Minnesota Department of Agriculture
C/O Teresa Cira
MDA Pesticide and Fertilizer Management Division

American Crystal Sugar Company
Joe Hastings General Agronomist
101 North Third Street
Moorhead, MN 56560

Minnesota Department of Agriculture,

I am Joe Hastings, the General Agronomist for American Crystal Sugar Company, and I am submitting comment on the "Draft Chlorpyrifos Special Registration Review Scoping Document" on behalf of American Crystal Sugar Company.

American Crystal Sugar Company is a grower-owned cooperative of 2,600 shareholders producing sugarbeets on approximately 400,000 acres in the Red River Valley in northwest Minnesota and northeast North Dakota. Sugar is extracted in our factories from the sugarbeets raised and then sold as refined sugar. The United States raises roughly 1.1 million acres of sugarbeets domestically. This is a relatively small acreage crop compared to other crops and keeping crop protection products labeled that work in sugarbeets is vital as there are very few tools and options available.

Chlorpyrifos is the most effective POST insecticide product that is used by our growers for the control of Sugarbeet Root Maggot (SBRM) flies. They are an insect pest in which their larvae feed on and damage sugarbeet roots. Where Chlorpyrifos is needed but is not used, we can see losses of up to 2,042 lbs. of Recoverable Sugar/acre and $300/acre in lost revenue. (Dr. Boetel NDSU Combined Analysis 2015-2018 Research).

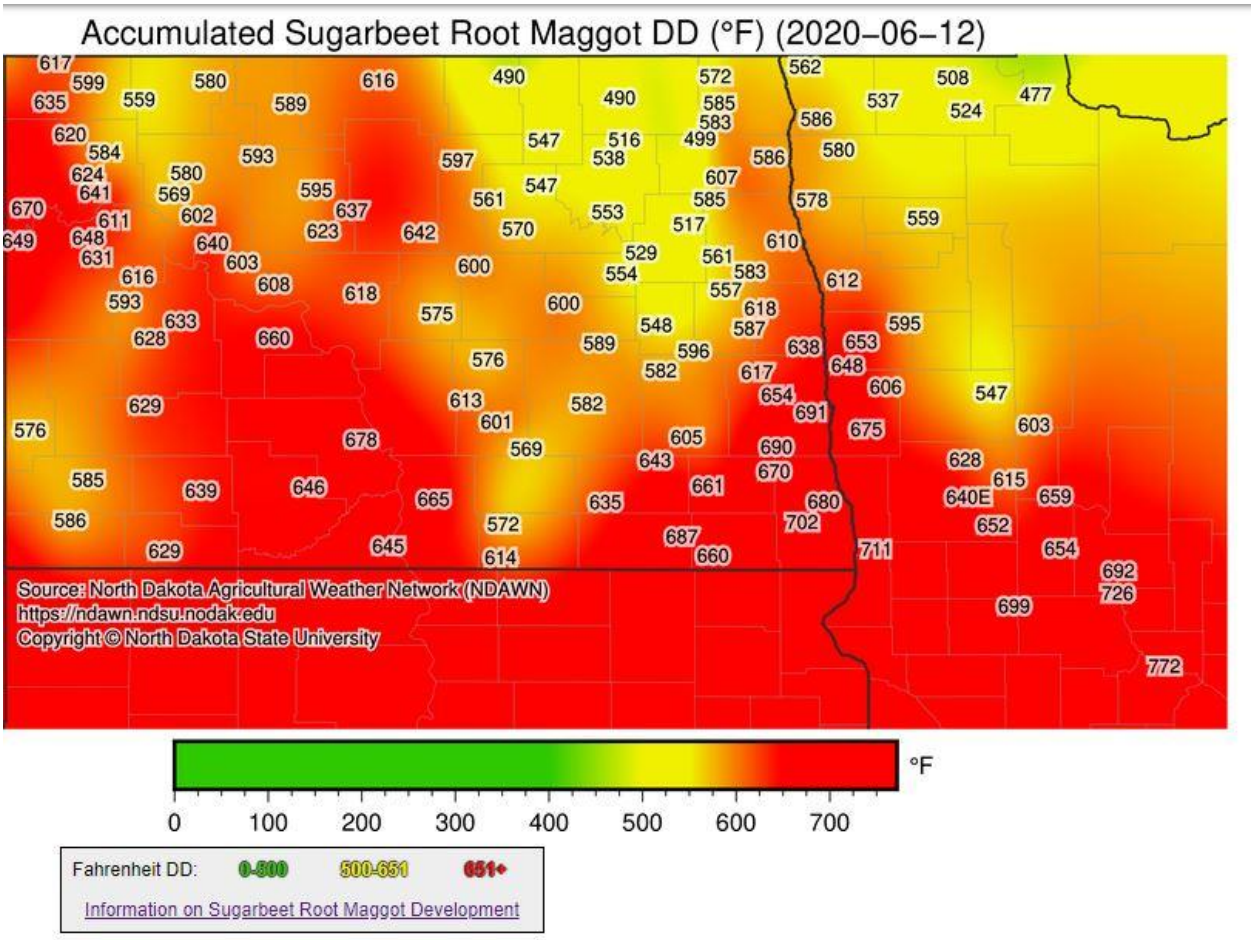
Pictures below show SBRM larvae and resulting damage from feeding.

