TOXIC CONCOCTIONS

HOW THE EPA IGNORES THE DANGERS OF PESTICIDE COCKTAILS.

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JULY 2016

Executive Summary

More than 1 billion pounds of pesticides are used in the United States each year, applied to agricultural fields and orchards, residential lawns, playgrounds and parks. Pesticides are often mixed with other pesticides and chemicals before application or after, and the individual ingredients in these mixtures can interact in such a way as to enhance their toxic effects. **This is referred to as "synergy," and it can turn what would normally be considered a safe level of exposure to people, wildlife and the environment into one that causes considerable harm.**

Although pesticide mixtures in the environment have been extensively documented, the Environmental Protection Agency generally only assesses the toxicity of pesticides individually, in isolation from potential real-life scenarios where these pesticides may interact with other chemicals. The EPA, which is tasked with ensuring that pesticides do not result in unreasonable harm to human health and the environment, often rationalizes this approach by stating that studies measuring mixture toxicity are often not available for analysis.

Our analysis, however, contradicts that claim by utilizing a publicly available information source (data from the U.S. Patent and Trademark Office) that provides a disturbing snapshot of pesticide synergy and the potential for widespread danger to people, waterways and wildlife — risks the EPA has repeatedly failed to identify and consider during its approval process.

For this report we conducted an intensive search of patent applications that were germane to all pesticide products containing two or more active ingredients approved by the EPA in the past six years from four major agrochemical companies (Bayer, Dow, Monsanto and Syngenta).

Among our key findings:

- 69 percent of these products (96 out of 140) had at least one patent application that claimed or demonstrated synergy between the active ingredients in the product;
- 72 percent of the patent applications that claimed or demonstrated synergy involved some of the most highly used pesticides in the United States, including glyphosate, atrazine, 2,4-D, dicamba and the controversial neonicotinoids thiamethoxam, imidacloprid and clothianidin, among others, indicating that potential impacts could be widespread.

This suggests that synergistic action between pesticide active ingredients is much better documented and more common than current EPA pesticide assessments would indicate. Further, it appears that pesticide companies are in fact collecting information about the synergistic effects of their products that they are not sharing with the EPA. Recognizing that pesticide synergy data are widely available and that the synergistic relationships between pesticides can have serious implications for human and environmental health, the EPA must now take action to properly consider the potential consequences of pesticide synergy.

Introduction

Pesticide Registration

Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), before a pesticide can be sold or distributed in the United States it must be registered — that is, approved — by the EPA. By law the EPA can only register a pesticide if its use will not cause unreasonable adverse effects on the environment.[1] To analyze whether any possible adverse effects may occur, the agency requires that toxicity studies be submitted to it by the chemical companies that plan to sell the pesticide (subsequently referred to as "pesticide registrants"). These studies typically analyze the relative toxicities of the pesticide to different taxa of plants and animals.[2] Once these data are analyzed, the EPA conducts a cost-benefit analysis that weighs the environmental costs with the purported economic benefits of pesticide use and decides whether or not to register a given pesticide.

The data that are required to be submitted by pesticide registrants almost always involve the use of a single pesticide in the absence of any other added chemicals. In reality pesticide exposures never occur in isolation. Pesticides are typically sold as formulations, meaning the pesticide is mixed with other chemicals in the bottle. These other chemicals can be other pesticides or "inert" ingredients, which are chemical additives that can affect the toxicity or absorption of the pesticide.[3] In addition, pesticide products are often mixed in the field before application with other ingredients called "adjuvants"[4] and/or other pesticide products. Pesticides that are applied on different geographic areas can also migrate away from the site of application and mix together in the environment.[5] The EPA toxicity data requirements from chemical companies that focus on a single ingredient, combined with the fact that government and academic researchers often don't have the means to study the vast landscape of mixture toxicity in sufficient detail, leads to an enormous gap in our knowledge of pesticide mixture toxicity.

Chemical Interactions

When chemicals mix in the environment, one of two things can happen: 1) the chemicals can interact in such a way as to change their toxicity profiles or 2) no interaction occurs. When chemicals do not interact, this is generally referred to as "additivity," which means that no chemical in the mixture influences the toxicity of the other chemical(s) and toxicity can be estimated by how the chemicals act on their own. Alternatively, chemicals can interact to increase or decrease toxicity beyond the sum of the individual effects, which is referred to as "synergism" or "antagonism," respectively.[6] Synergism is particularly worrisome from a regulatory point of view, because, if it is not properly taken into account, adverse effects on human health or the environment can be much greater than originally estimated.

The EPA's current guidance on how to assess mixture toxicity to humans directs the agency to assume that no interaction is occurring as a default unless available data indicate otherwise.[7] In practice, because of the enormous data gaps on mixture toxicity, the EPA almost exclusively ends up assuming "no interaction" when the agency analyzes mixture toxicity to humans. There is currently no guidance on how the EPA assesses mixture toxicity to plants and animals other than humans, and the ecological risk assessment process does not generally assess pesticide mixture toxicity.[6]

Patent Applications

The extensive gaps in our knowledge of mixture toxicity ultimately weaken the EPA's ability to effectively regulate pesticides, and new sources of data need to be identified. One new source of data was recently brought to the forefront with EPA's approval of Enlist Duo, a new pesticide product from Dow that combines glyphosate and 2,4-D into one formulation for use on second generation genetically engineered crops. Following its registration of Enlist Duo, in preparing to defend itself in subsequent litigation on the registration decision, the EPA came across a patent application from Dow that indicated glyphosate and 2,4-D result in synergistic toxicity to plants. This meant that the EPA's evaluation of the product at the registration phase lacked a full consideration of impacts to nontarget plants, including endangered species. The discovery of this patent application spurred the EPA to further request any relevant data from Dow about possible synergies and ultimately ask a court to vacate its decision to register Enlist Duo.[8]

When a company or individual wants to patent a chemical mixture in the United States, the United States Patent and Trademark Office (USPTO) has to determine whether there is something nonobvious about the mixture that could presumably only be found through research and development done by the applicant.[9] For chemical mixtures of pesticides, the applicant will often demonstrate this by claiming that the chemicals have synergistic activity. Therefore, when a chemical company applies for patent protection on a mixture of multiple pesticides, it is often accompanied by data that demonstrate synergistic toxicity to the organisms that are going to be targeted by the pesticide mixture.

