Transnational Environmental Law (2024) 1–26
doi:10.1017/S204710252400027X

TEL CAMBRIDGE UNIVERSITY PRESS

ARTICLE

The Role of Epistemic Communities in Formulating EU Policy: The PrecisionTox Project

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Abstract
The interface of science and law is a territory frequently occupied by policymakers. In facilitating this interface, epistemic communities have become significant influencers in policymaking, especially at the European Union (EU) level, as a result of its complex multilevel governance system. In this article we assess the quality and nature of interactions between epistemic communities and EU stakeholders on the Horizon-funded project 'PrecisionTox', by deploying the concept of epistemic communities developed by Haas, as well as the learning modes of epistemic communities as presented and adapted by Dunlop. The overarching goal of PrecisionTox is to advance the safety assessment of chemicals by establishing a new, cost-effective testing paradigm built from evolutionary theory, which entails reduction, replacement, and refinement of mammalian testing (the 3Rs). The study shows that EU-funded projects can provide an excellent platform for building epistemic communities and forging alliances with EU policymakers, especially when novel technologies may be unlocked and socialized. This study also explores the early interaction of policymakers with epistemic communities through different forms of learning to better understand the complexities surrounding these new technologies in order to set an agenda for policy interventions.

Keywords: Epistemic communities; Learning modes; PrecisionTox project; EU Horizon funding; REACH chemical risk assessment; Regulatory science; Policymaking

1. Introduction

The interface of science and law is a territory frequently occupied by policymakers. In facilitating this interface, epistemic communities have become, during the last four years, significant influencers in policymaking, especially at the European Union (EU) level, as a result of its complex multilevel and transnational governance system. Haas defines epistemic communities as a 'network of professionals with recognized expertise and competence in a particular domain and an authoritative claim to policy-relevant knowledge within that domain or issue-area'.[1] Their significance is particularly

[1] P.M. Haas, 'Introduction: Epistemic Communities and International Policy Coordination' (1992) 46(1) *International Organization*, pp. 1–35, at 3.

prominent in policy areas that are heavily informed and regulated by science, such as those protecting human health and the environment, where a major task is to ensure the translation of scientific findings into law and regulation through a joint dialogue with relevant stakeholders. The engagement of epistemic communities in the early stages of policymaking is especially prominent when new methods, processes, and technologies can advance the protective goals of EU regulation, as in the area of chemicals regulation. It is often the case that technological innovation is surrounded by high levels of uncertainty so that this discourse between experts and stakeholders allows for some degree of reflection and foresight regarding potential consequences of methodological change (such as to risk assessment) that might arise once translated and embedded into regulatory structures. Scientific innovation, including innovation in methodologies, is often funded and promoted by EU research programmes emanating from funding schemes such as Horizon 2020 and Horizon Europe (Horizon). Given this investment in research, there is a degree of oversight by and regular meetings with relevant institutional actors of the EU, including relevant departments and executive agencies, such as the Joint Research Centre (JRC). In this context, early conversations about technological innovation and science are facilitated in the EU through Horizon funding schemes. These create a structure and a venue for the work of epistemic communities in developing and translating research to address EU policies, with a particular focus on addressing major global challenges.[2]

This article examines the interaction of epistemic communities and relevant EU stakeholders in relation to the introduction of 'new approach methodologies' (NAMs) for assessing chemical safety.[3] Based on Haas' concept of epistemic communities, as well as the concept of learning modes within epistemic communities as adapted by Dunlop, we assess the quality of the discourse between experts and EU stakeholders. We also explore the manner in which they interact at the early stages of the policy process under Horizon funding to construct an agenda, in this case for chemical risk governance, to investigate the regulatory capacity of emerging methodologies based on environmental genomics and other 'omics' approaches.[4] Given that the science is not yet fully mature and that its development generates uncertainty alongside new knowledge, the work presented in this article focuses on the initial stages of policymaking to explore the role of epistemic communities in creating policy and guiding legal intervention.

The conceptual framework developed here is suitable for assessing the value and outcome of interactions from epistemic communities in transnational regulatory

[2] European Commission, 'What is Horizon Europe', available at: https://research-and-innovation.ec.europa.eu/funding/funding-opportunities/funding-programmes-and-open-calls/horizon-europe_en.

[3] PrecisionTox, 'Towards Precision Toxicology', available at: https://precisiontox.org.

[4] Haas, n. 1 above; C.A. Dunlop, 'Knowledge, Epistemic Communities and Agenda-Setting', in N. Zahariadis (ed.), *Handbook of Public Policy Agenda Setting* (Edward Elgar, 2016), pp. 273–96. It is worth noting that the concept of learning modes is further adapted by Dunlop on the basis of four genera of learning developed by Dunlop and Radaelli to reflect on the state of policy learning in political science literature: C.A. Dunlop & C.M. Radaelli, 'Systematising Policy Learning: From Monolith to Dimensions' (2013) 61(3) *Political Studies*, pp. 599–619; C.M. Radaelli, 'The Role of Knowledge in the Policy Process' (1995) 2(2) *Journal of European Public Policy*, pp. 159–83.

https://doi.org/10.1017/S204710252400027X Published online by Cambridge University Press

settings such as EU policymaking. Although this framework is not commonly deployed in legal scholarship, it is significant for environmental law scholars as it provides a framework to analyze how these interactions may contribute to and enhance legislative and policy processes. As suggested by Heyveart, this is particularly the case in EU policymaking areas such as complex risk regulation, where EU institutions regularly seek to directly regulate and influence the behaviour of Member States (MS) and private parties.[5] EU institutions (in particular, the European Commission) rely heavily on the input of epistemic communities through formalized and less formalized forms of interaction. Thus, this epistemological framework further allows legal scholars to assess how uncertainties and risks in particular areas, such as chemicals, can be addressed through interactions with policymakers.

The article focuses on the EU Horizon 2020 project PrecisionTox as a case study to discuss the interactions of policymakers with epistemic communities. This project brings together researchers in both the natural and social sciences who are regarded as traditional, though often separate, epistemic communities and, as such, offer different scientific and regulatory-focused examples to assess the interactions. The work on PrecisionTox is timely in that it aligns well with EU policy and legal developments such as the planned revision of Regulation (EC) No. 1907/2006 on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).[6] These groups of experts are called upon to address the environmental and scientific challenges in the development of NAMs, the novelty of which generates high levels of uncertainty. Within PrecisionTox, by employing a suite of model species that are distantly related to humans, including invertebrates, to investigate mechanisms of chemical toxicity, new methods can be developed to reduce, replace, and refine traditional reliance on mammalian testing (the 3Rs), which is one of the key EU commitments underpinning EU chemicals law.[7] Moreover, the work carried out on the project feeds into the revisions of REACH as the landmark piece of chemical law that deploys animal testing as a last resort. The findings of the researchers working on PrecisionTox are subsequently reviewed through a joint dialogue with EU stakeholders, particularly the European Commission and the JRC.

This analysis, based on the epistemic community conceptual framework and associated learning modes, provides an opportunity to study the process and impact of learning between experts and stakeholders within the Horizon research programme while developing NAMs to assess potentially hazardous substances. This analysis demonstrates the value of the conceptual framework in exploring how early phases of interaction through the Horizon framework provide a legal and policy structure to address novel issues, when contingency is high, and to analyze various interactions involving different learning modes. Although the early involvement of experts in EU

[5] V. Heyvaert, *Transnational Environmental Regulation and Governance: Purpose, Strategies and Principles* (Cambridge University Press, 2018), p. 35.

[6] [2006] OJ L 396/1. Details of the revision are available at: https://www.europarl.europa.eu/legislative-train/carriage/reach-revision/report?sid=8101.

[7] W.M.S. Russell & R.L. Burch, *The Principles of Human Experimental Technique* (Universities Federation for Animal Welfare, 1959).

https://doi.org/10.1017/S204710252400027X Published online by Cambridge University Press

decision making is greatly facilitated by the 'Better Regulation Agenda',[8] the mechanisms by which this occurs remain under-explored. We argue that, even though the involvement of epistemic communities through funded research is not part of the formal policymaking process, the design of research programmes can be instrumental in addressing complex scientific issues in the early stages of policymaking, leading to greater certainty in chemical risk assessment. To that end, the PrecisionTox case study demonstrates how early discussions between stakeholders are seen not only merely as a discourse but also as a structure for epistemic communities to help in shaping the regulatory relevance of their scientific work.

Finally, we conclude that the complexities of the learning process associated with new methods and technologies make it challenging, though possible, to classify modes of learning within PrecisionTox in the classification suggested by Dunlop. Modes of learning do not fall into discrete phases within the PrecisionTox project but, rather, they overlap throughout the project. Epistemic communities are simultaneously exposed to different modes of learning when exploring the new methods and, in this manner, these communities can comprehensively study regulatory, legal, scientific, and societal issues attaching to novel scientific methods such as NAMs, to co-create with EU stakeholders a platform for the science. Epistemic communities ultimately facilitate the quality of EU policymaking by promoting early discussions on new technologies before their policy uptake.