Our Ag Staff is trained and are Certified Crop Advisors (CCA's) and recommend the use of Chlorpyrifos as a precise, targeted application, only at the right time, right place, and in the right amount. To help us do this, we use tools to help us time the applications and find only the locations where the SBRM flies need to be controlled. We use Chlorpyrifos to knock down the SBRM fly population to decrease the amount of eggs laid by the flies and their resulting larvae that will feed on the sugarbeets. One item to note is that we had very high attendance by our Ag Staff to the Chlorpyrifos Use in Minnesota webinar the MDA put on April 8th, 2020.

Typically, SBRM fly activity occurs the first 2-3 weeks in June. To help in predicting when SBRM Peak Fly will occur, for proper timing of insecticide applications, North Dakota State University has developed a SBRM Growing Degree Day model. Peak fly activity occurs around 650 Degree Days for SBRM.

https://ndawn.ndsu.nodak.edu/sugarbeet-growing-degree-days.html

Below is a map from June 20th, 2020 showing SBRM GDD's at that time.



SBRM Monitoring Stake

In order to only treat areas that have SBRM activity with Chlorpyrifos, our Ag Staff sets up monitoring stakes. Staff from North Dakota State University does their own stake monitoring as well. In 2020 there were 150 total locations that were monitored every Monday, Wednesday and Friday during the SBRM fly season.

2020 SBRM Monitoring Locations

We also take into consideration the levels of fly activity to decide on whether to treat or not based on an economic threshold of the number of flies trapped. Dr. Boetel, entomologist with NDSU, is conducting work to further update and refine the SBRM Economic Threshold. Below is what we use in making treatment decisions.

Economic Risk based on Sugarbeet Root Maggot Fly Counts on Sticky-stake Traps

Daily **Capture (flies per stake)**	***Cumulative*** **Capture (flies per stake)**	**Risk Level***	**Suggested Management Tactic****
0-25	0-50	Low	Monitor fields closely.
26-50	51-100	Slight	A postemergence insecticide may be needed if an at-plant insecticide was used at a low rate or no at-plant material was applied.
51-75	101-150	Moderate	A postemergence insecticide is probably justified, even if an at-plant insecticide was applied to the field at a moderate or high rate (a granular insecticide can be used if 7 or more days before expected peak fly activity; use a liquid insecticide if within 4 days of peak fly).
76-100	151-200	Elevated	Apply a postemergence LIQUID insecticide as soon as possible (repeat if daily fly counts exceed 100 per trap.).
101-150	201-300	High	Apply a postemergence LIQUID insecticide immediately (apply it in 2 split applications, 7 days apart, at a moderate labeled rate.
151+	301+	Extreme	Apply a postemergence LIQUID insecticide at high labeled rate immediately (consider a 2nd application if daily counts resurge).

