



Formulating best practices for responsible innovation of nano-agrifoods through stakeholder insights and reflection

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ABSTRACT

Nanotechnology in food and agriculture (nano-agrifoods) may provide numerous benefits to society. At the same time, previous experiences have demonstrated the importance of innovating responsibly. This study reports on stakeholder-identified actions to address concerns about nano-agrifoods and actions to ensure their responsible innovation (RI). We find stakeholders largely supported actions to address risk and safety, followed by governance actions, the examination of 'need,' and identification of clear benefits. Participants also indicated no actions would address their concerns in several cases, largely for nano-in food products without a clear 'need' and risk/benefit comparisons. We conclude by highlighting four best practices to foster RI of nano-agrifoods, with relevancy for other novel agrifood technologies, including the institutionalization of RI, education and training next generation of researchers and innovators, use of tiered approaches to implement RI principles at different levels and degrees, and incorporation of monitoring and learning systems to improve RI practices.

1. Introduction

Nanotechnology in food and agriculture (nano-agrifoods) may provide numerous benefits to society. For instance, the use of nanotechnology and engineered nanomaterials may help achieve more sustainable food and agricultural production through harnessing unique physical-chemical properties and associated functionalities that occur at the nanoscale (An et al., 2022; Duhan et al., 2017; Rodrigues et al., 2017). Nano-fertilizers and nano-pesticides may offer more efficient delivery of agrochemicals, while reducing environmental run-off (Kumar et al., 2019; Sampathkumar et al., 2020), nanomaterials in foods and food supplements may provide enhanced nutritional value (Prakash et al., 2018), and nano-encapsulated veterinary medicines may provide more animal-friendly vaccine delivery for agricultural livestock (Renu et al., 2020). Given these potential benefits and the continued need to develop more sustainable agrifood technologies to feed a growing population (National Academies of Science, 2019), substantial investments in nano-agrifood research and development have been made alongside commercial interest (EstiCast Research & Consulting, 2018; Helmut Kaiser Consultancy, 2015; Parisi et al., 2015).

At the same time, previous experiences with other emerging agrifood technologies have also demonstrated the importance of innovating

responsibly, by factoring in environmental, health, and safety (EHS) aspects along with social and ethical concerns, stakeholder engagement, and ensuring trust and transparency (e.g., (Kuzma et al., 2008; Yue et al., 2015a). For instance, the first generation of genetically modified (GM) crops faced considerable backlash in some cases, due to a lack of transparency of GM ingredients in the food supply, lack of stakeholder involvement and openness, consumer attitudes and perceptions of safety, and lack of trust in industry and institutions (Kuzma and Roberts, 2018a). Building on these experiences and coupled with other scientific crises (e.g. Bovine Spongiform Encephalopathy (BSE) and mad cow disease, presence of dioxins in poultry, GM crops), the field of responsible innovation (RI) emerged in the early 2010s as a way to better align research and innovation with societal needs, values, and expectations (Owen et al., 2021). While numerous authors have proposed slightly different definitions of RI (Kokotovich et al., 2021), one of the most commonly cited definitions was proposed by Stilgoe et al. (2013), as "taking care of the future through collective stewardship of science and innovation in the present" and based on four pillars (anticipation, inclusion, reflexivity, responsiveness) (Stilgoe et al., 2013).

As a way to reap the potential benefits of nanotechnology and nanomaterials while also minimizing potential risks and learning from past experiences, various organizations in the US and other countries

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developed initiatives to pursue the responsible development and innovation of nanotechnology (European Commission (EC), 2020; National Nanotechnology Initiative (NNI), 2020; Organisation for Economic Co-operation and Development (OECD), 2020). These initiatives included substantial research investments at national and international scales to better understand potential EHS impacts as well as social, ethical, and legal implications (ELSI) of nano-enabled products and applications, including those in food and agriculture sectors. Among these studies are investigations into consumer and public attitudes, perceptions, and acceptance of nano-agrifoods (Brown and Kuzma, 2013; Brown et al., 2015; Chang et al., 2017; Chuah et al., 2018; Grieger et al., 2021; Siegrist and Keller, 2011; Yue et al., 2015; Yue et al., 2015b).

Despite substantial investments and research efforts conducted over more than 15 years, it has yet to become clear if the goals of pursuing RI have transferred into practice for many nano-enabled products and applications, including those in food and agriculture. Food and agriculture sectors, in fact, may be among the most sensitive to public scrutiny for nanotechnology applications compared to other fields (e.g. energy, electronics, medicine; (Porcari et al., 2019). This is a critical knowledge gap, as a clearer understanding of how RI has occurred for nano-agrifoods is important to not only evaluate the implementation of RI in nano-agrifoods, but also to reflect on best practices relevant for other emerging agrifood technologies that may be considered in the coming years (e.g. cell cultured meat, 3D printed foods, gene editing (Brunner et al., 2018; Post, 2012; Siegrist et al., 2020).

Only recently have published studies reported on if and how RI practices have been implemented within nano-agrifood sectors. For example, Kokotovich et al. (2021) found that researchers and innovators largely framed RI within the pillar of “anticipation” with a primary focus on ensuring nano-agrifood product safety, efficacy, and efficiency, with less emphasis on other pillars of inclusion, reflexivity, and responsiveness based on semi-structured interviews with 20 nano-agrifood researchers and innovators in the U.S. (Kokotovich et al., 2021). Using the same interview data, Cummings et al. (2021) also identified five key barriers to RI of nano-agrifoods according to researchers and innovators, including i) lack of data and prevalence of uncertainty, ii) lack of adequate product oversight, iii) need for ensuring marketability and use, iv) need for increased collaboration, and v) lack of adequate training and workforce (Cummings et al., 2021).

In addition, Grieger et al. (2021) recently investigated how diverse stakeholders in the U.S. viewed nano-agrifoods, including views of potential concerns, how well they aligned with principles of RI, and what challenges they foresaw in achieving RI of nano-agrifood products. Results from this work revealed that stakeholders viewed nano-agrifoods primarily within frames of considering EHS impacts, followed by the ability to respond to a larger societal need, and risk/benefit comparisons (Grieger et al., 2021). Participant views were also found to differ between case studies involving nano-agrifoods, whereby participants considered nano-agricultural (i.e., nano-ZnO particles to combat citrus greening) and veterinary medicine (i.e., chitosan nanoparticle-encased *Salmonella* vaccine) case studies as most adhering to RI, while nano-food (i.e., nano-titanium dioxide in infant formula) and food supplement (i.e., nano-copper dietary supplement) applications least adhering to RI. Stakeholders further expressed concerns and identified challenges to ensuring RI of nano-agrifoods including uncertainties in EHS studies, the need for public understanding and acceptance, adequate regulation, market-based pressures and funding levels, need for stakeholder engagement, among other obstacles (Grieger et al., 2021).

Building on this body of literature and leveraging recent results from Grieger et al. (2021), this paper identifies actions that academics, industry, and/or regulators could take, if any, to address stakeholder concerns of nano-agrifoods based on responses from 55 stakeholder participants in the U.S. This paper also reports on actions that could be taken by researchers and developers to ensure RI of nano-agrifoods as

identified by stakeholder participants. After presenting these results, this paper reflects upon these findings in a broader context of RI and identifies best practices for RI of nano-agrifoods with relevancy for other agrifood technologies. Overall, outcomes from this work may be relevant and useful for researchers, scientists, industry, and policy-makers to help ensure RI occurs within nano-agrifood sectors with relevancy for the overall sustainability of other emerging food and agriculture technologies.

