber characterized the request for animal experiments as a “reflex gut response” from reviewers and editors that his group has experienced many times.

Ingber identified some of the key goals for organs-on-chips, including:

- Predicting human responses to drugs using clinically relevant dose exposures for humans,
- Developing personalized disease models for individual patients,
- Creating models that replicate complex immune and inflammatory responses, and
- Replicating species-specific responses *in vitro*.

During the discussion following his presentation, Ingber commented on model validation and the limitations of organs-on-chips. He stated that the U.S. Food and Drug Administration has been very supportive of replacing animal tests as long as the nonanimal models are validated and at least as reliable. Since Emulate, Inc. and other biotechnology companies sell organs-on-chips, researchers can begin using these models now, which are similarly priced or less expensive than animal-based studies. (In addition, the authors of this report point out that considering the cost of translational failures associated with animal testing, nonanimal models may be substantially less expensive long-term (Meigs et al., 2018).) Further, Ingber expressed the opinion that because reviewers may prefer to see findings validated *in vivo* in animals, this can lead researchers to choose animal methods over *in vitro* methods to forward their careers.

4 “Publishing Biases and Their Impacts” by Pierre Deceuninck and Alicia Paini

First in this session, Deceuninck presented on monitoring innovation and the societal impact of European Union (EU) biomedical research through bibliometric analyses, a survey that assessed the relevance of animal and nonanimal methods, and follow-up interviews. Using publication data spanning 1991 to 2020, the number of studies published by EU affiliated researchers using animal or nonanimal methods were compared. Overall, studies using animal methods decreased slightly during that timeframe and studies using nonanimal methods increased and eventually surpassed them. Among studies investigating Alzheimer's disease, a majority consistently used animal methods in an increasing trend. There were fewer studies using nonanimal methods, but these also increased over time. Among studies investigating breast and prostate cancer, the majority used nonanimal methods and the number increased over time; the number of studies using animal methods also increased. Deceuninck then presented findings from a survey conducted to monitor innovation and the societal impact of EU-funded research, which assessed the relevance of different models to the research question investigated by EU projects. Respondents indicated that human cohorts and human-derived materials were the most relevant models, followed by animals and animal-derived material, then complex *in vitro* models. Follow-up interviews were also conducted to further explore notable themes from the survey, namely translatability issues with animals, the impression that the use of animals is still considered mandatory or unavoidable, and that human-based approaches are important for success (EC, 2021).

Next, Paini discussed her personal experience with reviewers requesting animal evidence for her project on investigating the estragole mode of action in DNA adduct formation and repair using solely *in vitro* methodologies. This work was carried out and drafted in 2010. In this anecdote, reviewers rejected the paper because of the lack of *in vivo* evidence to validate the *in vitro* findings. The authors did not comply to reviewers' requests to perform additional *in vivo* experiments and the work that elucidated the mechanisms of estragole *in vitro* was never published in a peer-reviewed journal. The work performed was ultimately not lost as it was still considered relevant and incorporated as a chapter in Paini's doctoral dissertation (Paini, 2012). More recently, the work was used in a new context to illustrate a case study in the application of the new OECD Harmonized Template 201, which was developed to report mechanistic *in vitro* data (Carnesecchi et al., 2022). Following Paini's presentation, participants discussed that this anecdote exemplifies several problems that commonly arise from animal methods bias in publishing. In this case, results were initially published in a manner lacking the same dissemination potential as a journal article, a PhD thesis; and while the work

was later used in a new context, the delay in the use of the results to other researchers was more than ten years. The time cost of rejection and resubmission can be prohibitive, especially for early career researchers, and this can lead to significant career-related consequences. *A priori* strategic thinking about how to frame a study's "narrative" in a complete, clear, and logical way, within the scope of a particular journal of interest, is essential. As such, correctly framing the narrative of an *in vitro* study is important for avoiding or addressing requests for animal data. Justification can be provided to editors and reviewers when such requests are made; responses to reviewers should always be positive, constructive, and respectful. However, it is well recognized that there is an existing bias against less established researchers and less prestigious institutions that may reduce the likelihood of these justifications being positively received (Tomkins et al., 2017).