Following this introduction, Section 2 of the article examines the scholarship on epistemic communities and its contribution to our understanding of policy evolution through learning, in order to set out the research framework that forms the basis of the article. Section 3 briefly outlines the PrecisionTox project and its objectives as part of the empirical base of this article. This section also provides an understanding of the main work undertaken for the project, which aims to introduce new technologies that might gradually lead to the replacement of animal testing. Section 4 reviews the contextual background surrounding the work on PrecisionTox and how work on the project aligns with major developments in EU chemical sectors, including the revision of REACH, as well as policy objectives promoted by the European Green Deal with regard to chemicals. Sections 5 and 6 explore the engagement of PrecisionTox experts with stakeholders in policymaking through the epistemic community framework. Section 5 examines specific ways in which epistemic communities interact with the policymakers while, at the same time, contributing to the regulatory process and being involved in reciprocated learning. Section 6 examines how project experts address uncertainties surrounding novel chemical testing methods through policy learning by analyzing short case studies of this interaction derived from data emanating from the project. Moreover, the case studies in Section 6 demonstrate some tangible outcomes of the policy interactions between the EU stakeholders and epistemic communities that display significant regulatory relevance. Section 7 concludes by reviewing the

[8] European Commission, Communication, 'Better Regulation for Better Results: An EU Agenda', COM(2015) 215 final, 19 May 2015, available at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52015DC0215; M. Weimer & A. de Ruijter (eds), *Regulating Risks in the European Union: The Co-production of Expert and Executive Power* (Hart, 2017).

https://doi.org/10.1017/S204710252400027X Published online by Cambridge University Press

main findings in terms of the nature of the epistemic community and its modes of learning. The article outlines the value of early interactions through funded research programmes, while suggesting new avenues of enquiry on epistemology and environmental policy development.

2. The Role of Epistemic Communities within the Research Framework

The concept of epistemic communities has a long lineage, albeit substantially refined from the 1980s onwards.[9] Today, this concept is widely deployed with regard to different aspects of such communities, including their scope, role, interaction, and the building of relations with both state and non-state actors.[10] Haas' definition of epistemic communities as a 'network of professionals'[11] includes experts 'from any discipline or profession who have a sufficiently strong claim to a body of knowledge that is valued by society'.[12] According to Haas, what creates the community is 'their shared belief or faith in the verity and the applicability of particular forms of knowledge or specific truth'.[13] Just as the notion of epistemic communities developed over time to include other experts beyond scientists, so too it was recognized that policymakers are dependent on species of knowledge in policy making. Cross recognizes a much wider group of experts – such as diplomats, judges, defence experts, high-ranking military officials, bankers, and international lawyers – who also possess valuable knowledge that may inform decision making.[14] This concept was further developed in EU studies as a result of increasingly intricate governance structures. For example, Zito regards advocacy coalitions as an additional expert group that can make a valuable addition to 'a wider esoteric knowledge community'.[15]

Epistemic communities may have an extensive remit with various roles in the policymaking process. With the rise in demand for expertise, those communities develop and proliferate.[16] There is a general understanding that these communities are key providers of knowledge and advice at the local, regional, national, or international level.[17] The extent to which epistemic communities will influence the policymaking process by providing knowledge from a broad range of domains may depend on a variety of internal and external factors, and this wider context may have an impact on their

[9] M.K.D. Cross, 'Rethinking Epistemic Communities Twenty Years Later' (2013) 39(1) *Review of International Studies*, pp. 137–60; Haas, n. 1 above. See further on epistemic communities A. Čavoški, 'The Impact of Brexit on Epistemic Communities in Agricultural and Environmental Sectors', in I. Antonopoulos et al. (eds), *The Governance of Agriculture in Post-Brexit UK* (Routledge, 2022), pp. 134–53.

[10] Ibid.

[11] Haas, n. 1 above, p. 3.

[12] Ibid., p. 16.

[13] Ibid., p. 3.

[14] Cross, n. 9 above, p. 155.

[15] A.R. Zito, 'Epistemic Communities, European Union Governance and the Public Voice' (2001) 28(6) *Science and Public Policy*, pp. 465–76.

[16] Haas, n. 1 above, p. 4.

[17] Ibid.

https://doi.org/10.1017/S204710252400027X Published online by Cambridge University Press

work.[18] With regard to internal factors, the quality of advice depends on internal capacity and expertise within an epistemic group, as well as the nature of a particular issue and the demand for a response. External factors are multifaceted and may lie beyond the control of the epistemic community, such as where social or public perceptions shape the policy discourse. In these situations, some epistemic communities have the ability to alter the perceptions and reframe the policy discourse by creating a collective response to emerging issues.[19] Their ability to influence the discussion in these situations will be highly dependent on the timeliness and readiness of stakeholders to be influenced by public perceptions.[20] One might suggest that the COVID-19 pandemic well illustrates this, as public health experts from a variety of disciplinary backgrounds became involved in advising state actors in a crisis, with epistemic authority tempered by the limits of social acceptance.[21]

In the environmental policy area, epistemic communities may negotiate complex scientific or technical issues using a dynamic evidence base. In areas such as chemical risk, as Haas points out, the role of these communities is often to convey the extent of uncertainty in an unbiased manner.[22] This may include shedding light on the cause-effects relationships or complex interlinkages between different issues, as well as evaluating the possible outcomes resulting from various interventions.[23] With scientific discovery, epistemic communities play a mediating role and act as channels for the dissemination of new ideas and concepts previously inhibited by inconclusive or conflicting evidence.[24] Cross also highlights the significance of globalized processes which, combined with varying degrees of uncertainty, create a demand for specialized knowledge.[25] This worldwide role of epistemic communities could aid in shaping state interests, crafting policies, setting the framework of political debate on an issue, and establishing diverse standards.[26] Haas identifies their value in the aftermath of an emergency or crisis situation, when they can assist in identifying causal factors and provide advice on the most appropriate action.[27] Again, the COVID-19 pandemic illustrated the necessity of involving experts with regard to a novel scientific phenomenon associated with lack of knowledge, to garner sufficient evidence to formulate an informed policy response, balancing technical solutions with social acceptability.[28]

[18] For the context of risk-related policymaking see O. Renn, A. Klinke & M. van Asselt, 'Coping with Complexity, Uncertainty and Ambiguity in Risk Governance: A Synthesis' (2011) 40(2) *Ambio*, pp. 231–46.

[19] E. Adler & P.M. Haas, 'Conclusion: Epistemic Communities, World Order, and the Creation of a Reflective Research Program' (1992) 46(1) *International Organization*, pp. 367–90. Our discussion is based on Haas' concept of epistemic communities as refined by this literature.

[20] Ibid., p. 383.

[21] A. Lavazza & M. Farina, 'The Role of Experts in the COVID-19 Pandemic and the Limits of their Epistemic Authority in Democracy' (2020) 8 *Frontiers in Public Health*, article 552192.

[22] Haas, n. 1 above.

[23] Ibid., pp. 2, 15.

[24] Ibid., pp. 27–8.

[25] Cross, n. 9 above, pp. 138–40.

[26] Adler & Haas, n. 19 above.

[27] Haas, n. 1 above, p. 15.

[28] Lavazza & Farina, n. 21 above.

https://doi.org/10.1017/S204710252400027X Published online by Cambridge University Press

In the environmental policy area, epistemic communities are well integrated in the entire policy life cycle, from early conception of policy issues to policy implementation, monitoring, and evaluation.[29] While their primary recipients are typically state actors, non-state actors have increasingly depended on their guidance in recent years.[30] At the EU level, epistemic communities participate at every stage of the legislative process, including legal drafting, adoption, implementation, monitoring, and enforcement. Their input is especially valuable in the planning and impact assessment phases, where epistemic communities have a key role in providing knowledge to substantiate the evidence behind planning and impact assessment determinations.[31] Epistemic communities form key components of the EU multilevel governance system, creating an epistemic dimension to European integration.[32] Rather than merely political, this process is equally epistemic, especially in areas heavily dependent on scientific input, where epistemic communities are said to provide scientific advice through a variety of formalized and less formalized scientific and professional fora.[33]

This policy discourse involves a learning process, which may include the acceptance of new ideas and an understanding of causality between a means and its ends.[34] This process of learning will vary according to the stakeholders, issues at hand, timing, and state of uncertainty. This latter variable is of great significance in addressing environmental issues. As Haas and Adler point out, it becomes 'crucial to know who learns what; whose learning gets translated into policy and why; whose learning gets a chance to affect other countries; and how political processes determine whose interpretations of reality are more viable in a particular historical context'.[35]

Dunlop further develops this conceptual framework by exploring how epistemic communities structure policy discussion through learning. To that end, Dunlop adapts four modes of learning that provide better insights into how epistemic communities contribute to the policy process. These four modes of learning are defined based on two conditions of decision making: problem tractability and actor certification.[36] The former condition encompasses the complexity and unpredictability of the problem, whereby some problems can be more difficult to grasp and solve. The latter condition of actor certification concerns when and how an actor can be regarded as having sufficient authority and recognition to address the problem in question. With regard to the four different modes of learning, the first mode suggests that 'epistemic communities are *teachers of frames*'.[37] In this learning process Dunlop sees epistemic communities as