In the case of Enlist Duo, the fact that publicly available data from a patent application was unknown to the EPA until it was working to defend itself in litigation highlights just how broken this process is. Enormous data gaps, coupled with nonconservative measures of mixture toxicity, have created a precarious framework of assumptions that, in many cases, underestimates the toxicity of pesticide mixtures to humans and the environment.

Analysis

Pesticide Products

For this analysis we sought to understand just how extensive the patent landscape was regarding claims of pesticide synergy. To ensure that our analysis was relevant to pesticide mixtures that were going to be encountered in the environment, we limited it to products that contain multiple pesticide ingredients (subsequently referred to as "active ingredients"). Specifically, we identified all of the products from four major agrochemical companies (Bayer, Dow, Monsanto and Syngenta — hereafter referred to as "The Big Four") the EPA approved in the past six years that contained two or more active ingredients.[10] This way we identified pesticides that were absolutely certain to be co-applied because they are sold together in a single product. A more detailed description of our methodology is outlined in Appendix A.

We found 140 products from The Big Four, approved between June 2010 and June 2016, that contained at least two active ingredients. Each product contained anywhere from two to six active ingredients, and all were characterized as an herbicide, insecticide or fungicide/nematicide. The largest group of multi-ingredient products from The Big Four that have been approved in the past six years was herbicides, accounting for 67 of the 140 products. A breakdown of the products by company indicates that Bayer, Dow, Monsanto and Syngenta had 49, 26, 5 and 60 products that were included in our analysis, respectively.

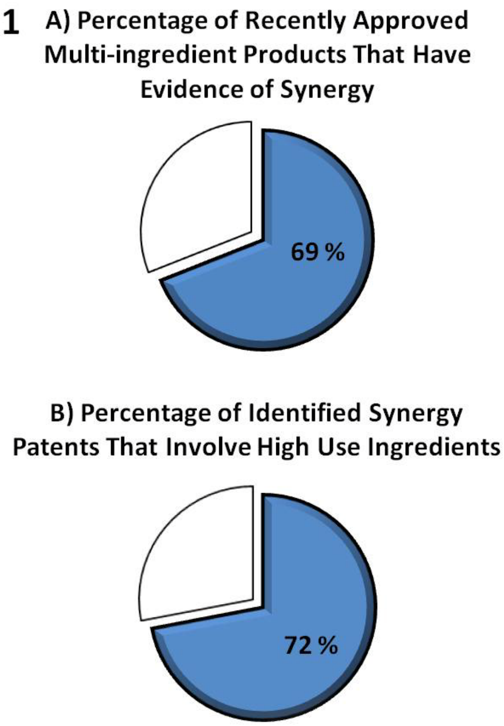
Synergy Patents

We then searched various databases for patent applications that made a claim of synergy for at least two of the active ingredients in the product (methodology outlined in Appendix A). Only patent applications submitted to the USPTO were included in this analysis; patent applications in other countries were excluded. All patent applications that were granted, denied or still in the application process were included in our analysis because the status of the application has no bearing on the underlying accuracy of the synergy claims. The USPTO generally does not pass judgment on whether synergy exists or not; it takes applicants at their word, only considering whether the claims are nonobvious and therefore patentable.

Remarkably, of the 140 pesticide products included in our analysis that contain multiple active ingredients, 96 had at least one patent application that claimed or demonstrated synergy between the active ingredients in the product, a total of 69 percent (Figure 1a and Appendix B). These 96 products had at least one patent application and as many as six, claiming or demonstrating synergy between the active ingredients in the product. The majority of patent applications contained experimental data that were included in the application as evidence of the claimed synergy. For all patent applications, synergy was claimed or demonstrated for target organisms (i.e. synergistic toxicity to target insect species for insecticidal ingredients). A breakdown of the patent synergy claims by company indicates that 71 percent (35/49), 46 percent (12/26), 40 percent (2/5) and 78 percent (47/60) of Bayer, Dow, Monsanto and Syngenta products had patent applications that claimed synergy between at least two of the active ingredients in the product, respectively.

As some of the approved products contained similar ingredients, many patent applications covered multiple products. There were a total of 47 patent applications that covered the ingredient mixtures in the products included in our analysis.[11] Many of the ingredients covered by these patent applications are very widely used, with 72 percent (34/47) of patent applications involving high use ingredients (more than 1 million pounds used per year in the U.S. agricultural sector) (Figure 1b).[12]

Fig 1



<u>Acuron, a case study</u>

In 2015 the EPA conditionally registered a pesticide product from Syngenta called Acuron (EPA Reg. No. 100-1466, Decision No. 470872). Acuron combines four different active ingredients — bicyclopyrone, S-metolachlor, mesotrione and atrazine — into a single formulation to control weeds in cornfields. The approval of the Acuron product was combined with the approval of the new active ingredient bicyclopyrone, and therefore went through public review and comment.[13]

In response to the Center for Biological Diversity's public comments regarding possible synergistic effects of Acuron, the EPA stated: "Concerning synergistic effects, the agency does not routinely include a separate evaluation of mixtures of active ingredients. However, there are some data available to the agency regarding synergistic effects and EPA believes it adequately addressed the issue of synergism between bicyclopyrone and atrazine."[14] But the EPA provides no information on how it addressed this issue of synergism as there is no mention of this analysis in the ecological risk assessment,[15] no separate analysis was provided to the public, and there was no mention of whether synergy was analyzed for ingredient combinations other than bicyclopyrone and atrazine. The agency further indicated that a study of acute toxicity of Acuron to mammals was analyzed and did not indicate synergy was occurring.[14] However, it did not analyze chronic toxicity to mammals or acute and chronic toxicity to all other taxa like birds, fish, invertebrates and plants as a result of Acuron exposure prior to approving this product.