5 Breakout Groups, Part 1: Exploring the causes and consequences of animal methods bias in scientific publishing

Participants were divided into four break-out groups to explore causes and consequences of animal methods bias in scientific publishing. Mural¹ was used as an online collaboration platform where the following questions were prompted to guide the group discussions:

1. What needs to happen to make organ chips and other nonanimal methods more available for researchers?
2. Should reviewers be dictating model selection?
3. Besides publishing, in what other areas might animal methods bias exist?
4. What are indicators or measures of animal methods bias in publishing?
5. What factors contribute to animal methods bias in publishing?
6. What are some impacts of animal methods bias in publishing?

After the breakout group discussions, participants reconvened to report and discuss the outcomes of breakout group discussions. Figure S1 shows the Mural output².

The majority of participants shared that, in their opinion, there exists a bias towards the use of animal methods. Adding to this, many described a general feeling that it is more difficult to publish studies containing only nonanimal methods in high impact journals. Participants felt that many reviewers lacked deep knowledge in nonanimal methods, an idea which also came across in their conversations with ethical review bodies.

It was postulated that the main cause of this bias is the fact that animal experiments are often seen as the gold standard in biomedical research and testing (Hamm et al., 2017; Bailey, 2021). Animals are seen as "safe" models to rely on due to historical use. In the participants' views, addressing this bias is difficult because: 1) peer review is a flawed process (starting with the lack of time given to reviewers to further understand the available models); and 2) in many regulations, the use of animals is still mandatory.

Nevertheless, it was unanimous among workshop participants that publishing peer reviewers should not be driving model selection. Reviewers are also researchers and might feel more inclined to suggest the models with which they are familiar. Instead of asking for a different model, reviewers could give constructive feedback, assess the quality of the model used, ask for a rationale or evidence of validity, and even suggest improvements based on their experience.

Editors also have a role in accepting and rejecting manuscripts and should be aware of possible animal methods bias and bias against early career researchers. Finally, authors should state their findings clearly, avoid overselling, and feel confident to rebut the decisions of reviewers when they feel it is necessary.

Workshop participants proposed some consequences of animal methods bias, including the use of animals where they may not be necessary or where nonanimal methods are appropriate, as well as an impression among early career researchers that they must use animals in order to publish (Tab. 1). These consequences are particularly concerning when animal use impedes translation to human outcomes, which can delay the progression of science, the acceptance of nonanimal methods, and effective patient interventions. Issues of poor translatability and the potential harms to both humans and animals that result from over-reliance on animal data in biomedical research have been discussed previously (Akhtar, 2015; Balls, 2021). Animal methods bias can affect public opinion on the use of animals in research, making it appear more critical to scientific progress than it actually is (Bailey and Balls, 2020); and it can influence public and private industry decisions, such as whether to make big investments in animal research infrastructure.

6 "The Journal Perspective" by Clare Stanford, Judith Madden, Alexandra Freeman, Christopher Cederroth

The Journal Perspective session comprised of a panel of four speakers followed by an audience Q&A. Speakers either had direct experience working with scientific journals as reviewers or editors or were working to improve the publishing process. The purpose of the session was to understand the considerations, pressures, and drivers of behavior of those involved in the reviewing and publishing process, and how they did or did not experience animal methods bias.

¹ <http://www.mural.co>

² doi:10.14573/altex.2210211s

Tab. 1: Animal methods bias in scientific publishing: Setting the stage

A summary of points made during breakout group discussions regarding what additional evidence is needed to demonstrate the existence and prevalence of animal methods bias, consequences of animal methods bias, and barriers to mitigating this problem

