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Risk and safety considerations of genome edited crops: Expert opinion

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ABSTRACT

It should come as no surprise that innovation is linked to uncertainty, especially when its effects are wide-ranging and can be difficult to quantify, as is the case for plant genome editing. Thus, scientific innovation should be conducted responsibly. Both regulators and companies seek ways to minimize inherent uncertainties regarding technological development. Risk assessment offers a basis to evaluate human, environmental and societal risks of fledging technologies and their application. This paper describes a range of potential issues related to the safety of genome editing as identified through a survey of a consortium of international experts in plant biotechnology. A key finding is that genome edited crops pose marginal risk to the economy, human health and the environment. Yet, regulations governing biotechnology and some advocacy groups tend to discourage the use of new gene technologies in agriculture. In effect, discussions concerning the risks associated with genome editing, and targeted breeding techniques generally, are driven more by socio-political factors than by scientific principles.

1. Introduction

The advent of targetable nucleases and the amalgamation of a number of scientific disciplines, has enabled scientists to develop a set of technologies that can alter an organism's genome with greater accuracy and celerity (Jinek et al., 2013; Schmidt et al., 2010; Turksen, 2016; Yamamoto, 2015). New plant breeding technologies (NBTs), including genome editing, provide technical and economic advantages over conventional breeding (Miao et al., 2018; Pfeiffer et al., 2018). In the face of mounting global food and fuel demands, the scarcity of water and land caused by global population growth, and the challenges climate change poses to agriculture, genome editing for crop improvement has tremendous potential (CAST, 2018).

The number of technologies that can be broadly classified as NBTs continues to expand. Most applications of NBTs to date are variants of genome editing, which is primarily represented by two distinct technologies: site-directed nucleases (SDN) and oligonucleotide directed mutagenesis (ODM). Unlike most agricultural applications of genetic modification (GM), genome editing does not necessarily entail the insertion of foreign DNA into the plant genome. SDN technologies encompass: meganucleases (MN), zinc finger nucleases (ZFN), transcription activator-like effector nucleases (TALEN) and clustered regularly interspaced short palindromic repeats (CRISPR). These molecular approaches can be used to deliver targeted short deletions or small insertions of endogenous deoxyribonucleic acid (DNA) (SDN 1 and SDN 2 approaches) or integration of long DNA sequences or entire genes into a desired site in the plant genome (SDN 3 approach). Products of SDN 1 and SDN 2 might be indistinguishable from naturally occurring mutations or conventionally-bred counterparts while SDN 3 yields transgenic outputs (BelgianBiosafetyServer, 2018; Woo et al., 2015). Calyxt high oleic soybean known as CalynoTM7 was the first genome edited soy distributed in the US (Calyxt, 2019). Other marketed genome edited products include Cibus' sulfonylurea (SU) herbicide-tolerant canola and waxy corn with enriched amylopectin. As with any new technology or scientific advancement, until sufficient data are provided about safety and efficacy, there might be reluctance to regulate with high degrees of confidence and certainty.

The safety of genome editing depends, in part, on whether the changes are directed to predetermined sites (which would reduce or eliminate unintended changes, so-called off-target mutations) or to targets (which would eliminate unintended effects of the intended changes) (SAM, 2017; Agapito-Tenfen, 2016). The precision and efficiency of genome editing is expected to lower the frequency of some sources of unwanted downstream events, and therefore to yield fewer potential hazards at the product level (SAM, 2017). Yet, for staple food crops with large and complex genomes, such as wheat, barley or maize, off-target editing is more likely to occur (Agapito-Tenfen, 2016). Similar to varieties derived from chemical or radiation mutagenesis, unexpected risks and negative externalities (i.e. potential harm to human health and the environment) cannot be ruled out. The current knowledge about the safety of genome editing in plants is relatively limited e.g. (Xie et al., 2014; Zhang et al., 2018; Nekrasov et al., 2013; Zhao

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and Wolt, 2017). In addition, current detection and identification strategies (e.g. bioinformatics) and emerging analytical tools (e.g. next generation sequencing) face potential shortfalls. This is complicated because reliable and harmonized procedures for the detection of unwanted editing are still lacking (Agapito-Tenfen, 2016).

This paper presents expert opinion regarding potential risks of using genome editing in agriculture. It reports the results of a survey in which a pool of international scientists and professionals involved in plant biotechnology were asked to describe the risks they believe genome edited crops could present in the environment, the economy, and for human safety. Though the technologies are different, genome editing comes into a world already shaped by genetic modification (GM). The survey also provides views on the role of biotechnology regulations and advocacy groups in promoting or impeding the use of targeted breeding in agriculture. There is significant evidence that the success of the new wave of technologies is much more a matter of socio-political considerations than technological competitiveness (Lassoued et al., 2018a; Araki and Ishii, 2015). We investigate this conflict.

The paper is structured in four parts. We briefly review the concept of risk and its two predominant (precautionary and flexible) approaches, the role of advocacy groups regarding biotechnology, and the significance of responsible innovation. We then present the method, detailed results, discussion and conclusions.

1.1. Risk management and plant breeding

Risk, an interdisciplinary and intensely studied phenomenon, is a key determinant of the application of new technologies, regardless of field of application (Anderson et al., 2012). van den Daele et al. (van den Daele et al., 1997) identified three types of risk that affect product safety and consumer perceptions of those risks. First, probabilistic risks involve those theoretically-grounded and empirically-demonstrated risks related to the product or its technology. Second, hypothetical risks embroil those possibilities that are grounded in accepted theory but lack empirical experience or evidence that can establish probabilities. Third, speculative risks, in contrast to the other two areas, have neither established theory nor experience to back them up. Based on this classification, risk can be foreseeable and/or unforeseeable depending on who defines it.

