Note that while we argue that ELSI research will benefit from taking results from the philosophy of science on board and, more specifically, that ELSI research *must* encompass the systematic investigation of epistemic issues, this does not imply that philosophy of science must provide final answers to epistemic questions to be of use for ELSI research.[4] As is the case for all subdisciplines of philosophy, including ethics, philosophy of science almost never provides final answers to issues under consideration and issues tend to remain susceptible to multiple viewpoints. What philosophy of science provides are *possible* answers, positions, perspectives, and so on regarding questions under consideration, thus providing a spectrum of possible ways of addressing questions. While debates in the philosophy of science occasionally do yield a dominant answer to a question (for example regarding the tenability of a traditional essentialist conceptualization of biological species, where the majority view is that such a conceptualization does not fit contemporary biology), in most cases no such majority view is achieved.

But philosophers of science often do much more than merely raise questions: they systematically map out the spectrum of possible positions regarding the questions they raise and highlight problems with each of these possibilities. That is, philosophy of science provides a spectrum of possible answers to a specific question along with an analysis of the strengths and weaknesses of these answers, on which other areas of work can build. For ELSI research, the clear benefit of such philosophical results lies in the achievement of a more solid basis for normative assessments: ELSI researchers can

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considered from an ontological, epistemological and/or methodological (i.e. partly normative) standpoint.

[4] We are indebted to an anonymous reviewer for raising this issue.

formulate normative claims *under the explicit assumption* of a particular position in the spectrum as mapped by philosophers of science. This allows ELSI researchers to formulate sets of normative claims, each under the assumption of a particular epistemic claim, and in this way to map out the normative spectrum in a systematic and perhaps even exhaustive way. Because final answers to epistemic questions are virtually impossible to achieve, framing normative claims under the explicit assumption of a particular answer to an epistemic issue is the best that can be achieved. But this is not a fundamental problem, as moral philosophy cannot typically provide final answers to moral issues either, such that ELSI research would not be able to provide final normative claims anyway. It thus is clear that ELSI research will benefit from the integration of work in the philosophy of science without requiring philosophy of science to provide final answers to epistemic questions.

In the remainder of the paper, we will defend our claims by taking ELSI research as an example and arguing for the potential of what we call *integrated E^2LSI research* for addressing normative questions related to the life sciences – i.e., we argue for the potential of ELSI research conducted in an integrative manner with research on the *epistemic* aspects of the relevant area of science (see the concluding section for discussion). We will proceed as follows. In section 2 we will highlight key aspects regarding the current division of labor between ELSI research and philosophy of science that are relevant for our discussion. In section 3 we will make some qualifications regarding the strength and the scope of our main claims, and illustrate and support our main claims by providing three examples (or “mini case studies”) from different areas of the life sciences and related normative issues – namely genome editing in plants, animal experimentation, and chimera research. We will end with a programmatic outlook in section 4.

2. The division of labor in ELSI research

An important motivation behind our proposal is the existence of a divide between mainstream ELSI research on the one hand, and philosophy of science on the other. This divide manifests itself in distinct research agendas and discourses, as well as, in many cases, in institutional separation with philosophers of science working in philosophy departments and ELSI researchers often having positions in life sciences institutes, medical schools, or dedicated ELSI/bioethics institutes. We suggest that this institutional separation is a consequence of at least three factors.

First, ELSI research has its roots in bioethics, which, although multidisciplinary from the start, was dominated by ethicists and moral theologians due to a "triggering" by moral questions[5] and scandals[6] in the 1950s/60s (Jonsen 2004; Kerasidou and Parker 2014). This shaped the landscape of later discussions and lead to the identification of "philosophical analysis" with "ethical analysis" in research on the normative questions in the life sciences. Second, institutional inertia and path dependencies are amplifying this tendency to the present day through, among other things, the anchoring of traditional bioethics components in undergraduate education in the biological and biomedical sciences (Willmott et al. 2004) and of dedicated ELSI modules in

[5] E.g. questions revolving around organ donation and end-of-life decisions as a consequence of the invention of the heart-lung-machine in the 1950s.

[6] E.g. the unethical cancer experiments at the Jewish Chronic Disease Hospital of Brooklyn in the 1960s (Arras 2008; Lerner 2004; Preminger 2002) and the infamous Tuskegee syphilis study from 1932-1972 (https://www.cdc.gov/tuskegee/timeline.htm).

prestigious graduate programs in the life sciences.[7] Philosophy of science does not have a comparable status in undergraduate and graduate programs in the sciences, and is hardly ever (if at all) included in the bioethics or ELSI courses offered to scientists. In addition, philosophers of science typically are not part of the target group of initiatives and funding programs that focus on the normative assessment of controversial life science research and biotechnology development, and have more traditional ELSI topics in view.[8] Third, for a long time there seems to have been a widespread aversion on the part of (theoretical) philosophers of science to embark too much on the "socio-ethical side of things".[9] This is a consequence of a mix of political and economic factors that for a long time promoted a value-free philosophy of science in line with Hans Reichenbach's ideal in the 20th century (Reisch 2005; Vaesen and Katzav 2019) – an ideal that only recently came under criticism within mainstream philosophy of science (e.g. Fehr and Plaisance 2010; Weaver 2019).

There are, of course, examples where research on the ethical/social aspects of scientific research and its epistemic dimension have been integrated to some degree, e.g.

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[7] E.g. at the University of Oxford (http://www.dtc.ox.ac.uk/courses-and-network/academic-modules.html, accessed May 14, 2019.

[8] Such as the NIH's *Ethical, Legal, and Social Implications (ELSI) of Genomics Research Project Grant Program* (https://grants.nih.gov/grants/guide/pa-files/pa-17-444.html), Genome Canada's *GE³LS* program, or the (terminated) joint German-Austrian-Finnish *ELSA-GEN* initiative.