Animal methods bias in scientific publishing: Setting the stage		
Evidence needed	Consequences	Barriers to mitigation
<ul style="list-style-type: none"> • Systematic reviews: for example, making the link between studies using animals, journals, and related impact factors • Large data analysis: for example, monitoring the journal publication process at the national and international level (comparing preprints to final versions of peer-reviewed publications) • Expanded data collection: survey a larger panel of researchers; journals could participate in surveying authors and reviewers • Use of natural language processing to inform scope, define criteria, and identify bias, and collect data 	<ul style="list-style-type: none"> • Requests for inappropriate animal methods • Conduct of unnecessary experiments on animals • Proliferation of flawed or less-translatable animal-based approaches, even where alternatives exist • Proliferation of a reliance on animals, which may influence public opinion and industry decisions • Less constructive manuscript review • Leniency in necessary requirements for reviewers' to be well-informed of developments in nonanimal methods • Delay of research publication • Publication in lower impact or less read journals, reducing research dissemination • Negative impact on career trajectory of early career researchers (provided the one or more of the previous consequences occur) 	<ul style="list-style-type: none"> • Career goals ("publish or perish;" the anecdotal reports that animal methods increase the chances of publishing in higher impact journals) • Ignorance of nonanimal methods and/or hostility to change, which may be based on psychological or technological "lock-in" • Institutional inertia (the educational system is slow to change) • Presence of a large number of stakeholders with varying interests • International inconsistencies between legislative mandates and guidelines regarding animal use

Madden outlined the roles and responsibilities of journal editors, including determining the scope and future direction of the journal, ensuring articles are relevant to the audience, and situating articles in the appropriate context. The editor in chief (EIC), associate or senior editors, and the editorial board work as team, the membership of which evolves to ensure that the team's expertise is reflective of the scope of the journal.

The journey of an article from submission to publication typically involves a preliminary assessment by the EIC to decide whether it is within the scope of the journal, seems scientifically sound, proposes a reasonable method to answer the question under investigation, etc. Associate (or senior) editors mediate the peer review process liaising between reviewers (who should deliver an unbiased report evaluating the manuscript and providing constructive feedback) and authors (who then respond to reviewers' comments). A significant challenge is securing high quality reviews; the work is usually unpaid, often unrecognized, and requires reviewers to commit a significant amount of time and to stay up to date, especially as authors may challenge the rationale for additional information they are being asked to provide. Simple training materials or readily accessible resources for reviewers could alleviate some of these problems.

As an editor, Stanford reported that she has not been aware of any prejudice towards animal experiments within her field. She stated that some papers do not pass the evidence threshold for publication, but that is usually because a study that involves completely *in vitro* techniques has made a claim about how the *in vitro* findings will generate a change in an animal (e.g., analgesia, antinociceptive), and there is no way to validate this claim without performing the test on an animal. In this circumstance, an author might be required to provide additional animal data.

However, she observed that similar scientific criticisms can be levelled at experiments using animal; for example, it is very rare for a single genetic mutation to completely recapitulate a human psychiatric disorder, yet there is an abundance of papers which claim to produce an animal to model multifactorial conditions such as depression. Papers that claim to use an animal to model a complex heterogeneous condition need to be able to explain how the model relates to the human diagnostic criteria, which usually require thresholds to be met across a range of symptoms or behaviors before the patient qualifies for a diagnosis. Indeed, some journals now have stricter requirements in their guidelines for authors about claims that can be made for animal experiments.

Stanford explained that publishers represent another stakeholder in the scientific publication process. Commercially, publishers have been very successful (financially and reputationally) as a result of the current research system and are resistant to introduce changes that might undermine confidence in the science they have been publishing for decades. They also worry about changes in journal policy that might lead to a reduction in manuscript submissions.

Freeman, who directs Octopus, a new, open by design primary research record, began by discussing how the incentives within the current academic system place all the power with publishers. This is a consequence of journal articles being viewed as the primary output of academic research and consequently the main way by which quality is judged. Therefore, publishers can influence what gets researched, how, and by whom. Octopus was founded on the belief that there are two functions for research

output and judging quality: 1) dissemination of relevant findings to audiences in easy-to-read narrative form, and 2) recording and quality checking of all the work that has been done. The current publishing system is effective at the former, but not the latter.

Octopus is designed to be a free, fast, and fair digital first primary research record. It launched in June 2022 and is supported by UK Research and Innovation and the UK Reproducibility Network. It is a public service with the sole purpose of improving science, thus removing the commercial incentives that arise from the current publishing model. It proposes abolishing the concept of the traditional journal article in favor of eight units: research problems, hypotheses/theoretical rationale, protocols/methods, data, analyses, interpretation, real-world implementation, and peer reviews. Each unit is treated as a publication or semi-independent output. In this model, a review is treated as any other type of publication in recognition of the fact that critiquing is an essential part of the scientific process, which helps to incentivize good peer reviewing. Readers can rate each element on what the community has defined as “good” for each publication unit and the system aims to reduce various biases by removing first names, photos, etc., and attempting to make it fully language agnostic.