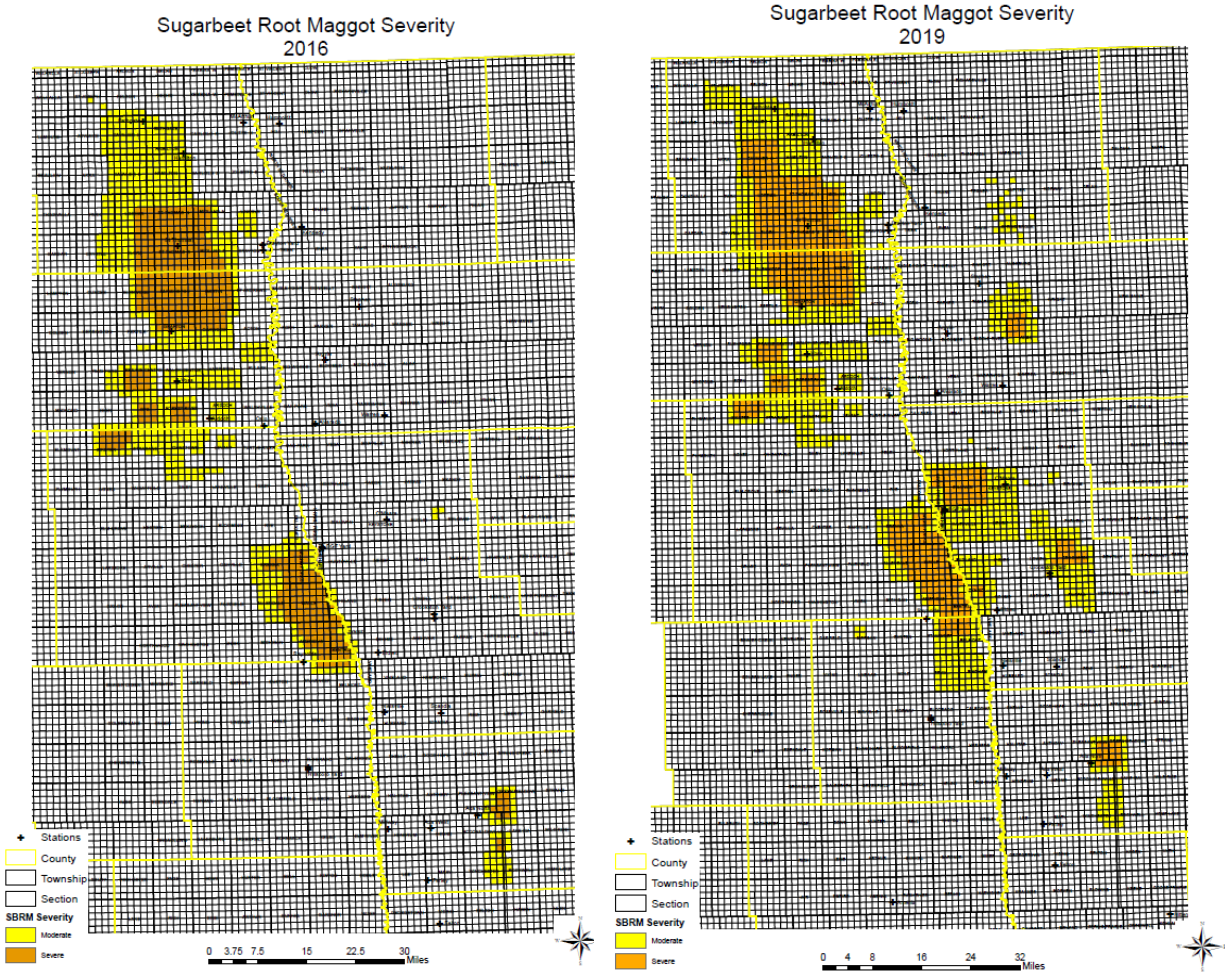
*Risk will vary based on actual peak fly activity date in a given field. Risk categories and corresponding management tactics in these tables are based on historical population levels and associated insecticide performance in research trials. Management suggestions are offered as general guidelines to assist growers with making informed management decisions; however, no guarantee can be made on whether economic return will be achieved from management tactics.

**Consult the "Sugarbeet Production Guide" (viewable on the internet at *http://www.sbreb.org/Production/production.htm*) for this year's sugarbeet root maggot forecast and management recommendations. Contact your local agriculturist or Mark Boetel, NDSU Entomologist (701-231-7901), for assistance with specific pest management decisions.

Updates on root maggot development and expected peak fly activity dates will be released on NDSU's Crop & Pest Report and the "Sugarbeet Growing Tips" program on several area radio stations (visit http://www.ag.ndsu.nodak.edu/aginfo/sugar/radio.html for a list of stations and broadcast scheduling).

Through all of this monitoring, our Ag Staff has been able to develop maps of the areas affected with SBRM and their severity. This helps us to dial in where to monitor for the potential need of a POST treatment of Chlorpyrifos for necessary SBRM control. We are seeing the areas affected by SBRM expanding in recent years as well as increases in the severity of the populations. This makes it critical that there is access to Chlorpyrifos as a control option.

Please see the maps below comparing observations from the 2015 crop year to 2019. In 2019, there were 134,000 sugarbeet acres in the Moderate to Severe SBRM areas. This represents a third of the acres of sugarbeets we produce.



We use all of this information to educate our grower/shareholders on the proper and effective use of Chlorpyrifos for SBRM maggot control. This is done through Grower Seminars put on by University staff as well as our own education class called “Your Way To Grow” given in the winter to our grower/shareholders by our Ag Staff. Here is a link to the presentation that was given this past winter on SBRM control.
https://www.crystalsugar.com/media/534488/sugarbeet-root-maggot-ywtg-2020.pdf

This presentation contains our recommendations of how to use Chlorpyrifos in combination with the other insecticides available. The most effective treatments in severely affected areas require an application of Counter (Terbufos) At-Plant, to help control larvae that come after the flies lay their eggs, followed by a Chlorpyrifos Post application to knock down the fly population.