2. Materials & methods

This study was conducted as a part of a larger U.S. Department of Agriculture (USDA), National Institute for Food and Agriculture (NIFA)-funded grant that focuses on the societal implications and RI of nanotechnology used in food and agriculture (Grant No. 2019–67023–29855; PI = Grieger, Co-PI = Kuzma). As a part of the grant, we developed and conducted an online stakeholder engagement platform to investigate diverse U.S. stakeholder views of nano-agrifoods and RI. We previously reported on the process and approach to develop the online stakeholder engagement platform in Ruzante et al. (2022), which includes an overview of the engagement platform and all tasks and activities that study participants completed. We also reported on a subset of the results from the stakeholder engagement study, in which we describe: i) stakeholder participant views of RI; ii) views of five nano-agrifood case studies, including potential concerns, iii) views of how well nano-agrifood case studies adhered to principles of RI; and iv) challenges identified by stakeholders in terms of achieving RI of nano-agrifoods (Grieger et al., 2021). Full details of this study are publicly available through Open Access here: (<https://www.sciencedirect.com/science/article/pii/S2452074821000744>).

This current paper reports on another subset of results from the online stakeholder engagement platform and is the first to report on stakeholder-identified actions that could be taken to address their concerns and those that could help ensure RI of nano-agrifoods overall. Based on a deeper reflection of the literature related to RI and nano-agrifoods, this paper concludes by highlighting best practices for RI of nano-agrifoods, with relevancy for other agrifood technologies. Below is a summary of the approach used to develop and conduct the online stakeholder engagement platform, with further details provided in Grieger et al. (2021), also publicly available at (<https://www.sciencedirect.com/science/article/pii/S2452074821000744>), and Ruzante et al. (2022), publicly available at (https://www.rti.org/rti-press-publication/nanotechnology-in-food?utm_source=Website&utm_medium=LinkedIn&utm_campaign=Food+and+Ag).

2.1. Online platform and stakeholder engagement study

The stakeholder engagement study was conducted using CMNTY (<https://www.cmnty.com/>), which is an online platform that can be customized for stakeholder engagement activities. As described in Ruzante et al. (2022), the CMNTY platform was chosen for this study since it provided a variety of options and tools to elicit information from study participants and have them engage with one another in a virtual setting. The platform included: (i) a home page with an overview of all activities and tasks for participants; (ii) an electronic consent form for participants; (iii) questionnaires to understand stakeholder participant views of RI and nano-agrifoods; (iv) group forum discussion boards for participants to respond to open-ended questions; and (v) a chat feature to provide an additional communication tool. The research team developed all content for the engagement platform, and tested it prior to its use. After all content was developed and finalized, the stakeholder engagement study was conducted over a three-week period in late October and early November 2020 (Ruzante et al., 2022). After the study was finalized, the engagement platform was closed and participants were no longer able to login to the site, and all results were then exported for analysis.

2.2. Stakeholder participants

We targeted stakeholders who represented a range of sectors in the U.S. that would be interested in nanotechnology in food and agriculture, including academic institutions, government agencies, non-governmental organization (NGOs), think-tanks, advocacy groups, and industry (Ruzante et al., 2022). Study participants were identified using peer-reviewed literature, publicly-accessible databases, conference registration lists related to new technologies in food and agriculture, and the research team's networks related to nanotechnology, food and agriculture, veterinary medicine, and governance of agrifood technologies. We identified and invited 466 potential study participant candidates (Grieger et al., 2021). We obtained IRB approval from the PI's university (NC State, IRB protocol 19,207) prior to reaching out to potential candidates. After inviting them to participate in our study via email, 62 participants responded and agreed to participate in the study, and 55 participants completed all tasks and activities on the engagement platform. Therefore, the total number of study participants was considered to be 55. These participants were distributed across academia ($n = 19$), government ($n = 9$), NGOs/think-tanks ($n = 7$), NGOs/advocacy ($n = 10$), and industry ($n = 10$) sectors, and received an honorarium for completing all study activities. See Ruzante et al. (2022) (available at https://www.rti.org/rti-press-publication/nanotechnology-in-food?utm_source=Website&utm_medium=LinkedIn&utm_campaign=Food+and+Ag) and Grieger et al. (2021) (available at <https://www.sciencedirect.com/science/article/pii/S2452074821000744>) for further details on stakeholder identification, recruitment, and final participation.

2.3. Questionnaires for stakeholder participants

As mentioned above, the online platform used a series of questionnaires to understand stakeholder views of nano-agrifoods and RI. As detailed in Grieger et al. (2021), participants reviewed five case studies involving nano-agrifoods, and then responded to a series of questionnaires on their views of the case studies and how well they adhered to principles of RI. Each case study included a 1-page description of the general context of the case study, how nanotechnology or engineered nanomaterials were used, as well as potential risks and anticipated benefits of the nano-agrifood product. The case studies included a range of nano-agrifood products that were either on the market or in final stages of research and development, and spanned sectors of food, agriculture, and veterinary medicine (see Grieger et al., 2021 for all details, including all information of the case studies):

- A Lemongrass nano-emulsions to prevent surface browning of fresh cut fruit.
- B Chitosan nanoparticle-encased Salmonella antigens for oral vaccine for laying hens.
- C Nano-copper dietary supplement.
- D Zinc oxide nanoparticles to help combat citrus greening disease.
- E Titanium dioxide nanoparticles as a color additive in infant formula.

After reviewing each case study, participants were asked to respond to a series of questions regarding their views of the nano-agrifood case study, how well the case study adhered to RI and associated rationale, and potential challenges they foresaw in ensuring RI of nano-agrifoods. After responding to these questions, the participants were asked to respond to the following question after each case study:

(I) "Given this case study you just read, what actions could academics, regulators, and/or those in industry take to address the concerns that you have (if any) about this nanotechnology application?"

Participants responded to this question in an open-comment field, and each response was linked to a nano-agrifood case study. In addition

and at the end of the stakeholder engagement study, participants were also asked to respond to the following question:

(II): "Overall, what do you think are the three most important actions that those conducting research and development for nanotechnology in food and agriculture should take to ensure they achieve responsible innovation for nanotechnology?"

Participants responded to this question in an open-comment field, and responses referred to nano-agrifoods on a general basis.

Stakeholder participant responses to these open-ended questions (I, II) are therefore the subject of the current paper, with results and discussion reported below.

2.4. Analysis of results

After the online stakeholder engagement study was completed, all participant responses to questions I and II were exported from the CMNTY platform and analyzed using qualitative software (Dedoose) to identify themes and subthemes using descriptive coding approaches (Saldaña, 2013). In this process, participant responses were reviewed by the research team, and codes/sub-codes were identified that related to the actions suggested by participants to address concerns they have (if any, in the case of question I) and to ensure RI of nano-agrifoods (in the case of question II). After codes/sub-codes were identified, figures were developed to visualize the codes/sub-codes against the number of stakeholder excerpts for Figs. 1A, B, 2 and percentage of stakeholders who mentioned each code/sub-code for Fig. 3. We chose to report on number of stakeholder excerpts in Figs. 1A, B, 2 to demonstrate the breadth and depth of themes/sub-themes related to actions to address concerns across the five nano-agrifood case studies, given that a single participant might provide multiple excerpts that touched upon several themes/sub-themes for a given case study. We also chose to report on the percentage of participants who mentioned an action as important to ensure RI in Fig. 3, given that this question was not case study-dependent, referred to nano-agrifoods more generally, and revealed the extent to which study participants identified common themes/sub-themes to ensure RI of nano-agrifoods more broadly. Finally, we identified exemplary excerpts for each theme/sub-theme for use in the results section.

