Episode Title: EPA's Proposed Registration of a Sprayable RNAi Biopesticide -- A Conversation with Meibao Zhuang, Ph.D.

Episode Number: 20231214
Publication Date: December 14, 2023

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Lynn L. Bergeson (LLB): Hello, and welcome to *All Things Chemical*, a podcast produced by Bergeson & Campbell, P.C. (B&C®), a Washington, D.C., law firm focusing on chemical law, business, and litigation matters. I'm Lynn Bergeson.

This week, listeners are in for a real treat as I sit down with Dr. Meibao Zhuang, Senior Scientist and Regulatory Consultant with B&C and our consulting affiliate, The Acta Group (Acta®), to discuss double-stranded ribonucleic acid interference, better known to some of our listeners as dsRNAi. dsRNAi is a technology that allows scientists to silence or, given the little "i," interfere with, a particular gene. In the agricultural sector, this genetic modification can be used to great advantage to control pests of all sorts with extreme precision and very little impact on the environment. Meibao will discuss EPA's proposed registration of the very first sprayable RNAi biopesticide and the exciting implications of this technology. Now here is my conversation with Dr. Zhuang.

Good morning, Meibao. I am so delighted that you're here with us in the studio today. I'm just extremely excited to talk about this very exciting technology and to do so with you, because you are such an expert in this space. But before we jump into this topic, a topic that I know you are deeply passionate about and very much engaged in, maybe you can give our listeners just a little background on you and your interest in RNAi.

Meibao Zhuang (MZ): Yes. Thank you, Lynn. Thank you so much for having me today. It is a true pleasure talking about RNAi today. I'm a Senior Scientist and Regulatory Consultant with B&C and also its affiliate, Acta. Before joining B&C, I have nearly two decades of working experience with agricultural and pest management industries. I am a scientist at heart, so the first time that I heard about RNAi was during my graduate school study, when Andrew Fire and Craig Mello discovered specific gene silencing by introducing double-stranded RNA in the roundworm [*Caenorhabditis*] *C. elegans*. That was in 1998.

Their discovery was truly amazing, as it was totally different from what people typically expected, that when you introduce RNA for a coding region, you will get protein. That was the norm that people expected, but that was totally opposite. When they introduced the double-stranded RNA for a coding sequence, they blocked the expression of that protein. The publication has triggered a lot of research in developmental biology and functional genomics. In 2006, the Nobel Prize in physiology or medicine was awarded to Andrew Fire and Craig Mello for their discovery of RNA interference.

Later, during my tenure with a major agricultural company, I learned more about double-stranded RNA, or RNAi, technology being used for development of certain genetically modified trade products. I was also directly involved in development, evaluation, and preparation for regulatory submission of a specific corn product containing RNAi technology. I got very excited and reached out to you in October, after I saw EPA announcing its proposed registration of the first sprayable RNAi product, containing a double-stranded RNA as the active ingredient. This is a significant, yet long-awaited milestone, as this will be the first sprayable RNAi pesticide product in the world, once registered.

LLB: Thank you for that background, Meibao, and for our readers' benefit, EPA issued a press release on September 29 of this year announcing a public comment period on this proposal to register what it considers a novel pesticide technology for potato crops.

I recall the day well, Meibao, because you were *so* excited about seeing this in the *Federal Register*. And it is! It's just super exciting. I think -- at least from my perspective -- I think many of us have heard a lot about RNAi over the past few years. I'm certainly excited to learn more about its application to the agricultural product community. Again, just based on my own really primitive understanding, RNA stands for ribonucleic acid, which is found in pretty much all living cells. The "i" part stands for interference, as you correctly noted.

As I understand it -- and I read some stuff over the weekend and saw some videos to help my very rudimentary understanding of this form of technology -- RNAi can be likened to recipes or directions to cells to do certain things. The "interference" part is basically a message, or a code, to turn off, or silence, certain genes. It's this discovery that has some just extraordinary game-changing implications for human and animal therapeutics. The topic of our discussion today is its game-changing implications for the agricultural community. Do I have that basically right, Meibao?