One-on-one conversations are also done between Agriculturists and growers throughout the year. These conversations become more frequent as SBRM populations start to appear and decisions need to be made on whether to make a Chlorpyrifos application as well as when and where it is needed.

Through this letter the main points I wanted to present are:

- Chlorpyrifos is our most effective POST insecticide available to control SBRM flies
- When Chlorpyrifos is used it is in a very precise, targeted manner and only where needed

It is vitally important to continue to have Chlorpyrifos available as insecticide in our arsenal to control Sugarbeet Root Maggot. We are a small industry in acres which inhibits the amount of effective insecticides developed for sugarbeets. Sugarbeets have a big impact on the viability of farms and production agriculture in our region, it is important to have Chlorpyrifos as an available tool to maintain this.

As I've demonstrated in this letter, we are good stewards in the use of Chlorpyrifos and we will continue to promote these good stewardship practices of only using Chlorpyrifos at the right times and places where it is needed.

Please feel free to reach out to me if I can be of any further help or if you have any questions.

Thank you,

Joe Hastings
General Agronomist
American Crystal Sugar Company

September 17, 2020

Theresa Cira (Theresa.Cira@state.mn.us)
MDA Pesticide and Fertilizer Management Division
Submitted Electronically

Re: Comments on MDA's Draft Chlorpyrifos Special Registration Review Scoping Document

The Minnesota AgriGrowth Council (AgriGrowth) appreciates the opportunity to comment on the Minnesota Department of Agriculture's (MDA's) Request for Comments on Draft Chlorpyrifos Special Registration Review Scoping Document, Minnesota State Register Vol. 43, No. 3 (July 7, 2020).

AgriGrowth is a nonprofit, nonpartisan member organization representing the agriculture and food systems industry. Our members produce the world's food, fuel, and fiber, and are some of the strongest advocates around for the environment and water quality. We represent a host of farmers, companies, and other entities that rely on chlorpyrifos for insect pest management due to its outstanding efficacy and favorable environmental and human health characteristics.

Products containing chlorpyrifos protect more than fifty valuable U.S. food crops from destruction due to a variety of insect pests. In addition, chlorpyrifos are highly effective in controlling a broad spectrum of both foliar-feeding and soil-dwelling insect pests. The need to maintain access to chlorpyrifos is vital to Minnesota producers from an insect resistance management (IRM) perspective as it relates to commodities grown in state including corn, soybeans, sugar beets, wheat.

Upon review of the MDA's "Draft Chlorpyrifos Special Registration Review Scoping Document," there are a host of references to historical USEPA-OPP (United States Environmental Protection Agency-Office of Pesticide Program) chlorpyrifos human health risk assessments. This includes a November 2016 updated human health risk assessment that varied greatly from the traditional approach for classifying pesticide products that was conducted in by the same agency in 2011 and 2014.

We believe this updated 2016 assessment has led to a misinterpretation of chlorpyrifos toxicity by officials in Minnesota. This may be due to the adherence to the USEPA-OPP's approach that the human health endpoint for chlorpyrifos should be based on epidemiology data. In fact, previous chlorpyrifos assessments by the USEPA-OPP in 2011 and 2014 used red blood cell acetylcholinesterase inhibition (RBC AChEI). This method of measurement is the most sensitive mammalian toxicology endpoint associated with exposure to chlorpyrifos and should serve as the definitive regulatory endpoint.

Due to this inconsistency, it is our belief that regulatory authorities should work within a standardized regulatory framework relying on specified regulatory studies conducted within the regiment of "Good Laboratory Practices" to set regulatory endpoints. It is our understanding that USEPA-OPP did none of this when they created their 2016 Human Health Risk Assessment for chlorpyrifos.

While the State of Minnesota relies on USEPA-OPP's 2016 chlorpyrifos human health risk assessment to characterize the mammalian toxicology of chlorpyrifos, it should also be noted that the USEPA-OPP is in the final steps of updating the Agency's human health risk assessment for chlorpyrifos – which is scheduled to be shared publicly later this month. In addition, the USEPA-OPP is in the process of updating their characterization of the toxicity, exposure and risk characterization associated with chlorpyrifos use in the United States.

AgriGrowth believes the uses of chlorpyrifos registered for corn, soybeans, sugar beets and wheat are an important tool used by farmers to combat pests that can ruin entire crops. They help farmers control some of their most difficult pests and are critical components in the proven, scientifically based method of pest control in which there is a lack of reliable and effective alternatives. The need to maintain access to chlorpyrifos is vital to producers throughout the state.