2.5. Identification of best practices for RI

After reviewing the results from stakeholder responses, the authors of this analysis also reviewed the broader literature on RI, nano-agrifoods and RI, challenges to conducting RI in practices, and associated recommendations to fostering RI in fields of agrifood technologies. After reflecting on these findings and the broader literature, we formulated a list of best practices for nano-agrifood RI with relevancy for other novel agrifood technologies.

2.6. Study limitations

We recognize several limitations of the approach taken in this work. First, this study was based on participation from a range of stakeholders in the U.S. that were within sectors of academia, government, NGOs, think-tanks, advocacy groups, and industry. We recognize that study participants from other countries may have provided different responses to the questions on actions to address concerns (if any) and actions to ensure RI of nano-agrifoods, due to e.g. cultural or socioeconomic differences. Second, we recognize that 55 participants completed the study, which is a relatively small sample number. Due to this number of study participants, it was not possible to perform statistical analyses across stakeholder groups in order to evaluate whether some groups provided certain types of responses compared to others. We realize that larger sample sizes may have allowed for more in-depth investigations of

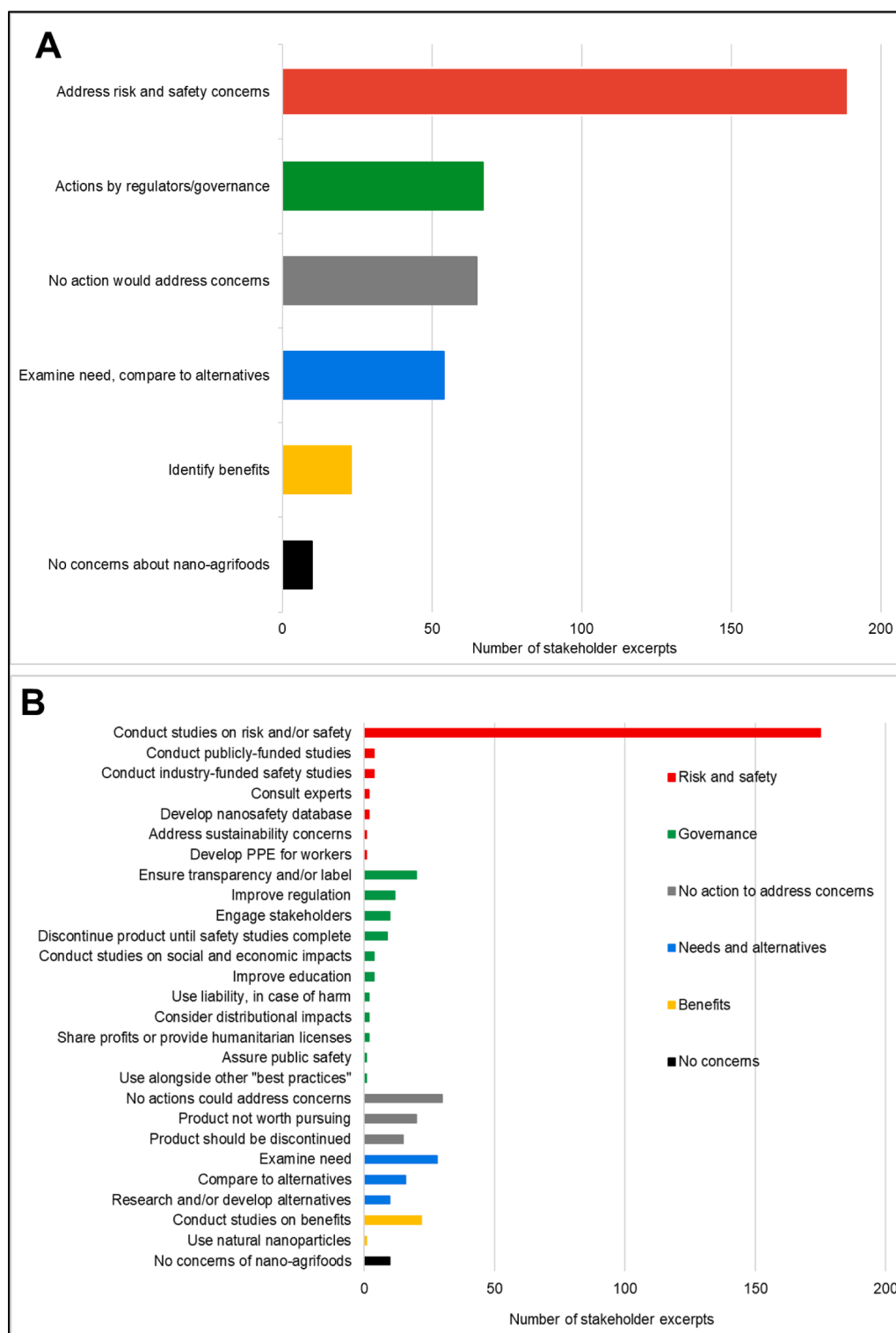


Fig. 1. Actions that academics, regulators, and/or industry could take to address stakeholder concerns regarding five nano-agrifood case studies. Responses to “Given this case study, what other actions could academics, regulators, and/or those in industry take to address the concerns that you have (if any) about this nanotechnology application?” Responses shown across six main themes (A) and sub-themes (B).

stakeholder responses to the posed questions. Nonetheless, we found the results obtained from the sample of 55 stakeholder participants to be interesting and informative in terms of their views on actions needed to address their concerns (if any) and actions to ensure RI of nano-agrifoods more broadly. Third, we conducted this study using an online engagement platform in October and November 2020, and during

the COVID-19 pandemic. While the engagement platform did not allow for in-person verbal dialog, and therefore in some ways may have limited stakeholder exchange and communication, study participants indicated that the platform worked well overall based on results obtained in an exit survey on the platform (as reported on in [Ruzante et al. \(2022\)](#)). Finally, the study participants were not provided with any