Cederroth described a slightly different experience he had had as an author having been asked to provide *in vitro* data to validate his *in vivo* findings, essentially the opposite of animal methods bias discussed here. He also described feedback from high impact journals that the more data generated with and corroborated between different methods, the more likely reviewers and editors are to view the findings as robust. Additionally, within his field (tinnitus and hearing loss), there have been substantial reproducibility issues known within *in vitro* research due to poor cell culture practices, undermining the perceived credibility of this methodology. In his role at Frontiers as a collection editor, he observed that there was more direct contact with authors than in some other journal structures and that one of his main functions as an editor is to listen to the difficulties authors are facing. Complying with requests to validate findings using other methods can be hugely time-consuming, expensive, and often simply not practical. The primary factors for deciding what model to use need to be the quality of the method, the appropriate choice of method for the hypothesis in question, and a clear description of experiments to aid reproducibility. Focusing on these areas would, in Cederroth’s opinion, reduce many types of bias.

Following these talks, a question was directed at Stanford: “Do you see a way of studying behavior and cognition directly in humans?” She responded that most researchers would much prefer to be working in humans and would not choose to use animals if it was possible to directly use the species of interest. The limitation on human studies is an ethical one with the ethical bar in the UK for conducting studies in animals considerably lower than that for humans. She noted that there were often two research strands usually running in parallel when considering any neurological or psychiatric condition which is how do we understand what is happening in terms of biochemistry and function, and how can we treat/cure or alleviate symptoms to enable “normal” functioning. She felt that nonanimal models might be particularly useful in finding treatments.

Cederroth added that there are substantial international variations in terms of the culture, ethics, and regulatory approval requirements for human versus animal research. Anecdotally, in the UK, some researchers’ grants expire before the ethical approval for human studies has been granted, causing research directly with human subjects to grind to a halt. In Sweden, the opposite has been observed; it may take substantially longer to get ethical approval for the use of animals than it would for studies involving human subjects.

7 “Animal Methods Bias Mitigation: What Can We Learn from Transdisciplinary Research?” by Merel Ritskes-Hoitinga

Merel Ritskes-Hoitinga spoke about the lessons from transdisciplinary research that we can apply in mitigating animal methods bias. She emphasized the importance of systematic reviews in the advancement of better science and the reduction and replacement of animal testing. SYRCLE was founded on the observation that systematic reviews led to better implementation of the 3Rs (replacement, reduction, and refinement of animal use) by bringing forth a more complete accounting and understanding of the limitations and low translatability of many animal studies (Ritskes-Hoitinga and Pound, 2022). The work of those at SYRCLE and others led to the founding of Transitie Proefdiervrije Innovaties (TPI; Transition to Animal-Free Innovations) in the Netherlands.

The history of animal use during crises, like the Elixir Sulfanilamide disaster among many others, seem to have played a role in the collective belief system biased towards animal testing (Swaters et al., 2022). This belief system can be challenged through transdisciplinary research by integrating knowledge across academic disciplines and with non-academic stakeholders to address societal challenges. Ritskes-Hoitinga pointed out how past successes can become counterproductive if there is unwavering belief in following them without asking critical questions. However, technological advances in human-relevant nonanimal methodologies have proved an efficient new solution to handling crises like the COVID-19 pandemic (Ritskes-Hoitinga et al., 2022).

Preclinical systematic reviews have concluded that 50-80% of animal study publications do not mention essential details, many animal experiments do not translate to humans, and there has been little progress in publication quality (Pound et al., 2004; Hyman, 2012; Leenaars et al., 2019). It is essential for regulators and funders to mandate preclinical systematic reviews before moving on to clinical trials, and to include systematic reviews as a part of investigator brochures for medical ethics committees, none of which is currently practiced.

Ritskes-Hoitinga made the case that systematic reviews should be incentivized through funding, like the support provided by the Dutch Health Funding Organization, ZonMw, which funded SYRCLE to teach, develop guidelines, and coach investigators on performing systematic reviews. A report on the ZonMw initiative revealed many positive impacts of preclinical systematic reviews, including better 3Rs implementation (Menon et al., 2021). Researchers who took the training reported that it had a major

impact on their own research, their view of the quality of animal study publications, and their decision whether to trust or continue to use animal tests in a particular field.