The complexity of risk is also due to the fact that it is a multi-attribute concept that is context dependent, and is as much a function of physical hazards as it is of perceptions. Formally, the term refers to the combination of two factors: “the probability that a potentially harmful event will occur; and the potential damage such an occurrence would cause” (OECD, 2003). Simply put, scientifically-based risk is computed as the probability of a hazard multiplied by exposure. Thus, risk is the potential of harm caused by an event or series of events (natural or man-made). Increased weediness or gene flow, resistance evolution, and herbicide carryover to rotational crops were among the potential risks of genome edited crops that have been observed in different regions for an important staple crop: rice. The mutagenic herbicide-resistant Clearfield rice was introduced in US in 2002 as an integrated weed management tool in rice fields and quickly spread in Central and South America, Asia and Europe (Sudianto et al., 2013). Its adoption has led to seed contamination as a result of outcrossing between Clearfield rice and weedy rice in countries like US, Cota Rica, Brazil and Italy (Sudianto et al., 2013; Burgos et al., 2014; Busconi et al., 2012; Gressel and Valverde, 2009).

Perceptions of risk, in contrast, involves subjective probabilities of likelihood and socially-adjusted perceptions of the acceptability of the harm. Thus, perception, analysis, and communications of any risk can vary both within and between nations. The United States' (US) and European Union's (EU) approaches to scientific risk with respect to biotechnology present a contrasting, yet similar enough example for the variation in approach to be documented.

1.2. The precautionary approach vs substantial equivalence

Two main principle-based approaches are used to regulate new technologies. Many systems are based on scientific assessments and delegate authority to scientific process (the so called scientific rationality), while others use science but consider other factors in the final judgement (the precautionary approach). In Canada, science-based regulatory intervention applies only to novel plants and foods (plants with novel traits: PNTs).

A recognized formulation of the precautionary approach dealing with environmental hazards is to be found in Principle 15 of the Rio Declaration of 1992: “Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation” (van den Belt, 2003). Since its origin in 1970s German environmental law, the precautionary principle's (PP) scope of application has broadened to the point of being incorporated into the national legislation of many European countries (Bourguignon, 2015). No universally accepted definition of the PP exists, and the criteria under which it can be invoked are unclear, despite European Commission (EC) efforts to set guidelines for its application (EC, 2019). However, empirical scrutiny of the ways in which it has been applied over the years shows the selective use of scientific evidence, and the susceptibility of the PP's applications to political influence (Tosun, 2013). Indeed, the application of the PP is held to belong to risk management: a political responsibility. According to Marchant (Marchant, 2001) the PP seeks to replace the factors (e.g. magnitude, distribution and uncertainty of risks, the extent of exposure, and the trade-offs and lost benefits in foregoing the risk) considered under the current risk-based approach. Nonetheless, Stirling (2007) and others argue that the PP is of practical relevance to risk assessment and risk management. As recently as 2018, the Court of Justice of the European Union (CJEU) invoked the PP to rule that new mutagenesis techniques should be regulated in the same way as genetically modified organisms (GMOs) (CJEU, 2018). Applications of the PP such as this, lead some to consider the principle is a conclusion, rather than an argument for greater security; some argue that the PP does not provide consistency, predictability, transparency, or accountability for regulation (Marchant, 2001; Garnett and Parsons, 2017).

Some argue the current approach to risk assessment is not designed to detect unintended consequences of employing NBTs (Christ et al., 2018). To address this, untargeted metabolomics could be incorporated as part of a routine protocol assessing future biotech crops. However, integrating untargeted metabolites in the characterization of crops derived from genetic engineering is not novel, and has been subject of criticism (Marchant, 2001; CJEU, 2018).

In contrast, the American science-based approach to biotechnology regulation is grounded on three elements (Marden, 2002). First, the emphasis is on the end product, not the method used to create it. Second, US policy holds that in the absence of verifiable ‘scientific risk’, there is no reason to delay technology. Finally, the approach maintains that GM technology (and now genome editing technology) should be compared with known risks of substantially equivalent products. Specifically for genome editing, the US reaffirmed it would use this approach in response to a petition made to the United States Department of Agriculture (USDA) for approval to commercialize a genome edited mushroom (Waltz, 2016). Given that the CRISPR-based mushroom involved small deletions (1–14 base pairs) but no foreign DNA, the Animal and Plant Health Inspection Service (APHIS) of the USDA concluded they were not plant pests and therefore did not fall under its scope of regulation.

The contrasting biotechnology regulatory approaches exemplify two different paradigms. The EU approach, with an eclectic outlook as to the sources of risk, considers it best to wait for evidence of no risk whatsoever in order to proceed. The US approach considers impeding technology only when there is evidence of risk. The difference in approach can be partly explained by the way through which biotechnology is perceived in both jurisdictions. Despite their difference, both governance methods are limited to scientific risk assessment of human and environmental safety and unable to resolve public and policy concerns (Hartley et al., 2016).

1.3. Risk framing

Events or issues have to be placed within an interpretative context before they can serve as a starting point for deliberation and action. How an

issue or event is 'framed' influences the perspective through which people see reality because it involves the inclusion, exclusion, and emphasis of different aspects of an event or reality (Hallahan, 1999). Entman (Entman, 1993) considers that frames, "*define problems* - determine what a causal agent is doing with what costs and benefits, usually measured in terms of common cultural values; *diagnose causes* - identify the forces creating the problem; *make moral judgments* - evaluate causal agents and their effects; and *suggest remedies* - offer and justify treatments for the problems and predict their effects." Framing can then be understood as the process of defining and delineating issues or events; how an issue is framed is of fundamental importance. Tversky and Kahneman (Tversky and Kahneman, 1981) have shown how logically equivalent scenarios framed alternatively as 'gains' or 'losses' can alter preferences significantly.

The seemingly intractable debate around GM crops shows how important framing can be (Lubieniechi et al., 2016). Despite numerous agronomic, environmental and economic assessments reaffirming the benefits that GM crops entail, there is still a polarized debate about whether countries should adopt them or not (Brookes and Barfoot, 2018; Kangmennaang et al., 2016). Why is it that even if people have similar understanding of a technology, they may have completely different interpretations about it? The synthetic biology public dialogue exercise in the UK demonstrated this challenge (Bhattachary et al., 2010). Based on their experience with GM crops, a UK research agency sought a different approach so as to engage the public on the nascent field of synthetic biology. Rather than opinion polls, they relied on a public dialogue. However, Marris (Marris, 2015) points out that this attempt was based on the dubious axis of the 'deficit-model' (i.e. that people only need more scientific knowledge to make the 'right' choice), and took for granted the socio-technical expectations put forward by scientific institutions. The 'dialogue' resulted in five central questions: 'What is the purpose? Why do you want to do it? What are you going to gain from it? What else is it going to do? How do you know you are right?' (Bhattachary et al., 2010). Members of civil society who participated in the dialogue focused more on the process of the technologies, rather than on the finished product.