[9] This has changed, but this change only happened during the past decade. Today the topic "science and values" occupies a prominent position in the philosophy of science (e.g. Kitcher 2011; 2003; Douglas 2000; Elliott 2017). Many of the more traditional ethical aspects of research in the life sciences (such as our moral responsibility towards laboratory animals), however, are still not on the agenda of mainstream philosophy of science.

in philosophical work on evidence-based medicine (Worrall 2008) and in discussions revolving around the meaning and social implications of genetics (Sarkar 1998). Such efforts at integration, however, often are initiated by philosophers of science who extend their work to address ethical, societal and practical issues. The field of philosophy of medicine that has emerged recently and currently is rapidly expanding is a good example of such integrative work initiated by philosophers of science (e.g. Broadbent 2013; Stegenga 2018; Valles 2018). Integration is not typically initiated from the side of ELSI research, though, such that more often than not contemporary ELSI research and philosophy of science are quite detached from each other, thereby depriving the normative analysis of the life sciences and biotechnology of important resources. The examples we provide in the next section should serve as motivation to change this situation and foster integrating philosophy of science into ELSI research.

3. Three examples

Before we proceed to our examples, we will explain the function of the selected cases for our argument. In recent years there has been a surge of papers on the use of examples and cases in philosophy of science (e.g. Pitt 2001; Burian 2001; Chang 2011; Currie 2015; Kinzel 2015; Pietsch 2016). Philosophers and historians of science have highlighted various epistemic roles that case studies can play in philosophy (and history) of science, such as providing counterexamples to philosophical theories, function as heuristic devices for research, or providing evidence for inductive generalizations about science (with the latter being criticised heavily from a methodological point of view, see Kinzel 2015).

In this paper we broadly follow Currie's (2015) idea of using cases as "illustrating conceptual tools". This means that we are not aiming for inductive generalizations based on the examples used. The main idea is to use the discussed cases to show *how* in concrete terms – and without relying on toy examples – philosophy of science can make important contributions to the normative analysis of the life sciences and in what way ethical, legal and social issues in the life sciences may depend on epistemic aspects or have an important epistemic dimension. Each of the three cases will be used to illustrate a different way in which philosophy of science can contribute. That way, the case studies can serve as paradigms for successful integrated research, showing its heuristic potential and acting as inspiring models for other cases. In Currie's words, cases are used here "to both illustrate how the machinery operates and demonstrate its potential" (Currie 2015, p. 566).

The first case (on genome editing) shows how the *clarification of scientific concepts* including their historical dimension can have normative bearing for the regulation of new biotechnologies. The second case (on animal experimentation) illustrates how a *(socio-)epistemological analysis of scientific practice* can help to identify latent normative issues and ethico-epistemic trade-offs that should be assed from an integrated point of view. The third case (on chimera research) is based on a best-practice example and shows how a philosophically informed *description of the actual scientific image of the world* – as opposed to scientific myth or an overly superficial view of what science tells us about the world – can help to debunk misguided ethical arguments and redirected our normative analysis in a fruitful way.

We should also make two important qualifications regarding our methodology, and the scope and strength of our main claim. (1) The primary function of the following "mini cases studies" is to substantiate our main argument. Therefore, we will not provide (too) many details but treat the cases mainly as paradigmatic examples – i.e., we are not aiming to provide full-blown case studies. (2) We do not claim that *each and* *every* ELSI project needs to integrate philosophy of science into its research. Our claim, in other words, is compatible with the existence of normative issues in the life sciences that can be addressed adequately within the standard ELSI framework. But we *do* want to claim that often integrating philosophy of science into ELSI projects is crucial, and that it is always a good idea for ELSI researchers to explore whether current philosophy of science should play an active role in their work.

3.1. Case I: Regulatory classification of genome editing

Genome editing is a general term for a series of techniques that allow precise alteration of the genetic material of a cell (somatic or germline), the most prominent being the molecular "scissors" CRISPR-Cas9. The technique can be applied without leaving any residual transgenic sequence in the target genome, only introducing a point mutation. Besides various somatic applications genome editing can be used to introduce alterations to the human germline (Howard et al. 2018) or to breed plants and animals (Hartung and Schiemann 2014; Van Eenennaam 2017) with unprecedented ease. Therefore, genome editing has recently received much public attention and has reinvigorated traditional ELSI discussions on genetic engineering and genetically modified organisms (GMOs).

There is a wide variety of new and emerging research on ethical, legal and social issues regarding genome editing as well as a long and entrenched debate about genetic engineering dating back to the 1970s (Berg et al. 1975). Most attention has been devoted to ethical, legal and social implications of human germ line editing – even more so recently, as news of a first successfully gene edited human baby provoked a global outcry (Cyranoski and Ledford 2018; Lovell-Badge 2019). Agricultural GMOs also have long been at the focus of public scrutiny and engagement for setting boundaries to applications of genetic engineering, and this topic has been strongly debated in recent years (Braun and Dabrock 2018; Kemper 2011) – even though the debate has been slightly less heated than in the case of human germline applications.

Debates on genetic engineering traditionally revolve around three broader issues: First, there is a debate rooted mainly in deontological ethics on the transgression of natural boundaries, involving considerations of human nature and dignity, or theological arguments and “playing god” (e.g. Comstock, 2014; Dabrock, 2009; De Vries, 2006; Menacher, 2012; Robert and Baylis, 2003).[10] Second, there is a very broad and interdisciplinary debate around precaution and risks emanating from genetic engineering, that focuses on the question of public participation and ideal political deliberation (e.g. Thompson 2018; Stirling, Hayes, and Delborne 2018; adding consumer choice issues to the list, see Bechtold 2018) as well as particular ethical or legal discussions on the justification and scope of the precautionary principle (Bogner and Torgersen 2018; Braun and Dabrock 2018; Dürnberger, Pfeilmeier, and Schleissing 2019). Third, there is a debate on social and ethical issues of distributive justice in societies that for example engage in unequal human enhancement (e.g. Buchanan and Brock 2007), or in an agrarian economy involving GMOs (e.g. Toft 2012; or as socioeconomic example Wesseler and Zilberman 2014). A much discussed topic at the fringes of distributive justice are legal and ethical issues regarding biopatents (Ossorio 2008; Storz 2018; Tvedt and Forsberg 2017). While traditional ELSI research focuses on analyzing issues from within the frame of its traditionally constitutive (thus focusing on topics such as distributive justice, democratic participation, inherent dignity, etc.),

[10] The case of chimera research discussed below (3.3) involves similar considerations on the transgression of natural species boundaries.

the case presented here tackles issues starting from scientific classificatory practice – a longstanding topic of discussion in philosophy of science.