In closing, AgriGrowth would respectfully ask that the Minnesota Department of Agriculture focus their Special Review attention on USEPA-OPP's scheduled 2020 assessment and registration review activities for chlorpyrifos. We appreciate the opportunity and thank you for your consideration of our comments.

Sincerely,

Tamara A. Nelsen
Executive Director

Minnesota Association of Wheat Growers
2600 Wheat Drive • Red Lake Falls, MN 56750
Phone: 218-253-4311 • mnwheat.org

September 17, 2020

Submitted via email to:
Theresa.Cira@state.mn.us

Theresa Cira
Pesticide and Fertilizer Management Division
Minnesota Department of Agriculture
625 Robert St. N.
St. Paul, MN 55155

Re: Comments on the Chlorpyrifos Special Registration Review Scoping Document

Dear Ms. Cira,

My name is Charlie Vogel, CEO of the Minnesota Association of Wheat Growers (MAWG). I work with and represent 700+ wheat grower members throughout Minnesota. I am submitting comments on the "*Draft Chlorpyrifos Special Registration Review Scoping Document*" on behalf of MAWG and its members. Maintaining crop protection products labeled that are effective is critical for us as there are few options available because of our relatively small number of acres compared to corn and soybeans across the United States

Wheat is produced on 1.45 million acres in Minnesota, valued at $375 million in 2019 (USDA). MAWG, in cooperation with the Soil Health Partnership and other organizations, is making progress by increasing the acres of wheat grown into southern Minnesota. These areas are traditionally corn-soybean rotations. Wheat is being added to increase the crop rotation, initiate cover crops to the farming system, and reduce herbicide use while improving soil health. Both traditional wheat growers, and those adding wheat to their farm system, occasionally rely on chlorpyrifos to control crop pests.

This year I spoke with multiple growers who said their only effective means of controlling army worm was chlorpyrifos. Without it they would have lost the crop. I spoke specifically with a farmer in Roseau, Minnesota. In 15 years of wheat production their farm has had infestations of army worms several times, but never at threshold levels that warranted the use of chlorpyrifos. However, this year those threshold levels where breached and without this tool both his wheat and grass seed crops would have been lost. One timely application at labeled rates of chlorpyrifos, specifically Lorsban, controlled the army worm and saved both crops. Chlorpyrifos, and other crop protection products, are diligently used by growers per label instructions. The profitability of their operations often relies on the appropriate use of these tools.

It is critical to wheat farms and MAWG members that we continue to have chlorpyrifos available as an insecticide to control army worm and other labeled pests. We are a relatively small industry, compared to corn and soybeans, and as a result do not receive a lot of attention from pesticide companies to develop new tools to use. Wheat is a critical rotational crop that supports many farms in NW Minnesota. We are making a concentrated effort to expand wheat into Southern Minnesota to improve soil health through increased crop rotation and utilization of cover crops. Both the wheat farmers in NW MN and those potential growers in Southern MN relay on tools such as chlorpyrifos to make wheat production a profitable proposition when pest pressure occurs.

Please contact me if you have any questions.

Sincerely,

Charlie Vogel
CEO

Minnesota Farm Bureau®
Farmers • Families • Food

September 17, 2020

Theresa Circa
Minnesota Department of Agriculture
625 Robert Street North
St. Paul, MN 55155
Theresa.Cira@state.mn.us

Submitted via email

Re: Request for Comments on the Draft Chlorpyrifos Special Registration Review Scoping Document

On behalf of the Minnesota Farm Bureau Federation (MFBF), we respectfully submit the following comments regarding the Draft Chlorpyrifos Special Registration Review Scoping Document and request the Minnesota Department of Agriculture (MDA) consider the concerns outlined below.

Chlorpyrifos is a critical tool used to protect agricultural crops and other plants from harmful pests. Farmers take stewardship of crop protection products seriously and use these tools, like chlorpyrifos, safely and in accordance with the label.

Currently, there is no comparable, effective alternative for farmers to utilize from an insect resistance standpoint. Without an alternative tool, it is vital to maintain access to chlorpyrifos to allow farmers the ability to protect their crops.

Specifically, MFBF opposes restrictions on the use of chlorpyrifos in the state of Minnesota.

MFBF appreciates the opportunity to provide comments on this important topic. If you have any additional questions, please do not hesitate to reach out.