[29] European Commission, n. 8 above.
[30] Cross, n. 9 above, p. 139.
[31] See also European Commission, 'How to Carry Out an Impact Assessment', 7 Dec. 2021, available at: https://commission.europa.eu/document/9c804cbd-e4bf-4267-9e3d-cef4516573bd_en?prefLang=it. See A. Čavoški, 'Science and Law in Environmental Law and Policy: The Case of the European Commission' (2020) 9(2) *Transnational Environmental Law*, pp. 263–95.
[32] T. Pfister, 'The Epistemic Dimension of European Integration' (2015) 28(1) *Innovation: The European Journal of Social Science Research*, pp. 11–7.
[33] European Commission, n. 8 above.
[34] Adler & Haas, n. 19 above, p. 385.
[35] Dunlop, n. 4 above, pp. 283–4.
[36] Dunlop & Radaelli, n. 4 above, pp. 602–3; Dunlop, n. 4 above.
[37] Dunlop, n. 4 above (emphasis added).

https://doi.org/10.1017/S204710252400027X Published online by Cambridge University Press

powerful teachers who are able to frame policymakers' understanding of the problem and their policy preferences.[38] Epistemic communities become powerful actors in this collaborative, but asymmetrical, relationship. Dunlop classifies the second mode of learning as '*reflexive learning*, where epistemic communities frame policy discourse through deliberation.[39] This mode of learning is associated with a high degree of uncertainty regarding issues at hand, and epistemic communities are seen as facilitators of social debate without having any hierarchical position in the learning process.[40] '*Learning through bargaining*', where epistemic communities act as agents, is the third form of learning. In these situations, epistemic communities are exposed to highly politicized environments and are required to 'become policy advocates and bargain for their understanding of the issue'.[41] Finally, '*learning in the shadow of hierarchy*' is the fourth mode of learning, where the activism of epistemic communities is heavily curbed by imposed standards that have already been set.[42] This may lead to a marginal contribution of experts. We further explore the models classified by Dunlop in Section 5 below, using PrecisionTox as a case study. Before doing so, it is necessary to explain the PrecisionTox research programme, its funding, and the interaction of researchers with EU stakeholders.

3. The PrecisionTox Case Study

This section provides a general background to the objectives and activities of PrecisionTox, a Horizon research programme on chemical hazard, which offers an effective base to assess the engagement of the European Commission as a key stakeholder alongside epistemic communities, drawn together through their scientific interest in the funding call.[43] The aim of Horizon funding is to facilitate collaboration among experts and thus improve the impact of research and innovation in developing and implementing EU policies.[44] The PrecisionTox initiative was one of the projects chosen in October 2020 in response to the call for proposals for the Health Societal Challenge, for the final year of Horizon 2020.[45] This project, together with two other projects, ONTOX[46] and RISK-HUNT3R,[47] form the **A**nimal-free **S**afety assessment of chemicals: **P**roject cluster for **I**mplementation of novel **S**trategies

[38] Ibid., pp. 283–4.
[39] Ibid., pp. 284–5 (emphasis added).
[40] Ibid., p. 284.
[41] Ibid., p. 286 (emphasis added).
[42] Ibid., p. 288 (emphasis added).
[43] See more in A. Čavoški et al., 'Precision Toxicology: New Approach Methodologies for Chemical Safety' (2024) 19(3) *Bio-Science Law Review*, pp. 101–7.
[44] European Commission, n. 2 above.
[45] European Commission, 'New Health Horizon 2020 Research Projects in 2020', available at: https://research-and-innovation.ec.europa.eu/system/files/2021-04/ec_rtd_new-health-h2020-projects.pdf.
[46] European Commission, 'Ontology-Driven and Artificial Intelligence-Based Repeated Dose Toxicity Testing of Chemicals for Next Generation Risk Assessment', available at: https://cordis.europa.eu/project/id/963845.
[47] European Commission, 'Risk Assessment of Chemicals Integrating Human Centric Next Generation Testing Strategies Promoting the 3Rs', available at: https://cordis.europa.eu/project/id/964537.

https://doi.org/10.1017/S204710252400027X Published online by Cambridge University Press

(ASPIS),[48] which aims to address different aspects of the safety assessment of chemicals without the use of animal testing. The overarching goal of PrecisionTox is to use evolutionary principles and their practical application to advance the safety assessment of chemicals without resort to traditional mammalian testing, by establishing a new, cost-effective testing paradigm. This new paradigm is 3Rs-compliant in that it seeks to replace, reduce, or refine animal testing. The project also responds to the urgent need to test the safety of around 350,000 registered chemicals and chemical mixtures.[49] Precision Toxicology focuses on identifying evolutionarily conserved pathways to toxicity and their biomarkers that are necessary components of an adverse outcome pathway (AOP), which can indicate chemically induced adverse health effects in many animals, including humans.[50] Despite different biomarker definitions, the World Health Organization defines a biomarker as 'any substance, structure or process that can be measured in the body or its products and influence or predict the incidence or outcome of the disease'.[51] The project will facilitate their uptake into regulatory and industry practice.

To that end, PrecisionTox deploys and trials the effective use of NAMs in chemical safety, which are defined by the European Chemicals Agency (ECHA) as 'an umbrella for various approaches utilising non-animal methods and technologies which may also allow multiple investigations from a high number of samples at the same time',[52] providing useful information on toxicodynamics, as well as useful and usable information for hazard screening and prioritization.[53] It is worth noting that NAMs include *in vivo* (using alternative animal models) for systemic toxicity, *in vitro* (human cell culture platforms) for measuring cellular toxicity, and *in silico* (computer modelling) methods of testing. PrecisionTox involves testing on five non-mammalian model species of fruit flies, nematodes, water fleas, and the embryos of clawed frogs and zebrafish, which share similar biological processes across different branches of the animal phylogeny by evolutionary descent and are, as such, highly relevant to human toxicology as predictors of harm to health.[54] This approach is advancing a

[48] ASPIS, 'Animal-free Safety Assessment of Chemicals: Project Cluster for Implementation of Novel Strategies', available at: https://aspis-cluster.eu.

[49] Z. Wang et al., 'Toward a Global Understanding of Chemical Pollution: A First Comprehensive Analysis of National and Regional Chemical Inventories' (2020) 54(5) *Environmental Science & Technology*, pp. 2575–84.

[50] M. Sachana, 'Adverse Outcome Pathways and Their Role in Revealing Biomarkers', in R.C. Gupta (ed.), *Biomarkers in Toxicology* (Academic Press, 2019), pp. 163–70.

[51] M. Memtsa, D. Jurkovic & E.R.M. Jauniaux, 'Diagnostic Biomarkers for Predicting Adverse Early Pregnancy Outcomes' (2018) 126(3) *Royal College of Obstetricians and Gynaecologists*, pp. e107–13. Other definitions are available in R.M. Califf, 'Biomarker Definitions and Their Applications' (2018) 243(3) *Experimental Biology and Medicine*, pp. 213–21.

[52] European Chemicals Agency, 'Non-Animal Approaches: Current Status of Regulatory Applicability under the REACH, CLP and Biocidal Products Regulations', Nov. 2017, pp. 15–6, available at: https://echa.europa.eu/documents/10162/22931011/non_animal_approcches_en.pdf/87ebb68f-2038-f597-fc33-f4003e9e7d7d.

[53] European Chemicals Agency, 'New Approach Methodologies in Regulatory Science', Proceedings of a Scientific Workshop, Helsinki (Finland), 19–20 Apr. 2016 p. 7, available at: https://echa.europa.eu/documents/10162/21838212/scientific_ws_proceedings_en.pdf/a2087434-0407-4705-9057-95d9c2c2cc57.

[54] J.K. Colbourne et al., 'Toxicity by Descent: A Comparative Approach for Chemical Hazard Assessment' (2022) 9 *Environmental Advances*, article 100287.

https://doi.org/10.1017/S204710252400027X Published online by Cambridge University Press

shift in regulatory toxicology away from detecting toxicity by observing the adverse effects of chemicals, and towards utilizing mechanistic knowledge about the chemicals' modes of action, thereby opening the door to biomarkers.

In order to identify biomarkers, the PrecisionTox project deploys different 'omics' approaches that fall within NAMs and which have been extensively developed over the last 15 years in precision medicine.[55] Omics approaches in toxicology consist of tools deployed to 'characterise and quantify the molecular and biochemical changes in cells, tissues, and organisms following exposure to chemicals and toxic substances'.[56] These technologies allow for the generation of large volumes of data on single or multiple biomolecules, including gene products and metabolites.[57] The aim is to replicate experiences from precision medicine that are underpinned by the knowledge of causal links between genes and disease, and develop ranges of different biomarkers that can be used in chemical testing. For example, diagnostic biomarkers, monitoring biomarkers, prognostic biomarkers, and predictive biomarkers have been identified in precision medicine.[58] In contrast, the development of biomarkers using omics technology for the purposes of precision toxicology is still in its early days and there remain many obstacles to the regulatory uptake of NAMs, some of which are social rather than technical.[59] Besides developing these different classes of biomarker, the ultimate objective is to translate this scientific knowledge on biomarkers into regulatory and industrial practices that better protect human health and the environment. This could lead ultimately to extensive changes to both hard and soft EU law governing chemicals.