1.4. The role of advocacy groups

Advocacy groups are actively engaged in debates about emerging technologies. The commercialization of GM crops has been especially controversial, with social development and environmental organizations questioning not only safety but a spectrum of issues including ethics, monopoly ownership, and corporate control of crop varieties and the food chain, consumers' and farmers' right to know, and the nuances around coexistence of various agricultural practices (Hartley et al., 2016; Wieczorek and Wright, 2012). In response, the science community has mobilized. In 2016, >100 Nobel Laureates signed a letter calling on Greenpeace to desist from campaigning against, and misleading the public about, agricultural biotechnology in general and Golden Rice in particular (Roberts, 2018). While some non-governmental organizations' (NGOs) opposition to GM foods and crops is grounded in strongly-based values and beliefs, NGO skepticism towards agricultural biotechnology has transformed into a more complex socio-political phenomenon, with emotion balanced with power struggles and commercial gain. Different motives generated different responses.

Helliwell, Hartley (Helliwell et al., 2017) engaged members of NGOs opposed to genome editing as a potential tool to guarantee food security and found their opposition to the technology is rooted in the frames through which they analyze the technology, and even the problem it sets out to address. Specifically, they first questioned why the problem is defined as a lack of food rather than a lack of access to food. Second, they questioned whether further entrenching intensive agriculture through science and technology can address political and socio-economic inequalities. Third, they wondered about the motivations for removing genome editing from GM regulations. In other words, scientists, political stakeholders, and NGO members are looking at the same problem and technology, but through different frames. No matter how much agricultural biotechnology is discussed, a harmonized understanding on the technology can never be reached if the framing of the issue is different. A promising starting point towards a harmonized understanding on genome editing is the characterization of risk that the use of this technology entails.

1.5. Responsible research and innovation (RRI)

Emerging technologies like NBTs often fall into an 'institutional void' (Hajer, 2003). At their emergence, rules governing NBTs including genome editing were lacking as derived products fell outside the scope of the conventional GM policy. New forms of anticipatory governance—led by responsible innovation (RI)—have evolved to guide science and innovation processes (Kerr et al., 2018). Stilgoe et al. (Stilgoe et al., 2013) define RI as "taking care of the future through collective stewardship of science and innovation in the present", where "responsible research and innovation is a transparent, interactive process by which societal actors and innovators become mutually responsive to each other with a view to the (ethical) acceptability, sustainability and societal desirability of the innovation process and its marketable products (in order to allow a proper embedding of scientific and technological advances in our society)" (Von Schomberg, 2013). In effect, different stakeholders have a co-responsibility to endorse research integrity in the science-society relationship (Mitcham, 2003). Lassoued et al. (Lassoued et al., 2018a) found that communicating information (e.g. benefits and related risks) about novel plant biotechnologies and derived output is a shared responsibility among scientists, regulators, industries and consumer and farmers organizations.

2. Method

An online survey was conducted between May and September 2018 to gather expert opinions on the potential safety issues surrounding NBTs, including genome editing. The survey was emailed to a panel of 487 international experts (scientists, government officials, agribusiness professionals, etc.) with related backgrounds and experiences in biotechnology. The survey instrument is part of a multi-year survey project investigating expert opinions regarding the opportunities and challenges on the application of NBTs and their potential to enhance global food security. The expert panel was obtained from a contact database that was created using emails of participants for several conferences on biotechnology organized by the researchers over the past 15 years, and of experts from online searches (i.e. websites of universities, research institutions, biotech companies and government agencies). In October 2015, an introductory recruitment effort involved contacting by email >4000 individuals and soliciting their participation. Those that enrolled in the research panel ($N = 720$) provided socio-demographic information and answers to a series of decision-making questions. Previous surveys covered different topics including: the top ranked NBTs for improving food security (Lassoued et al., 2018b), regulatory uncertainty surrounding NBTs (Lassoued et al., 2018a), costs of genome editing crops (Lassoued et al., 2019a), and related benefits (Lassoued et al., 2019b). As the survey topics varied, prospective panelists were not required to answer every survey. Due to the longitudinal nature of the survey project, the participation rate has decreased over time as survey relevance varies among prospective participants. This is expected as panel studies typically suffer from attrition which reduces sample size (Deng et al., 2013). Despite the gradual drop-off in response rates, this panel allowed us to reach a large number of international experts in the field of study and gather their views on the regulatory challenges surrounding novel crops. Expert opinions and judgments have been widely used to inform policy-related decision making, particularly for uncertain events where empirical data are lacking, and for emerging, complex and ill-understood problems e.g. (Martin et al., 2012). Unlike lay public, experts are deemed most likely to offer insights into future events as they hold certain knowledge or extensive scientific information on specific subjects (Lassoued et al., 2019a).

Our study (BEH 97) was exempted from full ethics review by the Behavioural Ethics Board at the University of Saskatchewan, on April 7, 2015 on the basis that the participants, as experts, were not themselves the focus of

the research.[1] 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 three parts (see Appendix A). The first part invited the respondents to offer opinions on current risk management frameworks and the importance of inclusion of socio-economic considerations. The second part included questions related to responsible innovation and its significance to the development of NBTs. The third part tested for the presence/absence of framing effects in expert risk choices adapted from the '*Asian disease*' problem (Tversky and Kahneman, 1981). It included two hypothetical questions describing the anticipation of severe environmental conditions. Subjects were presented with choices between two technologies (NBT A vs. NBT B) framed as gains (question 1) and losses (question 2) cast in terms of crops saved (positive frame) and crops lost (negative frame). As illustrated in Table 1, the outcomes of both technologies were logically equivalent under both frames. The positively framed question comprises a sure option of saving 17,250 producers' crops and a risky option of a 1/3 probability that all 51,750 producers would save their crops. Conversely, in the negative frame question, respondents were presented with a choice between allowing 34,500 farmers' crops to be lost or pursuing a risky alternative with a 2/3 probability that all would be lost. Both questions were manipulated within subject—presented to each respondent—but the question order was randomized to counteract the possible order effect and minimize transfer and learning across conditions.