As Acuron is a Syngenta product that was approved in the past six years, it was included in our patent analysis. We found three patent applications claiming synergistic toxicity to plants from exposure to the ingredients in this product: the combination of 1) S-metolachlor and mesotrione (app # 12374219), 2) mesotrione and atrazine (app # 12675156) and 3) atrazine and S-metolachlor (app # 08930901) (Appendix B). Since bicyclopyrone has the same mode of action as mesotrione,[16] it is likely that any synergy observed with mesotrione and other ingredients will be present with bicyclopyrone and those ingredients as well. Synergistic toxicity of mesotrione and atrazine to certain species of plants has also been extensively documented in the literature.[17-22] Finally, in publicly available promotional materials for Acuron, Syngenta has not only claimed that mesotrione and bicyclopyrone work synergistically with atrazine to kill plants, but they have mapped out the exact mechanism by which synergy occurs.[23]

It is clear that there are at least three and as many as five layers of synergy that result from the combination of ingredients in Acuron (Figure 2). This synergistic toxicity has been demonstrated for species of plants, and plant health is a very important part of the ecological risk assessment process. EPA's failure to accurately account for toxicity to nontarget plants can lead to damage of crops in nearby fields, harm to endangered or threatened species of plants and harm to vital aquatic and terrestrial plant communities and the wildlife that rely on them. The EPA is charged with ensuring that pesticide use results in no unreasonable adverse effects to the environment or harm to endangered or threatened species. It is still unclear how the agency came to its conclusion for Acuron without properly considering this publicly available, relevant information.[24]

Fig 2

Synergy Evidence for Acuron (mesotrione, S-metolachlor, bicyclopyrone, atrazine)

Line of evidence	patent claim	published studies	promotional materials	based on mode of action
S-metolachlor + mesotrione	X			
mesotrione + atrazine	X	X	X	
S-metolachlor + atrazine	X			
bicyclopyrone + atrazine			X	X
bicyclopyrone + S-metolachlor				X

Discussion

Our analysis indicates that there are patent applications claiming or demonstrating synergistic action for 69 percent of the recently approved products from The Big Four pesticide companies that contain multiple active ingredients. This percentage is very high and disconcerting. Synergy between chemicals is not generally thought to be a very common phenomenon, which is one reason regulatory agencies typically assume additivity. However, in the case of premixed products, this high percentage makes perfect sense. Combining synergistically acting chemicals into a single product not only allows a company to gain patent protection on the combination of ingredients in their product, but, from a product performance point of view, it makes sense to combine ingredients that will enhance each other's ability. Unfortunately enhancing toxicity to target organisms will often enhance toxicity to many nontarget organisms as well. Perhaps most worrisome is that 72 percent of the patent applications we identified claimed or demonstrated synergy with some of the most highly used pesticides in the United States, including glyphosate, atrazine, 2,4-D, dicamba and the controversial neonicotinoids thiamethoxam, imidacloprid and clothianidin, indicating that potential impacts could be widespread.

We're also certain that 69 percent is an *underestimate* of how many of these products have synergistic activity. There are multiple reasons for this conclusion:

1. We only took into account U.S. patent applications. In our search we found multiple relevant patent applications filed with other countries as well as with the World Intellectual Property Organization (WIPO). For example, a U.S. patent application could not be identified for the product combining methoxyfenozide and spinetoram (EPA reg No. 62719-666), however Dow submitted a patent application

to the WIPO claiming that this active ingredient combination works synergistically to kill an insect target organism.[25]

2. Many relevant patent applications may not be publicly available yet. The products that we analyzed were approved relatively recently, and it is therefore likely that some relevant patent applications were filed recently as well. The USPTO delays the publishing of patent applications for 18 months after the date of first filing.[26] So any patent applications filed within the past year and a half may not be publicly available and would not have been identified by our search strategy.
3. Because "inert" ingredients in pesticide products are not made available to the public, we were unable to search for patent applications that demonstrated synergy between the active ingredients and other ingredients contained in the pesticide product. We did come across many patent applications claiming synergy between the active ingredients in the analyzed products and commonly used "inert" ingredients;[27] however, the lack of ingredient transparency in pesticide products prohibited the inclusion of possibly relevant patent applications. Therefore, more layers of synergy may be present in these products than were identified in this analysis.
4. Searching for patent applications is surprisingly difficult. It is possible that our search strategy (Appendix A) missed relevant patent applications.
5. We only searched for claims of synergy in patent applications. As was the case with Acuron, some of these chemical combinations may have been demonstrated to act synergistically on target or nontarget organisms in peer-reviewed scientific studies. Any such study would not have been identified in our analysis. Furthermore, any unpublished, internal studies done by chemical companies would, of course, not be identified either.

Pesticide companies likely possess additional information regarding pesticide synergy that they do not include in their patent applications. Patent applications are very different from scientific studies, which are the typical data source used by the EPA to assess risk. The latter are very descriptive and data intensive, while the former provide the bare minimum of information required to demonstrate to the patent office that their claim is legitimate. This does not necessarily mean that experimental data provided in patent applications are somehow less scientifically valid than data from scientific studies, only that more data may be available from the patent applicant than was provided to the patent office. The EPA acknowledged this fact in the Enlist Duo case by not just relying on the information contained in the relevant patent application, but also requiring Dow to submit any relevant data on the synergy between glyphosate and 2,4-D that was in its possession.[8] In many cases the patent applicant will have additional data on synergism in their possession, as extensive experimentation is typically done before a company will invest the time and money to develop a product that they intend to market. It is important that this be kept in mind when scientifically evaluating the data contained in patent applications.

