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How should we regulate products of new breeding techniques? Opinion of surveyed experts in plant biotechnology

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ABSTRACT

The adoption of genome editing depends among others, on a clear and navigable regulatory framework that renders consistent decisions. Some countries like the United States decided to deregulate specific transgene-free genome edited products that could be created through traditional breeding and are not considered to be plant pests, while others are still challenged to fit emerging technologies in their regulatory system. Here we poll international experts in plant biotechnology on what approach should nations agree upon to accommodate current and future new breeding technologies and derived products. A key finding is product-based models or dual-product/process systems are viewed as potential appropriate frameworks to regulate outcomes of genome editing. As regulation of novel products of biotechnology is expected to impact research and trade, we test the impact of experts' worldviews on these issues. Results show that region influences worldviews of trade but not of agricultural innovation. In contrast, there was no effect of experts' worldviews on how products of novel biotechnologies should be regulated.

1. Introduction

Owing to advances in crop genetics, breeding efforts can potentially be reduced from approximately 7–25 years to as few as 2–3 years [1]. Site-specific genome editing approaches, spear-headed by clustered regularly interspaced short palindromic repeats (CRISPR), can be designed in a matter of weeks, if not days, and in the most economical case, for as little as 10 [1,2]. In less than a decade after CRISPR/Cas9 was first applied, genome editing—a subcategory of new breeding technologies (NBTs)[1] —has moved to the cusp of contributing to large-scale crop improvement [3,4]. However, for this occur, regulatory and social hurdles still need to be overcome [5]. That is, NBTs including genome editing, have revived tensions between process- and product-focused regulatory frameworks. The Atlantic Ocean once again serves as a major regulatory fault line separating the European Union (EU), a proponent of process-based regulations, and Canada, the United States (US) and Argentina, along with others, all proponents of the latter [5]. Given that NBTs may both introduce recombinant deoxyribonucleic acid (DNA) or could simply reorder the existing genetic structure [6,7], the debate around NBTs will be more complex than the debate on transgenic, genetic modification (GM). The possibility that multiple techniques can be used in combination reduces the adequacy of a comprehensive, one-size-fits-all regulatory approach. As genome editing is not a single technology but rather a molecular toolbox capable of yielding a spectrum of genomic changes, process-based regulation will be difficult. Product-based regulation, which is triggered by and assesses the nature of changes, the targeted crop variety, the new traits, and the environmental and societal impacts offers a pathway forward [8].

This paper presents the results of a survey of biotechnology experts on their views on whether the regulatory system needs to be reformed to accommodate existing and possible future NBTs and their resulting products. Non-governmental organizations (NGOs) are not within the scope of this study as they do not develop new crop varieties, nor do they make risk decisions based on the submitted data required to conduct a rigorous scientific risk assessment. A number of countries including the US [9] and EU [10,11] are proposing amendment and revision to existing

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[1] A comprehensive list of these techniques can be found at: https://op.europa.eu/en/publication-detail/-/publication/103eb49f-4047-11e7-a9b0-01aa75ed71a1/language-en/format-PDF/source-39042023

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regulations governing biotechnology. Polling knowledgeable experts (politicians, academics, physicians, etc.) has provided decision-makers with a trove of information for uncertain events where empirical data are lacking, and for emerging, complex and poorly understood problems [12,13]. Unlike the general public, experts are deemed most likely to offer insights into future events as they hold certain knowledge or extensive scientific information on specific subjects [2]. However, it is possible that decisions of experts—like other human beings—could be biased for a range of reasons, but especially under uncertainty which triggers a range of cognitive responses [14]. One particular source of bias is how people view the world, otherwise known as their 'worldview'. We test whether the worldviews of experts intervene in their opinions on regulatory decision-making. As the concept of worldviews is wide-ranging, we focus on those related to agricultural innovation and international trade—two matters that will be affected by how we regulate products of NBTs, including genome editing [5,10,15].

The remainder of the article is laid out as follows. First, we outline the regulatory status of NBTs worldwide, followed by a brief overview of the concept of worldview. Then, we explain our research design, including a discussion of the method employed in the study. Results are then reported, with a discussion of the implications of the findings, followed by concluding thoughts.

2. Novel breeding technologies and regulation of their use

The most common applications of NBTs use programmable nucleases to induce targeted (site-specific) DNA double strand breaks, and take advantage of DNA's natural repair mechanism to introduce desired modifications [16–18]. The three most common nucleases for genome editing are zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and Cas9 (part of the CRISPR mechanism). Most media, scientific and regulatory attention has focused on site-specific mutagenesis. However, as more plant genomes are sequenced, and plant physiological comprehension increases, more NBTs and variants thereof can be expected. For example, Klewer and Wu [19] discuss optogenetic systems, which use light to induce changes in genes, that can be coupled with CRISPR and some of its nucleases to genetically engineer an organism [see 20]. The debate about NBT regulation is complex, and is poised to become more so as the technology advances.