2.1. Results and analysis

The survey was completed by 113 participants, resulting in a response rate of 23%. The panel is dominated by males (80%), aged between 45 and 65 years (70%). Half of the participants reside in North America (NA), 30% in Europe, and 20% from the rest of the world (ROW: 6% Africa, 5% Asia, 4% Oceania and 5% Central and South America). The majority of subjects hold a PhD degree (71%) and 20% have a masters' degree. Eighty percent are employed and 14% are self-employed. Forty percent work for industry, 26% for university, and 20% for government. In the initial enrollment, panelists were asked about the type of crops and markets they work with. Main crops of interest include cereals (63%), oilseeds (43%), pulses (39%) and vegetables (25%). >70% of the panelists works with both food and feed, 43% on fiber, 37% on industrial ingredients, and 29% on environmental services. Fifty-six percent identified themselves as scientific experts, and 44% as social experts (lawyers, agribusiness managers, etc.). Contingency table analysis assessing expert opinion on different topics is reported for the total sample and on two categorical control variables: regions with three levels (NA, Europe and ROW) and expertise with two levels (scientific and social experts). Contingency analysis 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 associated. If the calculated p-value of Chi-square is lower than the critical value of 0.05, then that is evidence against the null hypothesis that the independent and dependent variables are not associated (i.e. the variables are causally linked).

2.2. Expert opinion on risks of genome edited crops

As identified above, genome editing can yield either transgenic or non-transgenic outcomes. Results of previous surveys within this project that experts agree that some genome edited crops are transgenic and thus should be regulated as GM technology while those free from exogenous genetic material should not (Lassoued et al., 2018a, b). Experts in this study were asked about the safety of genome editing. Table 2 shows the majority of experts consider that genome edited crops pose little to no risk to society (76%), the economy (71%), human health (75%) and the environment (71%). Less than a quarter of the sample believe that such crops present a moderate risk, compared to <5% who think they pose a high risk. One expert commented: "[risk] depends on the characteristics of the product and its intended use. In many cases for plants, there may be no/negligible risk (equivalent to conventional breeding), but in some cases risk may need to be assessed (case by case)." Expert responses in Table 2 were consistent between scientific and social experts ($\chi^2_{(13df)} = 9.986$; p-value = 0.695), and among regions ($\chi^2_{(26df)} = 21.385$; p-value = 0.722).[2] Regardless of their expertise or where they live, experts agree on the overall safety of site-edited crops.

The projected benign effect of genome edited crops is based on the efficiency and the accuracy of the technology that allows the precise inactivation of an endogenous gene, the conversion of an existing allele to a desired one, or the accurate insertion of an identified variant into additional breeds (Carroll and Charo, 2015). The application of these targeted breeding tools is intended to limit unwanted events when compared to random mutagenesis (SAM, 2017; Khandagale and Nadaf, 2016). Moreover, backcrossing and selection help to limit editing exclusively to the specific site without yielding other permanent changes in the plant genome (Wang et al., 2014). With high precision, genome editing yields fewer off-target events compared to classical mutagenesis. Nevertheless, off-targets are a focal point of criticism as they might cause genomic instability, cytotoxicity, and cell death (Agapito-Tenfen and Wikmark, 2015; Zhang et al., 2015; Kanchiswamy et al., 2016). Probabilities of risk exist with all forms of plant breeding. The precision of genome editing and selection of agronomic target genes are expected to help minimize undesirable effects (Khandagale and Nadaf, 2016).

2.3. Expert opinion on risk assessment and risk management regulatory frameworks

2.3.1. Familiarity with biotech regulation

Respondents were asked about their familiarity with risk assessment, risk management, and the regulatory frameworks governing biotechnology in their respective countries, using a five-point Likert scale (i.e. type of rating scale used to measure opinions on level of agreement, frequency, quality, likelihood and importance). Results show the majority (56%) were very or extremely familiar with them, and a quarter were moderately familiar. These results were consistent between scientific and social experts ($\chi^2_{(4df)} = 4.130$; p-value = 0.389) and among regions ($\chi^2_{(8df)} = 9.048$; p-value = 0.338). Regardless of their expertise and where they live, those consulted asserted they are informed about their country's biotechnology governing regulatory framework.

2.3.2. Precautionary levels of biotech regulations

Governance of biotechnology is heterogeneous around the world. Participants were asked to describe legislation governing biotechnology in their region. Table 3 shows that 56% of experts mainly from NA and ROW deem risk assessment and risk management regulatory frameworks as less precautionary[3] while almost all European respondents (29% out of 30%) judged them as more precautionary. This regional difference is statistically significant ($\chi^2_{(2df)} = 66.323$; p-value <0.001). Participants from the ROW were equally divided between those who thought biotech regulations are more precautionary and those who thought they are not.

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

[2] Chi-square statistics were generated based on a risk score calculated as the mean of the five-point Likert scale of the risk rates of genome edited crops taking into the account risks posed to society, the economy, the environment, and human health.

[3] Precaution in this application refers to both the precautionary approach and the precautionary principle.

Table 1
Structure of the choice scenarios.

Frame	Choice option	Outcome	Expected value	Risk preference
Positive	NBT A	17,250 saved	17,250 saved (34,500 lost)	Risk averse
	NBT B	(1/3) 51,750 saved	17,250 saved (34,500 lost)	Risk seeking
Negative	NBT A	34,500 lost	34,500 lost (17,250 saved)	Risk averse
	NBT B	(2/3) 51,750 lost	34,500 lost (17,250 saved)	Risk seeking

Table 2
Expert responses on the rates of risks of genome edited products (%).

Risk posed to:	No risk at all	Slight risk	Moderate risk	High risk	Extreme risk	Don't know
Society	**36**	**40**	15	2	1	6
The economy	**40**	**31**	18	3	1	7
Human health	**28**	**47**	12	4	1	8
The environment	**23**	**48**	21	4	1	3

Note: Each row adds up to 100%.

Table 3
Expert opinion on the precautionary levels of biotech regulation.