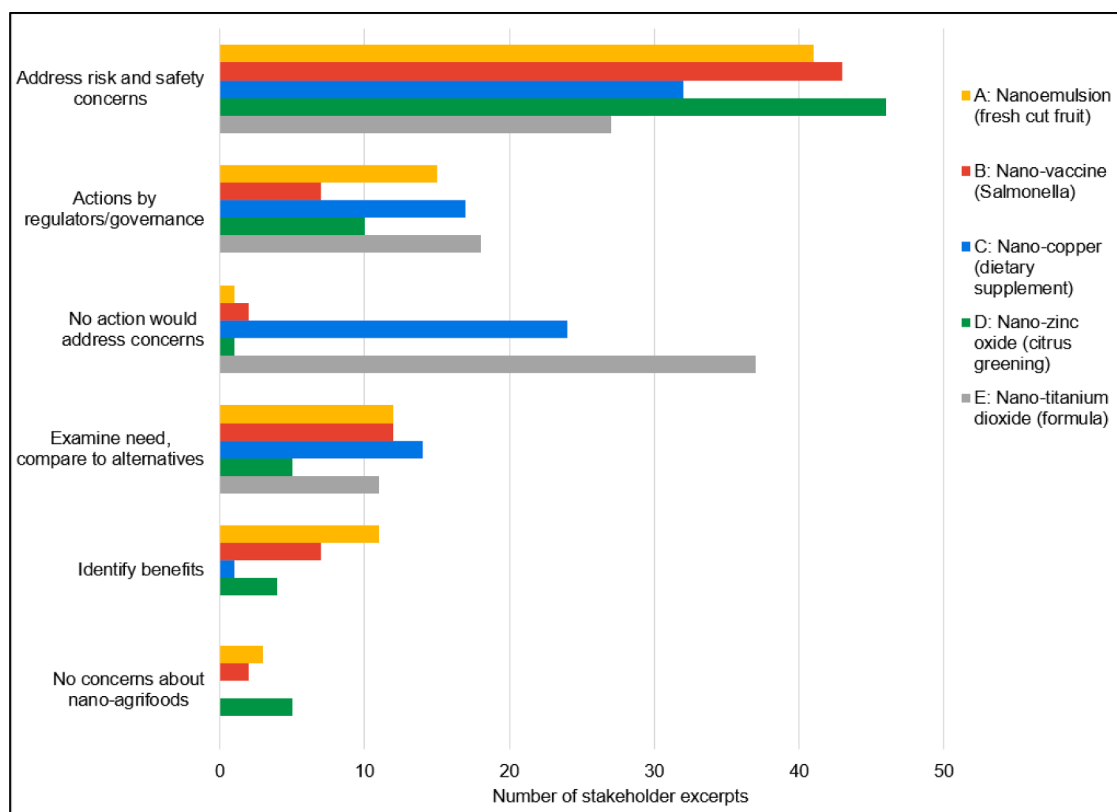


Fig. 2. Actions that academics, regulators, and/or industry could take to address stakeholder concerns regarding five nano-agrifood case studies and across six main themes. Results are similar to Fig. 1A, although shown across the five nano-agrifood case studies. Responses to “Given this case study, what other actions could academics, regulators, and/or those in industry take to address the concerns that you have (if any) about this nanotechnology application?”.

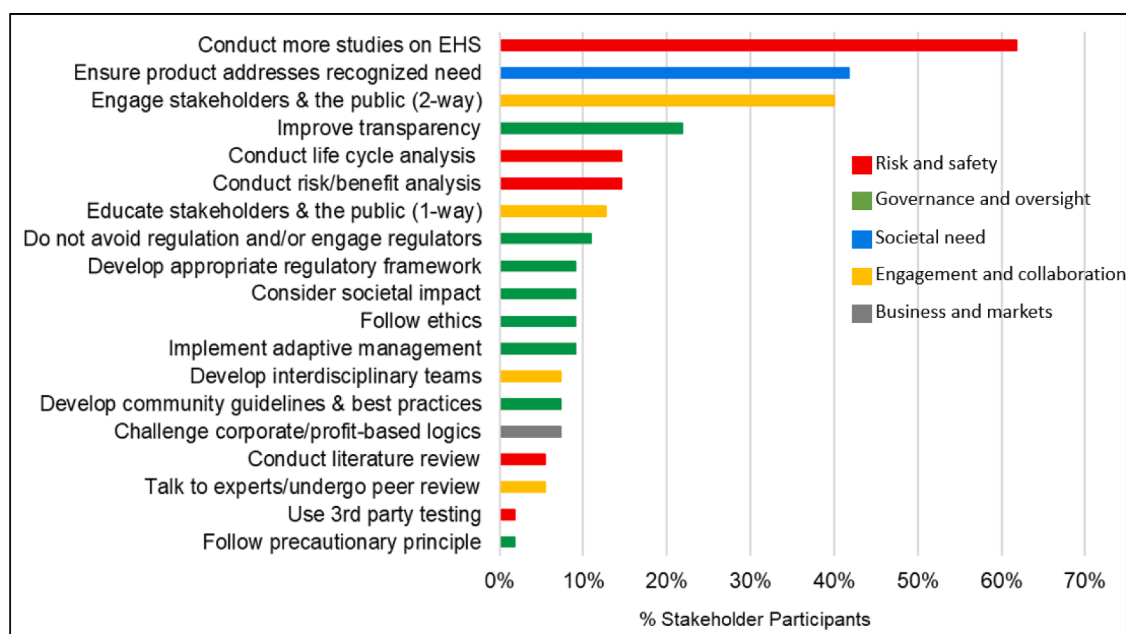


Fig. 3. Most important actions for researchers and innovators to ensure RI of nano-agrifoods according to stakeholder participants. Responses to “What do you think are the three most important actions that those conducting research and development for nanotechnology in food and agriculture should take to ensure they achieve responsible innovation for nanotechnology?” EHS = environmental, health, and safety.

background information on RI, which may have led to more limited responses directly relevant to the RI literature. However, we chose this approach deliberately since we were interested in investigating stakeholder views of RI and nano-agrifoods without prior scholarly

knowledge of RI and RI practices.

3. Results and discussion

3.1. Actions to address stakeholder concerns (if any) of nano-agrifoods

After reviewing each of the five nano-agrifood case studies, study participants were asked to indicate the actions that academics, regulators, and/or industry could take to address their concerns (if any) about the nano-agrifood case. Across all case studies, six major themes emerged from participant responses. The most common theme by far related to actions to *Address risk and safety concerns*, as expressed by 189 individual excerpts in open-comment responses by 55 study participants (Fig. 1A; Table S1). Next, participants indicated that *Actions by regulators and/or governance* would address their concerns (expressed in 67 participant excerpts) and *No action would address concerns* (65 excerpts). Participants also indicated actions to *Examine need or compare to alternatives* (54 excerpts), *Identify benefits* (23 excerpts), and *No concerns related to nano-agrifoods* (10 excerpts) would address their concerns (Fig. 1A).

Each of the six major themes to address stakeholders concerns about nano-agrifoods relate to a variety of sub-themes that provide further details and nuances (Fig. 1B). By far, the most common sub-theme across all participant responses was *Conduct studies on risk and/or safety* expressed by 175 participant excerpts and related to *Address risk and safety concerns* theme (Fig. 1B; Table S1). For example, one stakeholder indicated, “Further detailed studies of the impacts on the environment are needed. Studies of the environmental impacts based on particle dosage and location of application...should be conducted to better address the possible negative effects [of] nanoparticle use.” Also within the theme of risk/safety, other sub-themes were expressed to address stakeholder concerns but to a much more limited extent. These included *Conduct publicly-funded studies* and *Conduct industry-funded safety studies* (4 excerpts each), *Consult experts* and *Develop nanosafety database* (2 excerpts each), and *Address sustainability concerns* and *Develop personal protective equipment (PPE) for workers* (1 excerpt each) (Fig. 1B).

