

From: Watson Greg USGR  
Sent: Tuesday, September 20, 2005 1:45 PM  
To: McFarland Janis USGR  
Cc: Elder Andrea USGR  
Subject: FW: Janis, this article may be our best bet ...

As requested ...

Best Regards,

Greg Watson  
State Regulatory Affairs & Federal Label Support Team Lead  
Synfacts Regulatory Affairs  
ph 336 632 2993  
mobile 336 707 7162  
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From: Watson Greg USGR  
Sent: Friday, September 16, 2005 6:29 PM  
To: Janis McFarland (sabagomacs@ncr.com)  
Subject: Janis, this article may be our best bet ...

## Combination of two widely used pesticides linked to Parkinson's disease

University of Rochester

Scientists have shown that the combination of two widely used agricultural pesticides-but neither one alone-creates in mice the exact pattern of brain damage that doctors see in patients with Parkinson's disease. The research offers the most compelling evidence yet that everyday environmental factors may play a role in the development of the disease.

The latest findings of the team led by Deborah Cory-Slechta, Ph.D., professor of environmental medicine and dean for research at the University of Rochester School of Medicine and Dentistry, appear in the Dec. 15 issue of the Journal of Neuroscience. The scientists caution that more studies are necessary to explain the link, since it's probable that many factors contribute to a complex disease like Parkinson's, and they say it's unlikely that the pesticides on their own actually cause the disease.

Cory-Slechta's team studied the effects of a mixture of two very common agricultural pesticides, the herbicide paraquat and the fungicide maneb. Each is used by farmers on millions of acres in the United States alone. Maneb is applied widely on such crops as potatoes, tomatoes, lettuce and corn, and paraquat is used on corn, soybeans, cotton, fruit, and a variety of other products. In the experiment, mice exposed to either one had little or no brain damage, but mice exposed to both share a significant trait with people in the very early stages of the disease: Though they appear healthy, key brain cells known as dopamine neurons are dying. The mice exposed to the mixture carried nearly all of the molecular hallmarks of Parkinson's disease as seen in humans.

"The environmental reality is that several of these chemicals are used on the same crops and in the same geographical locations. You've got to get rid of the weeds. Then the insects. Then funguses. These are different chemicals that

Botham, Philip  
Exhibit 61  
6/17/2020

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do different things, but they're often applied in the same fields," says Cory-Slechta, who was joined in the research by graduate student Mona Thiruchelvam and faculty members Eric Richfield, Raymond Baggs, and A. William Tank.

The study is one of the first to examine the effects of such chemicals in tandem. Cory-Slechta notes that current regulations and determinations of safety levels are usually based on the effects of single chemicals. "In the real world, we're exposed to mixtures of chemicals every day. There are thousands upon thousands of combinations; I think what we have found is the tip of the iceberg," she says. "There are a dozen different fungicides related to maneb alone. I don't think we just happened to pick the right chemicals to see such an effect."

Maneb, paraquat, and many other pesticides are used in the same agriculture-rich areas of the country, including the Midwest, California, Florida and the Northeast. The map of their use mirrors areas of the country where people are more likely to die of Parkinson's disease.

Several epidemiological studies have hinted at a role for pesticides in the development of the disease. Studies have found that farmers, people who live in rural areas, and people who drink well water are more likely to have the disease than people who don't. In addition, just last month, scientists at Emory University presented evidence that rats given a steady dose of the natural pesticide rotenone, used on home-grown fruits and vegetables, develop Parkinson's-like symptoms. Cory-Slechta's study, which used much lower levels of chemicals than the Emory research, is the first to link a combination of more widely used pesticides to the disease.

"No one has looked at the effects of studying together some of these compounds that, taken by themselves, have little effect," says Cory-Slechta. "This has enormous implications."

Currently scientists have little understanding of what causes Parkinson's, where a tiny group of dopamine-producing neurons deep within an area of the brain known as the substantia nigra die. This cell death leads to a shortage of the neurotransmitter dopamine and to the tremors, rigidity, and slow movement that mark the disease as it progresses slowly over a period of years or decades. Parkinson's affects about 1 million people in North America. There is a growing consensus among scientists that both genetic predisposition and environmental agents may play a role in the disease. Doctors see a similar effect in heart disease, where a patient might have both a family history and a sedentary lifestyle, or in cancer, where certain genes may make one prone to develop colon cancer and a poor diet makes the disease even more likely. Cory-Slechta thinks it's unlikely that exposures to such chemicals actually cause Parkinson's on their own, but they may contribute to the development of the disease. "This is the first time that truly environmental risk factors for Parkinson's disease have been identified," she says.