In regulatory contexts the debate focuses on the legal status of organisms altered by genome editing, as well as on the questions whether it is scientifically accurate to classify genome editing techniques as a category of mutagenesis techniques, and whether (some) genome edited organisms should count as GMOs (Sprink et al. 2016). The European GMO-Directive (2001/18/EC) regulates the deliberate release of GMOs, such as genetically modified crops in agriculture, but prominently excludes organisms produced by mutagenesis from its scope of application (Art. 3 i.c.w. Annex IA). If the concept of mutagenesis is interpreted as including genome editing techniques (which is possible, as such techniques only induce point mutations), these would be excluded from the regulatory scope of European GMO law (which governs labelling, monitoring, environmental and toxicology assessments, liability, etc.). The question thus has far-reaching implications for what is planted on our fields and served on our plates.

An example may serve to clarify this. Along with many other seedless crops, our typical supermarket banana (e.g. the 'Grand Nain' Cavendish cultivar or, more colloquially, Chiquita-style banana) is a clonally reproduced variety. Each banana tree is genetically almost identical to the next and the artificial induction of mutations has been the only productive way of increasing variability for better pathogen resistance (Oladosu et al. 2016). This has been done in the past decades with a variety of techniques of mutagenesis, such as exposing whole organisms to a radioactive source to induce random mutations up to more recent techniques using in-vitro cell culture and molecular markers. None of the resulting cultivars has been commonly viewed as a GMO by the consumer. In the past few years however, genome editing has come up as a new technology for introducing mutations, in particular to confer resistance for the

Cavendish banana against new threatening plant pests (Tripathi et al. 2020). But are the new cultivars obtained by genome editing to be considered GMOs, as they are created by means of a molecular technology? Would they have to be considered GMOs even if they were to carry only mutations which also could have been obtained by conventional means?

In the relevant legal commentaries, the term “mutagenesis” appears to refer to a technical concept with a clear-cut definition. However, the term is neither legally defined nor further delimited anywhere else in European GMO law. In such a case, interpretation (of a term that is not defined within the relevant legal body) should be based on its common meaning (Beck 2019; Wasmer and Robienski 2018). For scientific concepts arguably the common meaning is the technical meaning of the concept as used in the relevant area of science. In sum, the epistemological as well as ontological question here concerns the clarification of the concept of mutagenesis for legal appraisal and discussion.

However, there is no standardized solution to determining the meaning of technical concepts in the sciences – and this constitutes a deeper problem for biotechnology law. On the one hand, the interpretation of terms that are not further defined within the law requires formal definitions or at least contextual information that allows a clear-cut delimitation of the meaning of relevant terms. On the other hand, in the practices of in the life sciences many terms are used without being sharply defined and with their meanings evolving over time (prominent examples are concepts such as ‘gene’, ‘species’, ‘function’ and so on – see, e.g. Wieben 2003; Reydon 2004; Stotz and Griffiths 2004; Griffiths and Stotz 2006; Reydon and Kunz 2019). This simple insight – that terms in the life sciences are seldom sharply defined and change as science progresses – has been a longstanding topic of study in (integrated) history and philosophy of science, and is an important insight for drafting of future biotechnology law.

For the case of mutagenesis it quickly becomes clear that no formal definition is available. An extensive survey of relevant dictionaries of biology and genetics as well as a keyword search for relevant publications using the term ‘mutagenesis’ as a technical term reveals considerable variation of use across disciplines (e.g. between plant genetics and oncology) and across time. For example, in the 1970s the term was used only to designate natural processes of mutation. In the 1990s (at the time of drafting the European Directive) the term was used often as a technical term in genetic engineering, while nowadays it is used exclusively in this context. A contribution to the legal discussion (Wasmer and Robienski 2018) pointed to variations in the use of the term and proposed a dynamic interpretation of the term “mutagenesis”, using the extension of the concept in current literature on agricultural breeding techniques, as a solution to determining the relevant meaning of the concept for legal discussion.

It is worth noting that each approach to defining the meaning of ‘mutagenesis’ for the case at hand depends on a choice that involves weighing different epistemic and non-epistemic values. For instance, basing the interpretation of the term on the most current scientific literature may be motivated by the desire for inclusion of the newest available scientific knowledge and weighing it above cautionary concerns regarding safety of new technologies. A precautionary stance, on the other hand, may justify choosing a historical interpretation of the term set at the time of the drafting of the GMO-Directive. The latter excludes the newest techniques already by definition, whereas the former values scientific and societal change over the original will of the legislator. Hence, even a conscious and well-informed interpretation of the term ‘mutagenesis’ will entail value-based choices, which ideally should be made transparent when scientific expertise is employed for legal interpretation. Making such value-based choices transparent in the context of the clarification of scientific terms is a job *par excellence* for philosophers of science in the context of integrated ELSI projects.

After a lengthy debate among opinionated legal commentators the European Court of Justice (CJEU 2018) ruled that the mutagenesis exemption only applies to techniques of mutagenesis that were considered to have a long safety record prior to instatement of the law in 2001 (Beck 2019; Wasmer 2019). Thereby the court ended the discussion about the exemption of all new techniques of directed mutagenesis such as CRISPR-Cas9. However, it inadvertently made the quest for the meaning of the concept of mutagenesis additionally a question of history of science (Wasmer 2019) such that an appropriate conceptual clarification now also must involve a historical component.

This case study shows how (integrated) history and philosophy of science can develop normative bearing in the context of underdetermined legal terms. Beyond simply defining a term as part of a scientific ontology, further questions of a more normative nature become relevant in the case of clarifying a concept for legal appraisal and discussion: Who has the prerogative of interpretation of such terms? Is there a consensus on the scientific definitions of the concepts involved? How stable are the scientific concepts in time and across different contexts? Where do legal definitions diverge from a common meaning of the concepts and where do misunderstandings arise in making reference to scientific concepts in legal (and ethical) debate?

These are important epistemological and ontological issues in the discussion of ethical and legal aspects with relevance for the interpretation and drafting of biotechnology regulation. Philosophy of science brings an additional skillset to such work in biotechnology regulation that is an essential addition to the methods of either biology or law. The reason for this is that legal methods alone do not suffice to identify the meaning of "mutagenesis", precisely because the question emanates from underdetermination of the legal meaning. Methods from the natural sciences alone do not suffice either, because the meanings of scientific terms are not primarily empirical issues but rather issues involving theoretical, normative and historical aspects. Philosophers of science have long been engaged in the reflection on such issues.