Within the theme of *Actions by regulators/governance*, there was a broad range of actions identified by participants that would address their concerns of nano-agrifood products (Fig. 1B). The sub-theme of *Ensure transparency and/or label* (of nano-agrifoods) was expressed by 20 participant excerpts and exemplified by the quote “The developers could address a lot of concerns by simply disclosing in plain language on the package what technologies are at work. That way people who are not comfortable with the risk could avoid them.” In addition, participants also indicated that actions to *Improve regulation* and *Engage stakeholders* would address concerns (12 excerpts each), with the former sub-theme exemplified by the quote “Advocate for better government oversight of dietary supplements.” Study participants also indicated that actions to *Discontinue product until safety studies are complete* (9 excerpts) and *Conduct studies on social and economic impacts* and *Improve education* (4 excerpts each). Additional sub-themes that were expressed to a limited extent included *Use liability in case of harm*, *Consider distributional impacts*, and *Share profits or provide humanitarian licenses* (2 excerpts each), as well as *Assure public safety* and *Use alongside other best practices* (1 excerpt each) (Fig. 1B).

As mentioned above, study participants indicated that *No actions would address concerns* of nano-agrifoods in some cases (Fig. 1B; Table S1). In fact, 30 participant excerpts were general expressions of this theme, as exemplified by the stakeholder quote “No actions could address my concern.” In addition, participants also expressed that the nano-agrifood *Product not worth pursuing* (20 excerpts) as exemplified by the quotes “This is not worth pursuing” and “Not sure that anything should be done as this is just totally an unnecessary product.” Participants also indicated that no actions would address their concerns in some cases, as the *Product should be discontinued* (15 excerpts) as exemplified by the quote “This should be banned, immediately.” These sub-themes were contrasted by the theme of having *No concerns of nano-agrifoods* (10 excerpts) as exemplified by the stakeholder quote “I don’t

have any concerns about this application of nanotechnology.”

Within the theme of *Examine need, compare to alternatives*, the most prevalent sub-theme was *Examine need*, expressed by 28 participant excerpts and exemplified by the quote “There should be a discussion of need for this type of product.” Participants also mentioned *Compare alternatives* (16 excerpts), as exemplified by the quote “Provide more information about what other options were considered and how did they compare with respect to both potential benefits and risks (including environmental as well as health impacts),” and *Research and/or develop alternatives* (10 excerpts). Finally, within the theme *Identify benefits*, most participants referred to actions to *Conduct studies on benefits* (22 excerpts), as exemplified by the stakeholder quote “I would want to see greater research focus on achieving nutritional benefits from nano-coatings,” in addition to 1 excerpt on actions to *Use natural nanoparticles* (Fig. 1B; Table S1).

Overall, these findings indicate that the study sample of 55 stakeholder participants identified a broad range of actions that academics, regulators, and/or those in industry could take to address their concerns (if any) regarding nano-agrifoods. The most prevalent set of actions identified by participants related to addressing risk and safety concerns, and in particular the need to conduct studies on nano-agrifood risks and/or safety. This finding is consistent with other results from the larger stakeholder engagement study (as reported in Grieger et al. (2021), in which participants predominantly framed concepts of RI within EHS considerations, and also expressed concerns with nano-agrifood case studies largely within aspects of risk, safety, and associated uncertainties. In addition to the emphasis on risks and safety, participants identified a broad range of actions that regulators or those involved in nano-agrifood governance could take to address their concerns, including a focus on ensuring transparency and/or labeling of nano-agrifoods. These results also reveal, interestingly, that no actions could address stakeholder concerns in some instances, as participants did not consider some nano-agrifood products as worthy of pursuit and in some cases should be discontinued, particularly if the benefits did not outweigh risks and there was no societal need for the product. Relatedly, the importance of examining whether the nano-agrifood product fulfilled a larger societal need was also highlighted, as well as the importance of identifying and demonstrating benefits of nano-agrifood products to address stakeholder concerns.

3.2. Differences between nano-agrifood case studies

In addition to identifying actions that could address stakeholder concerns collectively across all case studies, we also find value in investigating actions within and between case studies. These results are displayed in Fig. 2 and Table S2.

For case study A (Lemongrass nano-emulsions to prevent surface browning of fresh cut fruit), the greatest number of excerpts related to *Address risk and safety concerns* (41 excerpts), similar to most other case studies. This theme was followed by *Actions by regulators and/or governance* (15 excerpts), *Examine need or compare to alternatives* (12 excerpts), *Identify benefits* (11 excerpts), *No concerns related to nano-agrifoods* (3 excerpts), and *No actions would address concerns* (1 excerpt). Compared to the other case studies, case study A had the greatest number of excerpts related to *Identify benefits* out of all five case studies. This suggests that participants discussed more frequently the need to clearly identify benefits of this nano-agrifood case study in particular (Fig. 2, Table S2). Several participants also raised potential connections between nano-coatings on fresh cut fruit and a means to provide fresher, more nutritious foods to underserved populations. For example, one participant discussed the need to “examine societal benefits of potentially getting fresh(er) produce to regions that are food insecure or do not have access to healthy food alternatives - will this technology bring societal benefit to underprivileged populations, or will it just be an expensive gourmet item for privileged cohorts?” Also compared to other case studies, participants mentioned actions to *Examine need or compare*

to alternatives (along with case study B and C) and that they had *No concerns* (along with case study B and D) (Fig. 2), as exemplified by the quote “No actions. The materials, application, and potential dose pose no reasonable health or environmental concern.”

Similar patterns are observed for case study B (Chitosan nanoparticle-encased Salmonella antigens for oral vaccine for laying hens). For this case study, the greatest number of excerpts related to actions to *Address risk and safety concerns* (43 excerpts), which was the second highest number of excerpts related to the theme of risk and safety across all five case studies (following case study D) (Fig. 2). After this theme, participants mentioned the importance to *Examine need or compare to alternatives* (12 excerpts), *Actions by regulators and/or governance* and *Identify benefits* (7 excerpts each), and *No action* and *No concerns* (2 excerpts each) for this case study. In contrast to other cases, participants mentioned *Actions by regulators and/or governance* the least often for case study B, as this case had the least number of excerpts for this theme out of all five case studies (Fig. 2; Table S2). At the same time, several excerpts included the importance of considering animal rights and ethics of raising animals for livestock production in actions to foster RI of this case study. For example, one participant noted “An aggressive responsible innovation project could have the effect of simply bringing this technology to the attention of animal activists, who might have otherwise ignored it altogether.” Other notable patterns include the fact that this case study had the second highest number of excerpts related to *Examine need or compare to alternatives*, *Identify benefits*, and *No concerns* compared to the other case studies.

For case study C (Nano-copper dietary supplement), participants most frequently mentioned actions to *Address risk and safety* (32 excerpts) similar to other case studies. However, the next most frequently mentioned set of actions related to *No actions would address concerns* for this case study (24 excerpts), which was in contrast to most case studies, with the exception of case E. This theme was exemplified by the quotes “It’s not clear to me why anyone would pursue the development of this product other than greed” and “There already exist various copper supplements on the market, which fulfill the dietary needs. This product brings no innovation and the risks definitely do not outweigh the benefits.” These two themes were followed by *Actions by regulators and/or governance* (17 excerpts) and *Examine need or compare to alternatives* (14 excerpts). For example, one participant noted “There needs to be a better understanding of whether there is a population who is copper-deficient and who would actually be helped by such a product, more so than just a regular copper supplement.” Finally, stakeholder excerpts related to *Identify benefits* and *No concerns* were nearly entirely absent, with only 1 excerpt related to *Identify benefits* (and similar to case study E).