Genome editing technologies show tremendous potential for the rapid and precise improvement of crops and livestock. They can target nutrition (e.g. soybeans with healthier fatty acids) as well as productivity, including low-pesticide and sustainable agriculture traits (e.g. bacteria-resistant rice, fungus-resistant wheat, drought-tolerant corn) [10]. Whether this potential will be realized remains unclear, as experts and stakeholders disagree on how genome editing should be regulated [21]. It is becoming apparent that clear and navigable regulatory frameworks will determine whether genome editing contributes to food and nutritional security, climate change mitigation and prevention of further environmental degradation [22–27]. For the purposes of this discussion, regulation refers to rules, orders, norms and principles that are enacted by governments to prescribe or proscribe technological development [28]. Governments around the world have begun taking clear stances on NBT regulation and products derived from them; below we summarize the regulatory approaches various governments have reported.

2.1. European Union

Interestingly, although the EU's regulatory system is dual stream, with both process- and product- focused elements, it has been predominantly interpreted as a strict process-focused system [29]. This interpretation was amplified on July 25, 2018, when the Court of Justice of the European Union (CJEU) ruled that site-specific, targeted mutagenic crops should be subject to the EU's regulatory system in the same way as other GM organisms [30]. That is, the Court found that within the meaning of Article 2(2) of Directive 2001/18, all organisms obtained by mutagenesis are GMOs, in so far that the mutagenesis technique and method used to alter genetic material do so in a way that does not occur in nature.[2] This is made clear in Paragraph 29 of the CJEU judgement [30], where the Court reasons that certain techniques "alter the genetic material of an organism in a way that does not occur naturally." In essence, regardless of the genetic result, any unnatural process will deliver a GMO. Through the EU's regulatory framework, all genome edited plants are subject to regulation (be they developed by ZFNs, TALENs or CRISPR). While the CJEU ruling establishes regulatory certainty for products of site-directed mutagenesis, assessment of products of other NBTs is still ongoing. Many experts argue for amendments to the European genetic legislation including a revision of the GMO definition [10].

2.2. Canada

Agricultural crops and plants of biotechnology are subject to regulation of the product, not the process through what is known in Canada as plants with novel traits (PNTs)[3] . Canada's approach to all genome editing technologies is the same as for all technologies that have preceded it, in that regardless of the technology used to create a novel product Canada's PNT regulations are triggered. No standard or formal definition for what constitutes novel exists; each is negotiated in the context of the plant and its uses in Canada. Typically, if the specific trait expresses higher or lower than conventional varieties, then Canadian plant breeders contact regulators to determine the applicability of PNT regulations for that specific case. Novelty is largely defined by the plant breeding community. PNT regulations apply to all plant varieties possessing a novel trait, regardless of how they were developed. With this regulatory framework, Canada has already approved three GM genome edited products: non-browning apples (Golden Delicious and Granny Smith varieties), the Innate Potato [32] and two varieties of genome-edited herbicide tolerant canola, but only one has been commercialized [33].[4]

2.3. United States

In 1986, the US implemented a Coordinated Framework for the Regulation of Biotechnology to assess and regulate the products of biotechnology. The framework describes the roles and responsibilities of the Environmental Protection Agency (EPA), the United States Department of Agriculture's Animal and Plant Health Inspection Service (USDA-APHIS), and the Food and Drug Administration (FDA) [34]. These three government agencies are responsible for oversight of the products of agricultural modern biotechnology. Depending on its characteristics, a product maybe be subject to the jurisdiction of one or more of these agencies.[5] The underlying principles of the coordinated framework are that the product and not the process should be the focus of regulation, and that regulations should be based on 'sound science'. In 2016, these principles were reaffirmed when the USDA determined that a

[2] https://curia.europa.eu/jcms/upload/docs/application/pdf/2018-07/cp180111en.pdf

[3] http://www.inspection.gc.ca/plants/plants-with-novel-traits/eng/1300137887237/1300137939635

[4] https://www.cibus.com/crops.php

[5] https://www.aphis.usda.gov/aphis/ourfocus/biotechnology/sa_regulations/ct_agency_framework_roles

CRISPR-edited mushroom could be cultivated and sold without going through the agency's regulatory process [35]. Given that the CRISPR-based mushroom involved small deletions (1–14 base pairs) but no foreign DNA insertion, APHIS concluded that this modification did not involve plant pests and therefore did not fall under its scope of regulation. Numerous other genome edited crops, both publicly and privately developed, have been approved by the USDA, including corn, soybeans, wheat, tomatoes and rice, amongst others.[6] In 2019, the USDA proposed the revision of regulations regarding the movement (importation, interstate movement, and environmental release) of certain genetically engineered organisms, as a result of advances in biotechnologies and comprehension of plant pest risk these might entail [9]. The underlying philosophy of the proposed revision, is to reduce the regulatory burden for developers of novel genetically engineered organisms that are unlikely to pose plant pest risks. This proposed revision to regulations reaffirms the US supports a progressive risk-based regulatory framework for genome editing [36].