4. REACH Reform and Chemical Risk Assessment

This section locates the PrecisionTox research programme alongside legal and policy developments on chemical risk within the EU. As the article seeks to assess the nature and value of early interactions between epistemic communities on PrecisionTox and policymakers, understanding the EU legal and policy context is crucial for subsequent analysis. On 20 January 2022, the European Commission began a consultation on the reform of the EU's landmark chemical legislation, the REACH Regulation,[60] as part of a five-year review mandated by the Regulation. This move is part of the wider policy

[55] H. Quezada et al., 'Omics-Based Biomarkers: Current Status and Potential Use in the Clinic' (2017) 74(3) *Boletín Médico del Hospital Infantil de México*, pp. 219–26. See also J.J. McCarthy, H.L. McLeod & G.S. Ginsburg, 'Genomic Medicine: A Decade of Successes, Challenges, and Opportunities' (2013) 5(189) *Science Translational Medicine*, p. 189sr4.

[56] Organisation for Economic Co-operation and Development, 'Omics Technologies in Chemical Testing', 23 Nov. 2023, available at: https://www.oecd.org/chemicalsafety/testing/omics.htm.

[57] See A.J. Vargas & C.C. Harris, 'Biomarker Development in the Precision Medicine Era: Lung Cancer as a Case Study' (2016) 16(8) *Nature Reviews Cancer*, pp. 525–37. See also Quezada et al., n. 55 above.

[58] Califf, n. 51 above.

[59] A. Čavoški, L. Holden & R. Lee, 'Report on Socio-Technical Barriers to the Uptake of NAMs', 2023, available at: https://precisiontox.org/wp-content/uploads/2024/02/D6.1-Report-on-Socio-Technical-Barriers-26Jan.pdf.

[60] REACH Regulation, n. 6 above.

https://doi.org/10.1017/S204710252400027X Published online by Cambridge University Press

strategy embedded in both the European Green Deal[61] and the Zero-Pollution Action Plan,[62] which aims for a toxic-free environment by 2050. Moreover, in 2020, the European Commission published a Chemicals Strategy for Sustainability,[63] which points to the growing production of chemicals (forecast to double globally in 10 years between 2020 and 2030). The Strategy sets the objective of protecting health and the environment by the production of safe and sustainable chemicals. This includes producing chemicals that are safe by design; establishing a roadmap to prohibiting the most harmful chemicals by reviewing whether their use is essential; taking better account of the synergetic effect of chemicals; and establishing a simpler 'one substance; one assessment' process of risk and hazard assessment.

The revision of REACH should lead to its better alignment with the EU Chemicals Strategy and its aspiration for safe and sustainable chemicals in circulation in the European market. The Strategy emphasises the necessity of promoting the development of common standards and innovative risk assessment tools as the most appropriate way of gradually moving away from animal testing.[64] To that end, the Commission recognizes the significance of reinforcing the chemical science-policy interface to allow for better uptake of research findings and to better foster 'multidisciplinary research and digital innovations for advanced tools and methods'.[65] It is accepted that better assessment of chemical mixtures is required, and areas singled out for revision in the consultation to the Chemicals Strategy extend to fundamental processes under REACH. These include greater information requirements at registration, including for substances marketed at low volumes; dossier and substance evaluation, where there may be changes to the processes followed; and authorization and restriction processes, based on a balance of risk and essential use.[66]

REACH reform also provides the opportunity to advocate new testing methods, especially where such tests are 3Rs-compliant. Thus far, REACH has failed to deliver on its commitment in relation to the use of animals in chemical testing. Moving away from testing on vertebrate animals is prescribed in REACH;[67] its Article 13(1) allows for generation of information on intrinsic properties of substances by means of testing

[61] European Commission, Communication, 'The European Green Deal', 11 Dec. 2019, COM(2019) 640 final, available at: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=COM%3A2019%3A640%3AFIN.

[62] European Commission, Communication, 'Pathway to a Healthy Planet for All EU Action Plan: "Towards Zero Pollution for Air, Water and Soil"', 12 May 2021, COM(2021) 400 final, available at: https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=COM%3A2021%3A400%3AFIN.

[63] European Commission, Communication, 'Chemicals Strategy for Sustainability: Towards a Toxic Free Environment', 14 Oct. 2020, COM(2020) 667 final, available at: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=COM%3A2020%3A667%3AFIN.

[64] Ibid, p. 23.

[65] Ibid., pp. 21–2. Note that the PARC programme seeks 'to develop next-generation chemical risk assessment in order to protect health and the environment': European Partnership for the Assessment of Risks from Chemicals (PARC), 5 Nov. 2024, available at: https://www.anses.fr/en/content/european-partnership-assessment-risks-chemicals-parc.

[66] European Commission, n. 63 above.

[67] REACH Regulation, n. 6 above. See also Regulation (EC) No. 1272/2008 on Classification, Labelling and Packaging of Substances and Mixtures [2008] OJ L 353/1 (CLP Regulation); and Regulation (EU) No. 528/2012 concerning the Making Available on the Market and Use of Biocidal Products [2012] OJ L 167/1.

https://doi.org/10.1017/S204710252400027X Published online by Cambridge University Press

other than by animal tests, while Article 25 establishes that testing on vertebrate animals for the purposes of the Regulation shall be undertaken only as a last resort.[68]

This policy shift to greater non-animal testing is not surprising and it is part of the wider technology transition with regard to chemical risk assessment. As Geels has argued, opportunities for change may arise to abandon earlier reference points, as the system struggles to cope with contemporary pressures.[69] This may mean that values embedded in the system fail to meet a new set of expectations, such as, in our case, that animal welfare should be prioritized. Moreover, pressures for technological transition, according to Geels, may come from outside the system in place, but allow the niche activity at the system level the chance of breaking through to challenge the dominant regime, as doubts begin to emerge about its efficacy and effectiveness. In our case there are two main landscape pressures at play. The first is the commitment to eliminate environmental pollution and the adverse health impacts attributable to chemicals, which itself demands better understanding of chemical hazards. The second is the wish to eliminate the significant amounts of animal testing currently employed in chemical risk assessment.

There is also a global policy shift apparent among regional and national regulators moving away from animal testing, which for decades was regarded as the gold standard in testing.[70] A 2018 Strategic Roadmap encourages United States (US) federal agencies and stakeholders to adopt new approaches to safety and risk assessment of chemicals and medical products that improve human relevance and thus gradually replace or reduce the use of animals.[71] As a result, in its recent 2021 guidance, the US Environmental Protection Agency (EPA) waived toxicity tests on animal skin,[72] while the Toxic Substances Control Act stipulates the reduction of testing in vertebrates and greater use of NAMs.[73] In 2013, the EU introduced a full ban on animal testing for cosmetics,[74] while in 2021 the European Food Safety Agency (EFSA) Director

[68] REACH Regulation, n. 6 above.

[69] F.W. Geels, 'Technological Transitions as Evolutionary Reconfiguration Processes: A Multilevel Perspective and Case Study' (2002) 31(8–9) *Research Policy*, pp. 1257–74.

[70] See National Research Council, *Toxicity Testing in the 21st Century: A Vision and a Strategy* (National Academies Press, 2007), available at: https://nap.nationalacademies.org/catalog/11970/toxicity-testing-in-the-21st-century-a-vision-and-a; National Research Council, *Science and Decisions: Advancing Risk Assessment* (National Academies Press, 2009), available at: https://nap.nationalacademies.org/catalog/12209/science-and-decisions-advancing-risk-assessment.

[71] United States Department of Health and Human Services, National Toxicology Program, 'A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States', Jan. 2018, available at: https://ntp.niehs.nih.gov/whatwestudy/niceatm/natl-strategy/index.html.

[72] EPA, 'EPA Finalizes Guidance to Waive Toxicity Tests on Animal Skins', 19 Jan. 2021, available at: https://www.epa.gov/newsreleases/epa-finalizes-guidance-waive-toxicity-tests-animal-skin#:~:text=WASHINGTON%20(January%2019%2C%202021),whether%20pesticides%20lead%20to%20adverse.

[73] S.T. Parish et al., 'An Evaluation Framework for New Approach Methodologies (NAMs) for Human Health Safety Assessment' (2020) 112(2) *Regulatory Toxicology & Pharmacology*, article 104592.