Respectfully,

Kevin Paap
President

Minnesota Nursery & Landscape Association

1831 Lexington Ave. N. • Roseville, MN 55113
651-633-4987 • Fax 651-633-4986 • www.MNLA.biz

September 17, 2020

TO: Theresa Cira, Minnesota Department of Agriculture (MDA) Pesticide and Fertilizer Management Division

FROM: James Calkins, Minnesota Nursery and Landscape Association (MNLA)

RE: Draft Chlorpyrifos Special Registration Review Scoping Document – Public Comments

Dear Ms. Cira:

We have reviewed the draft *Chlorpyrifos Special Registration Review Scoping Document* and related materials and, on behalf of the Minnesota Nursery and Landscape Association (MNLA), we thank you and the Minnesota Department of Agriculture (MDA) for the opportunity to comment on the proposed MDA special registration review process for the organophosphate insecticide chlorpyrifos. Given the documented concerns about surface water contamination in some areas of the state and the potential human and environmental risks of exposures to chlorpyrifos via a variety of pathways, the MNLA supports the proposed special regulation review of chlorpyrifos and its use in Minnesota. At the same time, chlorpyrifos is the most widely used insecticide in the United States and in Minnesota as a consequence of its effectiveness in controlling a number of important insect pests and it is, therefore, important that the review be detailed and comprehensive and that any changes in registration be science-based, well documented, and justified. Although the use of chlorpyrifos in nursery and landscape situations in Minnesota is generally limited, important uses remain including the use of chlorpyrifos as an accepted dip and drench treatment for the control of Japanese beetle larvae (grubs) under the Japanese Beetle Harmonization Plan. In addition, limited use does not imply that a pesticide is not an important part of pest management under certain circumstances as part of an integrated pest management strategy, but does suggest that the potential for negative impacts would also be reduced so long as the product is used properly based on label requirements.

As for the review of any pesticide, it is imperative that the special registration review for chlorpyrifos includes documentation and a comprehensive review and understanding of the various, crop- and pest-specific uses of chlorpyrifos-based products in Minnesota, including nursery and landscape uses, and an analysis of the impacts of any additional restrictions that might be proposed. Determining the sources of chlorpyrifos contamination and whether these pathways can be effectively mitigated through enhanced best management practices should, of course, also be important components of the review. In all cases, if further restrictions or the elimination of certain uses are ultimately proposed, the availability and efficacy of alternatives should be addressed and should include a cost benefit analysis.

Finally, education, including certification programs, can be effective in reducing pesticide use and the human health and environmental impacts that can result from pesticide use and especially when pesticides are used indiscriminately and improperly. A detailed review and analysis of the MDA's education and outreach efforts related to chlorpyrifos will also be important in understanding and assessing the effectiveness of these educational efforts and in the planning and implementation of future education and outreach initiatives specific to chlorpyrifos and to pesticides in general. More specifically, are these educational efforts

effective, and if not why not, and how might they be improved? Meaningful outcomes are important and the effectiveness of educational and regulatory activities should be reviewed and assessed on a regular basis.

In summary, the MNLA supports the review of pesticides by the MDA and science-based restrictions on pesticide use when justified for the protection of human and animal health and the environment and this includes the proposed special regulation review of the insecticide chlorpyrifos.
Once again, we thank you for the opportunity to comment on the chlorpyrifos special registration review process and we offer our assistance if it would be helpful as the review progresses.

Respectfully submitted,

James Calkins

James B. Calkins, Ph.D.

Research Information Director – MNLA Foundation
Regulatory Affairs Manager – MNLA
jim@mnla.biz; 952-935-0682

Minnesota Nursery & Landscape Association (MNLA) & Foundation
1813 Lexington Avenue N., Roseville, MN 55113
651-633-4987
651-633-4986 (FAX)
jim@mnla.biz

MinnesotaCorn GROWERS ASSOCIATION

September 17, 2020

Theresa Circa
Minnesota Department of Agriculture
Pesticide and Fertilizer Management Division
625 Robert Street North
St. Paul, MN 55155

RE: Comments on draft Chlorpyifos special registration review scoping document

Dear Ms. Circa:

The Minnesota Corn Growers Association (MCGA) appreciates the opportunity to comment on the Minnesota Department of Agriculture's (MDA) draft chloryrifos special registration review scoping document. MCGA represents nearly 6,500 dues-paying corn farmer members and the 24,000 Minnesota corn farmers who contribute to the corn checkoff program.

Chlorpyifos is a critical crop protection tool for Minnesota farmers and it remains vital that growers have access to this tool through pesticide registration. Access to this tool is important for growers because there is a lack of reliable and effective alternatives to manage arthropod pests and maintaining access to chlorpyrifos is essential from an insect resistance management (IRM) perspective.