2.4. Argentina

Argentina's regulatory framework explicitly addresses products obtained from NBTs [37]. After a three year-long debate that examined the technical aspects of NBTs, the resulting framework considers genetic manipulation on a case-by-cases basis [38]. Underpinning this framework is Resolution 173/15, which establishes a procedure to determine whether a product derived from NBTs is considered under Resolution 701/11 to be a GMO [see 37 p. 29] [37]. Resolution 701/11 defines a "Genetically Modified Plant Organism" as "as any vegetable organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology," analogous to the Cartagena Protocol on Biosafety (CPB) definition of a "Living Modified Organism" which is "any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology." Thus, Regulation 173/15 does not modify pre-existing regulations regarding GM plants, rather, it clarifies whether a crop/plant obtained through NBTs is subject to pre-existing GMO rules and regulations [37]. It is important to note that both Argentinian regulations, and the CPB, define biotechnology in the same manner. Other important aspects of the Argentinian framework are that: there is no established list of NBTs (more can be added as they are applied); during the design stage, the developer can consult the regulatory Argentine Biosafety Committee (ABC) about the hypothetical product; and the ABC must perform the assessment within two months. Thus, a flexible, innovation regulatory system permits Argentina to remain at the forefront of advanced plant breeding, including NBTs and the subcategory of genome editing.

For a more in-depth view of various regulatory approaches to site directed mutagenesis and NBTs in various other jurisdictions see [5,36,39–41].

2.5. Worldviews

Knowledge, geography or space, time and society—with its cultural, political and economic systems—all shape worldviews [42]. The concept is a composite with no universally-accepted meaning. Depending on the discipline, different theories and models have emerged. As such, ambiguity still surrounds how the concept can best be operationalized in research and practice [43]. For the purpose of the analysis, we use the concept of worldviews as a behavioural proxy. More specifically, we conceptualize worldviews as heuristical[7] cues (mental shortcuts or processes to help solve problems) that assist in decision-making or judgment, especially under uncertainty. Indeed, worldviews are fundamental, cognitive assumptions for beliefs, emotions and interpreted experiences that inform and influence attitudes and behaviour [44,45]. In cultural anthropology, Paul Hiebert provides a preliminary definition of worldviews as "the foundational cognitive, affective and evaluative assumptions and frameworks a group of people make about the nature of reality which they use to order their lives" [46]. In short, worldviews define individual or collective core perceptions of reality.

As people have distinct preferences for how society should be organized, they hold divergent perceptions of personal and societal hazards and benefits. Agricultural, industrial and medical biotechnological innovations (e.g. GMOs, biofuels and vaccines) have prompted cultural polarization and at times political and economic deadlock. Some are concerned about potential risks, whereas others express their worldviews through cynicism or indifference. In response, some support that authorized experts should manage risk, while others prefer substantial social involvement in decisions. Research has demonstrated such societal reactions to innovative biotechnology are determined by an individual's cultural worldview [47,48]. In effect, the cultural theory of risk asserting that individuals selectively attend to risks and related evidence in a way that reflects and reinforces their cultural worldviews, or preferences about how society should be structured [49,50]. In effect, they reflect our values and beliefs.

Worldviews assist here in exploring divergent views of experts about international trade and R&D. We test whether expert worldviews influence their opinions on technology regulation. We consider three specific groupings of worldviews: the realist/hierarchical, liberal/individualist and critical/egalitarian perspectives (summarized in Table 1). The tripartite schema of worldviews is drawn from the international political economy literature [51,52], supplemented with the cultural theory of risk [48].

3. Method

Our multi-year survey project began in 2015 to investigate expert opinion regarding the opportunities and challenges on the application of NBTs and their potential to enhance global food security. Earlier survey topics included regulatory and social barriers around NBTs [15,53] and a set of probes about the costs of regulating NBT-derived crops [2], related risks [54] and benefits [55]. This paper presents the results of an online survey conducted between September 2018 and January 2019 designed to determine how biotech experts think policies should change in response to new NBTs and their resulting products. The survey was emailed to a panel of 479 international scientists, government officials, and agribusiness professionals with related backgrounds and experiences in biotechnology.[8]

The expert panel enrolled in the survey project was obtained from a contact database that was created using emails of participants for several conferences on biotechnology organized by the lead researchers over the past 15 years, as well as experts from online searches (i.e. websites of universities, research

[6] The list of deregulated articles can be found at: https://www.aphis.usda.gov/aphis/ourfocus/biotechnology/am-i-regulated/Regulated_Article_Letters_of_Inquiry

[7] The work of Tversky and Kahneman led to the development of the heuristics and biases research program.

[8] Initially enrolled panellists work with crops mainly cereals (63%), oilseeds (43%), pulses (39%) and vegetables (25%). More than 70% of them deal with both food and feed markets, 43% with fiber, 37% with industrial ingredients, and 29% with environmental services.

Table 1
The three dimensions of worldviews in a global political economy world.