[74] European Commission, Communication, 'Animal Testing and Marketing Ban and on the State of Play in relation to Alternative Methods in the Field of Cosmetics', 11 Mar. 2013, COM(2013) 0135 final, available at: https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:52013DC0135.

https://doi.org/10.1017/S204710252400027X Published online by Cambridge University Press

emphasized the ambition that 'by 2027, the large majority of [EFSA] requests for additional data will be based on alternative methodologies'.[75]

Such shifts in regimes of practice outside Europe, or within Europe but outside chemical policy, begin to create space, allowing PrecisionTox experts to address the wider use of NAMs as a regulatory tool. Some of the limitations of animal testing become useful in framing the discussion for furthering innovation in chemical testing. For example, certain pharmaceutical studies demonstrated that animal testing failed to predict adverse effects on humans.[76] Furthermore, there are economic and ethical considerations that would justify the use of non-animal alternatives. Animal testing is expensive and the costs of feeding, housing, and exposing animals under controlled conditions are increasing.[77] According to an EPA estimation, 'using the whole animal for testing for a single chemical can amount to 4 years of work and cost between US$ 1 million and $20 million'.[78] Ethical discussions about animal testing focus on animal welfare issues and prohibiting further suffering of animals exposed to testing. However, in framing this discussion, experts need to address certain concerns associated with the use of invertebrates as non-animal alternatives at the EU level. For example, the economic effects on potential manufacturers and importers who must first register the substance need also to be considered. Change may raise costs for industry, and it could be potentially coupled with a certain administrative burden being imposed on industry. Nonetheless, the ratcheting pressure of animal welfare, when combined with the wider REACH reform agenda, creates the space for policy engagement, which we now consider.

5. Engagement with Epistemic Communities through the PrecisionTox Project

PrecisionTox project experts must address the chemical law reform presented in the previous section. As we have shown, this may involve replacing the types of hazard assessment provided by animal testing by greater reliance on biomarkers that indicate pathways to adverse outcomes in the Annexes to the REACH Regulation.

The European Commission can capitalize on the knowledge of PrecisionTox epistemic communities within the ongoing legislative debate as set out in the 2020 EU Chemical Strategy for Sustainability. The European Commission is committed to reinforcing 'the REACH and Classification, Labelling and Packing (CLP) Regulations[79] as EU's cornerstones for regulating chemicals', which will include legislative reform, especially with

[75] J. Laperrouze, 'The European Parliament Must Protect the Animal Testing Ban on Cosmetics', *The Parliament*, 3 May 2021, available at: https://www.theparliamentmagazine.eu/news/article/the-european-parliament-must-protect-the-animal-testing-ban-on-cosmetics.

[76] Parish et al., n. 73 above.

[77] G. Marchant, 'Law – Not Science – Impedes Shift to Non-Animal Testing', *Bloomberg Law*, 18 June 2021, available at: https://news.bloomberglaw.com/us-law-week/law-not-science-impedes-shift-to-non-animal-safety-testing.

[78] M. Mondou et al., 'Factors Affecting the Perception of New Approach Methodologies (NAMs) in the Ecotoxicology Community' (2020) 16(2) *Integrated Environmental Assessment and Management*, pp. 269–81.

[79] CLP Regulation, n. 67 above.

https://doi.org/10.1017/S204710252400027X Published online by Cambridge University Press

regard to authorization processes and ensuring more comprehensive information concerning chemicals placed on the EU market.[80] Thus, PrecisionTox experts have been invited to discuss how REACH provisions on alternative non-mammalian testing might allow reliance on NAM-derived evidence of the safety of chemicals, while developing biomarkers that might gradually replace animal testing.

Alongside this legislative and policy process, the PrecisionTox project brings together epistemic communities with relevant expertise in NAMs to help to provide scientific advice for regulatory purposes. The project convenes a multidisciplinary pool of experts from disciplines such as toxicology, genomics, quantitative genetics, chemistry, data science, bioinformatics, economics, and law. They are tasked with providing scientific evidence that feeds directly into the EU policymaking process on chemical regulation as one of three projects in the ASPIS cluster, and as such are well placed to contribute to the ongoing legislative reform of EU chemical law.[81] Moreover, this potential contribution to policy process can be regarded as an opportune case, by the deployment of Haas' model of epistemic communities, to assess the quality and potential for engagement between the European Commission and the JRC as the main project beneficiaries, and PrecisionTox as an academic research community. Haas and Adler emphasize the role of epistemic communities through different stages of policy evolution, including four main steps: policy innovation, diffusion, selection, and persistence.[82] It is worth noting that Horizon convenes expert researchers outside the public governance setting whose work is directed to some degree by the funding programme. The created epistemic communities shared not only expertise but also beliefs in and linkages to the problem framing that underpins the research bid. Such problem framing in setting agreed goals and priorities is a first step in policymaking, alongside performative elements in terms of work programmes with promised 'deliverables'. Thus, research programmes like PrecisionTox may be constitutive in nature,[83] not merely researching NAMs but organizing their adoption in wider social settings such as chemical risk assessment.

The PrecisionTox project builds in a process of engagement with research and policy experts at different policy stages, as outlined by Haas and Adler. For example, there is a stakeholder advisory group (SAG), more than half of whom have policy or regulatory experience.[84] The main objective of PrecisionTox is to deploy NAMs in place of mammalian animal testing where possible. Although not part of the formalized decision-making system, interaction between experts and stakeholders throughout the Horizon project becomes a valuable component of the planning phase, because stakeholder input may direct attention to policymaking prior to any formalized process to consider this. It is worth noting that consideration of NAMs in chemical hazard

[80] European Commission, n. 63 above, p. 9.
[81] ASPIS, n. 48 above.
[82] Adler & Hass, n. 19 above, pp. 372–5.
[83] M. Callon, 'Introduction: The Embeddedness of Economic Markets in Economics', in M. Callon (ed.), *The Laws of the Markets* (Blackwell, 1998), pp. 1–57.
[84] PrecisionTox, 'Solution: Co-produce PrecisionTox with Key Decision Makers', available at: https://precisiontox.org/project.

https://doi.org/10.1017/S204710252400027X Published online by Cambridge University Press

assessment remains in the early stages of policy evolution, despite some appreciation of the potential of NAMs to produce alternative testing regimes. This innovative work is well aligned with the EU's wider European Green Deal policy agenda.

Alongside this, the PrecisionTox team offers social scientific input as the European Commission over time has sought to be more inclusive of soft science as well as natural science experts.[85] An interesting feature of this interdisciplinary endeavour is its ambition to make a significant contribution to regulatory science by translating and embedding the scientific knowledge of NAMs into the EU regulatory framework. This aligns with the Commission's efforts to revise and consolidate the legislative framework governing chemicals, and draws into policy circles the PrecisionTox social science and legal experts.

As Haas and Adler argue, epistemic communities play different roles within the policymaking process. Here, Horizon funding envisages a role as a provider of scientific knowledge. In PrecisionTox, this is to deploy NAMs to identify key pathways to toxicity that are evolutionarily conserved and thereby predictive of induced adverse health effects in humans. Once developed, these new testing methods can be taken up into risk governance frameworks. Haas points out that in certain instances, decision makers have limited understanding of complex issues and do not always recognize this limitation.[86] Here, however, the relevant directorates of the European Commission, together with the JRC as the Commission's in-house provider of scientific knowledge, exhibit high levels of expertise. The Commission and the JRC are already committed to the use of alternative techniques in chemical testing and are keen to explore further scientific options and opportunities.[87] However, new approaches to develop biomarkers are emerging rapidly and the provision of scientific evidence to EU stakeholders remains a key task of PrecisionTox experts.

Experts on the PrecisionTox project have an important role in framing the policy question about the usability of NAMs. The timing in opening a discussion on this issue is most fitting and is aligned with the European Commission's policy preferences in terms of both the European Green Deal and the explicit commitment of the Commission to reduce animal testing. We argue below that this falls within Dunlop's second category of framing through joint deliberation. However, to some degree, PrecisionTox experts advocate the use of NAMs as alternatives to animal testing, capitalizing on current policy shifts that fall within the remit of Dunlop's third mode of bargaining. Such bargaining is tempered, however, by wider policy considerations such as the regulatory burden that might be placed on the chemicals industry.

In creating policy discourse, both experts and stakeholders are involved in a learning process. This process allows for participants to learn about and understand different

[85] Čavoški, n. 31 above.

[86] Haas, n. 1 above, p. 14.

[87] ECHA, n. 52 above; ECHA, 'The Use of Alternatives to Testing on Animals for the REACH Regulation: Third Report under Article 117(3) of the REACH Regulation', 2017, available at: https://echa.europa.eu/documents/10162/13639/alternatives_test_animals_2017_en.pdf/075c690d-054c-693a-c921-f8cd8acbe9c3; European Commission, *Alternative Methods for Regulatory Toxicology: A State-of-the-Art Review* (Publications Office of the EU, 2014), available at: https://publications.jrc.ec.europa.eu/repository/handle/JRC91361.

https://doi.org/10.1017/S204710252400027X Published online by Cambridge University Press

linkages between causes and effects and means and ends.[88] Learning is particularly significant when addressing environmental issues carrying a high degree of uncertainty. Although NAMs have been actively pursued by different research organizations and companies, the pace of translation and acceptance into regulatory processes is lagging.[89] One possible reason for this delay is a lack of coordinated action in exploring the applicability of these new methods, resulting in delay and duplication of work.[90] However, limitations in uptake of NAMs are associated predominantly with uncertainties surrounding their functionality. Acting as an epistemic community, PrecisionTox seeks to narrow this uncertainty by presenting science openly, while identifying biomarkers with different levels of assurance based on omics.[91]

6. Learning Modes under Conditions of Uncertainty

Given that NAMs in chemical hazard and risk assessment are not widely established, both experts and policymakers are locked in a joint learning process to establish the credibility and wider acceptance of new testing methods as these technologies arrive with varying degrees of uncertainty. This final substantive section of the article explores the modes of learning engaged in such conditions of uncertainty, through a structured dialogue facilitated by Horizon funding. It does so empirically by drawing upon case studies taken from PrecisionTox data. As Haas points out, this process of learning, both for stakeholders and experts, will evolve over time depending on how this uncertainty is addressed, rendering it problematic to classify the learning process into the defined learning modes identified by Dunlop.[92] Nonetheless, documentary analysis of exchanges between the research team and wider stakeholders – in the form of emails, minutes, drafts of documents, etc. – has provided data for analysis to allow the authors to attempt to locate the work within the Dunlop categorization and demonstrate the outcomes of interactions between epistemic communities on the project and policymakers.