	Group type	More precautionary	Less precautionary	**Total**
Expertise	**Scientific experts**	33	24	**57**
	Social experts	11	32	**43**
	Total	**44**	**56**	**100**
Region	**NA**	5	45	**50**
	Europe	29	1	**30**
	ROW	10	10	**20**
	Total	**44**	**56**	**100**

Similarly, background has an effect on expert views regarding the precautionary level of biotech regulation ($\chi^2_{(1df)} = 12.571$; p-value <0.001). While a plurality of scientific experts (33%) view the regulation as more precautionary, the plurality of social experts (32%) view it as less precautionary. To measure the strength of association of the Chi-square test of independence, Phi (Φ, or the mean square contingency coefficient for the 2 × 2 table) and Cramer's V (for more a than 2 × 2 table) were checked. Opinion regarding biotechnology regulation as precautionary is strongly associated with region ($\Phi = 0.773$, $p < 0.001$) and moderately related to expertise (Cramer's V = 0.337, $p < 0.001$).

2.3.3. Biotech regulation and the use of genome editing in crop development

Overall, 51% of experts think that biotech regulation in their country moderately or completely discourages the use of gene editing in crop development. Close to one-quarter of the sample expressed a neutral opinion. Expertise is shown to have no effect on opinion regarding whether biotech regulation encourages the use of genome editing in plant breeding ($\chi^2_{(5df)} = 8.014$; p-value = 0.155). Yet, there is statistical evidence for a moderate regional effect ($\chi^2_{(10df)} = 32.500$, p-value <0.001 and Cramer's V = 0.379, $p < 0.001$). While a plurality of European participants (25%) indicated that biotech regulation in their country completely or moderately discourages the use of genome editing, a plurality of NA respondents (28%) point out that their regulation moderately discourages or has no effect on the use of genome editing.

2.3.4. Advocacy groups and genome editing

Results show that 64% of respondents believe that advocacy groups completely or moderately discourage the use of genome editing in agriculture in their region, regardless of their expertise ($\chi^2_{(5df)} = 8.762$; p-value = 0.119) or where they live ($\chi^2_{(10df)} = 12.777$; p-value = 0.236). However, some experts are more encouraged, with a plurality believing some advocacy groups offer a little or moderate support for the use of genome editing in their country (Table 4). There is evidence that neither an expertise effect ($\chi^2_{(5df)} = 2.837$; p-value = 0.725) nor regional effect ($\chi^2_{(10df)} = 8.706$; p-value = 0.560) is significant factor in opinion formation.

Different regional views—mostly related to the precautionary perspective, the flexibility of biotech regulations and their role in facilitating the use of genome editing in agriculture—were expected. At their emergence, NBTs including genome editing, were deemed outside the scope of the conventional GM policy, especially in regions that have process-based frameworks, which partly explains an unusually high number of experts without strong opinions. In the interim, North and South American countries moved to review genome edited products on a case-by-case basis, while many other regions remain undecided how to deal with them e.g. (Smyth, 2019). A range of socio-economic considerations are being considered alongside the science-based risk assessment of human and environmental safety. Mutual understanding and accommodation of different views will be essential to advancing more socially-responsible governance in agricultural biotechnology (Hartley et al., 2016).

2.3.5. Science vs socio-economic considerations

A key finding from previous surveys within this project is that the successful use of targeted breeding techniques is not grounded solely in science, but political attitudes and societal aspects are of substantial importance (Lassoued et al., 2018a). We were interested in what type of norms might be integrated into regulation to accommodate current and future technologies. Specifically, expert opinion was elicited on whether national biosafety policies governing NBTs including genome editing should be science-based or a combination of science and socio-economic considerations (SECs). Table 5 reports the results divided into three groups: (i) those who think that biotech regulation should be purely based on scientific evidence (33%), (ii) a plurality (44%) who think that some socio-economic factors such as consumer preference and animal welfare should be incorporated as secondary considerations, and (iii) those who think that the regulation should consider both science-based norms and non-science-based norms equally. These opinions are consistent across groups of experts ($\chi^2_{(2df)} = 1.430$; p-value = 0.489) and regions ($\chi^2_{(4df)} = 8.463$; p-value = 0.076).

Most experts (67%) believe that biotech regulation should not be solely based on science. Many now accept that science cannot solve disputes about risks of new technologies hosted in complex socio-technical systems

Table 4
Expert opinion on the impact of advocacy groups on the adoption of genome editing in agriculture.

Group type		Not at all successful	Slightly successful	Moderately successful	Very successful	Completely successful	Not sure	Total
Expertise	Scientific experts	9	13	14	7	1	12	56
	Social experts	7	13	14	3	1	6	44
	Total	16	26	28	10	2	18	100
Region	NA	6	16	15	3	0	10	50
	Europe	7	7	7	4	1	4	30
	ROW	3	3	6	4	1	3	20
	Total	16	26	28	11	2	17	100

Table 5
Expert views on what norms should be included in national biosafety policies governing NBTs.

	Group type	Only science-based norms	Mostly science-based norms with some non-science-based norms	Both science-based norms and non-science-based norms equally	Total
Expertise	**Scientific experts**	17	27	12	**56**
	Social experts	16	17	11	**44**
	Total	33	44	23	**100**
Region	**NA**	15	21	14	**50**
	Europe	10	18	2	**30**
	ROW	8	5	7	**20**
	Total	33	44	23	**100**

Table 6
Expert opinion on SECs that could be included in NBT risk assessment processes.

Socio-economic considerations*	%
Food security	**75**
Impact on conservation and sustainable use of biodiversity	**69**
Compliance with biosafety measures, including institutional costs	**67**
Economic impacts of changes in pest prevalence due to changes in farm management practices	**66**
Economic impacts of changes in application rates and effectiveness of pesticides and herbicides	**64**
Secondary health-related impacts, such as result from changes in the use of pesticides and herbicides	**58**
Farmers' rights	**55**
Coexistence of genetically modified organisms	**52**
Impacts on indigenous and local communities, livelihoods, traditional knowledge and biodiversity	**51**
Macroeconomic impacts, including those on sustainable development	49
General ethical norms	46
Impacts on consumer choice or consumption patterns	42
Microeconomic impacts at the individual, household or community level	19
Land tenure	18
Cultural and spiritual practices	18
Impacts on market access and trade at national and international levels	15
Labor and employment impacts	12
Gender impacts	10
Rural-urban migration	10

The list of SECs was adapted from (UNEP) (UNEP, 2019).
Total does not add up to 100% due to multiple responses.