In addition to funding, better collaboration among editors and funders can enable and accelerate human-relevant science. This is evidenced by: 1) the collaborative efforts of influential journal editors in the field of clinical research to mandate preregistration of clinical trials, and 2) the uniform setting of stringent guidelines by various journals to reduce the chances of manuscripts escaping to other journals with lower expectations; both of which have increased publication quality in the clinical sector.

Ritskes-Hoitinga went on to explain the workings of TPI, which is guided by the Ministry of Agriculture, Nature and Food Quality, and involves all possible stakeholders in the use of animals and nonanimal methods. This program recognizes that the transition to nonanimal methods is a multi-level process: niche (the level of innovations), socio-technical regime (legislation in place), and socio-technical landscape (the society at large). Transition analysis allows the identification of barriers, leverages, and opportunities at different levels that interact with each other. Five focus areas for the transition to animal-free innovation are: 1) identifying higher quality and more translatable medical research, 2) moving toward open science and increased transparency, 3) increasing funding for nonanimal methods and their validation, 4) advocating for legislative changes, and 5) increasing education, including through understanding and interacting with societal perspectives.

8 Breakout groups, Part 2: Exploring the barriers and solutions to addressing animal methods bias in scientific publishing

Participants were divided into five break-out groups to explore the barriers and solutions to addressing animal methods in publishing. Mitigation was also discussed during Breakout Groups, Part 1; those comments are included here for continuity. Mural¹ was used as an online collaboration platform where the following questions were prompted to guide the group discussions:

1. How can journals mitigate bias during manuscript submission and peer review?
2. What is the role of journals in ensuring research is done ethically?
3. What evidence is needed to demonstrate animal methods bias in publishing?
4. What are the barriers to addressing animal methods bias?
5. Who are other stakeholders in mitigating animal method bias and what is their role?
6. What actions should be given higher priority?

After the breakout group discussions, participants reconvened to report back. Figure S2 shows the Mural output².

The role of journals to mitigate bias

Many important points were raised in the group discussions about the role of journals in mitigating bias, which are summarized in Tab. 2. There was consensus that educating editors and reviewers is essential to mitigating animal methods bias, not only to increase knowledge about nonanimal methods but also to ensure that databases and tools are used by reviewers to assess whether animals are needed to answer a given research question. In addition, journals could provide stronger guidance to reviewers to assess claims and quality, and the review process could be made more transparent, for example by publishing reviewers' comments and authors' responses, or completely open, where the reviewing process is implemented by experts' comments and discussion.

To ensure that research is conducted ethically, there is an urgent need for journals to be more aware of relevant legislation and to not just rely on statements of approval from ethics committees, but also determine that animal use standards were met and require detailed justifications of model choice. Many participants mentioned the lack of details on animal testing methods in published articles, which can be solved by asking authors for more transparent and complete methods. Several obstacles were reported, such as the different and sometimes divergent definitions of the 3Rs, or the lack of international policy and guidelines on ethics and the publication process.

Animal methods bias in publishing is not widely recognized by the biomedical research community, and participants agreed that more evidence is needed to achieve broader recognition (Tab. 1). Systematic reviews, big data analysis, and surveys (targeting authors and editors/reviewers) were widely endorsed by participants as good approaches to provide more evidence of this bias. Artificial intelligence, especially natural language processing, was mentioned as an important and powerful tool for identifying and mitigating bias. For example, natural language processing can be used to automate the task of identifying different animal-based assays in large numbers of peer-reviewed publications. This data would allow researchers to identify strata that display a higher incidence of *in vivo* assays (e.g., journal, impact factor, discipline, lead author seniority).

Barriers, stakeholders, and concrete actions to mitigate bias

During the breakout session, participants also brainstormed how to identify barriers, stakeholders, and priority actions to mitigate prejudice. A non-exhaustive list of important points raised during the discussion is presented in Tab. 1 and Tab. 2.