Cory-Slechta heads a research center funded by the National Institute of Environmental Health Sciences where researchers study the effects of environmental agents like cigarette smoke, air pollution, and metals like mercury and lead on human health. She believes scientists must do more research on the effects of exposure to multiple chemicals. "It's a huge problem to start thinking about a nearly infinite array of mixtures of chemicals. Instead of the risk that a single chemical might pose," she says. She also says more work must be done to see how much of these chemicals people are actually exposed to. Usually it's not clear exactly how much of a pesticide remains on crops by the time they reach the dinner table. Maneb frequently shows up as a slight residue, she says, while paraquat usually shows up just in trace amounts; exposures can also occur via other routes.

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Often times the two are used at different stages of the growing cycle. "The real issue is what happens when they hit humans in the food chain. If they're both present, then you are exposed to the combination."

In the Journal of Neuroscience paper, and in an earlier paper in Brain Research, the scientists showed how mice injected with both maneb and paraquat differed from normal mice in many ways. Most obviously, the mice moved around much less; immediately after the last of 12 injections over six weeks, the mice ran around their cages just one-tenth as much as their normal counterparts. More importantly, the mice that received both chemicals showed brain damage in exactly the same way as humans with Parkinson's:

The amount of a key molecular marker, tyrosine hydroxylase, that is one measure of the health of the dopamine system was lower by about 15 percent in the mice, in the exact same areas of the brain that are damaged by the disease. Other closely related areas of the brain were spared, as in humans.

The mice had nearly four times as many "reactive astrocytes," structures which indicate brain damage, compared to the control mice, in areas affected by Parkinson's disease.

The mice had about 15 percent fewer dopamine neurons and ultimately produced about 15 percent less dopamine than normal mice.

The team is currently pursuing several new avenues of research, with funding from NIEHS. For instance, preliminary findings indicate that the Parkinson's-like effects on mice may be permanent, and that older mice may be more sensitive to the combination than younger mice. The team is also studying the effects of exposure to the mixture early in life, and they've shown that mice with the same genetic abnormality that causes some people to develop Parkinson's are especially vulnerable to the mixture.

Best Regards,

Greg Watson  
State Regulatory Affairs & Federal Label Support Team Lead  
Synfacts Regulatory Affairs  
ph 336 632 2993  
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Janis,

Know this would lead to a path targeting paraquat / Parkinsons ... Let me know how you'd like me to move forward ...

Best Regards,

Greg Watson  
State Regulatory Affairs & Federal Label Support Team Lead  
Synfacts Regulatory Affairs  
ph 336 632 2993  
mobile 336 707 7162  
fax 336 632 2884

am: Sturgess Nick GBAP  
sent: Friday, September 16, 2005 11:49 AM  
To: Elliott Barry GBAP; Clapp Mike GBAP; Watson Greg USGR  
Subject: RE: Comments on SAP nominations

Guy,

It is going to be very difficult to pin something really specific on D C-S, since it is more of an overall perception in her presentation style and language which is not strictly objective and lacks the complete story which would actually put her findings into a more relevant perspective. That said there may be some angles as follows.....

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SYNG-PQ-00353200

This has been done in some haste, but I can give you a few pointers. Attached are a couple of links to quotes from D C-S that you might find relevant.

<http://www.naturalworldtours.co.uk/articles2001/jan/jan06013.htm>

[http://www.panna.org/resources/panups/panup\\_20010928.dv.html](http://www.panna.org/resources/panups/panup_20010928.dv.html)

In addition she has made many verbal comments when presenting and answering questions following her presentation at the following scientific meetings.

20th International Neurotoxicology Conference (Little Rock, November 2002)  
21st International Neurotoxicology Conference (Honolulu, February 2004)

This has included words to the effect of:

"Our data support the need for the PQ human health risk assessment to be re-evaluated"

"Our data are in support of anecdotal evidence from e-mail communications I have had with farmers and their families who have used PQ and who have subsequently developed Parkinson's disease".

Unfortunately since I did not stand there with a tape recorder at the time she said this or words to this effect, I have no proof of this is what she said.