The first mode of learning, where epistemic communities act as '*teachers of frames*', does not occur in this project. There are several reasons. The relationship between PrecisionTox experts and EU stakeholders is not of a hierarchical nature with project experts acting as teachers, but is based on dialogue and negotiation between stakeholders and project experts in addressing uncertainty surrounding NAMs. Furthermore, the experts in the European Commission and the JRC are familiar with the issues of concern but require further assistance from PrecisionTox experts to address practically the regulatory relevance of NAMs.[93]

[88] Haas, n. 1 above.
[89] Parish et al., n. 73 above; Mondou et al., n. 78 above, p. 270; Čavoški, Holden & Lee, n. 59 above.
[90] Parish et al., n. 73 above.
[91] Haas, n. 1 above; FAIR data is a constituent element of the PrecisionTox project.
[92] Dunlop, n. 4 above.
[93] See recent Horizon call for the training and experience exchange for regulators, available at: https://www.horizon-europe.gouv.fr/gaining-experience-and-confidence-new-approach-methodologies-nam-regulatory-safety-and-efficacy.

https://doi.org/10.1017/S204710252400027X Published online by Cambridge University Press

At the same time, the fourth mode of learning – '*learning in the shadow of hierarchy*', whereby epistemic communities act as standard bearers, as adapted by Dunlop – is not immediately applicable to the PrecisionTox project.[94] This model is applicable to policy environments where knowledge is imposed from the top and epistemic communities are faced with highly developed standards or rules, which they can subsequently apply.[95] There is some of this in play. The adoption of NAMs involves a paradigm shift away from reliance on testing for adversity using mammalian animal testing in toxicological studies towards a mechanistic understanding of toxicity. There is considerable attachment to the traditional approach within both regulated and regulatory communities, which might potentially stifle the activism of epistemic communities in developing NAMs. The current context leads in a different direction, however, in which PrecisionTox experts are tasked to develop processes, rules, and standards that could be embedded into the regulatory context and enable the use of NAMs in chemical testing. Their activism and commitment are a necessary part of the achievement of policy goals.

A closer examination of the data reveals that the process of learning fits with the second and third modes identified by Dunlop, though these two phases are not distinct, and they overlap throughout the project. The second mode of learning, classified as '*reflexive learning*', is quite pertinent to NAMs that are associated with significant levels of uncertainty related to their applicability to chemical testing. This mode allows for a dialogue between stakeholders and experts on major scientific considerations, which should result in deliberation and better understanding of existing challenges. A main aim of the project is to integrate stakeholders in co-design and implementation. This is illustrated below by reviewing the work of experts in evidencing the value of non-mammalian model species for chemical risk assessment.

The third mode of learning is apparent in attempts to embed scientific innovation into the regulatory framework while addressing certain non-scientific barriers to the uptake of NAMs. This mode of '*learning through bargaining*' best describes the interchange between project experts and stakeholders. What is interesting to note is that the reflexive method of learning is led predominantly by natural scientists working on the project and addressing scientific concerns, while social scientists are more engaged in this mode of learning through bargaining and advocating the embedding of NAMs in the regulatory context. This mode of learning by bargaining is illustrated through experts' work in identifying both barriers and solutions to a wider uptake of NAMs.[96]

6.1. Reflexive Learning: Deliberating upon NAMs

A significant area of reflexive learning in the PrecisionTox project lies within research on barriers to regulatory acceptance of NAMs, including the lack of confidence in adopting omics methods as a form of NAM and employing model species, which

[94] Dunlop, n. 4 above, p. 288.
[95] Ibid.
[96] Čavoški, Holden & Lee, n. 59 above.

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carry a certain degree of scientific complexity and uncertainty. Stakeholders, including the European Commission and the JRC, are conscious of the limitations of using NAMs across different stakeholder groups and, in particular, NAMs methods based on 'omics', which are deployed by experts on the project. The reliability and reproducibility of omics data is one of the most significant issues. As with any testing, there is a need to prove causality between exposure to chemicals and adverse effects on humans. However, as this testing is done on non-mammalian species, experts need to demonstrate the relevance of omics data to human and environmental health protection, which calls for a clear connection and relevance of omics data to such health. This issue is closely linked with the perceived accuracy of NAMs as against traditional forms of testing by deployment of mammalian testing and the purpose for which NAMs are used. Omics data is often perceived as 'indicators' rather than definitive predictors of toxicity.[97] The extent to which this matters will depend on the purpose for which NAMs are used, which could include prioritization of chemicals of interest or early hazard identification, rather than full risk assessment.[98] Scientists also point out that it is unrealistic to expect a one-to-one replacement of traditional toxicity testing with non-animal assays for many endpoints.[99] Finally, the credibility of NAMs calls for a definition of the chemical applicability domains, reflecting the regulator's need to understand the performance of NAMs across diverse chemical classes.[100]

These questions are addressed through different stages of deliberation between the project experts and stakeholders and, as Dunlop points out, experts on PrecisionTox act as facilitators of this scientific discourse. In order to demonstrate the relevance of NAMs, the researchers accept that learning entails several steps of reflexive deliberation, especially around case studies that are co-produced with regulators. There are various NAMs – including, for example, the research on human cell lines – but PrecisionTox experts argue for the use of model species to assess the impact of exposure on the whole organism and thereby to better understand the systemic effects on human health. This leads to a need to also address a degree of scepticism outside the scientific community in associating humans with distantly related invertebrate model test species (such as fruit flies or water fleas). This can be addressed only through further dialogue and learning with policymakers. To that end, project experts suggest learning from extrapolating adverse effects of chemicals from one species to another to demonstrate how a diverse range of organisms might respond under exposure. In this project the concept of toxicity by descent is being explored. Here, the chosen model species represent some major branches of the animal kingdom and thus allow for mapping the evolutionary origins of toxicological pathways. With regard to human relevance,

[97] R.S. Thomas et al., 'The Next Generation Blueprint of Computational Toxicology at the U.S. Environmental Protection Agency' (2019) 169(2) *Toxicological Sciences*, pp. 317–32.

[98] See H. Prior et al., 'Reflections on the Progress Towards Non-Animal Methods for Acute Toxicity Testing of Chemicals' (2019) 102 *Regulatory Toxicology and Pharmacology*, pp. 30–3; and Parish et al., n. 73 above.

[99] Prior et al., n. 98 above, p. 32.

[100] Parish et al., n. 73 above.

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experts argue that despite 780 million years of evolution, over 65% of human genes that cause disease are found to have functional homologs in the genomes of invertebrate species.[101]

As part of this journey to demonstrate toxicity by descent from different species to humans, the project experts also need to address stakeholder concerns about the performance of NAMs across different classes of compound, by providing large toxicological datasets for experts and stakeholders to examine. This learning exercise of making a right choice of chemicals as a pre-condition in demonstrating toxicity by descent becomes even more important as we are faced with urgency to test the safety of around 350,000 registered chemicals and chemical mixtures.[102] To that end, the project experts, working closely with key stakeholders, are engaged in a specific case study to attend to this issue and demonstrate the use of omics-derived NAMs for chemical safety testing. Part of the learning process is to identify compound classes and class-representative compounds among the 210-chemical test set that will be used to model adverse outcomes in humans by deploying different invertebrate species. As pointed out by Dunlop,[103] this task exposes the need for reaching a broad social consensus as a result of there being a large chemical domain from which to select, and with many factors affecting this decision making.

The selection process was directed by PrecisionTox experts who provided initial recommendations of chemicals to be tested. This was followed by suggestions by different key stakeholders involved in the project who have their own agenda and preferences. The input of policymakers, beginning with the SAG, was significant in order to ensure that funded research would make direct policy contributions. The JRC, as the in-house provider of scientific knowledge for the European Commission, was fully involved together with the National Toxicological Programme, which is the US government programme responsible for developing and applying new approaches with the aim of advancing toxicological sciences.[104] Hence, learning by deliberation required PrecisionTox experts to reach out to different stakeholder communities to better understand how to 'exploit innovative methods' in attempting to prove toxicity by descent, while still ensuring that the direction of the project aligns with the policy agenda. Governmental bodies were particularly keen to test neurotoxicants, which are harmful to nervous tissue. Learning by deliberation involved identifying those chemicals that could be most harmful, while being realistic about the number of chemicals that can be tested during the life cycle of a project. PrecisionTox experts took account of testing undertaken by other ASPIS projects to avoid, but sometimes to encourage, overlaps with related work in other expert groups. Experts were also keen to maximize the information that could be generated on a specific

[101] Colbourne et al., n. 54 above, p. 2.
[102] Wang et al., n. 49 above, p. 2575.
[103] Dunlop, n. 4 above; R. Willis & J. Wilsdon, *See-Through Science: Why Public Engagement Needs to Move Upstream* (Demos, 2004).
[104] US Department of Health and Human Services, National Toxicology Program, 'Mission and Goals', available at: https://ntp.niehs.nih.gov/whoweare/about.

https://doi.org/10.1017/S204710252400027X Published online by Cambridge University Press

chemical as well as making it politically beneficial to examine common chemicals as part of the collaborative efforts to work with stakeholders through learning.

