wiley

Keith Matthews and Chris Wozniak: Talking Ag Biotech Episode 4

Wiley Podcasts
July 13, 2023

Wiley Podcast · Keith Matthews and Chris Wozniak: Talking Ag Biotech Episode 4

On this episode of Talking Ag Biotech, Keith Matthews and Chris Wozniak discuss the recent publication of the U.S. Environmental Protection Agency's Plant-Incorporated Protectants (PIPs) Exemption Rule. Keith and Chris offer background on the rule, discuss specific aspects of the rule that are of concern to technology developers, and briefly discuss an upcoming episode that will focus on the USMCA GE corn trade dispute.

Transcript

Keith Matthews

Hello everyone, this is Keith Matthews and Chris Wozniak with our latest version of Keith Matthews and Chris Wozniak: Talking Ag Biotech. Have not recorded one of these, this is our first one in 2023, so Chris, welcome, how are you doing?

Chris Wozniak

I'm doing very well, Keith, how about yourself?

Keith Matthews

Related Professionals

Keith A. Matthews
Of Counsel
202.719.4462
kmatthews@wiley.law

Practice Areas

Environment & Product Regulation

I'm doing great. So, how's the first half of 2023 treated you?

Chris Wozniak

Generally, pretty good. I have no major complaints. I'm happy that I'm retired, so every day is Saturday.

Keith Matthews

Yeah, you're retired but you're actually working pretty hard.

Chris Wozniak

Yeah, but you know it's good to be able to choose some things that you want to do so that's a plus. And I choose my schedule pretty much too. I don't have to get up at 6 am anymore, unless I want to.

Keith Matthews

Yeah, excellent. That's really good. So what we're going to focus on with today's recording is the recent release, recent publication, of EPA's PIPs Exemption Rule. And the EPA has been working on this since 2020, finally published it May 31st. I'm going to talk at the end a little bit about that publication date, some of the implications for that publication date, some of the implications for the publication date that weren't discussed in the rule. But nonetheless, so you actually worked on the rule while you were at EPA, going on before your retirement, so I know there's only so many things that you can say about it, but to the extent that you're able to discuss this and express this, what's your general impressions of the exemptions rule that was published in May?

Chris Wozniak

I have to say, like a lot of rules that come and go, one good thing is that, and you may recall this because you were at EPA at the time, I mean there are cases where you put in an enormous amount of time, and then through a variety of mechanisms, interagency review, OMB review, etc., things go nowhere. So you end up basically with nothing after all of that effort, and several people were involved in one of the earlier rule makings, so the fact that it's in the FR, it's getting placed into 40 CFR, that's one goal that I'm at least happy to see there's something to show for it.

There are certain aspects about the rule, the idea that you can move a gene from an older variety and don't have to go through all the linkage drag issues with conventional breeding, move that gene in and rely on the history of safe use, that's a great deal. I mean it's obviously to some degree low hanging fruit. It's not that challenging scientifically to see how this just makes sense, so it's good that that's in place. There are some other, it's always in the details, the finer details of expression of genes, for example. I'm a little concerned with 'hat in the description that I read, and the sense that I almost get the impression that some of the folks who put this together have a view of a late 1970s, what does a gene look like, or a simple bacterial gene, you've got a promoter, you've got a reading frame, termination sequence, and boom you make one protein. And we know now that many genes are so much more complicated. And if you think about it, just 15 years ago,

roughly when we really started examining RNA interference. I remember one of the companies coming in explaining to us that they found well north of 100,000 genes already that are dealing with miRNAs or siRNAs and all this within like a corn chunk. This was unknown. Well, originally in 1998 that started to evolve, but it wasn't until 2010, 2012 that this even appeared. So when I see this concern over the expression levels and not just the levels but the developmental stage and the tissues and organs in the plant, I worry that some of that is a little too simplistic, and it makes me wonder what will the developer do to prove to EPA that they meet the exemption, because you can't exceed the levels in, say, a whatever stage of soybean or corn you're talking about, in that leaf or in the root.