Other meetings include the Society of Toxicology and Society for Neuroscience meetings in 2001 & 2002. She also made controversial comments relating to the cause of Parkinson's disease in a forum which included lay people (Open Town Meeting) which was part of the 19th International Neurotoxicology Conference (held in Colorado Springs, August 2001) which Mike Clapp & Lewis Smith attended, but I was not present. They may have notes which relate to this specifically. Again proving she said anything at all would not be possible.

There are comments in the discussion sections of a few of her papers that may be relevant. Here are a couple of examples:

Thiruchelvam et al (2000) Brain Research 873: 225. Last sentence of the abstract - "These findings also raise questions about the adequacy of current risk assessment guidelines for these chemicals which are based on effect levels derived from exposures to single agents".

Specific conclusions in Thiruchelvam et al (2002) Neurotoxicology 23: 821. paper are not borne out by the data presented - it is claimed that effects are synergistic, but they appear just additive in combination. In the discussion of this paper they refer to this model representing an "environmental exposure mode" which it does not, since in human exposure scenarios the very young are not exposed to PQ + maneb.

If you view the detailed review of this and other D C-S papers I have written (these are with the PQ bibliography and also constitutes one of our very detailed position statements updated in the last few months) you will be able to see specific criticisms of papers, the way they were conducted and whether the conclusions drawn are supported by the data. I believe this is my biggest criticism of her work in that more is made of the data than is scientifically justified particularly when it comes to human relevance.

I hope this might help a little in trying to substantiate the statement that was made.

Regards,  
Nick.

From: Elliott Barry GBAP  
Sent: 15 September 2005 20:59  
To: Sturgess Nick GBAP  
Cc: Clapp Mike GBAP  
Subject: FW: Comments on SAP nominations

Further info

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SYNG-PQ-00353201

From: Watson Greg USGR  
Sent: 15 September 2005 20:41  
To: Elliott Barry GBAP; Clapp Mike GBAP  
Cc: McFarland Janis USGR; Carroll Beth USGR; Pastoor Tim USGR  
Subject: RE: Comments on SAP nominations

Sorry should have included the list of publications for her that we have pulled - I believe that quotes from meetings / popular press articles - like the items presented by Dr. Relyea's web site - would be of most benefit. I have looked at these sites briefly and cannot find anything that looks like what we need:

Dr. Deborah Cory-Slechta, is Professor and Chair, University of Medicine and Dentistry New Jersey-Robert Wood Johnson Medical School, Department of Environmental and Occupational Medicine, and serves as the Director of the Environmental and Occupational Health Sciences Institute.

Info at: <http://ehpsi.njmed.edu/faculty/staff/view.php?id=379>

and also at: <http://ehpsi.njmed.edu/about/ehpsi/director.shtml>

<< File: Cory Slechta pubs.doc >>  
Best Regards,

Greg Watson  
State Regulatory Affairs & Federal Label Support Team Lead  
Syngenta Regulatory Affairs  
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-----Original Message-----

From: Watson Greg USGR  
Sent: Thursday, September 15, 2005 3:15 PM  
To: Elliott Barry GBAP; Clapp Mike GBAP  
Cc: McFarland Janis USGR; Carroll Beth USGR; Pastoor Tim USGR  
Subject: FW: Comments on SAP nominations

Dear Barry & Mike,

Can you help us with this request?? I would like to have some of the requested examples - then make the regulatory call whether it is in our best interest to provide them (given that it will draw a pretty straight line to Syngenta).

On the other hand, for many, many of our projects it would be a real disaster to have her on the SAP!!

Thanks for your help with this!

Best Regards,

Greg Watson  
State Regulatory Affairs & Federal Label Support Team Lead Syngenta Regulatory Affairs ph 336 632 2993 mobile 336 707 7182 fax 336 632 2884

-----Original Message-----

From: McAllister, Ray [mailto:RMcAllister@croplifeamerica.com]  
Sent: Thursday, September 15, 2005 3:05 PM  
To: McFarland Janis USGR; Watson Greg USGR  
Subject: FW: Comments on SAP nominations

????

-----Original Message-----

From: Knott, Steven [mailto:Steven.Knott@epa.gov]  
Sent: Thursday, September 15, 2005 2:31 PM  
To: McAllister, Ray

Sent: Thursday, September 15, 2005 2:31 PM  
To: McAllister, Ray

Cc: Dorsey, Larry [mailto:epemall@epa.gov]  
Subject: Re: Comments on SAP nominations

Ray,

Thank you again for the additional information regarding CropLife America's public comments on the nominations for the FIFRA SAP. The information you provided for Dr. Relyea is very specific and helps to clarify the basis of your original general comment. Would it be possible for you to provide a similar level of specificity regarding your comments on Dr. Cory-Slechta? For example, can you point us to the specific presentations in meetings, appearances in the press, or publications that have formed the basis of your opinion?