MZ: Absolutely. You had it to the point. This is truly a game-changing technology because it allows you specifically to turn off a gene function by blocking or reducing the protein expression. Like you said, it has game-changing implications for human and animal therapeutics, and also in agricultural practice.

Before we go deeper on RNAi, let's just briefly review the flow of genetic information. This process involves DNA, RNA, and protein. DNA is the molecule that stores the genetic information. RNA is the messenger that carries that information to the ribosomes and then makes the proteins that are required for the development and functioning of an organism. The process of passing the genetic information from DNA to RNA is called *transcription*, and the process of passing the information from RNA to protein is called *translation*.

Let's take a look at how RNAi works. RNA interference actually is a natural biological process that cells use to regulate their gene expression by silencing specific genes. It works by introducing a specific double-stranded RNA, and then this double-stranded RNA works with other components in the target organism or in the cell to degrade the specific messenger RNA corresponding to the double-stranded RNA introduced. Since the messenger RNA carries the genetic instructions for making proteins, this degradation of the specific messenger RNA prevents the production of certain proteins, which can have a variety of effects on the cells, depending on the functionality of those proteins. This process is sequence-specific -- very important -- and only those specific sequences that match the double-stranded RNA are impacted.

LLB: Hence, the suggestion that this is just super-precise precision technology, which has extraordinary implications in the agrochemical community and agricultural product community for reasons that we will talk about. From my limited research, Meibao, I understand that RNAi-based technologies have been investigated for mosquito control purposes since the early to mid-2000s era. The *Aedes aegypti* mosquitoes provided what some regard as an early demonstration that RNAi could be introduced into mosquitoes and insects by topical application of double-stranded RNA, and from there, based on the literature references I've seen, the research just exploded. It took off, because the utility of RNAi-based technologies in plant protection products was early and immediately recognized, particularly since a lot of mosquitocides and other insecticides can be dispersive. So having a precision technology that has a high degree of control over the insect that it has targeted and has limited non-target implications obviously has tremendous commercial, environmental, and social value. Can you expand a little bit on that to make sure I've got it right?

MZ: Yes. Just like any product that eventually comes to market, it started from basic research, understanding how it works and figuring out the bottlenecks and overcoming the bottlenecks and bringing it to the market. It could be a pretty lengthy process, depending on the technology. Specifically for this one -- following Andrew and Craig's initial research on *C. elegans* -- *C. elegans* is usually used as a model organism for functional fundamental research. Following that publication, there has been quite a lot of research exploring potential employment of RNAi technology in agricultural industry for plant protection and for pest management, like mosquito control.

This actually includes the transgenic approach and the non-transgenic approach. The sprayable RNAi actually is a non-transgenic approach. Some of the research in this area includes focused work on understanding certain key elements, such as what works and how to make it work. As I said, demonstration of uptake of double-stranded RNA by mosquitoes via topical application is one of the key encouraging steps leading to the first sprayable RNAi product. This is not a very straightforward approach; it took us a long time to get there.

There are three key steps in the RNAi process, and it requires that all three steps work to produce a workable sprayable RNAi product. The first step is that the target organism can uptake the double-stranded RNA. The second one is that the target organism has appropriate enzymes to process the double-stranded RNA to a small interfering RNA, chopping from about 200 to 500 base pairs of the double-stranded RNA to 21- to 25-mer for small interfering RNAs. The third step is that the target organism has to have an appropriate protein complex to bind to these small interfering RNA and then guide them to specifically bind to and chop off the target messenger RNA, thus preventing the target messenger RNA from producing the target protein. This requires researchers to demonstrate that what they intended to control -- it could be a target insect pest or a weed -- it has to demonstrate that this target organism has the ability to uptake the double-stranded RNA and then has the appropriate RNA machinery to process the double-stranded RNA into small interfering RNA, and then eventually prevent a specific essential protein from expression, and then lead to the death of the target pest.

There are a lot of fundamental requirements required for this technology to work in a given organism. Scientists have focused a lot of research in this area to figure out what works, and also *how* it works. That's the genetic requirement. In addition to these key factors associated with this target pest, there are also critical technical challenges that the scientists or researchers have to overcome to make it work. The first one is that they have to be able to produce a large quantity of double-stranded RNA at a reasonable cost. The second one is to ensure that the produced double-stranded RNA is stable during the production process, to develop a workable, sprayable RNA product. That also makes it so amazing that we see the first product is coming to fruition.