And so, how much work will need to be done, under how many different geographic locations, environments that vary to prove to the risk assessment team that yes, we qualify for the exemption, we're not exceeding it. Now, before I finish on that thought, I'll say that in most cases, the vast majority of cases, there's not really a human health concern with that. You know very quickly if you select a gene, it's not hard to do a database search and know if it's a toxicant or allergen or whatever. So I don't have any real human health concerns there, I'm more concerned about the bureaucratic fallout in the sense that I come to EPA with all my data, and they say well yeah, it's not quite enough. You need to check this and this, it could become a PhD dissertation in itself to prove that.

Keith Matthews

Well, that's also a concern that I have, because quite frankly, I sometimes wonder if, in fact, some of the discussion in the preamble and in their response to comments, didn't really reflect the reality that technology producers face. And I wonder if, in fact, EPA is thinking that these exemptions as promulgated are going to make more of a positive difference to technology developers than, in fact, the reality is going to be. That's a concern for me because at the end of the day, I think what this should be about is burden reduction, reducing the burden on innovative technology producers to bring new products, necessary products, to the market. And if in fact, there are still going to be hurdles, maybe not insuperable hurdles, but unnecessary hurdles, to that process, and that this rule really isn't going to make as big of a difference as they're thinking that it will.

Chris Wozniak

Yeah, that's certainly a possibility, and again, I hate to be such a detailed person, but I think the proof is really going to be when we see developers coming in with these. Let's say they've found a wild tomato cousin in Bolivia, and they pulled the gene out, put it in there, and then they want some evidence. Well, what's the expression range in a certain developmental stage, or in the fruit versus the leaves and that. Again, those are a lot of difficult questions. You have to establish that range in order to meet the exemption. You have to be able to show that you're not exceeding it.

In many cases, at least what we know for example with the Simplot Innate potato, we were looking, they took a NT1 gene from a relative of solanum tuberosum, a potato, Irish potato, and I remember some of the risk assessors working on that and saying, wow, this thing is there at such low levels, that there's no way we could even get enough of it to do a tox study in a rat, for example. It's just not feasible. And so they found a

workaround and said basically there was some history of safe use. The protein was similar enough to another protein that we do consume. So, it wasn't an obstacle in that case. But for some of these plant disease receptors and things that detect fungal pathogens or bacterial pathogens, just actually quantifying the levels and all these things is not as simple as it sounds. Now, there is this indication here that you can modify regulatory sequences under this rule and still meet the exemption. But you do that with caution because you modify the regulatory sequences, you may well then exceed the level, as it's naturally found.

But in addition, I think, and hope, my former colleagues there understood this and kept this in the back of their mind, but it's not just the immediate promoter sequences. There are enhancer sequences and influences from even genes on other chromosomes, so when you take that gene from this wild tomato relative from Bolivia and put it into a commercial tomato variety in California, the expectation is as explained in the FR notice, is that it'll be the same or lower. Well, maybe and maybe not. That to me is still very much an open question. Again, I have no human health or ecological concerns that the level of that fungal disease receptor in that plant is going to cause any harm, but the rule talks about absolutes. You can't exceed the level.

Keith Matthews

Right. Yeah, and we know, in this context when you have absolute guidelines, absolute thresholds like that, they're problematic. It's biology. So they are problematic because biology tends not to be absolute.

Chris Wozniak

Right, true they do mention in the FR towards the end that they're going to be looking at broader genetic variation in plants because they understand that plants can vary based on not just the environment but the background genetics of it. And that's good, but my question is, given that this has taken many years to put this together, and this, by the way, for those who don't know, this rule, I don't know, I guess I could say it sort of started around roughly 2016-17 in its infancy, but the reality is, a lot of what came before that with other rulemakings that didn't succeed, influenced this. So it doesn't stand alone. So my question is, what is that, another five years or even longer before we see that further evolution?

Keith Matthews

Right, yeah that's always a concern. I mean this is just an aside, but that's always a concern. I mean we remember USDA's so-called secure rule. I think it was the first proposal for that rule was back in 2008, and who knows when that proposal started to be worked on. You know, maybe 2004, 2005, or earlier, and then it was promulgated I think it was 2018, so these things take time. Rulemaking takes time.

Chris Wozniak

So any time, you got to focus on rulemaking.

Keith Matthews

And again, that's just an aside. Substantively on the rule, there's two other aspects of it that I find to be of interest and perhaps of concern. One is loss of function and the other is plant regulators. And how are plant regulator PIPs going to be regulated by the agency?