The barriers to mitigating animal methods bias span the entire scientific process and involve many different stakeholders, presenting a complex challenge. Career development is a major barrier identified by workshop participants, as it is based on steep competition and high impact publication. There is an anecdotal link between high impact journals and the use of animals in studies; early career researchers may be advised that they must do animal experiments to publish their work in high impact journals and, due to time and the pressure to publish, operate on this often-misguided assumption, without testing it for themselves. Also, many stakeholders are reluctant to change and do not trust nonanimal methods, primarily due to a lack of knowledge about them, but also

Tab. 2: Workshop participants’ recommendations for actions that can be taken by the scientific community, journals, publishers, funders, governments, and policy makers to mitigate animal methods bias in scientific publishing

Animal methods bias in scientific publishing: Mitigation recommendations		
Scientific community	Journals & publishers	Funders, governments, & policy makers
<ul style="list-style-type: none"> • Build awareness about animal methods bias • Provide educational materials about nonanimal methods • Increase authors’ confidence in their ability to challenge reviewers’ requests • Perform systematic reviews and meta-analyses on animal- and nonanimal-based methods 	<ul style="list-style-type: none"> • Provide educational materials for editors, reviewers, and authors about nonanimal methods • Ensure that the guidance and enforcement of journal expectations are clear and consistent • Offer registered report paper types • Encourage preregistration of studies • Establish and enforce detailed requirements for justifications of model choice • Implement greater transparency in peer-review and publication, even to the extent that review is fully open • Implement different models for peer review and publishing • Change publishing incentives (i.e., less reliance on impact factor) • Encourage thorough reporting of methods and results (including negative results) • Mandate that requests for addition of animal methods be scrutinized by other reviewers 	<ul style="list-style-type: none"> • Prioritize funding for nonanimal methods, including for training and infrastructure • Provide support for early career researchers who wish to use only nonanimal methods • Advance the validation, standardization, and reporting of nonanimal methods, as is being performed by the International Council on Animal Protection in OECD Programs and the EU Reference Laboratory for alternatives to animal testing • Advocate for changes to animal welfare legislation and ensure that existing animal protective legislation is enforced • Change regulatory requirements regarding the use of animals in regulatory testing • Encourage the increased use of systematic reviews and meta-analyses on animal- and nonanimal-based methods

due to the need for validation studies, standardization across protocols, and consistent and comprehensive reporting. As reviewers are also researchers themselves, there may be a psychological or technological “lock-in” to the use of animal research: some reviewers may be unable to appreciate the capabilities of nonanimal methods and the limitations of experiments on animals because of their enmeshment in the animal research paradigm and their own perceived successes using animals. Furthermore, the education system is governed by more senior scientists, many of whom have relied on animals throughout their careers, making change very difficult. Mitigating animal methods bias may thus require a change in the mindset and education of early career scientists and for nonanimal methods to be made more accessible to researchers throughout their careers.

Researchers and publishers (including editors and reviewers) have already been widely mentioned as stakeholders in the use of animal methods, but the people carrying out this bias and those affected by it are not limited to these two groups. Participants identified other important actors like funding bodies, policy makers, companies in animal supply chains, as well as powerful and established industries using animals, the press and media, and the public (Fig. 1).



Fig. 1: Stakeholders in the use of animal methods, as identified by workshop participants

To act quickly and effectively against this bias, it is first essential to focus on the education of stakeholders with an emphasis on reviewers, editors, and publishers (Tab. 2). There is a clear need to increase awareness of nonanimal methods and to provide new guidelines to ensure that reviewers perform reliable, impartial, and ethical work. From a journal perspective, a priority action would be to increase transparency, by publishing more information on methods and negative results, making the peer review process open access (Tab. 2). It will also be crucial to provide more evidence of bias to raise awareness within a larger community of scientists. Ultimately, working with legislators and funding bodies may be necessary to generate change (Tab. 2). Finally, a strategic approach to combine efforts to reduce bias with the transition to nonanimal methods and interdisciplinarity could provide a concrete and solid solution, according to the participants. Workshop participants also reported having observed animal methods bias in other areas such as funding, regulation, and education. Therefore, mitigation efforts may need to be comprehensive and systemic.