The *realist* worldview	The *liberal* worldview	The *critical* worldview
Prioritization of the state/nationalism	Prioritization of the individual/individualism	Prioritization of groups/group identity
State power	Economic power	Relational power between groups
Politics over economics	Economics over politics	Conflictual view of politics and economics
Mercantilist view* of trade and globalization	Laissez-faire view** of trade and globalization	Dependency-based view*** of trade and globalization
State-driven process of innovation and economic development	Market-driven process of innovation and economic development	The need for socially-directed goals for innovation and economic development

Source: Adapted from Cohn [52] and Gilpin [51].
* Associated with policies which restrict imports (tariff/non-tariff barriers, quotas), increase stocks of gold and protects domestic industries.
** Free market with less governmental involvement.
*** Resources flow from undeveloped states to wealthy nations, enriching the latter at the expense of the former.

Table 2
Worldview survey questions on trade and R&D.

Topic	Worldview		
	Realist	Liberal	Critical
International Free Trade	It has some benefits but should be limited where it causes domestic problems (e.g. regional unemployment, security risks, or erosion of national sovereignty).	It increases overall wellbeing and states should trade as openly with one another.	It primarily benefits those who are already wealthy, deprives working people of their jobs, and perpetuates dependence and underdevelopment in poorer countries.
R&D and Innovation	My government should invest heavily and take a large role in setting the R&D and innovation agenda.	Most impactful R&D and innovation takes place in the private sector and the agenda should be determined by consumers in the market.	R&D and innovation should be aimed primarily at addressing social issues.

institutions, biotech companies and government agencies). In the initial recruitment, a snowball sampling was also applied: participants were asked to share the invitation with colleagues who might be suitable for the study. Snowball sampling is a non-probability method of survey sample selection used to locate hidden or hard-to-track populations such as experts. It relies on referrals from initially-sampled participants to other potential subjects thought to have the characteristics of interest [56]. Unlike household panels (i.e. consumer participants) and a few professional domains (e.g. healthcare) whose contact information are available to government agencies or private research institutions (albeit often at a high cost), we are not aware of any world-wide database source of contacts for international scholars and professionals knowledgeable in plant biotechnology. As our panel is a hard-to-track population, we strongly believe our sampling method is relevant given the subject of interest. Unlike with consumer populations, sample representativeness is less relevant in the context of this study. This approach has allowed us to reach a large number of international experts across a diverse set of fields.

Our study (BEH 97) was deemed exempt from full ethics review by the Behavioural Ethics Board at the University of Saskatchewan, on the basis that the participants, as experts, were not themselves the focus of the research.[9] Nevertheless, our online survey presented participants with a standard consent statement describing the study, identifying the absence of known risks associated with participation, and a reminder that participation was voluntary and responses would be anonymous and confidential. Upon expression of consent, participants were presented with the questionnaire.

The survey was administered in two parts. The first part invited the respondents to offer opinions on a number of questions related to the regulation of new biotechnologies. Participant's opinions were solicited regarding the 2018 ruling on mutagenesis by the CJEU, critical concerns surrounding the use and development of NBTs within existing rules, and approaches that should be adopted to regulate risks related to NBTs, including genome editing.

In the second part, participants were surveyed on their worldviews with respect to international free trade, research and development (R&D) and innovation. As justified earlier, we polled the expert panel about trade and R&D as regulation of novel biotech products has been shown to have implications on both areas [15,29]. We test whether worldviews related to trade and R&D shape preferences for policy governing emerging biotech crops. For each topic, participants were presented with three options that reflected different views—with the first, second and third options reflecting realist, liberal and critical worldviews. The multiple-choice task is illustrated in Table 2.

Contingency analysis is used as the analytical tool. It cross-tabulates the levels of the nominal independent variable (i.e. expertise) with the levels of the categorical dependent variable. The cross tabulation is a joint frequency distribution of cases based on two or more categorical variables that can be analyzed with the Chi-square statistic ($\chi^2_{(df=k)}$ with k degrees of freedom), which determines whether the variables are statistically independent or are connected. If the calculated p-value of Chi-square is lower than the critical value of 0.05, then there is evidence against the null hypothesis that the independent and dependent variables are not associated.

4. Results and analysis

The survey was completed by 113 participants, resulting in a response rate of 23.6 %. The panel is dominated by males (80 %), aged between 45 and 65 years (70 %). Forty-one of the participants reside in North America (NA), 34 % in Europe, and 25 % are from the rest of the world (ROW: 5% in Africa, 5 % in Asia, 6% in Oceania and 9% in Central and South Americas). The majority of respondents hold a PhD degree (71 %) and 20 % have a masters' degree. Forty percent work for industry, 26 % for a university, and 20 % in government. Seventy-one percent identified themselves as scientific experts, and 29 % as social experts (lawyers, agribusiness professionals, etc.). When asked about their frequency of

[9] Per the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, December 2014, Exemption Article 2.1

Table 3
Expert comments underlying their motives for opposing the 2018 CJEU ruling.