An internal negotiation process within the PrecisionTox Chemical Selection Working Group (CSWG) sought to consider the interests of stakeholders, such as those concerned with particular classes of chemicals, but of greater concern was the toxicity by descent objectives of identifying mechanisms of action and adverse outcome pathways. The selection of control substances, used to form comparisons in order to demonstrate test method efficacy, was also the subject of deliberation. Stakeholders working closely on a case study of selected compounds sought certain controls, but the CSWG challenged their appropriateness for the project's aims, taking into account the range of chemicals being tested, the varying levels of structural similarity across the controls, and the effects expected to be observed. The decisions of the CSWG were therefore made by PrecisionTox in consideration of, rather than in conjunction with, the needs of stakeholders, following a reflexive process. This example of chemical selection illustrates not only the value of reflexive learning but also the value of early interactions with policymakers as those interactions addressed uncertainty associated with chemical risk assessment. In this instance, the chemical selection demonstrates how the process of selecting chemicals did not as such resolve uncertainty, but it did allow experts to coalesce over what work might prove the most fruitful in resolving that uncertainty in the early phases of unlocking novel technologies.

6.2. Learning through Bargaining: Epistemic Communities as Advocates of NAMs

As suggested above, the project's experts are equally involved in advocating the uptake of NAMs. This mode of learning, through negotiating the value of NAMs, is well aligned with Dunlop's third learning mode of bargaining and allows an exploration of prominent economic, social, and regulatory barriers to the uptake of NAMs. This learning mode depicts epistemic communities as political actors shaping policy debates and aligns with the view of Haas and Adler of epistemic communities having the ability to alter perceptions and frame the context for collective responses.[105] 'Bargaining' in the EU context encompasses a multilevel governance system in which numerous actors interact in the transnational policy process. PrecisionTox consists of 15 European partners from seven countries, along with partners from the US, and is one of the three EU-funded ASPIS projects on chemical safety assessments. PrecisionTox experts are well placed to demonstrate the value of NAMs by suggesting solutions for roadblocks in the uptake of NAMs at both the EU and Member State levels, while seeking to alter wider social perceptions about NAMs across Europe. There is an assumption in the existing scholarship that most of these barriers are scientific and technical.[106] In contrast, research within PrecisionTox suggests that

[105] Adler & Hass, n. 19 above, p. 376.

[106] M. Mondou et al., 'Envisioning an International Validation Process for New Approach Methodologies in Chemical Hazard and Risk Assessment' (2021) 4 *Environmental Advances*, article 100061; V. Zaunbrecher et al., 'Has Toxicity Testing Moved into the 21st Century? A Survey and Analysis of Perceptions in the Field of Toxicology' (2017) 125(8) *Environmental Health Perspectives*, article 087024.

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many barriers are social and, in part, arise out of investments in and commitments to existing methodologies. Thus, changing that paradigm becomes complex as it involves addressing shared beliefs, values, and understandings, which actors are reluctant to abandon. Kuhn suggests that achieving paradigm shifts is fraught with difficulty, partly because it is uncertain whether either the old or the new paradigm will resolve future problems,[107] but also it requires some resort to advocacy in suggesting solutions, as scientists and policymakers begin to mobilize around a shift to a new paradigm.[108] Thus, through learning by deliberation with policymakers, PrecisionTox experts were engaged in another form of interaction with policymakers, which provided the platform for addressing uncertainty that inhibited reliance on NAMs. The aim was to address the social element of uncertainty rather than the technical, as this not only arises from knowledge shortfalls but can arise from social interactions, as one group challenges and seeks to undermine the views of another.

Throughout this interaction, the project experts acted as policy agents and advocated solutions for the wider uptake of NAMs. To that end, researchers firstly undertook an empirical study to better understand those barriers, and framed topics for semi-structured interviews to ensure the participation of stakeholders from relevant EU institutions and national jurisdictions.[109] Topic selection involved a degree of negotiation and bargaining, and the interviews explored divergent understandings about the regulatory readiness of NAMs, while revealing a wide range of other social barriers to the uptake of NAMs. This stage of learning, unlike the reflexive mode of learning, was led by social scientists on the project, who explored different socio-technical, legal, and economic factors for the translation of NAMs into the decision-making context.

This empirical study suggests that barriers were at least as likely to be social rather than scientific and technical. Barriers include regulatory acceptance and culture, societal expectations, lack of trust and expertise, jurisdictional differences, and validation processes.[110] This strongly suggests a social element rather than the barriers being within neat, technical domains. Interestingly enough, there was a stark difference of views as to whether the maturity of the science behind NAMs constituted a barrier to their uptake. These findings are, to some extent, at odds with the perceptions of the regulatory and regulated communities for whom the main contention is about the science. The research suggests that social and technical realms coalesce to create barriers to NAMs, each influencing the other to create ambiguity, inhibiting the uptake of these alternative approaches. Finally, the study demonstrated that stakeholders are more amenable and ready for incremental rather than wholescale change in chemical testing to adopt NAMs that are fit for purpose and offer high levels of protection.[111]

[107] T.S. Kuhn, *The Structure of Scientific Revolutions* (University of Chicago Press, 1962).
[108] G.M. Hilton et al., 'A New Paradigm for Regulatory Sciences' (2023) 145 *Regulatory Toxicology and Pharmacology*, article 105524.
[109] See more about the empirical research undertaken in Čavoški, Holden & Lee, n. 59 above.
[110] Ibid.
[111] Ibid.

https://doi.org/10.1017/S204710252400027X Published online by Cambridge University Press

A challenging part of learning through bargaining addresses levels of inertia and conservatism in institutional settings with regard to changes in culture, including legal culture.[112] Though the law is quite responsive to social change, legislators and regulators aim to ensure stability and permanence of law. Mobilizing legal and regulatory changes becomes an important part of learning through bargaining. As Dunlop points out, in these situations 'epistemic communities have to be politically proactive players to convey their message, interacting with a multiplicity of other actors'.[113] As a result, project experts need to ensure political consensus across a wide range of stakeholders.

As part of learning by bargaining, project experts are conscious of the policy preferences of EU stakeholders and aim to provide recommendations that might conform to established preferences. For example, of particular interest are economic barriers attaching to chemicals regulation where there is potential conflict between policy interests of the Directorate-General Environment, the work of which is underpinned by a legal commitment to a high level of environmental protection,[114] and Directorate-General Growth, which is interested primarily in reducing different burdens on companies (both chemical producers and chemical users) and improving their economic performance. A 'bargaining' approach might 'possibly discover smarter policy-making procedures or instruments',[115] and here actors each put forward their knowledge to negotiate how policy aims can be achieved. Learning by bargaining can occur to 'negotiate' formal conditions. Led by these goals, experts within PrecisionTox recognize the need to work within REACH, acknowledging that policymakers are likely to be more receptive to concepts that seek to improve chemical safety assessments under existing regulation rather than proposing the passing of new legislation. PrecisionTox focuses therefore on soft law modifications (for instance, to regulatory guidance), which might accommodate NAMs. The greater ease of adoption of such change demonstrates policy shifts through a bargaining process. Taking into account the feedback calling for incremental change, PrecisionTox began to focus on better deployment of NAMs for the purposes of 'adaptations' already permitted within REACH.[116] The concept of 'adaptations' under REACH is very useful as it allows applicants to deviate from the 'standard testing regime' of Annexes VII to X by reliance on some of the following mechanisms:

- the use of historical human data;
- a weight-of-evidence approach, where information from several independent sources is considered together to reach a reasoned justification;

[112] J.D. Carrillo & D. Gromb, 'Cultural Inertia and Uniformity in Organizations' (2007) 23(3) *Journal of Law, Economics, & Organization*, pp. 743–71.
[113] Dunlop, n. 4 above, p. 286.
[114] Art. 191 of the Treaty on the Functioning of the European Union (TFEU), consolidated version [2016] OJ C 202/1, available at: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A12016ME%2FTXT.
[115] Dunlop & Radaelli, n. 4 above, p. 611.
[116] M.R. Viant et al., 'Demonstrating the Reliability of in Vivo Metabolomics based Chemical Grouping: Towards Best Practice' (2024) 98(4) *Archives of Toxicology*, pp. 1111–23.