Philosophy of science will equally be helpful in other cases in which legal interpretation depends on epistemological or ontological questions. This may be the case when laws have to be drafted in a way that permits admitting for future scientific developments, or when terms are unclear or contested in science. Examples include taxonomic definitions and judgments based thereupon (Garnett and Christidis 2017) and the definition of ecological parameters such as biodiversity (Garson, Plutynski, and Sarkar 2016).

3.2. Case II: Animal experimentation and the 3R principle

Our second case concerns the practice of animal experimentation and the so called "3R principle". Tens of millions of vertebrate animals are used for scientific purposes all over the world per year (Taylor et al., 2008).[11] Animals are used in basic research, applied research, drug development, safety testing and for many other scientific purposes. There is a strong consensus in the life sciences and science policy and among the general public that these numbers are much too high and we need to improve scientific research and safety testing to reduce animal suffering. This should be done

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[11] According to the latest official numbers on animal experimentation by the EU commission, in 2017 there were 9.39 Mio. vertebrates and cephalopods used for scientific and regulatory purposes in the EU alone (European Commission 2020).

according to the influential 3R principle introduced by Russel and Burch (1959). The principle states that we should attempt to *replace* animal experiments with alternative methods (or "non-animal-methods"), *reduce* the numbers of animals that we use for a specific scientific purpose ("more information per animal"), and *refine* animal experiments to improve animal welfare and to make animals suffer as little as possible.

There are many long-lasting normative discussions revolving around the 3R principle and animal experimentation more broadly. One of the key questions concerns the legitimacy of (certain forms of) animal experimentation. Today's mainstream position is that animal experimentation is morally defensible if and only if (1) the benefits (e.g. biomedical knowledge, new biotechnologies, product safety) outweigh the harms done to the animals and (2) there is no valid alternative to animal experimentation for the scientific purpose. Naturally, there remain many unresolved questions within the mainstream position, such as whether we should define some kind of upper limit for animal suffering (Beauchamp and Morton 2015), and how we should approach the difficult task of a rational harm-benefit-analysis given that this involves comparing incommensurable goods (Arnason and Clausen 2016; Grimm, Olsson, and Sandøe 2018). These unresolved ethical questions also arise in the regulation of animal experimentation, where they appear as inconsistencies regarding upper limits for animal suffering and vague guidelines for the analysis of harms and benefits (Beauchamp and Morton 2015; Smith et al. 2018). The regulatory context of animal experimentation and best ways to implement the 3R principle using legal tools are, therefore, much debated topics in ELSI research. Next to the ethical, legal and governance questions, there is a line of sociological ELSI research that investigates, among other things, assessments of the practicability of the 3R principle by scientists (Franco, Sandøe, and Olsson 2018), and the influence of animal rights activism on science policy and legislation (Munro

2012). These issues are important in their own right and the respective discussions have been essential for advancing the implementation of the 3R principle. We believe, however, that there a number of important, albeit hidden, epistemic aspects missing from the picture and want to draw attention to socio-epistemic aspects of the status quo that have been neglected but have normative relevance for the 3R discussion and the regulation of animal experimentation and non-animal-methods. In our view, these aspects can best be reconstructed and analyzed through the lens of philosophy of science.

The implementation of the 3R principle in science policy and (self-)regulation has, in conjunction with scientific and technological progress, in the last two decades generated many new ways to replace animal experimentation with non-animal-methods. Prominent examples include in vitro systems for assessing adverse effects of drugs, disease models based on human embryonic stem cells, organ(s)-on-a-chip-systems and sophisticated "read-across"-computer algorithms to predict toxicological properties of unknown chemical substances (see Butzke et al. 2013; Polini et al. 2014 for an overview). Despite these developments non-animal-methods have not led to an extensive replacement of animal experimentation. Some of the inhibiting factors put forward in the scientific literature are a lack of awareness and expertise regarding new non-animal-methods in the scientific community, intrinsic limitations of non-animal-approaches for some research purposes and an inadequate funding infrastructure for the development of a more comprehensive array of alternative methods (Gruber and Hartung, 2004; Meigs et al., 2018). Another reason that is highlighted in regard to basic and translational research is a high degree of "scientific inertia": there seems to be a relatively low level of active engagement of the scientific research communities in the development and use of alternative methods (Cronin 2017). Two standard accounts attempt to explain this state of affairs: (1) Scientists who are active in the non-animal-research community and/or are known to be sceptics with regard to the current animal research regime tend to explain the relative lack of engagement with dogmatic attitudes of animal researchers and "scientific resistance" to new methods (Gruber and Hartung 2004; Knight 2011: pp. 98f). (2) Scientists who regularly use animals in their research, on the other hand, are more likely to make the case that the observed scientific inertia is best explained by the indispensability of animal experiments for scientific progress. Non-animal-methods, they argue, are just not as developed as their proponents like to believe and, hence, cannot replace many kinds of animal experiments (yet) (e.g. Barré-Sinoussi and Montagutelli 2015).

It matters for the normative assessment of the status quo who is right here (and to what extent). However, it is not obvious which side to pick, which is why ELSI researchers cannot – or rather: should not – take any side for granted in their research. In this situation, a philosophy of science perspective will be extremely helpful in providing an independent and critical analysis of the situation. Such an analysis would take scientific practice and its epistemic aspects seriously without taking the self-assessments of scientists at face value. There are two (socio-)epistemic aspects of animal-based research that seem to be particularly important if one is to shed some new light on the issue in question, namely (a) secondary epistemic functions of animal models, and (b) the socio-epistemic logic of risk management in the life sciences. In the following, we will focus on these aspects to indicate in what way philosophy of science can be illuminating for the 3R discussion.

Animal models serve a number of epistemic purposes in the life sciences (Weber 2014; 2018), including exploratory research, developing and testing hypotheses about biological mechanisms, animal-to-human extrapolations and many other things. Recent research in philosophy of science has, however, highlighted a number of purposes or functions of animal models that seem be somewhat different (Ankeny and Leonelli 2016; Hardesty 2018; Levy and Currie 2015). Animal models also have what we call secondary epistemic functions for life science research communities.[12] Here are three examples.