For case study D (Zinc oxide nanoparticles to help combat citrus greening disease), more than half of all excerpts were related to actions to *Address risk and safety concerns* (46 excerpts). In fact, the greatest number of stakeholder excerpts related to actions to *Address risk and safety concerns* were related to this case study. This theme was as exemplified by the quote “Further studies are needed to understand whether there would be any presence of zinc nanoparticles in fruit that people eat, and if those levels could cause adverse effects.” This theme was next followed by *Actions by regulators and/or governance* (10 excerpts), *Examine need or compare to alternatives* and *No concerns related to nano-agrifoods* (5 excerpts each), *Identify benefits* (4 excerpts), and *No action would address concerns* (1 excerpt). Compared to other case studies, case study D had the highest number of excerpts related to *No concerns related to nano-agrifoods*. One participant noted this in the exemplary quote “Nano-enabled agriculture is going to be critical to combatting global food insecurity this should move toward deployment.” At the same time, case study D also had the lowest number of excerpts related to actions to *Examine need or compare to alternatives* and *No action would address concerns* (Fig. 2) across all case studies.

The most pronounced theme related to Case study E (Titanium dioxide nanoparticles as a color additive in infant formula) by far was *No*

actions would address concerns (37 excerpts). In fact, this case study had the highest number of excerpts related to this theme across all case studies (Fig. 2). Exemplary quotes include “I am not sure that anything could address my concern regarding use of any chemical for esthetic reasons in an infant formula” and “No actions could address my concerns since this product is unneeded and therefore not worth taking any risk.” After *No actions would address concerns*, participants identified actions related to *Address risk and safety concerns* (27 excerpts), *Actions by regulators and/or governance* (18 excerpts), and *Examine need or compare to alternatives* (11 excerpts). There were, in fact, no excerpts that related to actions pertaining to *Identify benefits* or *No concerns related to nano-agrifoods* (similar to case study C). These absences may indicate that participants did not identify any benefits and that some participants had serious concerns about this case study.

Overall, these findings reveal that the study sample of 55 stakeholder participants emphasized the need to *Address risk and safety concerns* across all five nano-agrifood case studies in order to achieve RI. Participants discussed how to address risk and safety concerns most frequently for case study D (Nano-zinc oxide for citrus greening), B (Nano-vaccine for Salmonella), and A (Nano-emulsion for fresh cut fruit). For case studies C (Nano-copper as dietary supplement) and E (Nano-titanium dioxide in formula), participants overwhelmingly indicated that *No actions would address concerns* compared to other case studies. Participants also found value in *Identify(ing) benefits*, mostly for case study A (Nano-emulsion for fresh cut fruit). Further, participants expressed the least concerns with case study D (Nano-zinc oxide for citrus greening) out of all case studies (i.e., *No concerns about nano-agrifoods*). These findings are consistent with those reported in Grieger et al. (2021), in which stakeholders viewed nano-food case studies (C, E) as least adhering to RI, and nano-agriculture (A, B, D) as most adhering to RI, based on factors of risk/safety, responding to a societal need, and risk/benefit comparisons.

3.3. Actions to ensure RI of nano-agrifoods

At the end of the stakeholder engagement study, participants were asked to identify the most important actions that those conducting research and development should take to ensure they achieve RI of for nano-agrifoods. Across responses from 55 study participants, five major themes emerged, relating to actions to address risk and safety, improve governance and oversight, ensure a societal need, improve engagement and collaboration, as well as respond to businesses and market forces (Fig. 3; Table S3).

Consistent with other participant responses that revealed an emphasis on actions to address risk and safety, 62% of participants mentioned that actions to *Conduct more studies on EHS* would help ensure RI of nano-agrifoods (Fig. 3). This theme is exemplified by the stakeholder quotes “Consider safety for multiple potential exposure pathways and receptors (e.g. human safety of nanotech applied to fruit, as well as runoff into the environment from nanotech applied to fruit)” and “Ensure that potential health and environmental impacts of nanotechnology innovations are comprehensively assessed prior to introduction of the technology and negative impacts are mitigated as feasible.” Other actions relating to risk and safety included actions to *Conduct life cycle analysis* and *Conduct risk/benefit analysis*, mentioned by 15% of study participants, as well as *Conduct literature review* and *Use 3rd party testing*, mentioned by 5% and 2% of participants respectively.

The second-most frequently mentioned set of actions were to *Ensure product addresses recognized need*, reported by 42% of participants (Fig. 3). For example, one participant suggested to “Prioritize R&D for nanotechnology in food and agriculture applications that are likely to provide substantial benefits to society if successful in addition to offering an attractive rate of return, ideally solving important problems through nanotechnology that have proven difficult to address through other means.” Another participant emphasized a “focus on needs that aren’t being met - don’t just do nano for the sake of nano.” This theme

was followed closely by *Engage stakeholders & the public (2-way)*, mentioned by 40% of participants. For example, one participant mentioned “Engage with stakeholders to ensure that there is a true need for the product and that it will be accepted” while another participant suggested to “Engage the public for help in identifying the needs and ensure that products really are making a difference.” Other actions relating to engagement and collaboration included *Educate stakeholders & the public (1-way)* (mentioned by 13% of participants), *Develop interdisciplinary teams (7%)*, and *Talk to experts/undergo peer-review (5%)* (Fig. 3; Table S3).

Participants also mentioned a number of actions related to improving governance and oversight of nano-agrifoods. Nearly a quarter (22%) of participants suggested actions to *Improve transparency* (Fig. 3), as exemplified in the quote to “Equally and clearly share all information of products to the public, including the advantages, disadvantages or unknowns.” Other actions included *Do not avoid regulation and/or engage regulators (11%)*, *Develop appropriate regulatory framework*, *Consider societal impact*, *Follow ethics*, and *Implement adaptive management* – all mentioned by 9% of participants. Participants also mentioned actions to *Develop community guidelines & best practices (7%)* and *Follow precautionary principle (2%)*. In addition to these themes, 7% of participants mentioned actions that would *Challenge corporate/profit-based practices*. For instance, one participant mentioned “don’t pursue applications for purely financial gain.”

Collectively, these findings provide insights on the most important actions that researchers and innovators could take to ensure RI of nano-agrifoods according to stakeholder participants. Across the five major themes that emerged from this work, participants again emphasized the importance of addressing risk and safety. In fact, nearly two-thirds of participants suggested that conducting more studies on EHS was important to help ensure RI of nano-agrifoods. After this dominant theme, nearly half of participants mentioned actions to ensure the nano-agrifood product addresses a recognized societal need and engage stakeholders and the public in two-way communication. Further, nearly a quarter of participants supported actions to improve transparency of nano-agrifoods, among other actions relating to governance and oversight, engagement and collaboration, and business and market based actions. Overall, these actions identified by stakeholder participants to ensure RI of nano-agrifoods align with RI pillars of *anticipation* (i.e., evaluating risks and safety), *inclusion* (i.e., engaging stakeholders and the public), and some degree *responsiveness* (i.e., responding to a societal need), with more limited focus on *reflexivity* (i.e., reflecting on goals of nano-agrifood innovation).

3.4. Best practices for pursuing RI of nano-agrifoods

Based on the previously-identified actions, while also reflecting upon the broader field of RI (e.g. (Grieger et al., 2021; Owen et al., 2021; Roberts et al., 2020; Shelley-Egan et al., 2018; van de Poel et al., 2020), we identify four best practices to foster the RI of nano-agrifoods with relevancy for other agrifood technologies (Fig. 4). Each of these are described below.