(Sarewitz, 2015). We invited those who believed that the system needs to incorporate SECs to prioritize a selection of the SECs identified by the UN Development Program. Table 6 shows the responses. The majority of those wanting SECs in the system agreed that nine considerations should be targeted, including: food security; conservation and sustainable use of biodiversity; compliance with biosafety measures; economic impacts of changes in pest prevalence; economic impacts of changes in application rates and effectiveness of pesticides and herbicides; and secondary health-related impacts due to changes in the use of chemicals; farmers' rights; co-existence of GMOs; and impacts on indigenous and local communities.

2.4. Responsible innovation

The accelerated development and widespread use of genome editing requires an international dialogue to resolve gaps or inconsistent decisions and to ensure responsible innovation (RI) (Fears and Ter Meulen, 2018). Experts were presented with a definition of RI proposed by Stilgoe et al. (Stilgoe et al., 2013) and asked about the importance of the concept in the development of NBTs and genome editing, using a five-point Likert scale. The majority of experts indicated that responsible science is very (46%) or completely (17%) important for the development of emerging technologies in agriculture; a further 21% agreed the concept is moderately important; only 12% believed it is only slightly important and just 6% declared it was not at all important. In the same vein, most respondents indicated that conduct consistent with RI is very (20%) or completely (16%) encouraged in their work environment, and 26% thought it is moderately encouraged.

Experts were also consulted on the role of the researcher and research institution in setting the rules for developing novel plant breeding tools. Table 7 reports the majority agree or strongly agree that scientists are ultimately responsible for developing technologies that are socially desirable, safe and useful in addressing socio-ecological challenges. Responsible innovation requires scientific experts to be open and transparent about their knowledge and practices. According to Hartley et al. (Hartley et al., 2016) commitment to candour is one of the five pillars of responsible practices of agricultural innovation. This should include disclosure of the scope and quality of available scientific knowledge, the feasibility of claimed benefits and the range of concerns at stake. Stilgoe, Owen (Stilgoe et al., 2013) advocate that both inclusion and anticipation are among the fundamental dimensions of the RI framework that addresses social and ethical concerns. Tansparency of innovators and inclusion of societal actors help foster public trust in science.

2.5. Experts' risk preferences

The survey also investigates expert risk preferences regarding NBT applications. It tests for a relationships between framing and risk choice, using the H0 that framing and choice are independent. Tabulated statistics and Chi-square analysis assessing expert risk preferences with respect to choice of technology (NBT A versus NBT B) are reported for the total sample by region and by expertise.

2.5.1. Overall results

As in many other studies, we found that our panel was generally risk averse. However, we found that changing the framing had a significant effect. When the choices were presented in positive terms (i.e. the number of producer crops saved), the majority of experts (64%) preferred a sure outcome of saving 17,250 crops threatened by the onset of severe environmental conditions (i.e. NBT A) versus a risky option of taking a one-third chance of saving all 51,750 crops (i.e. NBT B). When the options were negatively framed (i.e., number of producer crops lost), only 58% selected the risk-free option. Thus, even though the options were logically equivalent,

Table 7
Role of the researcher/research institution while developing NBTs.

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree	Don't know
Target to develop a NBT that is socially desirable	4	6	27	34	28	1
Be inclusive, involving representatives of society in the research process	5	13	21	50	10	1
Comprehensively explain its activities to the public	1	1	8	47	43	0
Proactively investigate NBT's unintended impact(s)	2	4	13	41	39	1
Be held responsible of the outcomes of the NBTs	3	9	21	36	28	3
Target to develop NBTs that will address critical challenges such as food insecurity	1	1	15	30	52	1
Be transparent (i.e. share knowledge widely)	0	2	8	31	59	0

Table 8
Rates of technology choice by frame type among groups of experts.

Expertise	Frame type		Negative		Total
			NBT A	NBT B	
Scientific experts	Positive	NBT A	51	19	70
		NBT B	6	24	30
		Total	57	43	100
		χ^2 (1df); p-value	14.469; <**0.001**		
		Φ; p-value	0.479; <**0.001**		
Social experts	Positive	NBT A	48	8	56
		NBT B	10	34	44
		Total	58	42	100
		χ^2 (1df); p-value	20.065; <**0.001**		
		Φ; p-value	0.633; <**0.001**		

most experts demonstrated risk aversion in the positive frame and in the negative frame.

Some participants (6%) exhibited a choice shift in their risk preferences as they switched from being risk averse in the positive scenario to risk seeking in the negative scenario. Such a shift is statistically significant ($p < 0.05$) at a 99% confidence level with a moderate to strong effect of 0.54 ($p < 0.05$). In other words, framing has a moderate to strong effect on expert risk choices within the overall sample. This result is in line with a string of previous research that has shown the presence of framing effects in experienced, professional decision makers e.g. (Fu et al., 2018).

2.5.2. Results by expertise

Table 8 shows that both scientific and social experts opted for the certain outcome under both frames. The tests led us to reject the null hypothesis that the type of frame and the choice preferences are independent among groups of experts. In fact, 13% of scientific experts shifted from being risk averse in the positive scenario to risk seeking in the negative scenario, while only 2% of social experts switched, in this case in a somewhat perverse search for more risk when the outcomes were framed as gains. In other words, framing has a moderate to strong effect on expert risk choices within the overall sample.

2.5.3. Results by region

Table 9 shows the majority of participants from NA, Europe and the ROW opted for the certain outcome under both frames. Results also show evidence against the null hypothesis for both NA and the ROW that the type of frame and the preference choices are independent ($p < 0.05$), but not among European respondents ($p > 0.05$). While 15% of European experts shifted from being risk averse in the positive scenario to risk seeking in the negative scenario, the shift was not statistically significant. Thus, there is insufficient evidence against H0—risk choices appear independent from framing within the European region. From Table 9, we can observe that tolerance for risky choices was higher in North America and the ROW than the EU and that we could reject the hypothesis of independence of frame and choice in NA and the ROW. Our respondents from Europe were unaffected by risk framing.