- the use of valid computer models on qualitative or quantitative structure-activity relationships ((Q)SARs);
- *in vitro* methods, using, for example, cells or tissues; or
- by grouping substances with reference data together on similar properties and 'reading across' to predict whether a test substance falls between known data points within the group, rather than testing each substance.[117]

For instance, based on the flexibility provided by the concept of 'adaptations' under REACH, PrecisionTox developed a 'group first regulate better' (GFRB) approach to improve efficiency in assessing chemical safety. Adaptations available in Annex XI of REACH to avoid testing every substance allows for chemicals that are structurally similar to be grouped together, so that adverse outcomes may then be predicted using data from reference substances to conclude for target substances (known as 'read across'). Additionally, the ECHA uses a grouping approach based on structural similarity to improve efficiency in selecting substances to assess their regulatory needs, such as for a substance evaluation. The GFRB approach moves away from grouping based on chemical structure and instead integrates observations of bioactivity gained from omics technologies, which will allow a higher throughput for screening, strengthen grouping predictions, and lead to fewer animal tests. Bioactivity as a concept provides further insight into the effects of a substance on a living organism or tissue by seeking a comprehensive understanding of the biological system under exposure. Learning by bargaining is considered by Dunlop and Radaelli to be more unstructured[118] and GFRB has developed through discussions about this approach at project-related fora, including ASPIS Regulatory Fora (made up of project experts, regulators, and policy institutions); workshops at the PrecisionTox and ASPIS Annual Consortium Meetings; and ad hoc meetings with stakeholders. This has progressed from introducing the GFRB concept, to interactions with stakeholders that led to reflection on and refinement of the approach, so that it could be shown to meet different policy objectives without extensive legislative change. Furthermore, the recent work undertaken by PrecisionTox scientists in close dialogue with the ECHA as a key regulator in this field has demonstrated tangible policy outcomes resulting from the structured dialogue on GFRB. This work has shown how the use of omics applied to the assessment and measurement of biological responses of the chemicals leads to better grouping of chemicals for regulatory purposes.[119] This research allows regulators to read across potential harmful effects, predicting the adverse outcome of other chemicals based on their similar biological response. Finally, learning by bargaining allowed for an agenda-setting initiative in relation to GFRB, whereby bringing new disciplinary insights within the epistemic community and early grouping of chemicals according to their

[117] REACH Regulation, n. 6 above, Annex XI.
[118] Dunlop & Radaelli, n. 4 above, p. 610.
[119] Viant et al., n. 116 above; Labmate Online, 'Metabolomics Study Heralds Change in Animal Testing', 12 Mar. 2024, available at: https://www.labmate-online.com/news/Laboratory-research-news/126/university-of-birmingham/metabolomics-study-heralds-change-in-animal-testing/62271.

https://doi.org/10.1017/S204710252400027X Published online by Cambridge University Press

bioactivity helps to utilize existing data on substances, which can be read across to substances in the newly formed group.

Thus, these project activities are pertinent examples of how the epistemic communities' work with the regulator on scientific design through research initiatives can lead to solutions that are applicable in chemical risk assessment. This demonstrates that, while with 'bargaining' it may be 'difficult to predict how learning can occur or when it takes place', it does mean that 'the actors involved in the learning process can set their own goals – they are strategic about where they want to go with their learning process'.[120] The development of the GFRB concept is therefore fluid, taking into account knowledge and opinions to build a proposal within the confines set. The long-term aim within PrecisionTox is for GFRB to be accepted as a primary method of regulatory grouping, so that this advocacy process is seen to have allowed better regulation and reduced animal testing by a more confident resort to read across.

7. Conclusion

In this article we examined the participation of epistemic communities on the EU-funded PrecisionTox project to develop new approach methodologies that could gradually inform the EU regulatory regime for the identification of chemical hazards and the assessment of chemical risk. To that end, we deployed Haas' concept of epistemic communities, as well as the concept of learning modes of epistemic communities adapted by Dunlop, to measure the quality and nature of the discourse between experts and EU stakeholders at different policy levels. This conceptual framework is particularly salient in assessing the discourse between different actors in introducing new technologies in the environmental policy area. Several significant findings emerge. Firstly, research programmes under EU funding schemes such as Horizon provide a platform to form an epistemic community in line with the concept set out by Haas, as well as to forge alliances with stakeholders over time that lead to new ways of addressing current regulatory challenges. There are certain features of PrecisionTox that may make the development of an epistemic community more likely, not least the fact that the research bid followed a targeted call for research that might introduce alternative, 3Rs-compliant research methodologies into chemical testing regimes. This is enhanced by the regulatory context in which PrecisionTox operates, as this project comes at a time of review and possible reform of chemicals regulation and a further push to meet commitments to diminish reliance on animal testing in the process of chemical risk assessment. These contextual factors, which were reviewed, provide an arena in which the NAMs put forward by PrecisionTox can receive serious consideration by policymakers. Notwithstanding the political commitments to reform, the work within the PrecisionTox programme remains epistemic, negotiating, as it does, uncertainties around science.

Secondly, by reference to categorizations of learning modes identified by Dunlop, this study indicates that the quality of the discourse between EU stakeholders and

[120] Dunlop & Radaelli, n. 4 above, p. 611.

https://doi.org/10.1017/S204710252400027X Published online by Cambridge University Press

epistemic communities depends heavily on learning processes within EU funding schemes. Depending on the type of learning mode, epistemic communities may have varying impacts on the policy process regarding risk assessment of chemicals. Though these are still being shaped within the programme and while there are overlapping learning modes, some conclusions are possible. Given shared expertise between researchers and policymakers, the learning is not hierarchical in the sense of experts leading by teaching, as in one categorization offered by Dunlop. In addition, while there is room for a second Dunlop characterization of 'learning in the shadow of hierarchy', given the primacy and hold of certain risk governance methods and processes, the contextual factors suggest a move away from this form of hierarchy. Of Dunlop's learning modes, then, the PrecisionTox case study falls primarily in the less hierarchical middle-ground of learning through reflexive deliberation and learning through bargaining. Reflexive learning allows epistemic communities to shape and drive the discourse on the value of NAMs in enhancing the quality of risk assessment, reducing test burdens and animal testing, and providing data on new chemicals entering the market. Moreover, this learning mode enables policymakers to address and understand degrees of scientific uncertainty surrounding NAMs that will gradually inform the incorporation of those new methodologies into existing regulatory frameworks.

In PrecisionTox, as a case study, this learning mode did not immediately resolve all uncertainty. Still, it did create priorities in how uncertainties might be reduced as we show from our analysis of chemical selection. In addition to this highly reflexive mode of learning, the contextual background for 3Rs-compliant regulatory reform, and the aims of the research programme to translate the omics-based NAMs into the chemical testing process, involve a degree of advocacy for the NAMs. Positing epistemic communities as advocates of NAMs gradually builds their mandate on this policy issue to become, over time, a recognized stakeholder in bargaining for acceptance of these new technologies.

Furthermore, this study suggests, significantly, another avenue of research by exploring the value of interactions between EU stakeholders and epistemic communities in less formal policy settings within EU funding schemes such as Horizon. This article assessed the value of these interactions by examining the work and progress made on the PrecisionTox project, which aims to apply the novel concept of toxicity by descent to chemical risk assessment and which will, in time, render this process more efficient. In this instance, Horizon funding has created a structure and venue for an early discourse between different groups when faced with new concepts and technologies that have the potential to enhance regulatory processes significantly and offer a better understanding of how regulatory science emerges from the laboratory. Here, early discussions between stakeholders and epistemic communities helped to shape the regulatory relevance of the scientific work that followed.

Just as the contributions of the epistemic communities within PrecisionTox have been enhanced by the regulatory context in which PrecisionTox operates, it would be valuable to assess the quality of interactions between epistemic communities and policymakers in other EU-funded instrumental projects by deploying the same

epistemological framework. This might also provide a more comprehensive analysis of the value of Horizon funding within EU transnational regulatory settings. Considering the scale and diversity of EU-funded research programmes, exploring how interactions within them become more than a vehicle for dialogue to augment other processes – such as oversight, reporting, and dissemination – becomes pertinent. The contextual setting of PrecisionTox and its links to the EU Chemicals Strategy for Sustainability and to REACH revision suggest, too, that there is room to explore the place of law reform in creating and sustaining epistemic communities. These can then enhance the quality of subsequent phases of the policy and legislative process, including regulatory impact assessment, by capitalizing and testing existing scientific knowledge before policy uptake.

Acknowledgements: We would like to thank our colleagues Jonathan Freedman and Fiona de Londras for their valuable feedback.

Funding statement: This project received funding from the EU's Horizon 2020 research and innovation programme under Grant Agreement No. 965406: European Commission, 'Towards Precision Toxicology: New Approach Methodologies for Chemical Safety' (Horizon 2020), available at: https://cordis.europa.eu/project/id/965406.

Competing interests: The authors declare none.

Cite this article: A. Čavoški, R. Lee & L. Holden, 'The Role of Epistemic Communities in Formulating EU Policy: The PrecisionTox Project' (2024) *Transnational Environmental Law*, pp. 1–26. https://doi.org/10.1017/S204710252400027X