3.4.1. Develop and embed mechanisms to institutionalize RI principles, practices, and oversight

One of the main barriers to realizing RI within research and innovation settings has been the lack of practical methods, processes, frameworks, and other mechanisms to institutionalize RI (Kuzma et al., 2018a; Roberts et al., 2020; Timmermans et al., 2021). In fact, our previous investigations into RI of nano-agrifoods also highlighted many institutional barriers faced by researchers and innovators to pursue RI, including barriers to collaborating with external stakeholders and outside parties, sharing and reporting data, being transparent about nano-agrifood innovation processes, and engaging regulators (Cummings et al., 2021). In other words, nano-agrifood researchers and innovators have also reported needing to navigate several institutional barriers to pursue RI more broadly (Cummings et al., 2021), even when they were motivated by RI goals and pursuits (Kokotovich et al., 2021). In order to overcome these barriers for RI of nano-agrifoods, mechanisms (e.g. processes, procedures, policies) to institutionalize RI principles and practices will need to be developed and embedded within organizations, companies, and other institutions involved in nano-agrifood research, develop, and innovation (Fig. 4). These types of mechanisms will likely be relevant for RI of other novel agrifood technologies as well, given that the need to better institutionalize RI practices has been cited by authors more widely (e.g. (Owen et al., 2021)).

In order to be effective, mechanisms to institutionalize RI should be implemented in normal, everyday practices for conducting research, development, and innovation, and will likely not be successful if they are viewed as interesting side-projects or even distractions (Shelley-Egan et al., 2018). For instance, Owen et al. (2021) suggest a series of processes that span from early stages of implementing RI within current institutional settings (e.g. creating incentives, having an experimentation period, ensuring adequate resources), to sustained institutionalization (e.g. dedicated leadership, continued institutional commitment and work), to having mechanisms for oversight and compliance (Owen et al., 2021). The institutionalization of RI should also not be a ‘one-size-fits-all’ approach, but rather customized for different organizations, projects, or initiatives. Some authors have also suggested starting this process of institutionalization by building on current approaches

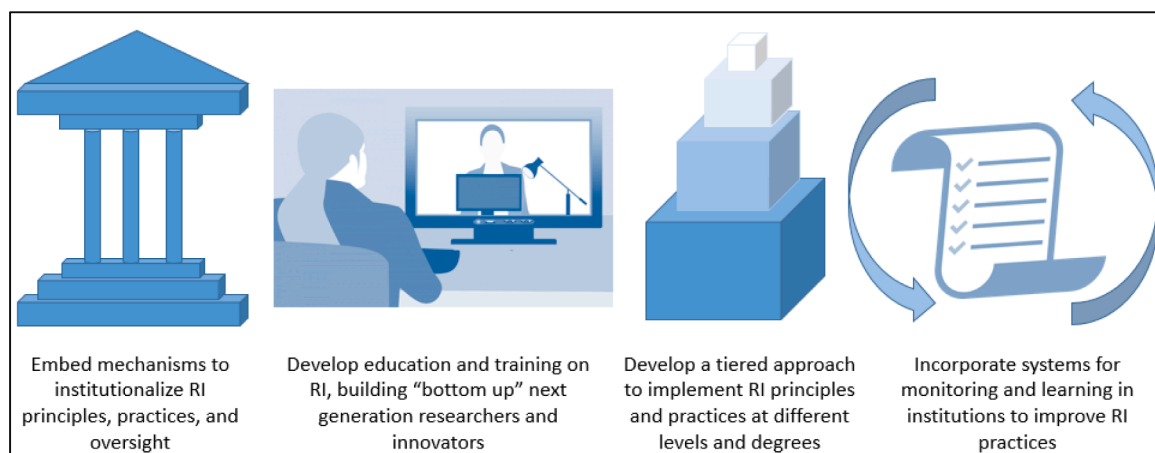


Fig. 4. Identified best practices for fostering RI of nano-agrifoods with relevancy for other novel agrifood technologies.

already used within an organization, rather than starting with completely new approaches brought in from the outside, and placing organizational values on “center stage” (van de Poel et al., 2020). After RI practices are implemented, mechanisms for oversight are also needed (e.g. use of research councils to perform national assessments) to ensure that institutions are committed and following RI principles (Owen et al., 2021).

In the case of nano-agrifoods, stakeholder participants in our study identified a range of actions that researchers and innovators could take to achieve RI (Fig. 3). Many of these same actions could be conducted within current research and innovation settings, including the top four actions identified by stakeholders: *Conduct more studies on EHS*, *Ensure product addresses recognized need*, *Engage stakeholders & the public* (2-way), *Improve transparency*. For example, while EHS studies continue to be conducted on a range of nano-agrifood products, researchers and innovators could implement practices to discuss what it means to innovate responsibly and what practices help foster RI of nano-agrifoods as a first step (Kokotovich et al., 2021). Second, researchers and innovators could institute reflective practices in these conversations to ensure their product of innovation responds to a recognized societal need, and if possible, compare to existing alternatives. Third, researchers and innovators could implement strategies and mechanisms to engage stakeholders and the public, such as utilizing extension and outreach programs, engaging with the public via museums and science exhibits, and working with social scientists and educators on other ways to interact and engage with broader members of the public. Fourth, nano-agrifood researchers and innovators could develop mechanisms to share data among stakeholder groups to improve transparency, while also protecting confidentiality and confidential business information (Grieger et al., 2019). One option could be to share data in an open-access data registry on nano-agrifoods, similar to the approach described for in Kuzma & Grieger (2020) for biotech crops (Kuzma and Grieger, 2020). Fifth, nano-agrifood researchers and innovators could implement practices to revise and update their innovation strategies in light of new data, information, regulatory requirements, and/or findings from stakeholder engagement and outreach programs, as a way to be responsive within their own research and innovation practices. Overall, many of these aforementioned actions outlined for nano-agrifoods are likely applicable to researchers and innovators of other agrifood technologies as well.

3.4.2. Develop education and training on RI, building “bottom up” next generation researchers and innovators

Coupled with efforts to develop and embed mechanisms to institutionalize RI principles and practices is the need to develop and implement education and training on RI within organizations and institutions conducting nano-agrifood research and innovation. This education and training on RI principles and practices will essentially develop “bottom up” strategies to train the next generation of researchers and innovations who work in complex, interdisciplinary fields of nano-agrifoods and RI. The need for more professionals and researchers who can span fields of emerging technologies, food and agriculture, and RI was also identified in our previous work, as one of the key barriers to RI of nano-agrifoods (Cummings et al., 2021). Such “bottom up” education and training could start with graduate student training programs that implement RI principles within their own research and laboratory practices, while also participating in education and training on RI theory and transitions to practice. For example, graduate students interested in developing various nano-agrifoods could implement the five strategic actions outlined above (Section 3.4.1) within their own research groups. This could include collaborations with other graduate students (or researchers) to i) conduct EHS studies on nano-agrifoods (or at the very least, review published studies on potential EHS impacts); ii) reflectively discuss what RI and RI practices entail within nano-agrifood contexts; iii) tap into extension and outreach programs to connect with broader stakeholder groups; iv) share data between research groups aiming to develop

nano-agrifood products and those interested in their impacts; and v) revise research strategies in light of new information. In addition, graduate students could also participate in a variety of workshops and symposia focused on RI theory, including RI definitions and principles (e.g., (Stilgoe et al., 2013) as well as lessons learned from putting RI theory into practice for various fields including those involving nano-technologies (e.g. Cummings et al., 2021; Kokotovich et al., 2021; Kuzma & Roberts, 2018; Kuzma and Cummings, 2021; van de Poel et al., 2020). Since graduate students working in nano-agrifoods and RI will inherently be involved in interdisciplinary, “wicked” challenges, other workshops and symposia could include aspects of working in interdisciplinary teams, engaging and communicating with stakeholders, as well as science and risk communication, among other topics. Such strategies will be applicable to educating and training the next generation of researchers working on other novel agrifood technologies as well.