Perceived problems with the EU system	Politics vs Science
The problem lies with the **process based** regulation **not product based**, and the 20 year history of safe usage should be highly relevant. The EU system is **process**-based, which relies on arbitrary definitions of what is and isn't a GMO, and was already dysfunctional with its extreme interpretation and application of the **Precautionary Principle**. The regulation of the event by the technology used, **not by the trait** created will have serious long term consequences for the stewardship of events and the management of environmental impact. Mutagenesis/editing is a regular, natural process that will not change the "risk" profile of crops, should be regulated **based on outcome not process**. EU laws on agricultural biotechnology are scientifically unjustified. The EU laws focus on **process and precaution** whereas I believe that the regulations should focus on product and risk. Ruling is in line with **old GMO legislation** in EU, taking the **precautionary principle** and regulating technologies (**processes**) for which there is no history of safe use (as there was for conventional mutagenesis). However, it did not take into account the increased knowledge on plant genomes' variability and the 20 years of safe use of recDNA technologies.	The ruling is based on **politics**, and **not**, as they claim, on **science and scientific evidence**. The ruling was driven by **politics and not the science.** Having said that there needs to be a regulatory framework and science based driven risk based approach to the evaluate risk. This ruling is **not based on good science**, or risk assessment, but rather on a **political position**. EU is **not science-based**. There is no technical reason to consider all techniques using genetic information as Transgenic The ruling also goes **against individual member state** stated position on NBT's. The ruling **ignores the science** behind new plant breeding technologies. **No scientific evidence** was taken into consideration and only vague unfounded fears of the public and NGOs are served by this ruling. It goes **against scientific opinion** and also regulatory approaches in other countries - Argentina, Brazil, USA, Japan. . . . . the ruling appears to be more **political than scientific.** I believe there is **no scientific evidence** to support the EU's decision that mutagenesis-like genome edits are analogous to plants that would be defined as GMOs. Did **not take Advocate General's opinion** into account. The justices have demonstrated that they lack a basic **understanding of the biology** underpinning genome editing by declaring the products as GMOs. It is an interesting development that reflects that the science is not clear cut. Decision **not based on scientific facts**, solely based on how to interpret existing laws - decision should be based on scientific facts.

engagement in regulatory activities, 44 % reported they are often or almost always engaged during the course of their work, 46 % are occasionally involved (Sometimes: 28 %, Rarely: 18 %) and 10 % are almost never involved in such tasks. Engaging in regulatory activities include providing input data (24 %) and/or input analysis (32 %), contributing to decision-making (25 %) and rule-making (15 %).

Tabulated statistics and Chi-square analysis assessing expert opinion on different topics are reported for the total sample and on two categorical control variables: region with three levels (NA, Europe and ROW) and expertise with two levels (scientific experts and social scientists).

4.1. Expert opinion on the CJEU judgment of directed mutagenesis

Experts were asked whether they were aware of any recent updates or changes in biotechnology rules, precisely those related to targeted (gene-specific) plant breeding techniques, and to identify where these changes have occurred (region/country). Seventy-nine percent of the participants provided a positive answer. Among these, 62 % mentioned the CJEU ruling alone, 31 % mentioned regulatory changes in the EU and in other countries including the US, Argentina, Japan, Brazil and Australia (that decided to deregulate foreign DNA-free genome edited products), and 6% referred just to updates in the US. Participants were then presented with a brief background on the CJEU ruling stating that: "On July 25th 2018, the Court of Justice of the European Union ruled organisms obtained by mutagenesis are GMOs within the meaning of the GMO Directive. Other countries (e.g. USDA in USA) have been exempting products of modern forms of mutagenesis (e.g. genome editing) from regulatory oversight as long as they are not plant pests", and were asked whether they support or oppose the ruling, using a five-point Likert scale. Results show a majority of 75 % were not in favor of the CJEU judgment. A number of participants considered the ruling in their own words "problematic" and "scientifically inappropriate". One respondent argued: "It condemns plant scientists to working behind unnecessarily high restrictions". Another expert asserted: "Mutations, regardless of how they occur, are part of the conventional genetic improvement." These expert comments and the wording of them, highlight the degree of frustration at the ruling, which was a legal interpretation of existing EU law, nothing more. Many experts observed the ruling as 'non-scientific' or 'politically biased', which given the lack of technical legal expertise among the expert panel, is not unexpected. In August 2019, the Council of the European Union requested the European Commission to submit a study on the legal challenges on the regulation of new breeding techniques to respond to some of the criticisms.[10]

Based on participant comments (see Table 3), the impetus behind criticizing the ruling is twofold. First, many participants were concerned about the rigid nature of EU policy governing biotechnology, namely a process-based system guided by the precautionary principle (PP). Second, several respondents claimed that the ruling was politically motivated and ignored scientific evidence. Purnhagen et al. [31] note that the CJEU is not legally allowed to go on a fact-finding mission and must make rulings solely based on the materials presented to them by the referring court—in this case, by the French Council of State—and by other public parties consulted. The authors conclude that the CJEU's decision on site-specific, targeted mutagenesis has merely drawn attention to the imperfections and inadequacies of the EU regulatory system.