We cannot say with absolute certainty that the patent data on synergy that we identified were not used in making registration decisions for these products. There are multiple reasons for this. The first is that, unlike Acuron, many individual products are given approval without public review and comment, so the analysis that went into the product approval, if any, is not shared with the public. Second, even when products do go through public review and comment, a mixture toxicity analysis is either not performed or not outlined in sufficient detail for the public to understand all of the lines of evidence that were used. However, given that, in the case of Enlist Duo, the EPA indicated that it just recently become aware that patent data on synergy exist and the fact that it is not common practice to do a mixture analysis for the ecological risk assessment, we think it is extremely likely that most, if not all, of these product approvals were made without taking into account this relevant patent information.

It is also unclear why the EPA has not previously been made aware of these patent data by pesticide registrants. Registrants are required to submit information to the EPA that could raise concerns about the continued registration of a product or about the appropriate terms and conditions of registration.[28] For example, pursuant to 40 CFR §159.195(a)(3), the registrant is required to submit information that indicates "[u]se of a pesticide may pose any greater risk than previously believed or reported to the Agency." Data on chemical synergy would certainly fall into that category. It appears that chemical companies are using synergy to demonstrate that chemical combinations have some sort of novelty associated with them and are, therefore, patentable — yet when it comes to the toxicities associated with this synergy, this information never makes it to the EPA.

Recommendations

Searching for patent applications can be a difficult process that takes considerable time and knowledge. Often the pesticide is not referred to by its common name in the patent application, making a simple keyword search insufficient to identify all relevant patent information. The EPA cannot rely on stakeholders to provide all of the necessary information from patent applications, but rather the EPA must place the burden to produce and submit information related to synergistic effects squarely where it belongs: on the pesticide registrant or applicant.

1. Registrants or applicants need to be made aware that failure to submit relevant data to the EPA will be a violation of their duties under Section 6(a)(2) of FIFRA.[29] When applicable, enforcement should be pursued when registrants fail to provide those data.
2. To identify patent data that are not affiliated with the pesticide registrant, the EPA needs to use a stepwise approach of doing a keyword <u>and</u> structure search for patent applications concerning the pesticide of interest followed by a rigorous analysis of the claims in the patent application.
3. Any claims of synergy need to be assessed for relevance given the label restrictions for the pesticide (or lack thereof) and the inert ingredients that are present in any formulation up for approval.
4. Appropriate measures need to be taken to ensure that any registration decision is compliant with FIFRA. This may include label restrictions on mixing, increased in-field buffers, lower application rates or even product cancellation.

A full analysis of mixture toxicity needs to be taken into account for both the human health and ecological risk assessments. When patent applications or other data demonstrate synergistic toxicity to target organisms, that synergy needs to be assumed for all other nontarget organisms within that taxon. For instance if a mixture results in synergistic toxicity to a target insect, like an aphid, then that synergy needs to be assumed for all insects and possibly all other invertebrates in the ecological risk assessment unless available data indicate otherwise. This would be consistent with EPA's current use of surrogate species to estimate toxicity to other species within the same taxon for the human health and ecological risk assessments. This is one way that the EPA can begin to take into account mixture toxicity given the extensive data gaps that are currently present.

Conclusions

The human health and ecological risk assessments are a key part of the EPA's pesticide-approval process; without them the agency cannot justifiably conclude that a pesticide can be used without unreasonable harm. When relevant data are not included in the risk assessment, and nonconservative assumptions are made about mixture toxicity, it diminishes the process and ultimately underestimates harm to humans and the environment.

The patent applications identified in this analysis are just the tip of the iceberg. The patent landscape on pesticide mixtures is vast and in no way limited to pesticides that are sold together in formulations. In fact, the implications of this analysis should extend far beyond that of multi-ingredient product approval. The entire pesticide-approval process is designed to narrowly assess the toxicity of individual active ingredients one at a time; yet when most of these active ingredients are being routinely co-applied on agricultural fields across the country, the initial analyses that were done are no longer relevant to real-world exposure scenarios and are not an appropriate estimate of true risk.

This analysis highlights the shortcomings of such a narrow approach. Since mixture toxicity is such a low priority for the EPA, it is no surprise that relevant information was missed for so long. Clearly pesticide synergy is not a rare occurrence and should no longer be treated as such. The EPA must take into account relevant patent data and other lines of evidence and fundamentally alter its approach to assessing pesticide mixtures.

Appendix A

Methodology of Product Search

We used the EPA's Pesticide Product Label System database to conduct our search.[30] In the "company name" search box we searched for "Bayer," "Dow Agrosciences LLC," "Monsanto Company" and "Syngenta Crop Protection," which identified 685, 369, 176 and 539 products respectively. These are all of the pesticide products with "active" status for these four companies as of June 23, 2016 (a total of 1769). To identify the products that had their initial approval in the last six years *and* had multiple active ingredients, we found all active products that that had a date on or after June 23, 2010 in the "current status" column. We then searched the pesticide labels of each of those products. If the label indicated two or more active ingredients were present in the product, it was included in our analysis. Of the 1769 active products for these companies, 140 had multiple active ingredients and were first approved by the EPA in the past six years. All of these products are listed in Appendix B.

Methodology of Patent Search

To identify all applicable patent applications, we used a multi-layered search strategy. First, we used the search engines from Google Patents,[31] FreePatentsOnline[32] and the USPTO[33] to do simple keyword searches. The common names of each pesticide were searched concomitantly with the words "synergy," "synergistic" or "synergism." We found many relevant patents using this strategy, but quickly became aware of the limitations of doing a simple keyword search. Many patent applicants do not refer to pesticides by their common name but instead use a common core structure along with various possible side groups to describe the chemicals they want to patent. In order to identify these patents, we used a search engine called SureChEMBL.[34] This allows the user to search patent applications for the chemical structure of the pesticide in conjunction with keywords. In addition, we used SciFinder[35] to search patent applications by the pesticide's Chemical Abstracts Service (CAS) number and filtered results by other pesticides mentioned in the patent or by the word "synergistic."