(1) Animal models can have a paradigm-like function for research communities. Certain mouse models, for instance, are often used to study cancer immunotherapy. In a common procedure, immunodeficient mice get engrafted with human tumor tissue to study the effects of different kinds of treatment. This general procedure can serve as a blueprint for similar research projects. Researchers can use different immunodeficient mouse strains, or mouse models with humanized immune systems, or humanized mice with individualized immune properties; they can experiment with different kinds of tumor tissue, try different forms of immunotherapy and so on (see Choi et al. 2018 for an overview). The upshot of this is that specific animal models and standard research procedures applied to them provide research puzzles to solve and, at the same time, offer implicit guidance on how to solve these. Animal models can, in other words, be important in defining the problem space and a corresponding research perspective in an area of research.

(2) A closely related function of animal models is that they are important in establishing shared techniques/methods and standards in various sub-disciplines. There are, for instance, standard protocols for antibody production in rats or mice (e.g. Kishiro et al., 1995). And animal models can display certain characteristics that may serve as a

[12] Strictly speaking it the *use* of animal models as key elements in “repertoire-like systems of scientific practice” that manifests these functions (see Lohse 2020 for a more detailed analysis).

benchmark for scientific success, e.g. a phenotypic response by mice or rats in reaction to a new drug is often considered important in biomedical research (Huber and Keuck 2013).

(3) Finally, animal models and their surrounding infrastructure can function as anchors and stabilizers for research communities on a more institutional level. First of all, research communities tend to align themselves with certain animal models (Lewis et al. 2013). Moreover, there exist animal-based communication and knowledge hubs for researchers (such as the Mouse Models of Human Cancer Database, http://tumor.informatics.jax.org/mtbwi/index.do), which provide a digital infrastructure for sharing knowledge on an international level. Professionalized providers for standardized, high quality animal strains (such as Jax Mice & Services, https://www.jax.org/jax-mice-and-services) and companies that specialize on the creation of transgenic animals (such as PolyGene Transgenics, https://www.polygene.ch) have an additional stabilizing effect on research communities via the robust deployment of standardized resources for experimental work.[13]

These secondary epistemic functions of animal models contribute to the establishment of a joint research perspective/agenda, stabilize research communities in the life sciences and promote scientific progress. At the same time, their working together generates scientific and infrastructural path dependencies and is likely to convey a strong sense of indispensability of animal experimentation in the relevant scientific research communities.

Scientific progress is always uncertain, though, and in many cases it is unclear whether a new and promising line of research or method will turn out to be more

[13] See Ankeny & Leonelli (2011) for the case of model organisms.

successful in dealing with a persistent scientific obstacle than established lines of research and methods. An important epistemic reason for this is that new and promising approaches can always fail and that traditional approaches can always turn out to be flexible (or "upgradable") enough to overcome given scientific problems. Kuhn (1977) and D'Agostino (2010) have shown that scientific communities address this dilemma by using a "risk-spreading strategy". In light of persistent obstacles in research some researchers try to modify existing approaches ("the traditionalists") while others attempt to develop or apply new, alternative approaches to the problem ("the iconoclasts"). Although only one of the approaches might be successful in dealing with a given scientific problem and the others might fail, the scientific community as a whole is more likely to be successful this way.[14] In our context, the traditionalists' approach is based on animal experimentation, so it is important to note that the epistemic usefulness of animal models in experimental settings is not fixed. If anything, their epistemic flexibility seems to be quite high. First of all, animal models, although standardized organisms, are extremely complex natural systems to be *explored*; i.e. animal models can in many cases act as "generators of surprises" in that they yield new and unexpected properties (after scientists have had (more) time to interact with them and to tinker with the experimental systems of which they are an element) (Rheinberger 1997; Weber 2014). Secondly, the scientific questions that can be investigated using animal experimentation very much depend on the available technologies and tools in the life sciences and, hence, are also not fixed. Examples for "disruptive technologies" that opened up new epistemic opportunities include new imaging technologies (such as

[14] This description is not *completely* in line with Kuhn's and D'Agostino's ideas (see Hoyningen-Huene and Lohse 2011), but it is very much inspired by them.

fMRT) and gene-editing technologies (such as CRISPR-Cas9) that can be used to create, amongst others, fluorescent zebrafish for in-vivo tracking or mice with humanized immunological properties for biomedical research.

The risk-spreading strategy seems to give life scientists very good *epistemological and methodological* reasons for pursuing the traditionalist animal-based approach next to (new and promising) non-animal-approaches. What is more, the epistemic flexibility of animal models seems to incentivize holding onto traditional forms of animal experimentation to a special degree. From a purely epistemological point of view, it would be risky to discontinue animal experimentation as it has in many cases turned out to be a highly adaptable research approach.

This sketch of (socio-)epistemic aspects of animal-based research offers a fruitful perspective on the status quo of animal experimentation. It provides an illuminating explanation of the relative low level of engagement of the scientific community in the development and use of non-animal-methods. This explanation, though in need of further elaboration, is rooted in widely-accepted insights from (a historically informed) philosophy of science. It helps to uncover scientific inertia as a consequence of the general logic of life science research, and it makes the above-mentioned opposing impressions of “scientific resistance” vs. “indispensability of animal research” appear in a new light: There are good reasons for sticking to a traditional research approach in an attempt to modify or upgrade it, although this can (from the outside), appear to be nothing more than dogmatism; and working within the current animal research regime (and being subjected to the described research-stabilizing secondary epistemic functions) can lead scientists to the impression that animal models are indispensable, not only within current practice, but for doing life science research *per se*.

Our account immediately suggests a number of normative questions regarding the 3R principle, the (self-)regulation of science and related issues: If we want to accelerate the replacement of animal experimentation in basic and applied science, how can we do justice to the epistemic complexity of the situation, and which stakeholders need to be on board for systemic change? To what extent would a stricter regulation of animal experimentation (as, e.g. in the Netherlands) need to take the risk-spreading strategy in science into account? How should a rational science policy regarding animal experimentation deal with trade-offs between epistemic values and ethical demands? Addressing questions like these is important for a well-informed discussion of opportunities and limitations of animal experimentation, and it is crucial for a more efficient regulation of animal experimentation. It is the integration of philosophy of science into ELSI and related research that enables us to identify and to address these issues in an appropriate manner – a manner that is sensitive to the (socio-)epistemic details *and* to the normative implications of animal-based research.