Table 9
Rates of technology choice by frame type among regions.

Region	Frame type		Negative		Total
			NBT A	NBT B	
NA	Positive	NBT A	50	11	**61**
		NBT B	9	30	**39**
		Total	**59**	**41**	**100**
		p-value ($F_{(1df)}$)	<**0.001**		
		Phi; p-value	0.592; <**0.001**		
Europe	Positive	NBT A	47	27	**74**
		NBT B	12	14	**26**
		Total	**59**	**41**	**100**
		p-value ($F_{(1df)}$)	; **0.264**		
		Phi; p-value	0.175; **0.307**		
ROW	Positive	NBT A	52	4	**56**
		NBT B	0	44	**44**
		Total	**52**	**48**	**100**
		p-value ($F_{(1df)}$)	<**0.001**		
		Φ; p-value	**0.919**; <**0.001**		

p-Values of Fisher's exact test were used instead of Chi-square test as a couple of cells **have less than five observations.**

3. Conclusion

The majority of experts surveyed conclusively agree genome editing poses no significant risks to the economy, environment, human health or society. This sample of experts thought existing national regulations work to discourage genome editing in many countries; a view that was strongly held in Europe.

The current generation of genomic technologies, including genome editing, challenges existing precautionary-based governance approaches. The 2018 CJEU ruling on mutagenesis and the resulting experts' reaction reflect such challenges. A number of EU states are calling for a coalition to update the EU GM legislation with regards to NBTs (Fortuna, 2019). This signals that respective regulatory systems are dysfunctional as they do not support advancement of innovative plant breeding. Our expert panel suggest this is because discussions concerning the risks associated with genome editing, and targeted breeding techniques generally, are driven more by socio-political factors than by scientific principles.

While the experts in this survey overwhelmingly support the safety of genome editing and the resulting products, they also acknowledge that rigid adherence to science-based regulatory frameworks will not facilitate the commercialization of future innovations. Experts are aware of the 'pushback' coming from environmental NGOs (eNGOs) opposed to the use of new genomics tools in crop breeding. This opposition is based on speculative risks, those that have no established theory or evident data. The challenge of attempting to reconcile speculative risks with risks grounded in theory and evidence, is that speculative risks can be very fluid and dynamic, changing at will and frequently at the whim of eNGO political motives.

Decision-making in the real world is complex. The final risk assessment decision is often not based solely on technological aspects (as expressed by experts) but involves some consideration of social issues and perspectives (raised and articulated by the lay public). Our results show that a majority of 67% of experts are in favor of incorporating a number of SECs in regulatory frameworks which would be a dramatic shift from current practices in an effort to address the gap in opinions between scientists, regulators and end-users (adopters and consumers). Moving from objective guidelines and tests (scientific evidence) would imply introducing more room for cognitive and politically motivated biases to enter the regulatory system. Key challenge will be handling risk framing, which could lead to significant divergences within and between regulatory systems. Experts are not immune as shown by our results. If SECs were to be considered for inclusion, measurable objectives would need to be established, validated methods to be identified and the risk framing to be normalized for the choices in the system (set negative frame or positive frame for reviews, rather than let individuals and groups choose whatever supports their perspective). Preference would need to be given for negative framing, thus supporting innovation.

Innovations face commercialization challenges in some markets due to the role of advocacy groups, leading to the question of whether it may be the time to reconsider the RI model? The challenge of incorporating SECs is that many of the eNGOs advocating them argue that they must be assessed from a zero risk perspective, that is, if any one individual is made worse off, then the innovation in question should be rejected. Additionally, many of the SECs are included in the present global risk assessment framework developed by the OECD and to explicitly remove them from science-based risk assessment methodologies would simply be a duplication of effort and add needless costs to the risk assessment process. The lack of rigourous methodologies and consensus on factors of inclusion create high levels of uncertainty, which is negatively correlated to innovation investment. As an example, there is no globally accepted definition on how to measure improvements in food security, the leading SEC factor survey experts identified could be included in the risk assessment process.

One of the consistent impacts of innovations is that they create 'winners' and so-called 'losers', those that do not, or will not, adopt. The concern about including SECs into a science-based regulatory system is this results in a rigourous application of the precautionary principle, raising commercialization uncertainties beyond acceptable levels, driving R&D investments to other jurisdictions that regulate solely on science-based frameworks. The EU has tried to integrate SECs into their regulatory framework, with the result being one GM crop approval since 2003. This is not the record of success that is going to reduce food insecurity, or contribute to the global acceptance of genome editing technologies.

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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Declaration of competing interest

The authors declare no conflict of interest.

Appendix A. Biosafety risks of NBTs survey

Consent

Dear participant,

We appreciate your participation in our seventh quarterly survey that includes questions related to **risk/safety of New Breeding Techniques (NBTs)**. The questionnaire is part of a three-year project on risk decision-making regarding NBTs. You have already completed at least one survey with us, and your responses have been invaluable in moving the project forward.

The multi-year survey project is investigating risk preferences among knowledgeable experts regarding innovative technology applications in the agri-food industry. The lead researchers for this project are: Dr. Stuart Smyth (stuart.smyth@usask.ca, (306) 9662929) and Dr. Peter Phillips (peter.phillips@usask.ca, (306) 9664021). They can be contacted should you have any questions or comments. Any questions regarding your rights as a participant may be addressed to the University of Saskatchewan Research Ethics Office ethics.office@usask.ca; (306) 966–2975. Out of town participants may call toll free (888) 966–2975.

As an expression of our gratitude, we will ensure you are granted access to all publications, reports and press releases prior to their publication.

This survey is hosted by Voxco, a Canadian-owned and managed company whose data is securely stored in Canada. Please consider printing this page for your records.

There are no known risks to participating in this survey; however, as with any online activity the risk of breach of confidentiality is always possible.

In order to complete this survey, you may be required to answer certain questions; however, you are never obligated to respond and you may withdraw from the survey at any time by closing your internet browser.

By selecting next and completing this questionnaire, your free and informed consent is implied and indicates that you understand and accept the above conditions of participating in this study.