All of the patents we identified were further scrutinized. First, any patent application that was not submitted to the USPTO was discarded. This is because many of the patent applications submitted to other countries that we identified were in a language other than English; however, we note that this discarded information could likely be useful to the EPA. We then went through each of the identified patents and verified that claims of synergy were made for at least two of the active ingredients in the product. If it was stated anywhere in the patent application that a mixture of chemicals acted synergistically to produce toxicities to any organism, that patent was used in our analysis. However, we note that a strong majority of patent applications also contained experimental evidence of synergy.

Notes were taken on each patent included in our analysis, including:

1) The company that was listed as the applicant or assignee of the patent application and whether this was different from the registrant of the product.
2) The taxa of the organism(s) for which synergy was claimed (plants, insects, fungi, nematodes).
3) If there was a possible difference in stereoisomer content of the chemicals in the pesticide product and the patent application. Since lambda-cyhalothrin is a mixture of enantiomers, one of which is gamma-cyhalothrin, any claims of synergy for one was assumed for the other. Similarly, since mefenoxam is one of the two enantiomers that are present in metalaxyl, any claims of synergy for one was assumed for the other.
4) If any experimental evidence of synergy was provided in the patent application as well as the magnitude of the synergy as measured by the Colby equation.[36] If experimental data were provided in the application and a Colby analysis was performed, the extent of synergy (low, medium and high) was noted for each patent application. The observed response (C_{obs}) and the expected response (assuming no interaction) (C_{exp}) were used to make this determination. If the difference of C_{obs} and C_{exp} was less than 10, that was considered low synergy. If the difference of C_{obs} and C_{exp} was between 10 and 20, that was considered medium synergy. And if the difference of C_{obs} and C_{exp} was greater than 20 or if C_{obs}/C_{exp} was greater than 2, then that was considered high synergy. Also, if experiments were performed but no data were provided, or if experimental data were given but no Colby equation was done, we took note of that as well (Appendix B).

Appendix B

First App	Reg	Reg #	Active Ingredients	App #	notes	Taxa	Appl	App #	notes	Taxa	Appl	App #	notes	Taxa	Appl
7/14/2010	D	62719-616	penoxsulam; cyhalofop												
7/20/2010	S	100-1369	thiamethoxam; fludioxonil; azoxystrobin; mefenoxam	10496187	3	F	S	10170902	1, 7	F	S				
7/25/2010	B	72155-90	2,4-D; dicamba; mecoprop-p; indaziflam	13841457	3	P	B	12506456	3	P	B				
7/26/2010	B	72155-91	dicamba; penoxsulam; indaziflam	14026902	2, 7	P	D	12506456	3	P	B				
7/26/2010	B	72155-89	2,4-D; dicamba; mecoprop-p; indaziflam	13841457	3	P	B	12506456	3	P	B				
8/2/2010	B	264-1103	Iodosulfuron-methyl-sodium; mesosulfuron-methyl												
8/3/2010	D	62719-617	aminopyralid; metsulfuron methyl	12945099	6	P	D								
8/5/2010	S	100-1366	difenoconazole; thiamethoxam; *lambda* -cyhalothrin	12633063	1, 4	I	S	9968173	3	I	M, S	14215205	8	I	S
8/5/2010	S	100-1367	difenoconazole; thiamethoxam; *lambda* -cyhalothrin	12633063	1, 4	I	S	9968173	3	I	M, S	14215205	8	I	S
8/6/2010	D	62719-612	penoxsulam; isoxaben												
9/3/2010	S	100-1352	fludioxonil; mefenoxam; azoxystrobin; thiabendazole	11563240	6	F, N	S	10496187	3	F	S				
10/14/2010	B	432-1513	trifloxystrobin; triadimefon												
10/29/2010	S	100-1384	thiamethoxam; mefenoxam; fludioxonil; azoxystrobin	10496187	3	F	S	10170902	1, 7	F	S				
11/24/2010	S	100-1385	fomesafen; glyphosate												
1/20/2011	B	352-846	aminocyclopyrachlor; chlorsulfuron												
1/20/2011	B	352-848	aminocyclopyrachlor; metsulfuron-methyl	14172201	2, 4	P	D								
1/20/2011	B	352-847	imazapyr; aminocyclopyrachlor; metsulfuron-methyl	14172201	2, 4	P	D								
2/16/2011	S	100-1389	pinoxaden; fluroxypyr												
3/2/2011	S	100-1396	fomesafen; glyphosate												
3/10/2011	D	62719-630	2,4-D; aminopyralid	13014909	6	P	D								
3/10/2011	D	62719-628	2,4-D; aminopyralid	13014909	6	P	D								
3/11/2011	S	100-1377	azoxystrobin; propiconazole												
3/11/2011	S	100-1378	azoxystrobin; propiconazole												
3/24/2011	S	100-1393	fludioxonil; mefenoxam	8799310	1, 3	F	S								
4/10/2011	D	62719-629	2,4-D; aminopyralid	13014909	6	P	D								
4/12/2011	S	100-1364	chlorothalonil; acibenzolar-S-methyl												
4/12/2011	B	72155-98	indaziflam; diquat dibromide; glyphosate	12506456	6	P	B								
4/12/2011	B	72155-99	indaziflam; diquat dibromide; glyphosate	12506456	6	P	B								
4/12/2011	B	72155-100	indaziflam; diquat dibromide; glyphosate	12506456	6	P	B								
4/12/2011	B	72155-101	indaziflam; diquat dibromide; glyphosate	12506456	6	P	B								
4/26/2011	B	72155-104	2,4-D; dicamba; mecoprop-p; indaziflam	13841457	3	P	B	12506456	3	P	B				
4/29/2011	B	264-1132	clothianidin; Bacillus-firmus I-1582	12936700	3	I, F, N	B								
5/2/2011	B	72155-102	indaziflam; diquat dibromide; glyphosate	12506456	6	P	B								
5/2/2011	B	72155-103	indaziflam; diquat dibromide; glyphosate	12506456	6	P	B								
5/5/2011	D	62719-637	triclopyr; fluroxypyr												
6/3/2011	S	100-1402	*lambda* -cyhalothrin; chlorantraniliprole												
6/13/2011	B	72155-105	2,4-D; dicamba; mecoprop-p; indaziflam	13841457	3	P	B	12506456	3	P	B				
6/15/2011	S	100-1399	thiamethoxam; abamectin; thiabendazole;	11028776	7	I	S	11563240	6	F, N	S	11028769	7	F, N	S
			fludioxonil; mefenoxam; azoxystrobin	14183671	6	F, N	S	10496187	3	F	S	10170902	1, 7	F	S
6/27/2011	D	62719-640	glyphosate; 2,4-D	14567574	6	P	D	12147853	6	P	D				
8/12/2011	B	72155-106	2,4-D; isoxaben; mecoprop-p; dicamba	13841457	6	P	B								
8/17/2011	B	264-1134	Iodosulfuron-methyl sodium; thiencarbazone-methyl	12824951	6	P	B								