A number of experts forecast dire consequences of the ruling, notably its potential to stifle innovative research that will force EU farmers to miss breeding opportunities. Others were concerned it will amplify the global food gap, hurt sustainability, and disrupt international trade. Potential problems arising from the EU

[10] https://data.consilium.europa.eu/doc/document/ST-11347-2019-INIT/en/pdf

Table 4
Respondents' familiarity with biotech regulation, segmented by region and expertise (% of total).

	Regions			Total	Expert groups	
	NA	Europe	ROW		Scientific	Social
Not at all/Slightly familiar	8	2	–	**10**	3	7
Moderately familiar	14	9	8	**31**	24	7
Very/Extremely familiar	18	23	18	**59**	44	15
Total	40	34	26	**100**	71	29
Chi-square statistic	χ^2 = 11.087, p = .026				χ^2 = 11.236, p = .004	

Note: To increase the cell count, the scale options "Very familiar" and "Extremely familiar" were grouped together. Similarly for "not at all familiar" and "Slightly familiar".

Table 5
Critical factors related to the use of NBTs to develop new crops.

List of critical factors	Score (%)
Public attitudes to public confusion about food safety and health risks	38
Cost of regulatory approval	34
Market access/trade rules	32
Cost of international biosafety compliance	29
Confidence in the science of modern genome-specific technologies	21
Cost to develop new variety	21
Consistency between domestic regulatory authorities	19
Rules related to environmental protection	16
Cost for firm compliance with risk management	13
Consistency between products	12

The percent score is a weighted sum value (%) of the 5 ranked responses where 1st, 2nd, 3rd, 4th and 5th choices were weighted 0.5, 0.4, 0.3, 0.2 and 0.1, respectively.

regulatory approach include limiting small farmers' access to low-cost technology with low-environmental impacts, increased difficulty for small/start-up companies to develop new varieties and a range of impacts inside and outside the EU [e.g. 5,15,57,58]. According to Purnhagen et al. [31]: "If anything, the CJEU's judgment underscores is the need for regulatory reform in the EU".

4.2. Familiarity with biotech regulations and engagement in related activities

Respondents were asked about their familiarity with the rules and agencies regulating plant biotechnology in their respective countries, using a five-point Likert scale. Overall, the majority (59 %) were very or extremely familiar with them, and 31 % were moderately familiar (our earlier survey [49] found similar results). Table 4 reports the results of a Chi-square Test of Independence performed to examine the relationship between an expert's region (and background) and his/her familiarity with biotech regulations. The relationship between a respondent's familiarity and region is statically significant (p = .026). While the plurality of the participants from Europe (23 %) and the ROW (18 %) were very or extremely familiar, the plurality of NA respondents (22 %) were moderately, slightly or not at all familiar. Similarly, expertise is found to affect responses (p = .004). The plurality of scientific experts (44 %) were very or extremely familiar, whereas social experts were equally divided into those who were very or extremely familiar (15 %) and those who were moderately, slightly or not at all familiar (14 %). These results suggest that experts' familiarity with biotech regulation is both region- and background-specific.

4.3. Regulation of the use of NBTs

Participants were asked to rank the five most critical concerns they have related to the ability to use NBTs to develop new crops. As illustrated in Table 5, surveyed experts view public confusion about food safety and health risks (38 %), the cost of regulatory approval and biosafety compliance (34 %), and trade (32 %) as key challenges. Since the emergence of NBTs, regulatory uncertainty has been a burden to many broadly applicable technologies. Countries like the US, Brazil, Argentina and Australia[11] amended their rules to exempt targeted genome-edited products as long as the repair mechanism occurs naturally rather than using foreign genetic material. Other countries have tougher measures. One expert commented: "I am more concerned about the time and uncertainty for regulatory approval - in particular Import Countries (i.e. China) that block new innovations from being introduced into the agriculture system in countries like, Canada, US, Argentina, Brazil, etc. that have approved the technology."

Results of previous surveys within this overall project show that experts actively distinguish between genome edited crops that are free of foreign DNA and those that are transgenic, which are appropriately regulated as GM [53,55]. The majority of experts surveyed (Table 6) chose product-based regulation—either stand-alone (59 %) or combined with some process-based (i.e. dual/hybrid) system (26 %)—as 'ideal' approaches nations should adopt to regulate any risks related to transgenic outcomes of NBTs including genome editing. The cross-tabulations reported on Table 6 show no statistical difference by region (p-value = 0.981 > 0.05) or by background (p-value = 0.129 > 0.05). Most participants from NA (23 %/39.5 %), Europe (19 %/34.5 %) and the ROW (17 %/26 %) converged on a common view; moreover, scientific (43 %/71 %) and social experts (16 %/29 %) generally agreed.

For many participants, the outcome of a technology (either crop type or end-product) matters the most for farmers and consumers as it is the use that determines how risky or valuable a new trait actually is. Experts generally agree that the final product—regardless of how it is developed—can generate potential risks.

[11] https://www.nature.com/articles/d41586-019-01282-8

Table 6
Expert opinion on how NBTs should be regulated by region and by background (% of responses).