3.3. Case III: chimera research

Our third case concerns the creation of chimeric organisms. As living beings that incorporate genetic or bodily material from multiple species, chimeras are widely met with discomfort or even outright rejection. Much of this discomfort is due to lack of clarity regarding the question what chimeric beings *really* are, that is, to which groups in the whole realm of biodiversity they in fact belong. For example, are human-animal chimeric embryos a kind of human embryos, or non-human animal embryos, or a category *sui generis*? And if they are human embryos, should we treat them as *fully* human embryos, enjoying the same rights and the same protection as regular human embryos, or does their partially non-human nature give them lower degrees of protection and fewer rights? Both ethically and legally, such questions are important – and they result from questions regarding the classification or chimeric beings.

Another often heard argument, in particular in earlier debates, is that the production of chimeras is ethically problematic because is consists in the transgression of presumed natural boundaries between species and in violations of the natural integrity of species. That is, the boundaries between species, in particular between the human species and other animals, are "given" by nature and disrupting the natural order by technological means is something we aren't allowed to do. Such ways of arguing are found for example with authors who argue in a religious context, authors who argue on the basis of human dignity, and as a "gut feeling" with the general public (for a recent review of the literature, see Kwisda et al., 2020; furthermore: Hübner 2018; Mirkes 2006; Schaub 2006; Robert and Baylis 2003; Streiffer 2003; Comstock 1998). In such a way of arguing, too, ethical, legal and social issues arise due to classificatory issues – albeit that here it is no lack of clarity about the classification of chimeric beings, but rather assumptions about there being fixed boundaries between species.

Both kinds of argumentation rest on the assumption that biodiversity comes in fixed, well-delimited groups – that there is a natural order in the living world. The assumption is that species exist as groupings of organisms that are "given" by nature, that have fixed boundaries that are not transgressed in nature (but might be transgressed by us using particular technologies) and that every organism has its proper place in nature as a member of one species. An open question, though, is whether such an assumption should indeed give rise to the aforementioned ethical concerns, and in what way it could legitimately give rise to ethical concerns at all.

Here we highlight research that answers this question and can be seen as a "best practice" example of the sort of integrated research that we suggest should be done more generally, namely Robert & Baylis's (2003) widely cited paper on the topic and extensions of Robert and Baylis's work by other authors. We also show how this work can be extended further.

Robert and Baylis suggested that four main categories of the production of chimeras can be distinguished: human-to-animal chimeras (created by e.g. inserting human cellular material into non-human animal embryos), animal-to-human chimeras (in which the authors notably include human recipients of animal organs by means of xenotransplantation), human-to-human chimeras (where the authors include recipients of conventional organ transplants as well as recipients of stem cells from other humans in stem cell therapy), and animal-to-animal chimeras.[15] This fourfold categorization of chimeras provides us with a theoretical framework that allows a deeper analysis of ethical, legal and social issues than would have been possible when simply considering these issues *tout court*.

Robert & Baylis's categorization clearly highlights an easily overlooked issue in the debate: that the four overarching categories of chimeric organisms are perceived as problematic to different extents and for different reasons. The focus of ELSI debates so far has been on the acceptability of human-to-animal and animal-to-human chimeras (e.g. Mizuno, Akutsu, and Kato 2015; Hyun 2016). Human-to-human chimeras are widely perceived as unproblematic and any ethical issues involving human-to-human organ transplantation are discussed as an issue *sui generis*. That is, human-to-human chimeras are not typically seen as giving rise to ethical problems due to their nature as chimeric beings but ethical problems are seen as originating elsewhere (e.g., questions

[15] Next to these four categories of chimeras, Robert & Baylis distinguish hybrids and transgenic animals as additional categories of controversial living beings. Here, we will not consider these.

regarding fair allocation of organs intended for transplants; the question whether harvesting organs after death requires a declaration of consent from the individual, or the absence of a declaration of refusal would suffice; and so on). Most people would probably not even think of a human who has received an organ from someone else as an actual chimeric being at all (even though from a strictly scientific perspective they are). The category of chimeras is usually thought to encompass organisms created by transfer of material between organisms of *different* species, i.e., human-to-animal, animal-to-human, and animal-to-animal (as long as two different animal species are involved).

Robert and Baylis's work thus shows that what lies behind ethical worries regarding the production of chimeras is connected to the species identities of the organisms involved in the making of chimeric beings. The problem is not so much that organisms carry (genetic or tissue) material that is not originally their own, but that they carry material that "belong" to different species. As Robert & Baylis (2003, p. 2) observe, the "the prevailing view appears to be that species identity is fixed and that species boundaries are inappropriate objects of human transgression." But they go on to point out that such assumptions about fixed boundaries between species, and about species having intrinsic natures, are in conflict with the current (as well as older) state of knowledge in the biological sciences, such that these assumptions cannot in fact support the ethical concerns that often are thought to follow from them.

Robert and Baylis, however, do not hold that the creation of chimeric beings should not give rise to *any* ethical concerns. Rather, they argue that that ethical debates on chimera research are driven by an "inexorable moral confusion" that results from profound lack of clarity regarding to how chimeric beings should be classified. The argument is that the introduction of moral categories (chimeras, the moral status of which is debated) that fail to connect to biological categories (species, the moral status of which is presumed to be clear) causes deep confusion regarding how chimeras should be treated. Lacking stable reference groups that support moral categories, there is no way of determining whether the moral categories we use in the debate are well-founded. This point could only be made by making strong connections to the large literature on classificatory issues in the philosophy of biology and in biology itself – and in this sense Robert and Baylis's article exemplifies how work in the philosophy of science can be crucial for assessing whether ethical concerns are well-founded.

In what follows, we show how such an analysis of ethical concerns by using results from philosophy of science can be extended. Thinking of chimera research as transgressing naturally given species boundaries presupposes clarity on what biological species *are* and in what ways their boundaries might be given by nature. Historians and philosophers of biology (as well as philosophically inclined biologists) have long addressed these issues, with a result that calls such presuppositions of clarity into question. Currently, more than 20 definitions of the term "species" are available in the literature. These give different accounts of what species are, what makes individual organisms members of "their" species, and how the boundaries of species are delimited (Reydon and Kunz 2019; Ereshefsky 2014; Wilkins 2011; 2009; Mayden 1999; 1997). Different definitions sometimes lead to very different assessments of the number of species that exist in a particular geographic region or in a particular domain of biodiversity (Reydon and Kunz 2019; Reydon 2019; Agapow et al. 2004). In biological research practice, multiple definitions of the term "species" are used and we are very far removed from a general agreement on a preferred definition, or on the question what species *really* are. As already mentioned above, many concepts in the life sciences are not sharply defined and undergo profound changes in meaning as science progresses. The notion of species is one of the concepts that is perhaps the most problematic in this respect. It is safe to say that the assumption that species boundaries are unequivocally given by nature stands on a very weak footing, as Haber and Benham (2012) have also pointed out. Rather, species boundaries should be seen as made by us – i.e., taxonomists are the ones who sort organisms into species – on the basis of various aspects of the living world that we intend species to represent (Reydon and Kunz 2019). Or, as Ankeny put it, "our working notion of fixed species boundaries is just that: a working model that allows biologists to get on with their work" (2003, p. 32). But then concerns about alleged transgressions of natural species boundaries do not make much sense.