First App	Reg	Reg #	Active Ingredients	App #	notes	Taxa	Appl	App #	notes	Taxa	Appl	App #	notes	Taxa	Appl
10/19/2011	S	100-1405	thiamethoxam; abamectin; thiabendazole;	11028776	7	I	S	11563240	6	F, N	S	11028769	7	F, N	S
			fludioxonil; mefenoxam; azoxystrobin	14183671	6	F, N	S	10496187	3	F	S	10170902	1, 7	F	S
11/16/2011	S	100-1410	S-metolachlor; mesotrione	12374219	6	P	S								
12/6/2011	B	264-1135	thiencarbazone-methyl; pyrasulfotole; bromoxynil	12824951	4	P	B								
12/14/2011	S	100-1414	S-metolachlor; mesotrione; atrazine	12374219	6	P	S	12675156	6	P	S	8930901	3	P	S
1/11/2012	S	100-1415	azoxystrobin; thiamethoxam												
1/26/2012	B	432-1519	thiencarbazone-methyl; foramsulfuron; halosulfuron-methyl	13902364	5	P	B	12824951	5	P	B				
2/1/2012	S	100-1433	azoxystrobin; difenoconazole	10496185	8	F	S								
2/2/2012	S	100-1427	thiamethoxam; mefenoxam; fludioxonil	13209926	2, 3	F	Bf	8799310	1, 3	F	S				
2/2/2012	S	100-1426	thiamethoxam; mefenoxam; fludioxonil; thiabendazole	11563240	6	F, N	S	8799310	1, 3	F	S				
2/2/2012	B	264-1091	fluopyram; tebuconazole												
2/2/2012	B	264-1090	fluopyram; trifloxystrobin												
2/2/2012	B	264-1085	fluopyram; pyrimethanil												
2/2/2012	B	264-1084	fluopyram; prothioconazole												
2/7/2012	D	62719-646	acetochlor; atrazine												
2/14/2012	S	100-1429	pinoxaden; fenoxaprop-p-ethyl												
2/15/2012	D	62719-645	clopyralid; aminopyralid	13715230	6	P	D	14102818	6	P	D				
2/22/2012	S	100-1428	difenoconazole; mefenoxam												
4/23/2012	S	100-1436	thiamethoxam; *lambda* -cyhalothrin	12633063	1, 4	I	S	9968173	3	I	M, S	14215205	8	I	S
4/23/2012	S	100-1437	thiamethoxam; *lambda* -cyhalothrin	12633063	1, 4	I	S	9968173	3	I	M, S	14215205	8	I	S
4/27/2012	B	72155-107	metsulfuron-methyl; thiencarbazone-methyl; indaziflam; dicamba	12824951	6	P	B	12506456	3	P	B				
4/30/2012	S	100-1438	thiamethoxam; mefenoxam; fludioxonil; azoxystrobin	10496187	3	F	S	10170902	1, 7	F	S				
5/11/2012	B	264-1125	penflufen; clothianidin	11912773	6	I	B								
5/11/2012	B	264-1123	penflufen; prothioconazole	13061976	3	F	B								
5/11/2012	B	264-1122	prothioconazole; penflufen; metalaxyl	10508208	2, 3	F	Bf	12663273	5	F	B				
5/11/2012	B	264-1124	penflufen; trifloxystrobin	12663273	4	F	B								
5/11/2012	B	164-1121	clothianidin; penflufen; trifloxystrobin; metalaxyl	11793763	6	I	B	10486663	6	I	B	12663273	5	F	B
				13209926	2, 3	F	Bf	11912773	6	I	B				
6/20/2012	S	100-1383	sedaxane; difenoconazole; mefenoxam; thiamethoxam	12306870	1, 2, 6	I	B	13209926	2, 3	F	Bf	12278731	6	F	S
6/21/2012	S	100-1440	abamectin; thiamethoxam	11028776	7	I	S								
8/2/2012	S	100-1442	S-metolachlor; mesotrione; atrazine	12374219	6	P	S	12675156	6	P	S	8930901	3	P	S
8/23/2012	S	100-1449	thiamethoxam; mefenoxam; fludioxonil; azoxystrobin	10496187	3	F	S	10170902	1, 7	F	S				
10/31/2012	S	100-1441	chlorothalonil; difenoconazole	12066894	8	F	S								
12/6/2012	S	100-1455	mesotrione; prodiamine	12374195	6	P	S								
1/15/2013	M	71995-57	glyphosate; diquat dibromide												
1/15/2013	M	71995-56	glyphosate; diquat dibromide												
1/15/2013	S	100-1457	abamectin; thiamethoxam; mefenoxam; fludioxonil	11028776	7	I	S	8799310	1, 3	F	S				
1/22/2013	B	432-1528	indaziflam; diquat dibromide; glyphosate	12506456	6	P	B								
1/23/2013	S	100-1458	*lambda* -cyhalothrin; thiamethoxam	12633063	1, 4	I	S	9968173	3	I	M, S	14215205	8	I	S
1/30/2013	S	100-1459	thiamethoxam; mefenoxam; fludioxonil; sedaxane	12306870	2, 6	I	B	13209926	2, 3	F	Bf	8799310	1, 3	F	S
				12278731	6	F	S								
1/30/2013	S	100-1460	thiamethoxam; mefenoxam; fludioxonil; sedaxane	12306870	2, 6	I	B	13209926	2, 3	F	Bf	8799310	1, 3	F	S
				12278731	6	F	S								
3/5/2013	D	62719-655	2,4-D; picloram												
3/7/2013	D	62719-653	2,4-D; picloram												
4/2/2013	D	62719-673	glyphosate; 2,4-D	14567574	6	P	D	12147853	6	P	D				