We would really appreciate it if you could provide any additional information at your earliest convenience. Also, if there is anyone else you believe we should contact regarding the specifics of your comments, please let me know.

If you have any questions regarding this request, I would be happy to discuss them with you.

Thanks again for your time and consideration.

Sincerely,

Steve Knott  
Assistant Executive Secretary  
FIFRA Scientific Advisory Panel  
202-564-0103

McAllister,  
Ray  
<RMcAllister@croplifeamerica.com>  
To: Steven Knott/DC/USEPAUS@EPA  
cc:  
09/12/2005  
10:31 AM  
Subject: Comments on SAP nominations

Mr. Stephen Knott  
USEPA Headquarters  
Ariel Rios Building  
1200 Pennsylvania Avenue, N.W.  
Mail Code: 7201M  
Washington, DC 20460

Dear Steve:

In response to your inquiry about comments submitted by CropLife America on nominees for the FIFRA Scientific Advisory Panel, I am providing the following additional details.

RICK RELYEA

Dr. Relyea's web site (<http://www.pitt.edu/~relyea/>) has links to numerous of his press statements that are demonstrably inaccurate and thus cast doubt on his scientific objectivity.

1. The observation that surfactants, including those in Roundup brand agricultural herbicides and many other products, may cause adverse effects in amphibian and other aquatic species is not at all new. The fundamental conclusions from Dr. Relyea's studies on a Roundup branded herbicide's effects on tadpoles were already well-known, initially from Dr. Bidwell's work that was reported in Australia ten years ago, which had received considerable coverage in the scientific press. Therefore, his press statements, such as the following, were completely inaccurate misrepresentations of the state of knowledge in the literature:

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SYNG-PQ-

"This is really the first discovery that something made to kill plants really can be extremely lethal to amphibians, which of course, comes as a complete surprise to a lot of people that apply Roundup."  
[http://www.pittsburghlive.com/x/search/s\\_319779.html](http://www.pittsburghlive.com/x/search/s_319779.html)

"It's fair to say that nobody would have guessed Roundup(r) was going to be so lethal to amphibians."  
[http://www.umc.pitt.edu/media/pcc060411/sci1\\_pesticide.html](http://www.umc.pitt.edu/media/pcc060411/sci1_pesticide.html)

"It's much deadlier than we thought," Relyea said.  
<http://www.stloday.com/stloday/news/stories.nsf/sciencemedicine/story/E50D65CDBEEFE65988257057001FC5A8?OpenDocument>

2. Dr. Relyea has repeatedly promoted his work through sound bites, interviews, and speculation in the public press. He has suggested, through extrapolation of his laboratory findings, that perhaps Roundup branded herbicides might be the cause of global amphibian decline: "If these frogs are declining from a pesticide effect we never new [sic] existed, then what are the other effects that pesticides are having that we don't know about because we haven't done the tests yet?"  
[http://www.pittsburghlive.com/x/search/s\\_319779.html](http://www.pittsburghlive.com/x/search/s_319779.html)

Through such unfounded and inflammatory statements, he exacerbates public concerns without really providing a realistic appraisal or risk assessment. This is not the hallmark of a scientific adviser that EPA should select to provide advice on potentially controversial regulatory issues.

#### DEBORAH CORY-SLECHTA

Dr. Cory-Slechta has been active in examining the effect of chemicals in a mouse model. This short-term model uses intraperitoneal administration of chemicals over a relatively short timeline and at relatively high doses. For obvious reasons intraperitoneal exposure of agents creates some concerns about extrapolation of the results of the research. Although the animal model is simply a research tool with clear limitations in reflecting a chronic progressive disease in humans (i.e., extrapolation issues regarding short term intraperitoneal exposure), Dr. Cory-Slechta's presentations have reported conclusions beyond what the data reasonably support. Her presentations in meetings, appearances in the press, and publications often include overly-dogmatic statements and over-interpretation of data with subsequent conclusions that are, in reality, speculation. Overall, we feel that Dr. Cory-Slechta is not an appropriate candidate for the scientific advisory panel, based on these reservations.

Sincerely,

Ray S. McAllister, Ph.D.  
Regulatory Science & Policy Leader  
CropLife America

SYNG-PQ-00353204