The same holds for presuppositions that species or their member organisms have an inherent nature that *all* members of the species share, and that is *only* shared by members of the species. Fox, for example, put it thus: "Genetic engineering makes it possible to breach the genetic boundaries that normally separate the genetic material of totally unrelated species. This means that the telos, or inherent nature, of animals can be so drastically modified […] as to radically change the entire direction of evolution" (1990, p. 32).[16] On this assumption, creating chimeras from material from organisms of different species would amount to mixing the natures (or essences) of different species, thus somehow causing the evolutionary pathway of the species to go off its natural track. While genetic engineering of course does affect the future evolution of the population, the assumption that a species has an inherent nature that determines its natural course of evolution is mistaken. Moreover, what would such natures consist in? The assumption here seems to be that the inherent nature of a species consists in the genetic makeup that all a species' member organisms share, but biological research has

[16] Fox's claim pertains to genetic modification and genome editing, not to the creation of chimeric beings, but the discussion exhibit strong parallels and involve very similar conceptual issues.

long ago shown that this assumption is flawed: for all species there is a large genetic diversity among the organism of one species, while at the same time there are large genetic similarities between different species (with larger similarities between closely related species). In a response to Robert & Baylis's paper, Haber & Benham (2012) address this issue. Haber & Benham deepen the conceptual analysis by showing that the assumed connection between moral and biological categories is highly problematic, as it rests on essentialist views of species that deeply conflict with the current state of biological knowledge (see Ereshefsky 2014, for an introduction to the literature on this matter). Thus, they strengthen Robert & Baylis's analysis by adding still more considerations from the philosophy of biology.

The preceding discussion shows how work from the history and philosophy of biology – in this case the historical and philosophical analysis of the scientific term "species" and of the foundations of biological classification – helps ELSI research as well as the public debate by providing insight into how well-founded (or not) particular concerns regarding specific technologies actually are. It shows how connecting the ELSI debate on chimeras with the long-standing debate in the philosophy of biology on the nature of species brings aspects of the debate to light that would have remained overlooked otherwise. The role of history and philosophy of biology in the chimera debate is to clean up misconceptions that have their roots in how we as human beings tend to perceive the world: as ordered into well-delimited kinds of things (kinds of chemical substances, kinds of rock, kinds of fruit, kinds of trees, kinds of animals, and so on) that all have something internal or innate to them that makes them into what they are. Philosophical analysis of classificatory concepts shows that the world is not as well-ordered as it often seems to be and that some of our commonplace assumptions about what the world is like are mistaken. Examining central assumptions behind our concerns about certain technologies shows these concerns to be unfounded, but also shows how they arise in the first place (i.e., as a result of moral confusion). Such an analysis clears the way for a more subtle and more adequate examination of why the creation of chimeric beings could be problematic.

One way in which integrated research could build on Robert & Baylis's (2003) work is by refining the categories the authors use. The highlighting of humans and nonhuman animals as the two relata in the "transfer from … to …" relation in Robert & Baylis's (2003) paper serves the authors' purposes by reflecting widespread ethical worries: animal-to-animal chimeras could be problematic as they affect sentient beings that might suffer from the procedures they are subjected to or from being a chimeric being, while human-to-animal and animal-to-human chimeras could be problematic for those reasons and because they affect *our* species. But the framework can easily be extended to other parts of biodiversity: plants (where natural hybridization is common, and artificial hybridization in agriculture is common practice), fungi, and prokaryotes (where horizontal gene transfer between different species is not uncommon). Strictly speaking, for example, Bt-corn plants are chimeras (even though the amount of genetic material from *Bacillus thuringiensis* inserted into *Zea mays* is very low). Acknowledging that there are many more actual and potential categories of chimerism – e.g. prokaryote-to-plant chimeras, plant-to-plant chimeras, animal-to-plant chimeras, human-to-plant chimeras, prokaryote-to-human chimeras, prokaryote-to-prokaryote chimeras, etc. – will probably make it even more clear that ethical, legal and social concerns regarding chimera research are not linked to the creation of chimeric beings *per se*, as not all categories are equally perceived as problematic. Rather, they presumably are linked to more specific worries concerning technologies that affect our species, that affect sentient beings, that affect agriculture and the environment, etc.

Thus, an extended categorization should yield more subtle discussions of the actual concerns, such as harming sentient beings, harming the environment in which chimeric plants grow, potentially creating “super-bacteria” that we cannot keep under control once they have been realized, etc.

An additional extension could also take into account the fact that not all animals are equally sentient beings or are equally capable of suffering: many animals are not sentient in any relevant sense at all. Pig-to-gorilla chimeras would in this respect give rise to very different concerns than flatworm-to-roundworm chimeras. In addition, it is worthwhile to highlight that chimeric beings also occur naturally (i.e., hybrid organisms such as mules), such that chimeric beings should not be ethically problematic *merely* because they are chimeras. Robert & Baylis’s framework, then, is an excellent first step towards a better, deeper and more subtle debate on the acceptability of chimera research, as it allows us to connect ethical, legal and social concerns to specific kinds of chimera production. The further development of their work must involve work in the (integrated) history and philosophy of biology (for instance on the question of animal sentience, or the way in which hybrid organisms are usually grouped in relation to their parent species). Thus, we suggest, the case of chimera research shows how history and philosophy of science played and must play a crucial part in achieving more clarity on the normative aspects of this area of research, and why these areas of the humanities should be an integral part of further ELSI research on this topic.