And so with respect to loss of function. So, hypothetical here. So let's say a technology producer goes in, they find that the cessation of protein expression for a particular protein will have a beneficial impact, maybe not even in the context of preventing, destroying, repelling, or mitigating a pest, maybe a beneficial aspect in terms of plant life cycle, and they somehow alter the gene so that that protein is no longer expressed. Well, according to the rule, that is regulated, that action by the product developer, is regulated as a pesticide. Now, when I look at it from a legal standpoint, well what is, how does FIFRA define pesticides, well as a substance or mixture of substances that act to prevent, destroy, repel, or mitigate a pest or act as plant regulators, desiccants, or defoliants.

So, if in fact, what we're doing now, what the technology producers are doing, is they're eliminating the expression of a protein, so there is no substance there. But, however, what EPA says in the rule, where will the substance that will be regulated as a protein, is the altered DNA that results in cessation of expression of a substance. I find that to be an interesting question. Any thoughts on that or the philosophy or the logic behind that?

Chris Wozniak

Yeah, I can't say too much for the logic behind it because I think I agree with you in the sense that, as one of my former mentors at EPI said, show me the risk. Where's the risk? Well one of the ways we look at risk or examine it is we do toxicological studies. Some of them can be done in silico, on a computer looking at databases, some of them require rats and birds and whatever. You have nothing to test, so the question becomes what risk are you mitigating? And when you don't see that, to me that's a great time for enforcement discretion. I've seen this several times at FDA, both in Center for Veterinary Medicine and in Center for Food Safety and Applied Nutrition, and also at APHIS, where they basically have said, we don't need to regulate this, even though statutorily we probably can. I think that is a time for EPA to say well, if it's a knockout and the company can demonstrate to me that that's the only change, they made some insertion or deletion or something in a gene, and again, it's like trying to prove a negative, proving this gene or a family member in that gene family elsewhere in the genome are not expressing some, it takes a little bit of work, but it's certainly not impossible. But again, where is the risk and what are you going to evaluate? It just doesn't add up to the intent of FIFRA, in my opinion.

Keith Matthews

Right. And from my perspective, and I think that's why these conversations between you and I are so very helpful because you get the scientific perspective, you get the legal perspective. From my perspective, looking at it from the legal side, I say, listen, this is the definition of pesticide under FIFRA, and does this really fit the spirit of what is intended if you, in fact, have a plant that is no longer producing a substance? So we'll see, and I will note that because it's a legal question, there may be an issue as to, well, should we try to let a

court figure this out? Is this an acceptable interpretation of FIFRA? And I'm going to get to that toward the end of our discussion today because there are some fairly interesting issues that the rule raises with respect to judicial review, so we'll talk about that a little bit as well. And then the other thing that I wanted to mention was, well, plant regulators. So what's a PIP regulator, and there seems to be an awful lot of confusion about that. And I will just say this, I try to be fairly reserved in these discussions, but the statement and the response to comment that what constitutes a plant regulator PIP is outside the scope of this rulemaking I just found really astounding. I mean how can that be outside the scope of a PIPs exemption, rule because for some technology producers, that's central to what they're working on. Is the modification or the product that I'm working on, is it going to be regulated as a plant regulator? So, I found that really baffling.

Chris Wozniak

Yeah, I agree it is somewhat baffling, Pure speculation here on my part but the other thing that's been going on, and I actually worked on this at one point when I was with the agency, is some guidance on plant regulator compounds, some of which may be used as biostimulants, some of them are used as pesticides under FIFRA, and that is going on in the background where there's a guidance document people are working on. And it's not out yet, I've been retired a year and a half, it's not out yet, so I know they're still working on it, and it makes me wonder if there was concern that what you're looking at in this rule, this PIPs exemption rule, if you're to venture into the area of plant regulators, then that could impact what we're doing over here with the biochemicals and even some engineered bacteria and naturally occurring microbes on the other side of the fence, so to speak.