The draft scoping document relies on the U.S. Environmental Protection Agency's Office of Pesticide Program (EPA-OPP) 2016 chlorpyrifos Human Health Risk Assessment to characterize the mammalian toxicology of chrlopyrifos. However, EPA-OPP is in the final stages of updating the Human Health Risk Assessment for chrlopyrifos and should be publically available soon. Additionally, U.S. EPA-OPP is scheduled to post a proposed Registration Review Interim Decision for chlorpyrifos October 2020. In order to have the best available information for the MDA special registration review, MCGA urges MDA to focus on the latest EPA-OPP assessments of chlorpyrifos.

In summary, MCGA urges MDA to maintain grower access to chlorphyifos as a crop protection tool and use the most up to do information from U.S. EPA-OPP assessments of chlorpyrifos.

Thank you for considering our comments on the draft Chlorpyifos special registration review scoping document.

Sincerely,

Les Anderson
President
Minnesota Corn Growers Association

RED RIVER VALLEY Sugarbeet GROWERS ASSOCIATION
Minnesota • North Dakota

1401 32nd Street SW • Fargo, ND 58103 • Phone: 701-239-4151 • Fax: 701-239-4276
email: information@rrvsga.com

September 17, 2020

Theresa Cira
Pesticide and Fertilizer Management Division
Minnesota Department of Agriculture
625 Robert St. N.
St. Paul, MN 55155

Submitted via email to:
Theresa.Cira@state.mn.us

Re: Comments on the Chlorpyrifos Special Registration Review Scoping Document

Dear Ms. Cira,

I am Neil Rockstad, the President of the Red River Valley Sugarbeet Growers Association (RRVSGA) and a sugarbeet farmer from Ada, Minnesota. I am submitting comments on the "*Draft Chlorpyrifos Special Registration Review Scoping Document*" on behalf of the RRVSGA and its members.

The RRVSGA represents the 2,600 sugarbeet growers who own American Crystal Sugar Company. Our members represent over one third of the total sugarbeet production in the United States. Maintaining crop protection products that are labeled for and work in sugarbeets is critical for us as there are very few options available because of our relatively small number of acres across the United States.

Chlorpyrifos is the most effective POST insecticide product that is used by our members for the control of sugarbeet root maggot (SBRM) flies. The SBRM is an insect pest whose larvae feed on and destroy sugarbeet roots. Where Chlorpyrifos is needed but is not used can cause losses of up to 2,042 lbs. of Recoverable Sugar/acre and $300/acre in lost revenue (Dr. Boetel NDSU Combined Analysis 2015-2018 Research). SBRM has continued to expand in severity throughout our growing region and it is vital we maintain the use of Chlorpyrifos to control SBRM.

Like the vast majority of our members, I only use Chlorpyrifos when it is absolutely necessary to control the damaging SBRM. As a best management practice, sugarbeet growers only make precise, targeted applications. If we apply a product too early, too late, or in the wrong amounts,

we are only hurting ourselves. We use “monitoring stakes” from agriculturalists from the American Crystal Sugar Company and routinely visit with them to ensure we make timely applications when SBRM are at the economic thresholds. American Crystal agriculturists use research and data from North Dakota State University (NDSU), our local agriculture university, to base their recommendations. Additionally, our Cooperative, the American Crystal Sugar Company, and NDSU produce maps and records populations of SBRM to ensure we know where to scout for the pest. We also attend numerous seminars hosted by American Crystal trained agriculturalists and the University system which fully explain how to make safe applications.

It is critical to my farm and the RRVSGA members that we continue to have Chlorpyrifos available as an insecticide to control SBRM. We are an exceedingly small industry, which does not receive a lot of attention from pesticide companies to develop new tools to use. As a result, our members have few, if any, alternative products to use. Sugarbeets are the only thing that is keeping me profitable at the farm, without them I may not continue to farm. And without Chlorpyrifos, I may not continue to raise sugarbeets.

Please reach out with any additional questions.

Sincerely,

Neil Rockstad

President
Red River Valley Sugarbeet Growers Association
Ada, Minnesota

Southern Minnesota Beet Sugar Cooperative

Minnesota Department of Agriculture
625 Robert Street North
St. Paul, MN 55155
September 8, 2020

Dear Minnesota Department of Agriculture Officials,

I am writing this letter in support of the continued registration of chlorpyrifos. My name is Mark Bloomquist and I am the Research Director at Southern Minnesota Beet Sugar Cooperative in Renville Minnesota. Southern Minnesota Beet Sugar Cooperative is a cooperative of 500 shareholder growers in west-central Minnesota. Our producers raise approximately 120,000 acres of sugar beets for processing into sugar and feed by-products each season. Chlorpyrifos is an important tool for sugar beet production in our growing area.