First App	Reg	Reg #	Active Ingredients	App #	notes	Taxa	Appl	App #	notes	Taxa	Appl	App #	notes	Taxa	Appl
4/3/2013	D	62719-671	atrazine; acetochlor												
4/4/2013	D	62719-668	atrazine; acetochlor												
4/4/2013	D	62719-670	atrazine; acetochlor												
6/11/2013	B	432-1527	imidacloprid; beta-cyfluthrin	9968175	2, 3	I	M								
6/12/2013	S	100-1444	thiamethoxam; fludioxonil; difenoconazole	7792845	4	F	S								
6/17/2013	S	100-1470	glyphosate; mesotrione												
6/19/2013	B	72155-110	imidacloprid; beta-cyfluthrin	9968175	2, 3	I	M								
7/22/2013	D	62719-666	methoxyfenozide; spinetoram												
8/8/2013	B	352-845	aminocyclopyrachlor; sulfometuron-methyl; chlorsulfuron												
8/29/2013	D	62719-667	methoxyfenozide; spinosad												
2/3/2014	D	62719-648	cyhalofop; fluroxypyr	12913235	6	P	D								
2/6/2014	S	100-1421	cyantraniliprole; thiamethoxam	11628145	2, 5	I	Du								
2/7/2014	S	100-1422	cyantraniliprole; thiamethoxam	11628145	2, 5	I	Du								
2/7/2014	S	100-1424	cyantraniliprole; thiamethoxam	11628145	2, 5	I	Du								
2/27/2014	D	62719-679	acetochlor; flumetsulam; clopyralid	12074809	3	P	D								
2/27/2014	M	524-614	acetochlor; flumetsulam; clopyralid	12074809	3	P	D								
2/27/2014	S	100-1508	thiamethoxam; mefenoxam; fludioxonil; sedaxane	12306870	2, 6	I	B	13209926	2, 3	F	Bf	8799310	1, 3	F	S
				12278731	6	F	S								
4/22/2014	M	524-616	dicamba; glyphosate	13099552	2, 6	P	D	13751021	7	P	M				
5/16/2014	D	62719-680	sulfentrazone; cloransulam-methyl												
5/29/2014	S	100-1527	thiamethoxam; difenoconazole; mefenoxam; fludioxonil; sedaxane	12306870	2, 6	I	B	13209926	2, 3	F	Bf	8799310	1, 3	F	S
				7792845	4	F	S	12278731	6	F	S				
5/30/2014	S	100-1526	difenoconazole; mefenoxam; fludioxonil; sedaxane	8799310	1, 3	F	S	7792845	4	F	S	12278731	6	F	S
6/10/2014	B	264-1168	fenoxaprop-p-ethyl; pyrasulfotole; bromoxynil octanoate; bromoxynil heptanoate												
7/16/2014	S	100-1540	propiconazole; azoxystrobin												
7/29/2014	B	432-1533	foramsulfuron; iodosulfuron-methyl; thiencarbazone-methyl	13902364	5	P	B	12824951	6	P	B				
9/29/2014	B	264-1170	spirotetramat; imidacloprid	13790375	7	I	B								
10/10/2014	S	100-1555	cyantraniliprole; thiamethoxam	11628145	2, 5	I	Du								
10/15/2014	D	62719-649	glyphosate; 2,4-D	14567574	6	P	D	12147853	6	P	D				
11/12/2014	B	432-1530	imidacloprid; spirotetramat	13790375	7	I	B								
12/2/2014	S	100-1530	sedaxane; difenoconazole; mefenoxam; thiamethoxam	12306870	1, 2, 6	I	B	13209926	2, 3	F	Bf	12278731	6	F	S
12/22/2014	S	100-1549	azoxystrobin; propiconazole; *lambda* -cyhalothrin; thiamethoxam	12633063	1, 4	I	S	9968173	3	I	M, S	14215205	8	I	S
12/23/2014	S	100-1550	azoxystrobin; acibenzolar-S-methyl												
1/12/2015	S	100-1506	azoxystrobin; difenoconazole	10496185	8	F	S								
1/14/2015	S	100-1554	azoxystrobin; difenoconazole	10496185	8	F	S								
2/6/2015	B	264-1171	imidacloprid; fluopyram												
4/13/2015	M	524-620	acetochlor; fomesafen												
4/21/2015	B	72155-112	dicamba; penoxsulam; indaziflam	14026902	2, 7	P	D	12506456	3	P	B				
4/21/2015	B	72155-113	dicamba; penoxsulam; indaziflam	14026902	2, 7	P	D	12506456	3	P	B				
4/24/2015	S	100-146	atrazine; bicyclopyrone; S-metolachlor; mesotrione	12374219	6	P	S	12675156	6	P	S	8930901	3	P	S
4/27/2015	D	62719-689	cloransulam-methyl; flumioxazin												
7/17/2015	B	72155-114	tau-fluvalinate; tebuconazole												
8/5/2015	S	100-1561	sedaxane; mefenoxam; fludioxonil	8799310	1, 3	F	S	12278731	6	F	S				
8/23/2015	S	100-1450	thiamethoxam; mefenoxam; fludioxonil; azoxystrobin; thiabendazole	11563240	6	F, N	S	10496187	3	F	S	10170902	1, 7	F	S
8/28/2015	D	62719-685	clopyralid; fluroxypyr; pyroxsulam												