Approach	Region			Total	Expert group	
	NA	Europe	ROW		Scientific	Social
Process-based regulation	2.5	2.5	1	**6**	4	2
Product-based regulation	23	19	17	**59**	43	16
Hybrid regulation	10	10	6	**26**	15	11
Tailored regulation	3	2	1	**6**	6	–
Other	1	1	1	**3**	3	–
Total	39.5	34.5	26	100	71	29
Chi-square statistic	$\chi^2 = 2.001$; df = 8; p = .981				$\chi^2 = 7.142$; df = 4; p = .129	

Table 7
Factors that can improve transparency around biotech regulation: expert responses (%).

	Not at all important	Slightly important	Moderately important	Very important	Extremely important
Efforts of regulators to communicate/report on own activities	1	6	18	45	30
Academic involvement	0	3	23	40	34
Farmers/growers involvement	2	7	23	45	23
Public engagement/consumer consultation	3	10	22	46	19
Voluntary corporate commitment	2	16	26	41	15
Access through freedom of information requests	10	13	28	35	14
NGO participation	10	21	43	19	7
Relaxed confidential business information	15	22	37	18	8

Note: Each row sums to 100 %.

Table 8
Participants' worldviews of trade by region and by expertise.

Worldviews	Region			Total	Expert group	
	NA	Europe	ROW		Scientific	Social
Realist*	8	13	12	**33**	27	6
Liberal	34	22	11	**67**	43	24
Total	42	35	23	**100**	70	30
Chi-square statistic	$\chi^2 = 8.075$; df = 2; **p = 0.018**				$\chi^2 = 3.438$; df = 1; p = 0.064	

* We could have realist and critical WV responses merged together as both views are less optimistic (more pragmatic) compared to the liberal view regarding trade. In Table 8, we did not account for the critical responses (4%) as the proportion is insignificant.

Experts further agree that each trait should be comprehensively characterized, including its social impact, ethical considerations and sustainability One justification is that the process-based system may be unable to keep pace with emerging technologies. One view is that a product-based safety assessment is the "only scientifically valid approach". One respondent stated that: "Focusing on the process, in transgenesis, has led to bad decision-making, especially in Europe, and groundless fears in parts of the general public." Another added: "The process can be performed under controlled settings and thus any risk mitigated at the site of execution of the process. Products are released to the public . . . it makes most sense to regulate what reaches the public." According to one expert, a product-based approach would help overcome the problem of defining a GMO, debates around novel crops, and thus consumer acceptance and understanding of the technology.

Only 6% of those surveyed viewed pure process-based systems as suitable. The process-based regulatory systems may have been adequate at the end of 20th century when other methods of characterization were not available. But knowledge has advanced. There are now over 4300 regulatory risk assessment decisions from 70 countries that have approved GM crops for food and feed use, none identifying risks that differ from conventional crop production [59]. GM products. The experts in our survey that utilize new tools to characterize products and monitor the environment, are virtually unanimous that process-based regulatory systems are completely unjustifiable.

A range of alternatives are supported. Tailored regulation (i.e. case-by-case) was recommended by 6% of the respondents. All early regulatory applications for products of genome editing (e.g. using CRISPR/Cas9) have been reviewed case-by-case in countries like Canada and the US, with some codification of the rules since then (see discussion above).. Supporters of the case-by-case assessment argue that as applications of NBTs, including genome editing, vary so does the resulting trait or product and its potential impact(s). One respondent commented: "It depends on the trait. Increases in starch or oil content in a crop would not be as much of a concern as the production of novel seed protein that could be a potential allergen." Another expert stated: "The diversity of each crop is specific for each environment and the risk factors vary

Table 9
Participants' worldviews of R&D and innovation by region and by expertise.

Worldviews	Region			Total	Expert group	
	NA	Europe	ROW		Scientific	Social
Realist	20	21	13	**54**	37	17
Liberal and Critical*	20	13	13	**46**	34	12
Total	40	34	26	**100**	71	29
Chi-square statistic	$\chi^2 = 1.008$; df = 2; p = .604				$\chi^2 = 0.242$; df = 1; p=.623	

* For statistical reasons (i.e. relatively balanced groups), liberal and critical responses were merged. We believe this is reasonable as both views consider more the social inclusion compared to the realist view regarding R&D and innovation.

Table 10
The effect of trade and R&D worldviews on regulatory decision-making.

Approach	Worldviews on trade		Total	Worldviews on R&D	
	Realist	Liberal		Realist	Liberal/Critical
Process-based regulation	1	5	6	3	3
Product-based regulation	17	41	58	31	27
Hybrid regulation	12	15	27	16	11
Tailored regulation	2	4	6	3	3
Other	1	2	3	1	2
Total	33	67	100	54	46
Chi-square statistic	$\chi^2 = 3.189$; df = 4; p = .527			$\chi^2 = 1.353$; df = 4; p = .852	

according to the event to be introduced and evaluated. Another expert asserted: "Because risk does not depend on the technology but on the product and the area where it will be released. Hence every new variety can have its special risks and benefits." One expert advocates for the dual/hybrid system because: "A pure process based system is inadequate since it is nearly always the product that counts for safety impacts. A pure product based system is an inadequate trigger for regulatory actions since it is difficult to define 'novelty'." One view is that process-assessment may be best suited to environmental concerns while product-based review can most effectively address food safety concerns. In other words, the systems can complement each other; embracing one of them might not be the best strategy in the long run.