LLB: Which just -- I mean, that's an amazing summary of a wide variety of factors that the stars need to align to make this work. Do you have any idea, Meibao, how they landed upon the Colorado potato beetle as a suitable candidate for this new technology? Because, as a non-scientist, I'm always just gobsmacked that smart people can figure out how to make all of these moving parts coalesce to be efficacious and perfectly suited to combat what has proven to be an extremely costly pest. I think -- I read some accounts that the Colorado potato beetle can do maybe about a half billion dollars of crop loss in any given period. It's just very, very destructive, so this is a huge new tool for the agricultural community. But why this bug, and why this technology?

MZ: Yes, that's a very good question, Lynn. Why this bug? Because I think that basically, some previous research shows that this bug has the three things that we talked about to make it work: it can uptake the double-stranded RNA, so once they spray it on the crop tops, the beetles chew on them, chew on the leaves, right?

LLB: Exactly, yes.

MZ: As they chew on the leaves, the double-stranded RNAi sprayed on the leaves gets taken up into the gut of the beetle. The gut actually has the appropriate protein, usually called a dicer, to process this long double-stranded RNA to small interference RNA. Then this small interference RNA can also work with other proteins existent in this beetle to get to the specific region to bind to the specific target that the double-stranded RNA corresponds to, and then eventually degrade this messenger RNA, because the target -- the double-stranded RNA that was introduced in this first product -- corresponds specifically to a key functional protein. Then once you block this key functional protein from producing, the beetle actually dies. It works.

So as a summary, first, they figured out that it works fundamentally for this beetle, for this insect species -- and then they were able to overcome the other key challenges we mentioned briefly: able to pick a target that is very specific for Colorado potato beetle but not impacting the other, beneficial insects around the potato. The final product will be very specific, as it doesn't impact the other, non-target, organisms.

LLB: That's what makes this just so incredibly targeted.

MZ: Exactly. The stability to produce a sufficient amount of dsRNA and stabilize them during the process -- remain intact -- so when you spray it on the potato crop, the active ingredient, the dsRNA, remains intact and that allows potato beetle to take it up and then use it against itself.

LLB: No, it is just incredibly cool.

MZ: It's just so incredible with specific work against the pest-- using a key gene that is from the Colorado potato beetle and using it against itself, to kill it specifically.

LLB: We had mentioned a couple of different RNA-type based technologies. What are the key ones for use in the plant protection area? Are there several, or some of them just more prominent than others because of their suitability for this market?

MZ: Yes, based on the research. There are various types of RNAi technology, including the small interfering RNA [siRNA], microRNA [miRNA], or small hairpin RNA, or dicer-substrate small interfering RNA [DsiRNA]. They have all those fancy acronyms, along with the double-stranded RNA. The double-stranded RNA is the most common one that a lot of researchers are focused on because it has just proved that it works.

The other types of RNAi also work by similar, yet different, mechanisms and can be used for silencing expression of specific proteins, but just -- we have not seen as much research focused on the other type of RNAi, compared to the double-stranded one.

Also, sprayable RNAi products can be used to silence a very specific or just a very wide variety of genes in plants, in insects. We have talked about insects, but it can also work in other organisms. Application approach-wise, it can be applied for foliar application -- that's the sprayable RNA, the first product for foliar application, but also some research is focused on other application methods -- such as soil drench, seed treatment, trunk injection -- that can also work. But those application methods are still currently in the experimental phase. Regardless what method the product uses, it just needs to make sure there is a sufficient amount of double-stranded RNA being taken up by the target organisms.

LLB: Got it. No, it sounds like, given the fundamentals, if you hit all of the markers that you identified -- a sufficient amount, in a sprayable form, the little critter can absorb it, and the double-stranded RNAi can silence the gene -- or the protein -- that causes the critter to die. I mean, then you're in business, so the applications seem to me, based on my layperson's perspective, to be just almost unlimited. I kind of wish they'd hurry up and get that weed one out there, since weeding is not my favorite thing in the whole wide world to do. I'd love a more effective weed tool. But maybe you can answer this, Meibao. How is sprayable RNAi different from other types of RNAi, or other types of less novel, more conventional pesticides?