First App	Reg	Reg #	Active Ingredients	App #	notes	Taxa	Appl	App #	notes	Taxa	Appl	App #	notes	Taxa	Appl
10/8/2015	B	432-1544	imidacloprid; beta-cyfluthrin	9968175	2, 3	I	M								
10/19/2015	S	100-1556	thiamethoxam; fludioxonil; difenoconazole; sedaxane	12306870	2, 6	I	B	7792845	4	F	S	12278731	6	F	S
10/19/2015	S	100-1559	thiamethoxam; mefenoxam; thiabendazole; fludioxonil; sedaxane	12306870	2, 6	I	B	11563240	6	F, N	S	8799310	1, 3	F	S
				12278731	6	F	S								
11/10/2015	B	11556-186	diflubenzuron; permethrin												
12/9/2015	B	264-1182	penflufen; trifloxystrobin; metalaxyl	12663273	5	F	B								
1/6/2016	D	62719-693	acetochlor; mesotrione; clopyralid	12074809	3	P	D								
2/3/2016	S	100-1564	thiamethoxam; difenoconazole; mefenoxam; sedaxane;	12306870	1, 2, 6	I	B	13209926	2, 3	F	Bf	12278731	6	F	S
			cytokinin; gibberellic acid; indole butyric acid												
2/8/2016	S	100-1568	bicyclopyrone; mesotrione; S-metolachlor	12374219	6	P	S								
2/17/2016	B	264-1184	dicamba; tembotrione												
2/24/2016	D	62719-702	penoxsulam; oxyfluorfen	13014869	6	P	D								
4/11/2016	B	432-1583	imidacloprid; beta-cyfluthrin	9968175	2, 3	I	M								
4/12/2016	S	100-1563	thiamethoxam; thiabendazole; sedaxane; mefenoxam; fludioxonil	12306870	2, 6	I	B	11563240	6	F, N	S	8799310	1, 3	F	S
				12278731	6	F	S								
6/16/2016	S	100-1587	fludioxonil; sedaxane; thiamethoxam	12278731	3	F	S	12306870	2, 5	I	B				
6/20/2016	B	432-1537	fluopyram; trifloxystrobin												

Column 1: Date that the product was first approved by the EPA
Column 2: Registrant of the approved product (D=Dow, M=Monsanto, S=Syngenta, B=Bayer)
Column 3: Registration number of the product. Information on products can be found by searching the registration number on the EPA's Pesticide Product Label System found here:
https://iaspub.epa.gov/apex/pesticides/f?p=PPLS:1
Column 4: A list of the active ingredients found in each product
Column 5: The patent application number. Patent applications can be searched by application number on USPTO's Public Pair Portal found here:
http://portal.uspto.gov/pair/PublicPair
Column 6: Notes taken on the patent. **For more detailed information see Appendix A**
1 = Stereoisomer content of a pesticide in the product may differ from that analyzed in the patent.
2 = Applicant/assignee of patent application differs from the registrant of the product
3 = No experimental evidence was provided in the patent application
4 = Experimental evidence was provided in the patent application, which indicated low synergy
5 = Experimental evidence was provided in the patent application, which indicated medium synergy
6 = Experimental evidence was provided in the patent application, which indicated high synergy
7 = Experimental evidence was provided in the patent application but no Colby equation was performed
8 = Experiments were said to be performed but data were not provided in the patent application
Column 7: Taxa for which synergistic toxicity is claimed or demonstrated (P=Plants, I=Insects, F=Fungi, N=Nematodes)
Column 8: Applicant/assignee of the patent (D=Dow, M=Monsanto, S=Syngenta, B=Bayer, Du=DuPont, Bf=BASF)
Columns 9-12: Repeat columns 5-8
Columns 13-16: Repeat columns 5-8

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[1] 7 U.S.C. § 136a(c)(5)(C), (D); 40 C.F.R. § 152.112(e).
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[8] Respondents' Motion for Voluntary Vacatur and Remand filed in N*atural Resources Defense Council, Inc. v. U.S. EPA*, No. 14-73353 (consolidated with 14-73359), ECF Dkt. No. 121 (filed November 24, 2015 9th Cir.).
[9] 35 U.S.C § 103.
[10] Instead of identifying all of the products that were approved in the last six years that have multiple active ingredients, we decided to focus our analysis on just four companies. Our reasoning is that the EPA's pesticide product label database is of limited utility. The only search terms are "product name," "company name" or "EPA registration number." The only way to identify all products approved by date is to search by company, so we focused our analysis on the major players in the agrichemical business.
[11] The 47 USPTO patent application numbers are: 13014909, 11028776, 12074809, 14172201, 12945099, 12675156, 8930901, 12066894, 9968175, 13715230, 14102818, 12936700, 11793763, 13209926, 10486663, 11628145, 12913235, 9968173, 12633063, 14215205, 13099552, 13751021, 10496185, 10170902, 10496187, 7792845, 12147853, 14567574, 12506456, 13841457, 8799310, 11028769, 11563240, 14183671, 12374195, 12374219, 11912773, 12663273, 13061976, 14026902, 13014869, 10508208, 12278731, 13790375, 12306870, 13902364 and 12824951.
[12] Usage information was collected from the USGS National Water-Quality Assessment (NAWQA) Program. Pesticide National Synthesis Project – annual pesticide use maps 2013. Available here: https://water.usgs.gov/nawqa/pnsp/usage/maps/compound_listing.php. High use ingredients (defined as more than one million pounds active ingredient used in the agricultural sector per year in the U.S.) covered by the identified patent applications include: 2,4-D, thiamethoxam, acetochlor, clopyralid, atrazine, mesotrione, S-metolachlor, chlorothalonil, imidacloprid, clothianidin, dicamba, glyphosate, azoxystrobin, bromoxynil.
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[24] The Center has initiated litigation challenging the EPA's failure to consider the impacts of this approval on threatened and endangered species. *See* https://www.biologicaldiversity.org/news/press_releases/2015/pesticides-06-18-2015.html.
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[28] 40 C.F.R. § 159.195(a).
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