4. Conclusion: From ELSI to E^2LSI

Let us re-evaluate our initial claims in light of the presented mini case studies. All three cases show that research on ethical, legal and social issues is concerned with fundamental normative questions that either are to a significant extent dependent on epistemic issues or have a significant epistemic dimension. Therefore, these normative questions cannot be adequately addressed without in-depth clarification of the epistemic issues involved – which is the proper purview of philosophy of science. In case I the question of the legal status of genome-edited organisms is shown to crucially depend on epistemic considerations regarding the nature of scientific terms – specifically the term "mutagenesis" and its varied history and use. Case II illustrates how existing perspectives on ELS-issues of animal experimentation must be supplemented by completely new avenues of normative analysis for ELSI research based on an analysis of scientific practices involved in animal experimentation. Case III is a best-practice example in which the relevant epistemic issues *were* to some extent taken into account. This case shows how connecting an ELSI debate to relevant debates in the philosophy of biology helps to uncover certain concerns as unfounded, and it also shows how the available research can be extended into a more fine-grained conceptual structure with which the foundations of ongoing debates on chimera research can be assessed. Each of these cases thus shows ways in which ELSI research can benefit from (more) philosophy of science.

Note, though, that even though we have only argued that ELSI research needs to incorporate the results from work done in the philosophy of science, we want to suggest that *both* sides will benefit from closer interaction. The philosophy of science will also benefit from closer connections with ELSI research in several ways. First, closer connections to ELSI research will likely open up new avenues for research in the philosophy of science by bringing new topics for investigation to the attention of philosophers of science. This will both increase the scope of topics that philosophers of science work on and increase the relevance of philosophy of science for other parts of academic scholarship. It will however also contribute to increasing the relevance of philosophy of science as an academic (sub)discipline for areas outside academia. Recently, philosophers of science have begun to explore ways to make their field of work more socially relevant due to "a keen sense of missed opportunities for philosophy of science to have a broader social impact" (Fehr and Plaisance 2010, p. 301).[17] This has resulted in institutionalized efforts to increase the social impact of scholarly work in the philosophy of science, such as SRPoiSE (the *Consortium for Socially Relevant Philosophy of/in Science and Engineering* – see http://srpoise.org), SEPOS (the *Socially Engaged Philosophy of Science* group at Michigan State University – see https://sepos.cal.msu.edu), and the E^2LSI group (at Leibniz University Hannover's Centre for Ethics and Law in the Life Sciences – see https://www.cells.uni-hannover.de/e2lsi). Closer connections with ELSI research (which scholars in the aforementioned groups are already actively seeking to establish) will clearly further the aim of making philosophy of science more socially relevant.

Because of these expected benefits for philosophy of science, but more importantly because philosophy of science is the go-to-discipline for understanding and reflecting on the (socio-)epistemic aspects of science, philosophy of science should be systematically and routinely integrated into ELSI (and related) research. One could for instance think of research programs that address *E*pistemic, *E*thical, *L*egal and *S*ocial *I*ssues in the life sciences in an integrated manner – that is, the systematic

[17] See also the special issue of *Synthese* on "Making Philosophy of Science More Socially Relevant" (Vol. 177, Issue 3, guest edited by Plaisance and Fehr), Cartieri and Potochnik (2014) or Elliott (2018). In the mentioned special issue, Tuana argued that philosophy of science can increase its social impact, highlighting the "contributions philosophers of science can make to an enriched understanding of the complexity of the ethical dimensions of scientific research, to policy-relevant science, and to epistemically and ethically adequate science based policy" Tuana (2010: pp. 489-490).

transformation of ELSI research into E^{2}LSI research (from which topics for research as well as results would be fed back into philosophy of science more broadly). This demand does not only hold for the discussed examples but also for similar cases, i.e. for cases where the analysis and clarification of epistemic elements of scientific practice has the potential to reveal aspects with hidden normative dimensions or implications.

While we have provided arguments for a transformation of ELSI into E^{2}LSI research, we have not addressed the question *how* such a transformation could take place. We will conclude by briefly addressing this issue. Primarily, because of the differences between the involved areas of science, technologies and applications, and in the ELS-issues that arise with respect to the different technologies and applications, there can be no one-size-fits-all way of establishing an integrated E^{2}LSI approach. The ELSI debate on, say, genome editing in plants, differs fundamentally from the debate on, for instance, the use of genomic testing in personalized medicine or by health insurance companies. The technologies are different in important respects, the biological knowledge base on which these are founded in part differs between cases, the applications are different, and therefore the ethical, legal and social issues under debate are different. When considering ELSI debates on highly divergent technologies, e.g. chimera research and nanotechnology, the differences in the issues that are addressed are even larger. Therefore, we are *not* suggesting that ethicists, theologians, social scientists, legal scholars, philosophers of science, historians of science, and so on, should join forces at a *global* level: we are not pleading for a merging of fields of research. What we are suggesting, rather, is a joining of forces by researchers from relevant fields at a *local* level – i.e., that the integration of relevant fields into E^{2}LSI should take place on an *issue-driven* basis.

Starting with a specific debate, the broader community should first identify which areas of science and the humanities, and which aspects of these areas of research, are relevant to the issue under debate. This means that work on different ELS-issues calls for the participation of researchers working on different specialized topics in the philosophy of science, and research teams should be assembled on an *ad hoc* basis, bringing in expertise required for the issue under consideration. Note that philosophy of science is not special in this respect – the same holds for ethics, theology, social science, legal scholarship, and so on, as different issues require different expertise. Thus, what we are advocating is a view of E^2LSI research in which scholars from relevant areas come together into integrated interdisciplinary research teams to work on specific issues, with different teams addressing different issues. We do not aim to provide overarching guidelines for how such teams should be established, however. Our proposal merely implies that researchers on the normative dimensions of science and technology should be deeply aware of the epistemic aspects of the topics they address and take time to reflect on potential contributions of pertinent fields (such as philosophy of genetics or philosophy of animal research). It will prove to be essential, in many cases, to integrate (relevant parts of) philosophy of science with ELSI research into interdisciplinary E^2LSI projects[18] in which the history and philosophy of science is positioned on an equal footing with the other fields of scholarship that participate in such projects.

[18] While we have only discussed ELSI research, educational aspects should also be taken into consideration, for example in the form of bespoke E^2LSI modules in graduate programs, in postdoctoral training and in the continuing education of advanced scientists.

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