Background: Our previous survey covered questions on the benefits of the new breeding techniques (NBTs), specifically gene editing crops. In this survey, we want to understand what **risks or safety issues** can be posed by these new technologies and by their derived crops.

1. People often disagree about the nature of technological risk. Please rate how much risk you believe gene editing tools pose to:

	No risk at all	Slight risk	Moderate risk	High risk	Extreme risk	Don't know
Society	☐	☐	☐	☐	☐	☐
The economy	☐	☐	☐	☐	☐	☐
Human health	☐	☐	☐	☐	☐	☐
The environment	☐	☐	☐	☐	☐	☐

2. How familiar are you with the risk assessment and risk management regulatory frameworks governing biotechnology set by your country?
   - ☐ Not familiar at all
   - ☐ Slightly familiar
   - ☐ Moderately familiar
   - ☐ Very familiar
   - ☐ Extremely familiar
3. Would you describe legislation (risk assessment, risk management frameworks) governing biotechnology in your country/region as?
   - ☐ More precautionary/protective (such as in the European Union)
   - ☐ Less precautionary/protective (such as in the United States and Canada).
   - ☐ I don't know
4. As you consider commercializing gene edited crops, how strict or flexible do you think that the current risk assessment and risk management regulatory frameworks in your country are:
   - ☐ Far too strict
   - ☐ Moderately strict
   - ☐ Neither strict nor flexible
   - ☐ Moderately flexible
   - ☐ Far too flexible
   - ☐ Not sure
5. To what extent do you think **biotech legislation** in your country **encourages** the use of gene editing tools in crop development?
   - ☐ Completely discourages
   - ☐ Moderately discourages
   - ☐ Neutral (Neither encourages nor discourages)
   - ☐ Moderately encourages
   - ☐ Completely encourages
   - ☐ Not sure
6. To what extent are **advocacy groups** encouraging the use of gene editing in agriculture in your country?
   - ☐ Completely discouraging
   - ☐ Moderately discouraging
   - ☐ Neutral (Neither encourage nor discourage)
   - ☐ Moderately encouraging

- Totally encouraging
- Not sure

7. To what extent are advocacy groups' **successful in encouraging** the use of gene editing in your country?
   - Not at all successful
   - Slightly successful
   - Moderately successful
   - Very successful
   - Completely successful
   - Not sure

8. New breeding techniques and their derived products may fall outside the scope of exiting regulatory frameworks on biotechnology in some countries that have process-based frameworks. Do you think that national biosafety policies governing new breeding technologies including gene editing should include:
   - Only science-based norms
   - Mostly science-based norms with some non-science-based norms including such socio-economic factors as consumer preference and animal welfare
   - Both science-based norms and non-science-based norms equally
   - Mostly non-science-based norms with some science-based norms
   - Only non-science based norms

9. Which socio-economic considerations do you feel are very important to include in the risk assessment process of NBTs, including gene-editing:
   - Impacts on market access and trade at national and international levels
   - Macroeconomic impacts, including those on sustainable development
   - Microeconomic impacts at the individual, household or community level
   - Compliance with biosafety measures, including institutional costs
   - Coexistence of genetically Modified Organisms (GMOs)
   - Secondary health-related impacts, such as result from changes in the use of pesticides and herbicides
   - Gender impacts
   - Labor and employment impacts
   - Impacts on consumer choice or consumption patterns
   - Food security
   - Land tenure
   - Rural-urban migration
   - Farmers' rights
   - Cultural and spiritual practices and
   - General ethical norms
   - Economic impacts of changes in pest prevalence due to changes in farm management practices
   - Economic impacts of changes in application rates and effectiveness of pesticides and herbicides
   - Impacts on indigenous and local communities, livelihoods, traditional knowledge and biodiversity
   - Impact on the conservation and sustainable use of biodiversity
   - Other (Please specify) ……

We are interested in your opinion about the concept of: **Responsible Innovation** (RI). According to Stilgoe et al., 2013, "responsible innovation means taking care of the future through collective stewardship of science and innovation in the present." (Source: https://doi.org/10.1016/j.respol.2013.05.008)

10. In your opinion, to what extent is Responsible Innovation (RI) important in the development of new breeding technologies (NBTs)—including gene editing in agriculture?
    - Not at all important
    - Slightly important
    - Moderately important
    - Very important
    - Completely important
    - Not sure

11. Do you agree or disagree that while developing new breeding technologies (NBTs), including gene editing, the researcher/ the research institution should:

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree	Don't know
Target to develop a NBT that is socially desirable						
Be inclusive, involving representatives of society in the research process						
Comprehensively explain its activities to the public						
Proactively investigate unintended impact(s) of the NBT						
Be held responsible of the outcomes (positive or negative) of the NBT						
Target to develop NBTs that will address critical challenges such as food insecurity						
Be transparent (i.e. share knowledge widely)						

12. In your work environment, to what extent is conduct consistent with Responsible Innovation (RI) encouraged?
    - Not at all encouraged
    - Slightly encouraged
    - Moderately encouraged
    - Very encouraged
    - Completely encouraged
    - Not sure
    - Not applicable

13. Finally, we would like you to answer the following **hypothetical** scenarios about two technologies.

13.1. Imagine that your country is preparing for the onset of severe environmental conditions, which are expected to destroy 51,750 producers' crops. Two alternative new breeding technologies (NBTs) have been proposed. Assume that the scientific estimates of the consequences of the technologies are as follows:

- If Technology A is adopted, 17,250 producers' crops will be saved.
- If Technology B is adopted, there is 1/3 probability that 51,750 producers' crops will be saved, and 2/3 probability that no producers' crops will be saved.

Which of the two technologies would you favor?

o Technology A
o Technology B

13.2. Imagine that your country is preparing for the onset of severe environmental conditions, which are expected to destroy 51,750 producers' crops. Two alternative new breeding technologies (NBTs) have been proposed. Assume that the scientific estimates of the consequences of the technologies are as follows:

• If Technology A is adopted, 34,500 producers' crops will be lost.
• If Technology B is adopted, there is 1/3 probability that no producers' crops will be lost, and 2/3 probability that 51,750 producers' crops will be lost.

Which of the two technologies would you favor?
o Technology A
o Technology B

14. Any comments you would like to share with us?

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