MZ: Yes. That's a good question. Let's talk about sprayable RNAi first. I think we mentioned about -- during my earlier tenure with a different company, I have seen -- and helped develop -- some others containing RNAi technology, but that was a transgenic approach. The transgenic approach is very different from the non-transgenic approach, as we talked about sprayable RNAi. RNAi actually has been employed in the United States as a transgenic approach before the non-transgenic approach.

There have been multiple genetically engineered crops containing RNAi technology that have been reviewed and approved by EPA, USDA, and FDA in the past around ten, 20 years. These transgenic products can increase plant nutritional value and improve overall quality and can also confer resistance against pathogens, disease, and insect pests. This approach has been employed in corn, cotton, potato, and soybean. Talking about sprayable RNA, this is a non-transgenic approach for Colorado potato beetle control. This non-transgenic approach is unique compared to a transgenic approach: First, by definition, it does not produce a transgenic product. As a result, from the regulatory authorities' perspective, it only requires approval by EPA; you don't involve USDA and FDA in this case. For sprayable RNAi, compared to chemical pesticides, this approach is more effective, and we can control the design to make it very, very specific. Depending on what target gene you choose to make your double-stranded RNA, the target organism can be as narrow or as wide as you wish.

It can also be used to control some pests that already developed resistance to other traditional chemical pesticides, which has been a concern for the community. Because this one works by a totally different mechanism, so by introducing this new mechanism of action, it can be used to control certain species that already developed resistance to current methods. Also, the sprayable RNAi -- the active ingredient in the RNAi is the double-stranded RNAi. That is a substance that is generally safe -- or considered safe by FDA and EPA -- because of the history of safe use and the history of safe consumption.

Nucleic acid is part of the diet; it occurs in everything. So that being said, the specific tolerance requirement for this type of product is generally exempted. Lynn, we know how expensive and how time-consuming it is to obtain -- to apply for -- a tolerance petition for a new active ingredient. A tolerance exemption saves a lot of time and effort compared to traditional new chemical active ingredients for pest management.

LLB: You've already answered one of the questions I was going to ask you, Meibao, which is what are the key potential benefits -- and to some extent, too -- the risks of sprayable RNAi? But before I get to that, something you just said piqued my curiosity because this strikes me as a very new and novel technology that EPA's Office of Pesticide Programs (OPP) has, as noted before, proposed to register this new technology. We do an awful lot of work with OPP and have nothing but great respect for all of the scientists and regulatory entities at work over at OPP. But we *know*, based on our very significant experience, that sometimes really new novel technologies don't fit squarely within the more conventional boxes of technologies that EPA has reviewed and approved and on which their vast experience is based. So I did not check in advance of my conversation with you, but has this application lingered at EPA, or are the data so compelling that this is a registration application that was submitted relatively recently and EPA reviewed it and is presumably on track to getting it to market absent significant adverse public comment in a relatively short period of time? How long has this been pending over at EPA? And has the newness and the novelness of the technology delayed its review and presumptive approval, since EPA opened public comment on it back in late October or late September of this year?

MZ: Lynn, yes. As we all know, before approving a new technology, EPA takes its time to make sure that the product is safe for humans and the environment. You may not use the word *safe* actually, it is described as "does not pose unreasonable risks to humans and the environment," in EPA's words. EPA follows its process for this product review. It appears, based on the publicly available information, that the product was first submitted to EPA in 2020, along with a comprehensive set of data to support its registration. It does not show on the record, but we probably would all agree that the applicant probably already had engaged with EPA before its submission, such as pre-submission consultation, to make sure that the products that they intend to launch -- the data that they submit and generate to support this product launch -- was specific.

LLB: Sure, something that we would strongly support.