4.4. Transparency and biotech regulation

Not only have technological advances been altering the landscape of the products of biotechnology but it has also led several nations to revisit their current regulatory frameworks in order to ensure public confidence and improve transparency. Our expert panel is of the opinion that transparency can be improved through improved regulator communications (75 %), involvement of academics (74 %), increased growers involvement (68 %) and better engagement processes with the public (65 %). Participation of non-governmental organizations (NGOs) is moderately important according to 45 % of respondents (Table 7).

4.5. Panel worldviews and their effect on regulatory decisions

The mix of worldviews held by surveyed experts on trade and R&D are displayed in Tables 8 and 9, respectively. Most respondents (67 %) agree free trade increases overall well-being but there are significant differences based on their location. North American participants (34 %/42 %) appear to be most attached to the liberal view, followed by European experts (22 %/35 %). But respondents from the ROW are statistically less optimistic about international markets ($p < 0.05$). Those experts coded as realists viewed trade as beneficial (12 %/22 %), but acknowledged the limits imposed by regional unemployment and security risk. Few of our respondents aligned with the critical worldviews (0% for NA, 1% for European and 3% for ROW respondents). Disciplinary specialization does not appear to influence worldviews of trade ($p > 0.05$). Indeed, a majority of scientific (43 %/70 %) and social scientists (24 %/30 %) revealed liberal views.

Regarding R&D and innovation, 54 % of the sample view their government as the primary player in investing and agenda setting. Overall, 46 % of the population surveyed ascribed to a liberal/critical view that would support more social/public inclusion. Europeans tend to display a somewhat more realist worldviews (21 %/34 %), but given our sample size that is not statistically different from other regions ($p > 0.05$). To sum up, region and expertise appear to influence worldviews of trade but not of R&D and innovation.

The question then is whether the worldviews on trade and innovation align with the stated preferences of our respondents on regulatory choices. As presented in Table 10, none of the results were statistically significant ($p > .05$). The product-based model or a dual-product/process system are believed to be appropriate frameworks to regulate outcomes of genome editing in the eyes of experts, regardless of their worldviews. We might expect our results would be different if non-experts were involved.

We explicitly tested whether our respondents' views on the CJEU ruling were influence by their worldviews s. We found the panel was homogenous in its overall opinion: the majority of experts opposed the ruling regardless of their worldviews on trade ($\chi^2 = 5.400$; df = 3; p = .145) or innovation ($\chi^2 = 1.349$; df = 3; p = .718)

5. Conclusion

Genome editing regulation will guide, or discourage, the use of novel technologies that might contribute to mitigating a number of major problems afflicting society. Food security and environmental sustainability both might be improved by appropriate use of new technology.

One of our goals was to test to see if worldviews might drive some of the divergence in our regulatory outlook. Our assessment of worldviews suggests the division of opinions, if any, are not the result of disciplinary background but may be a result of location. We found relatively consistent worldviews between scientific and social scientists about both trade and innovation, and could not discern any unique regulatory preferences driven by worldviews of either factor. In spite of expert consensus on the importance of trade and innovation, there are divergent worldviews based on which region one lives in. While those do not uniquely map onto preferences, one might infer they are part of the policy conundrum separating parts of the world.

Each specific way of genome editing is complex and the probability that different tools will be used together simply amplifies the complexity of regulating. There is some evidence that R&D funding is beginning to move from jurisdictions with process-based regulatory systems, such as that of the EU, to countries that utilize a product-based system, such as that used in most of the Americas. This would simply amplify the challenges of asynchronous use of crops derived from different technologies.

Our expert survey reveals that there is an emerging consensus that the regulatory processes need to innovate to address the challenges resulting from new technical opportunities. Our finding that experts operating in their professional capacity in the context of research and innovation can, and do, find middle ground is positive. The challenge will be to reconcile any resulting consensus with the divergent views held based on where one lives. Experts think the key to realizing genome editing's potential is in regulatory transparency and open dialogue but the notion that an open dialogue with society on genome editing will lead to

greater understanding needs to be validated, as recent structured dialogues have not led to greater acceptance or use [60].

We remain partially pessimistic about the future for NBTs. Experts seem both able and willing to look for solutions but even they reflect the biases of their home. Reconciling these conflicting interests will remain a challenge for the foreseeable future.

Declarations of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

CRediT authorship contribution statement

Rim Lassoued: Conceptualization, Methodology, Formal analysis, Writing - original draft. **Diego Maximiliano Macall:** Conceptualization, Methodology, Writing - original draft. **Stuart J. Smyth:** Conceptualization, Methodology, Writing - review & editing, Supervision, Funding acquisition. **Peter W.B. Phillips:** Conceptualization, Methodology, Writing - review & editing, Funding acquisition. **Hayley Hesseln:** Conceptualization, Writing - review & editing.

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Appendix A. Supplementary data

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