And again, pure speculation but it makes me wonder if, and you remember this I'm sure as well as I do, one of the things that I always found somewhat incongruous at EPA and in the Office of Pesticide Programs, is just that things that we did in the Biopesticides and Pollution Prevention Division, which handles biochemicals and biologicals, the microbes and the PIPs, were somewhat dictated by what had been done previously in the conventional realm and the registration division, for example. And I always thought, well, the two are quite different in many ways, substantive ways. But, from a legal standpoint, I can kind of understand the OGC saying, well, but the regulations say this, FIFRA says this, they didn't make that distinction. And so it could be that this whole plant regulator thing, which as you know is very poorly defined statutorily and on the regs, it really, it needs a lot of work, and I can only somewhat surmise that maybe they didn't think it was ready for prime time. But you're absolutely right, it would have been helpful.

Keith Matthews

Well, I would just say, again I try to be restrained here, but I would have preferred that sort of an explanation as to saying it's outside the scope of the rulemaking, but nonetheless I get what you're saying, and yeah, they've had that draft plant regulator guidance. I think it was first released in spring or late winter of 2020.

Chris Wozniak

That was 2019.

Keith Matthews

2019, and we're still kind of waiting on that. I wonder, this is completely off topic here, but I wonder if, you know, they're waiting to see what happens with the Plant Biostimulant Act, which has been introduced into Congress, and seeing if that actually makes it through, because it was introduced in the last Congress, and the last Congress ended, and so now it's been reintroduced. And of course we have the Farm Bill that's being worked on now, and so we'll see. Maybe that ends up as a part of the 2023 Farm Bill. We don't know. But anyway, plant regulators are an issue, and they're certainly an issue with respect to PIPs, and they're certainly an issue with respect to this particular rule. So we'll have to see how that plays out.

Chris Wozniak

Sure, and I agree, I'm definitely waiting for that. And something of a potentially unrelated note, we don't know because we don't have the details, but one of the things, on a positive note I should say, that I saw in the description in the FR where they talk about off-target mutations, so if you're using CRISPR you have a guide RNA that directs you to a specific sequence, but we know from work in animals and plants and fungi that CRISPR CAS9 is not perfect, and there are a variety of these CAS-type enzymes. And so if it hits outside of your target sequence, and some people refer to it as a scar, but I just call it an off-target alteration in the DNA, there was a lot of concern over that, and my feeling was that, particularly on the plant side of things, that it was an unnecessary concern.

I spoke with a gentleman at Harvard a few years ago that fortunately I happened to sit next to at a meeting, and he's developed a couple of really complex software programs that go in to detect these off-target scars. And he's got some more advanced ones now that he told me are more robust, and when I asked him with these plants, I said we're talking about domesticated plants like corn and soybean and sorghum and whatever - should we be concerned that one of these off-target effects occurs and we have this so-called scar or this little insertion, mini deletion somewhere, could create de novo some sort of toxin? And he just laughed. He said you're kidding me. He says you guys are concerned about that? And I said well, some people are, and he said basically the chances of that happening are so astronomical. He says I wouldn't worry about it. He says yeah, you could potentially disrupt another gene elsewhere, but to create some sort of toxicant that's going to harm people or animals, that's just far-fetched. Now, he explained in his work – he works more on the clinical side, dealing with human beings – and so there you have to take these little scars and other, I call them off-target effects, a little more seriously because the stakes are just so much higher. But I thought it was interesting in here and the FR notice, they say that CRISPR or some other related modification technique will be no more risky than point mutations that arise from tissue culture, plant tissue culture, or from conventional breeding. And I totally agree with that. It was nice to see that. It was a little bit of a surprise that was not brought out in the EPA webinar, but I think it's an important point, that as a group they're starting to look at this CRISPR-based editing a little differently.

Keith Matthews

Yeah, and I think you make a good point. We have to be careful that we focus on the negative aspects of the rule. But there are some positive aspects of the rule. And I think the world is better with the rule than it was without the rule. I think the world could be a lot better with a different rule or with certain interpretations. I specifically speak to on that in plant regulators because during the webinar last week Mike Mendelsohn said that they're thinking of doing a guidance. I guess he said more than thinking, I think he said they're going to do a guidance on plant regulators and so we'll see where that comes out. We'll see how long it takes, and we'll see what the details are, but that could be very important.

Chris Wozniak

No doubt. And I look forward to some further guidance associated with this, as well as you may be aware that APHIS put out some guidance on engineered microbials.