MZ: Exactly. So they did submit a comprehensive set of data, including information required for the human health risk assessment, and also the non-target organism assessment -- this is very important -- and then for the environmental risk assessment, along with some other standard information. The submission was made in 2020, and then in May 2023 -- so this year -- EPA approved the experimental use permit -- EUP -- for ten states. Then following that EUP announcement, EPA proposed to register this product in September this year. It appears that EPA has reviewed the information and then felt comfortable moving forward with the EUP, and encouraged by the EUP information and proposed its registration in September. We have yet to see the actual registration yet, but it looks like it's on track, based on what we can see.

LLB: Thank you for pointing out to our listeners that an EUP for -- did you say up to ten states?

MZ: Yes, ten states.

LLB: Wow. Wow. That must have been a huge shot in the arm for the agricultural community growing taters, right?

MZ: Yes. The ten states -- those are key growing states for potatoes, right?

LLB: Yes.

MZ: Idaho, right?

LLB: Yes, and it's way beyond Colorado.

MZ: Idaho, Maine, Michigan, Minnesota, New York, North Dakota, Oregon, Virginia, Wisconsin, and Washington.

LLB: Excellent. Getting back to the potential risks and benefits of sprayable RNA, if you could comment on that, Meibao, that would be great. Then I also wanted you to circle back on the fact that a lot of different -- well, I don't want to say a lot -- but pesticide products, species can develop an immunity to them, which would blunt their effectiveness. In your mind, is there any opportunity for at some point an RNAi technology to also have developed some sort of resistance down the road? Is that even a possibility? I honestly don't know the answer to that question.

MZ: Thank you, Lynn. Let's get back to the first part: the potential benefits and risks for sprayable RNAi, and why it's so exciting. Seeing the first sprayable RNAi product getting to the market, it *is* a very exciting milestone. First, this is the first of this kind of biopesticide approved by a regulatory body worldwide. This step signifies that the bottlenecks for the technology, including double-stranded RNA production and product stability, delivering technology, and efficacy, and also the related benefit, have been resolved. The second, based on the double-stranded RNA design, the activity spectrum can be very narrow, as we mentioned. It can be -- only target a, say, that this one only targets Colorado potato beetles. But if they modify the spectrum, it could potentially target other beetle species, as well. It can be narrow, or slightly expanded, based on how you choose your double-stranded RNA target to modify the activity spectrum.

We briefly mentioned that this technology can be designed to target pests that have already developed resistance to other chemical pesticides on the market and then can become a very, very valuable tool in resistance management. We also know from our previous discussion that it does not result in a transgenic product, so that development costs and process and time can be significantly reduced. We also mentioned that the active ingredient for this technology is RNA; that is a substance that's very common in the human diet and is generally exempt from tolerance requirements. That also adds a benefit for this product.

Talking about the potential risk associated with this technology: One potential risk is the possibility of off-target effects. What is an off-target effect? Off-target effects occur when the RNAi molecules silence genes other than the intended gene, but also based on how this is designed. These issues can be minimized by careful design of the double-stranded RNA target based on genomic information for the target organism and also available from the other beneficial species that you intend to protect, to make sure that there is very minimal overlapping with other genes from the other species that you do not want to kill, so only specific to what you intended. Lynn, you mentioned about resistance potential, and that is possible.

LLB: It *is* possible? Okay, I didn't realize that.

MZ: It is possible for -- I would say, probably for any given chemicals, or pesticides, even biopesticides. Because this is just how biology works and evolves. But this, too, I think with the history of using different generations of pesticides, either chemical or non-chemical, we know that there are ways, strategies we employ to slow down the development of resistance. For this one, for RNAi technology being a new mode of action, it's best to use this new mode of action only when it's required, and make sure that your product is as effective as possible so you'll kill them all when you intend to kill.

LLB: That's the goal, right.

MZ: Yes. You kill them all that you intend to kill, so there's no escape to slow down resistance development. Then you also rotate different modes of action. For example, one season, you use this sprayable on it, and then you use the other mode of action, other chemicals in the second rotation; that would help to slow down resistance development. That is a practice that I think the industry has been promoting as part of their integrated pest management approach.