9 Polling at the beginning and end of the workshop

A Slido³ poll was conducted by Dr. Sofia Batista Leite during the introduction of the workshop on day one and its conclusion on day two. The objective of this interactive exercise was to better understand the participants' interest in the topic of animal methods bias in scientific publishing and to gauge whether the workshop discussion had changed their perspective on this subject at the end of the event. Full questions and answers can be found in the supplementary file².

Results

On the first day of the workshop five questions were asked. The first question was a ranking poll: "As an author or reader, how do you use scientific publishing?" 17 participants responded and each response received the following ranking score: "to share my scientific findings" (3.24); "to learn about methods" (2.47); "to stay up-to-date" (2.29); "to push my field forward" (1.65); "to build trust in the methods I use" (1.00) and finally, "to demonstrate my productivity and advance my career" (0.29). The second question was a multiple-choice poll asking participants "Why did you come today?" 50% of the 20 respondents answered "to broaden my knowledge" and "to try to make a difference", while 25% of them wanted to share their experience and 20% were there for networking. To the third question on publication process satisfaction, which was a rating poll from 1 to 5 (1=not satisfied at all, 5=extremely satisfied), 30% of the 20 respondents gave a 2; 60% gave a 3, while 10% gave a 4 to the publication process. The fourth question was another rating poll, querying participants about "How much of an impact do you think animal methods bias has on scientific publishing?" (1=no impact; 5=very large impact) and received 21 responses. More than 60% of the respondents reported that animal methods bias has large to very large impact on scientific publishing (ratings 4 and 5). And 24% were neutral (rating 3) while only 14% replied that the impact was small (rating 2) (Fig. 2). The last question of the day was "What do you expect from this meeting?" Results were represented as a word-cloud (Fig. S3), with "new ideas, data, change, solutions, and swap experience" as the most repeated responses.

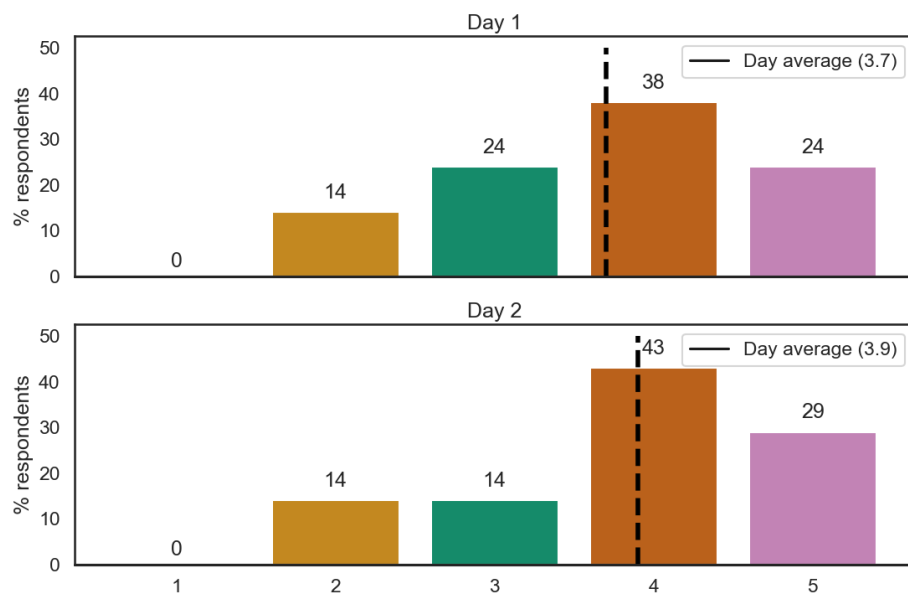


Fig. 2: Comparison of answers to the question "How much of an impact do you think animal methods bias has on scientific publishing?" (1=no impact, 5=very large impact) asked at the start and again at the end of the workshop

Respondents' ratings increased slightly over the course of the workshop. Day 1: n=21; Day 2: n=14.

³ <https://www.slido.com/>

On day two, three additional questions were asked to assess the impact of the workshop. The rating poll “How much of an impact do you think animal methods bias has on scientific publishing?” was proposed again and there was an increase of 10% in the responses reporting that animal methods bias has large to very large impact on scientific publishing. Several post-workshop actions activities (immediate and long term) were proposed, and participants indicated they were willing to participate in a follow-up meeting (18%), join a taskforce (41%), draft the workshop report publication (35%), or participate in another way (6%). The final question of the workshop asked participants to share the main take home message of this meeting. Themes that emerged from the answers to this question included that more evidence of animal methods bias is needed, as well as training, education, and collaboration to mitigate this bias.