Keith Matthews

Mhmm, yep.

Chris Wozniak

And that, as far as I know the comment period is over, and there could be some changes coming in the next month, two, three months something like that. So I'm excited about that because some of the folks that I've been working with, it's very clear that, in terms of synthetic biology, but even just, I hate to say it, traditional genetic engineering of a bacterium, there are so many things going on and not just in agriculture. You know, talk to people that are say DARPA is funding some of this work, not only repairing but enhancing the strength of concrete with these engineered microbials. There's all kinds of things where they want to actually physically put them into clothing. They could be as sensors, they could be as mosquito repellents, the engineering of the microbiome of the human skin, the military is very interested in that. All these things coming down the pike. I have to agree with the national academies a few years back when they said we're not so sure the regulatory system is ready for this.

Keith Matthews

Right.

Chris Wozniak

And I totally agree with that.

Keith Matthews

Yeah, well I will say that I've spent a fair amount of time this year talking with Subray Hegde over at APHIS, and we've been at different conferences, and yes they are putting a lot of work into this, and I think they're making a really good faith effort to try to update their regulatory system to make it more risk-based and more

relevant to the technological world that we live in today.

Chris Wozniak

Yeah, I agree. I think APHIS overall has done a good job with moving towards not just less regulatory burden, but providing some explanation. And just the other day I was looking at a, it was a short stature quorum they have on their website, their request letter from the developer, and then their response to go through the regulatory review status, and that's the way it should be. Explain to the public what you received, how you responded, and there were at least 3-4 of these on the website that are just coming in the last few weeks. And APHIS in all cases said we don't need to regulate this under the Plant Protection Act.

Keith Matthews

Right. And that does, again, that gets us back to plant regulators and what is it that EPA should be focusing on. If it's a plant regulator and it is a change, the new trait is not intended to prevent, destroy, repel, or mitigate a pest, you're working on plant architecture or some other aspect of plant physiology. What's the risk? And even if they get to that, if they don't get to the point where these sorts of modifications are presumptively exempt from registration, from the requirement of registration, they really hopefully will get to the point where a company doesn't have to go through a full-fledged registration review, that's going to take years and years for them to complete.

Chris Wozniak

Sure, and the other aspect I don't think we've discussed before, but I was talking to a friend who's a crop consult in Nebraska, and it's a fairly large cooperative he works, and they handle hundreds of farmers' needs, including his own. He's also a farmer. And I can sense the frustration. We're losing all of these conventional chemicals either through revocation or food tolerance or whatever and there just aren't many more arrows in the quiver. So I think the reliance on the biologicals is going to be so much heavier as we move forward,

Keith Matthews

Right

Chris Wozniak

I hate to sound dramatic, but Rome is burning. There's not a lot of time to sit around and talk about what should we do? We know what we have to do. And I think biotech both with plants and with microbes and even, not genetic engineering, but just even use of naturally occurring microbes, I think has so much more potential. There's obviously a marketing issue, I can remember speaking with some farmers over dinner one night and mentioning that I worked with biopesticides, and they said oh yeah, we tried those, those don't work. Someone they knew tried one product, one time, don't even know if he applied it correctly, wrong time of day, whatever, it didn't work so they wrote that off. But as more and more of the conventional insecticides, nematicides, and even some herbicides fall by the wayside, I think farmers and the developers are aware of this. The farmers are going to have to give them another look.

Keith Matthews

No, absolutely. Absolutely and let's say, let's give the biopesticides credit. The biopesticides industry credit, where credit is due. They are developing new products. The products that are on the market now are not, what you can buy now, they're not your grandfather's or your father's biopesticides. The products that are being developed now are much more sophisticated and I think much more efficacious.

Chris Wozniak

Yes, I believe they are, and not to knock EPA again, but one of the things that has come to light, both when I worked for the agency and even afterwards, I have a couple colleagues that are actually retired like me, but they still are working in the biopesticide industry, and occasionally they'll just send me products. Every time they say, do you notice that this isn't registered by EPA? Look at all of the FIFRA intent-type claims on the label. And so I pass it on through channels to get it to enforcement, but my sense has always been, I've only worked on two or three enforcement cases when I was there, there just isn't enough resources put into OECA, the Office of Enforcement and Compliance Assurance. Because some of the folks have told us, some of the developers, well, you know that fungal product's out there? I'm like actually, no, I don't. It's the farmers who go shopping and go to these seminars and webinars on these products, whether it's California and it's grapes, or whether it's sweet potatoes in North Carolina. They're the ones who are seeing this, and they need to make somebody at EPA aware that these products are illegal, because those could very well be the products that give the farmers the wrong impression.