LLB: Got it. You mentioned the EUP that was approved in May of this year for the ten states that you enumerated, Meibao. Are there any data that have come back that would help demonstrate the efficacy of this technology? We're recording this in mid-November, so I'm guessing that might not be publicly available, but it's usually the case that when EPA even considers granting an EUP, that's based on a pretty strong showing that this particular unapproved pesticide, because it's an experimental use, is going to do what it claims it *can* do. Any early signs of those data yet, or too soon to tell?

MZ: Lynn, that's a good point. Those data may not be publicly available, but just based on how EPA reviews this type of application and what it takes to get to the EUP, it appears that EPA felt very confident when they issued the EUP in May. Because before they issued the EUP, EPA would review a lot of information, including probably small-scale field trials that do not require an EUP -- such as in a confined environment, to make sure that it works, and it does not pose unreasonable risk to the environment or to the health of humans, to the applicators, and to other species around the crops. EPA -- and also based on the data submitted to EPA for review, it appears that EPA sees no unreasonable risk before they issued the EUP. Then from the time of the EUP to its proposed registration -- that's four months; it'll be over four months -- I would expect that the data coming back from the EUP will confirm its efficacy and also confirm there is no unreasonable risk to humans and to the environment. Basically, I would say this -- from EUP to the proposed registration, that looks like it works as expected, and that is very exciting.

We would be able to see more real-world testing results once this product is approved and used by more potato producers. Then we would probably have some more information, but right now, based on the time and the information we can see, it looks really good and on track.

LLB: Great. I know, Meibao, you've been at this, perfecting your craft and sharing your brilliance as a Ph.D. scientist on *our* team now, but you've been in this space for maybe 15, 20 years now? I think you can tell our listeners what some of the challenges might be to commercializing a new technology, this sprayable RNAi. Do you speculate, Meibao, that there at every step of the process, including generating funds, investment resources, through the experimental stage and the development of data, then most importantly from our perspective, once you submit that registration application to EPA, especially a new technology, what are some of the challenges an entity might expect to confront at the EPA registration level?

MZ: Yes. Similar to many products of technology, there are technical challenges. Then there are challenges for getting it to the market. There are regulatory challenges that we need to face. For sprayable RNAi technology, the technical challenges include producing a large-scale double-stranded RNA at a reasonable cost and to be able to stabilize them during the production process. Those could be very challenging for new players in the space. But once --

LLB: -- Meibao, when you say "stabilize," maybe you can help our listeners understand. Does that mean there isn't an explosive potential, or it has to remain potent during production and intended use? But what does that mean, that stability issue for double-stranded RNA?

MZ: Yes. That's a very good question, Lynn. The active ingredient being a double-stranded RNA, just being an RNA molecule, you know that there are so many RNase -- an enzyme that could chop off RNA, that exists in the environment. Like the sweat that we have on our hands, it could just degrade RNA. It's very important for these produced double-strand RNA to remain intact during the production process.

LLB: Got it.

MZ: If it were chopped into pieces by an enzyme, or anything that you may have introduced during the production stage, then it would become small pieces that would not work as you intended for it to be.

LLB: Got it. That's very helpful. Thank you.

MZ: Then the next step, once you solve those technical challenges and then you are able to have a concept for the exciting product, then we need to talk about the regulatory challenges. The regulatory challenges -- actually, for a sprayable RNAi technology, we mentioned that it's a non-transgenic product. This actually has its own advantage in the regulatory space because transgenic products, to get the approval, require approvals by USDA, FDA, and EPA, in general. This includes transgenic products containing the RNAi technology. But for a sprayable RNAi, that is under EPA's regulation as a biopesticide.

EPA actually has very specific data requirements for registering such products. Like we said earlier, EPA needs to make sure that the product works and that it does not pose unreasonable risk to humans and the environment. So developers actually can engage with EPA during the product development and evaluation process to ensure that the information generated can be used effectively to support such evaluation in a timely manner.

There are a lot of data to generate, and you have to follow specific guidelines to generate those data, and you also need to be able to interpret those data to support your product registration. At B&C, we have the knowledge and expertise to help our clients to understand what it takes, what data are needed, when and how to generate that information, and how to register this type of products with EPA.