3.4.3. Develop a tiered approach to implement RI principles and practices at different levels and degrees

As mentioned above in Section 3.4.1, the implementation of RI principles and practices should be customized for different organizations, projects, or initiatives, as a one-size-fits-all approach will not be appropriate for all the different types of nano-agrifoods in research, development, or in commerce. In response, a tiered approach could be developed for nano-agrifoods that implement RI principles and practices at different levels and to different degrees, depending on the specific nano-agrifood product and context under consideration.

For example, some nano-agrifoods may have very limited uses, do not appear to pose health or environmental risks based on current studies, and would not be expected to be distributed or used by the broader population (within current or foreseen uses). One example of these limited-use nano-agrifoods might be nano-vaccines intended for specific applications within veterinary medicine (Maina et al., 2020). Primarily for illustrative and conceptual purposes here, such nano-agrifood products could be considered as “Tier 1” cases, given that they have limited exposures, low/no hazards to health/environment, do not appear to raise significant societal or ethical issues based on current knowledge, and respond to a greater societal need. In these cases, nano-agrifood researchers should still follow the five strategies outlined earlier (described in Section 3.4.1) to implement RI practices in their own research. This could include i) investigations into potential EHS impacts, particularly for known-unknowns and unknown-unknown impacts under different scenarios; ii) institute reflective practices on RI within their own research; iii) investigate whether, or to what degree, their nano-agrifood product responds to a societal need and compares to alternatives; iv) share data when appropriate, particularly with researchers interested in investigating potential risks and impacts; and iv) consider ways to engage and/or reach out to various stakeholders (e.g. to receive feedback, understand perceptions, potential concerns). On the other end of the spectrum would be nano-agrifoods that would have much wider distributions among more (sub)populations, and/or show signs of being potentially problematic for health, the environment, or society, and do not appear to respond to a greater societal need (e.g., engineered nanoparticles used as food additives to primarily enhance colors). Again, for illustrative and conceptual purposes here, such nano-agrifood products could be considered as “Tier 3” cases, given that they have wider exposures/distributions, medium-to-high hazards to health or environment, raise significant societal or ethical issues based on current knowledge, and/or do not respond to a greater societal need (with Tier 2 cases in between Tier 1 and 3, in this conceptual example). In fact, our research has shown that stakeholders viewed nano-food products less favorably, less in line with RI, and had greater concerns compared to nano-agriculture products, based on factors of risks/safety, whether the product addressed a societal problem/need, and risk/benefit comparisons (Grieger et al., 2021). Further, this current paper also revealed that the two nano-food products were those where participants indicated that no actions would address their concerns, again over issues

of risk/safety, whether the product responded to a need, and risk/benefits. In these cases of Tier 3 nano-agrifood products, researchers and innovators of nano-agrifoods could implement the five strategies mentioned above, but to a much greater depth and breadth compared to lower-tiered nano-agrifoods that had more limited uses, clearer benefits, more demonstrated safety and ethical considerations taken into account. Further, Tier 3 nano-agrifood products could also be reviewed by independent third parties or external review boards, which could also provide an external validation and/or certification of the approach taken, similar to the approach previously suggested for the oversight of biotech crops (Kuzma & Grieger, 2020).

Overall, such a tiered approach would not only help the implementation of RI practices using customized methods, but it would also be more time and resource-efficient to target more in-depth efforts towards nano-agrifoods that would require greater investigations and engagement. Tiered approaches to implement RI for nano-agrifoods at different levels and degrees could be highly applicable to other novel agrifood technologies as well (e.g. CRISPR-based genome editing in agricultural crops (Kuiken et al., 2021)).

3.4.4. Incorporate systems for monitoring and learning in institutions to improve RI practices

Along with customized approaches to implement RI principles, systems for monitoring, learning, and improving RI practices should be the incorporated into RI best practices (Hartley et al., 2017; van de Poel et al., 2020). Monitoring systems will allow for iterative feedback mechanisms to provide information on what RI practices and processes are working and those that need to be modified to achieve the goal of embedding RI within an organization. Monitoring systems will also improve transparency regarding the actions, processes, and procedures taken by an organization and nano-agrifood researchers and innovators. Such systems should monitor the RI practices related to the previously-described best practices, including: i) mechanisms to institutionalize RI principles, practices, and oversight, for evaluation, learning and updating of these mechanisms; ii) education and training programs to develop the next generation of researchers and innovators; and iii) tiered approaches to implement RI practices at different levels and degrees, depending on the nano-agrifood and specific context. Finally, outcomes from such monitoring programs need to be the foundation for institutional learning on how best to implement practices of RI. These systems for monitoring and learning on how best to implement RI practice are relevant not only for organizations involved with research, development, and innovation of nano-agrifoods but other novel agrifood technologies as well, as noted by several authors (Owen et al., 2021; Shelley-Egan et al., 2018; van de Poel et al., 2020).

4. Conclusions

In conclusion and based on responses from 55 stakeholder participants in the U.S., we find that stakeholders identified a broad range of actions that could be taken to address their concerns of nano-agrifoods, if any, with a predominant focus on actions to address risk and safety. Stakeholders also identified actions related to regulation and/or governance of nano-agrifoods, the examination of 'need' and comparison to alternatives, and identification of benefits. In some instances, no actions would address concerns of stakeholder participants, largely in cases in which the nano-agrifood product did not fulfill a recognized societal need and potential risks outweighed benefits. Stakeholders also identified five major sets of actions to ensure RI of nano-agrifoods more broadly, again largely framed within actions to address risk and safety, followed by ensuring a societal need, actions focused on stakeholder engagement and collaboration, governance and oversight, as well as business and market-based actions. Finally, we identify and describe four best practices for ensuring RI of nano-agrifoods with relevancy for other agrifood technologies. These include: i) develop and embed mechanisms to institutionalize RI principles, practices, and oversight; ii)

develop education and training on RI, building "bottom up" next generation researchers and innovators; iii) develop a tiered approach to implement RI principles and practices at different levels and degrees; and iv) incorporate systems for monitoring and learning in institutions to improve RI practices. Overall, outcomes from this study may be relevant for researchers, scientists, industry, and policy-makers to help ensure RI occurs within nano-agrifood sectors with relevancy for the overall sustainability of other emerging food and agriculture technologies. For example, researchers and innovators could institute reflective practices to discuss strategies to foster RI of nano-agrifoods, engage stakeholders and the public, and improve transparency through data sharing, among other activities. Academics, faculty members, and scholars could develop graduate training programs to implement RI principles within their own research and laboratory practices, and funding agencies and policy-makers could develop and implement institutional mechanisms for monitoring and learning to improve RI practices.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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