Keith Matthews

That's right.

Chris Wozniak

There's no quality control with some of these. They're used. They don't do anything, and then the farmers dismiss the entire lot.

Keith Matthews

And yeah, actually, that's a really good point, because I work with a number of companies. In fact, they come to me, and they say all right, this is what our product is, these are the claims that we want to make. Do we have to get this product registered? And they try to do the right thing. If their claims are pesticidal, then they say okay fine. We're going to go through the registration process. And so it really behooves the agency to actually take action against these scoff laws because if they don't, then that disadvantages the companies who come to me and say we want to do the right thing. And if we're making claims that require to be registered then we're going to go through the regulatory process, or if we don't want to do that then we're going to adjust our claims. And there are companies that in good faith, are making those types of decisions and so yeah, the ones that aren't we really should be worried about.

Well, we've spent a fair amount of time, and one thing I do want to say, so there's a couple of things I want to say before we close out. I did mention that there is a problem with the rule with respect to the fact that EPA says that the effective date of the rule is July 31st, which is true for the FIFRA portion of the rule. EPA, however, also promulgated under section 408 of the FFDCA, a tolerance exemption provision related to the PIPs FIFRA exemptions, and those aspects of the rule are not effective as of July 31st because that's not how section 408 of the FFDCA works. And so the reason why that may be important is that that in fact could have a significant effect on the judicial review provisions because FFDCA, FIFRA have very different judicial review provisions for rules that are promulgated related to pesticides. And so it may be that the reality is that if there's an entity that wants to seek judicial review of this rule that they will have to do so by July 31st, which is what EPA says is the effective date. So I'm kind of getting to the weeds here from a legal standpoint, but it's very important because if an entity does want to accompany, or an individual, does want to challenge a rule, if they don't do so in the right time, they could actually lose that opportunity. So we want to keep an eye on that.

Chris Wozniak

Sure.

Keith Matthews

And then the second thing that I wanted to mention is, so we're not going to be able to get to it today, but there's a lot going on with respect to the biotech corn dispute between the US, Canada, and Mexico. And I do want to get into that, I do want to delve into that in some detail. And so we have an associate here, Kimberly Reynolds who's in our trade group. And Kimberly joined Wiley from USTR, from the USTR Council's office, and so what I'm really looking forward to in the near future is the three of us getting together for another podcast. So last podcast was about six months ago. We're not going to go six months before our next one, we probably won't even go a month before our next one, we're going to come back because of the importance and the topicality of that issue. We're going to come back fairly soon to do another podcast on the USMCA trade dispute between Canada, the US, and Mexico related to biotech corn, which is a big deal.

Chris Wozniak

Yeah, it is a big deal. It's at least $3 billion worth of corn we're talking about. And I'll hold my comments, but I did have some activity, shall we say, with some of the consulates in Mexico before I retired, where we dealt with this issue with GMO cotton in Mexico. And all I'll say is that there's clearly a lack of scientific credibility in some of their arguments, and I'll leave it at that for now.

Keith Matthews

Okay, sounds good. Well, to the audience we will be back in fairly short order to talk about Ag Biotech trade and some of the disputes. And this is a big issue for US growers because the more markets they have, the better off they are, and shutting off markets to a very near and significant trade partner like Mexico is a big deal, so we'll be back to talk about that. And with that I think we will sign off. Chris, thank you very much.

Chris Wozniak

My pleasure, Keith.

Keith Matthews

Always good to talk. And many thanks to our producers and the folks who work to make these podcasts happen. We have an excellent staff behind the scenes, and they do the hard work. We just sit up here and have a nice conversation, which is always wonderful, and I'm looking forward to doing it again.

Chris Wozniak

Sounds good.

Keith Matthews

All right, take care.

Chris Wozniak

You too.