LLB: Thanks to you and your colleagues, Meibao, you have significant experience in integrating these data elements, along with fitting those data within a regulatory and legal construct that ensures EPA's comfort level in its ability to make the registration decision required under FIFRA Section 3 with regard to those data. We're very lucky to have you, and I'm so pleased to understand your past experience with your prior employer on these RNAi issues. That's just hugely exciting for us institutionally. I know EPA's signaling that it was likely to approve this RNAi sprayable product generated a lot of excitement in our shop as a result.

My last question relates to just the commercial prospects for this technology, for sprayable RNAi generally. My guess is that the sky's the limit. It has enormous commercial potential. But what are your views on that question?

MZ: Yes, Lynn, the sky's the limit, but let's start from small.

LLB: Got it.

MZ: Yes. This is a very exciting technology that, like we mentioned before, the first step is just we need to make sure what organism has those three things to make it work built in. Based on the published research, RNAi technology actually may work on several insect orders, such as grasshoppers -- it's also Orthoptera, so grasshopper -- is one from a different insect order, cotton bollworm, from Lepidoptera, the moth and butterfly, that's lepidopteran, and we mentioned the mosquito -- that's a dipteran -- and also this one, the Colorado potato beetle. That is a Coleoptera. At least from what we have seen from literature, at least four or more insect orders -- it can work for these four or more insect orders to develop targets for the next product. Besides insecticides, it's also reported that the plants, like weeds, can also uptake double-stranded RNA and process double-stranded RNA to small interfering RNA. Lynn, there's a potential for an herbicide development using the sprayable RNAi technology in the future.

LLB: That's very good news.

MZ: Yes. Then also, besides the insecticides and herbicides, we also know that RNAi can be used for disease control, including preventing fungal and virus infection and parasite damage to crops, and also to protect beneficial insects, such as honeybees, from damage by parasites, such as Varroa mites. The list may not be long, for now, but given the unique advantage of this technology and that there are so many target genes, you can select a form to produce a very specific pesticide and biopesticide, and also the potential to target species that already developed resistance for existing chemical pesticides.

This technology has a great potential to be part of the integrated pest management tool, given its unique mode of action and then the generally safe profile for humans and the environment. There's less concern for human health and the environment. Just all those unique advantages associated with this technology and then the unique list that we mentioned above can be potentially used for this technology. We would expect to see more and more exciting products, sprayable RNAi products, come to the market to deal with those unique challenges that we face.

LLB: That is very good news indeed. Meibao, I want to thank you for bringing this issue to our listeners' attention. I fear I would not have focused as much as I think it deserves, given the novelty of the technology, its potential application in *so* many different areas, and its immediate relevance for purposes of farmers having to combat the Colorado potato beetle in the ten states that warranted the EUP. I know I will be looking for a notice in the *Federal Registe*r when and if this is approved.

As noted, the EPA press release came out September 23. The comment period closed, ominously, on Friday, October 13, so we'll be looking to see if there are any adverse comments, because when I read about novel technology, sometimes I worry that the novelness might make people uncomfortable, and there might be some optical issues that people need to address. But EPA does its homework. Sounds like an extraordinarily promising technology with high precision and low adverse environmental impact, and I look forward to having EPA issue that notice of approval.

In addition to the *Federal Register* notice and the press release, I just wanted to bring our listeners' attention to one [Organization for Economic Cooperation and Development] OECD report that I found very helpful in preparing for this podcast, and that's "Considerations for the Environmental Risk Assessment of the Application of Sprayed or Externally Applied dsRNA-Based Pesticides." This is a series that OECD issues. It's numbered 104 and was issued on March 17, 2023. We'll list it when we post this podcast.

Meibao, thank you for your brilliance, your enthusiasm, and for bringing this to our attention so we can all learn more about this fabulous new technology.

MZ: Thank you, Lynn. It's a pleasure talking about RNAi today, and thank you all very much.

LLB: The pleasure is all ours, Meibao. Thank you.

MZ: Bye-bye.

LLB: My thanks to Dr. Zhuang for speaking with me today about the brave new world of sprayable dsRNAi and what EPA's registration of an RNAi biopesticide could mean for the agricultural sector.

All Things Chemical is produced by Jackson Bierfeldt of Bierfeldt Audio LLC.