In conclusion, the poll showed the participants came from backgrounds where scientific publications are used in very diverse ways (Q1.1.) but that they were bound by common motivations of learning more about animal methods bias in publishing through sharing experience and data and exploring how to make a difference in tackling this issue (Q1.2. and Q1.5). It is apparent that the participants were very satisfied with the outcome of the workshop and strongly engaged in the activities, considering that many of them were willing to pursue post-workshop actions, including joining a task force (41%) (Q2.2.). The activities and discussions offered also convinced several participants that animal methods bias has more of an impact on scientific publishing than previously thought (Fig. 2). Finally, the very diverse ‘take home messages’ offered by the participants (Q2.3.) reflect the variety of topics discussed during the lectures and the group discussions, as well as the comprehensive nature of the challenge posed by animal methods bias in publishing.

10 Discussion

During a two-day workshop, researchers, journal editors, scientific publishers, and animal advocates gathered to examine the newly identified problem of animal methods bias in scientific publishing, defined as the preference for animal-based methods where they may not be necessary or where nonanimal-based methods may already be suitable, which affects the likelihood of a manuscript being accepted for publication or introduces a significant delay to manuscript acceptance. Invited speakers illustrated the evidence for this problem and the current state of nonanimal methods and their suitability for answering many research questions; provided information on trends for the publication of animal versus nonanimal methods; described responsibilities of journal editors, models for scientific publishing, authors’ experiences, and lessons from transdisciplinary research and systematic reviews; and discussed the multi-factorial nature of nonanimal methods uptake.

Conversation among participants took place at the conclusion of each day’s talks and was facilitated by prompts from workshop organizers. Participants overwhelmingly agreed on the existence of animal methods bias from the start of the workshop, but their view on how much impact the bias has on scientific publishing differed, and on average increased slightly over the course of the event. A theme that emerged from the workshop was that different research domains (infectious diseases, neuroscience, etc.) have different needs for model systems and have made progress in the development and uptake of nonanimal models at different rates, likely owing to differences in factors including disease complexity, phenotypic nature, and accessibility of human tissue.

Workshop participants discussed recommendations to address animal methods bias in scientific publishing, including building awareness about animal methods bias; educating editors and reviewers about nonanimal methods; implementing different models for peer review and publishing; requiring study preregistration; implementing open science and open review; prioritization of nonanimal methods by funders; advancing validation, standardization, and reporting of nonanimal methods; and changing regulatory requirements (Tab. 2).

Barriers to mitigation were identified as being the high-pressure nature of the research environment, the intense pressure to publish research findings in high-impact journals, the persistence of animals as a so-called “gold standard” for answering many research questions, lack of knowledge or lack of desire for knowledge about nonanimal methods, and the presence of a large number of stakeholders with varying—and sometimes conflicting—priorities (Tab. 1). Nevertheless, participants were optimistic that steps can be taken to address the problem and were motivated to continue learning about and working on this issue.

11 Conclusion and future directions

This workshop was successful in its charge of generating discussion about the causes, consequences, and potential solutions of animal methods bias in scientific publishing and created an ongoing taskforce committed to addressing this issue. Two major working groups were formed following its conclusion. The Evidence Building Working Group is gathering additional data on animal methods bias in scientific publishing through a follow-up survey to Krebs et al., 2022 and by analyzing publication data. The Mitigation Working Group is planning to work with journal editors and publishers to improve policies and is developing educational materials and support for authors wishing to avoid experiments on animals.

It was clear from the workshop that animal methods bias likely extends beyond publishing, and solutions therefore need to be targeted both at publishing and at other systemic levels of research policy, funding, and education. More evidence demonstrating animal methods bias in publishing and beyond and exploring its causes and impacts will help generate buy-in among important stakeholders. These efforts will contribute to necessary cultural change in biomedical research and testing that will lead to more ethical and effective research.

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Conflict of interest

The authors have no conflicts of interest to declare.

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