The most common insect pests of sugar beets in our growing area are various species of cutworms in the spring, and lygus bugs during the summer months. These insects can reduce the production potential of fields and thus the potential income for our shareholders. Alternative insecticides are available for these two insects; however, the most commonly available alternatives are both in the pyrethroid family. The loss of chlorpyrifos would place increasing selection pressure on the pyrethroid insecticides and risk the development of pyrethroid resistant or tolerant insect pests on our sugar beet crop. The continued registration of chlorpyrifos allows for effective insecticide choices in an integrated pest management system.

In the southern Minnesota growing area, sugar beet root maggot is not an issue for sugar beet production. In the Red River Valley however the root maggot is a major sugar beet production issue. The availability of chlorpyrifos is an important tool for effective management of this insect pest. The continued registration of chlorpyrifos will be important for sugar beet production in Minnesota.

Thank you for the opportunity to express the importance of chlorpyrifos for sugar beet production in Minnesota. Feel free to contact me with any questions.

Sincerely,

Mark Bloomquist
Research Director

Email: info@smbsc.com Website: www.smbsc.com

Good afternoon Theresa,

Chlorpyrifos is a critical tool for me as a farmer. This is especially true when I am controlling the soybean aphid. Chlorpyrifos Is one of the most effective control tools I have. This is even more true when I also have spider mites at the same time as soybean aphids. This is one of the few chemicals that control both pests.

If you need to limit the use of chlorpyrifos, please do so on a use by use basis. Out options are limited in pest control in soybeans!!

Thank you for your consideration!

Paul Groneberg

Dow AgroSciences*
9330 Zionsville Road
Indianapolis, IN 46268
USA

September 17, 2020

Theresa Cira
Minnesota Department of Agriculture
Pesticide and Fertilizer Management Division
625 Robert Street North
St. Paul, MN 55155-2538

COMMENTS ON CHLORPYRIFOS SPECIAL REGISTRATION REVIEW SCOPING DOCUMENT

Dow AgroSciences LLC appreciates the opportunity to comment on the draft Chlorpyrifos Special Registration Review Scoping Document (July 20, 2020). Our response is outlined in the attached document, "The Minnesota Department of Agriculture Proposal for a Chlorpyrifos Special Registration Review. Comments by Dow AgroSciences LLC, September 17, 2020".

Summary of Comments:

1. Minnesota Department of Agriculture (MDA) relies on USEPA-OPP's 2016 chlorpyrifos Human Health Risk Assessment to characterize the mammalian toxicology of chlorpyrifos. MDA should be aware USEPA-OPP is in the final steps of updating the Agency's Human Health Risk Assessment for chlorpyrifos which is scheduled to be shared publicly soon. In addition, USEPA-OPP is scheduled to post a proposed Registration Review Interim Decision for chlorpyrifos in October 2020. To keep the MDA Special Registration Review current, we ask MDA to focus on the contemporary USEPA-OPP assessment of chlorpyrifos.

2. By relying on the USEPA's assessment from 2016, MDA mischaracterizes chlorpyrifos's mammalian toxicity. In 2016, USEPA-OPP felt the human health endpoint for chlorpyrifos should be based on (and calculated from) epidemiology data which was an unprecedented and inappropriate approach. In 2019, USEPA signaled they may be moving away from this unusual approach they took in 2016.

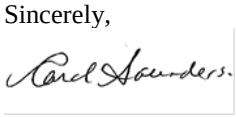
3. Regulatory authorities should work within a standardized regulatory framework relying on specified regulatory studies conducted within the regiment of "Good Laboratory Practices" to set regulatory endpoints. USEPA-OPP did not follow this approach when they created their highly unusual 2016 Human Health Risk Assessment for chlorpyrifos which differed greatly from their previous chlorpyrifos assessments (e.g. 2011 and 2014).

4. For nearly 50 years, Red blood cell acetylcholinesterase inhibition has been and remains the most sensitive mammalian toxicology endpoint associated with exposure to chlorpyrifos and should serve as the definitive regulatory endpoint.

5. It is critically important to maintain currently approved crops and pests on chlorpyrifos labels for growers in MN. Key reasons supporting this include a lack of reliable, effective alternative products and the importance of having chlorpyrifos (Group 1B) available for resistance management in insecticide spray programs.

We would be pleased to further discuss our comments on chlorpyrifos with MDA Pesticide and Fertilizer Management Division. If you have any questions or require additional information, please contact me at (403) 481-6939 (carol.saunders@corteva.com).

Sincerely,



Carol Saunders
North and West State Regulatory Leader
US Regulatory & Public Affairs - Crop Protection
(403) 481-6939

Enclosures

cc: B. Houtman, 308/2E
C. Saunders, 308/2E
K. Shears, 308/2E
H. Reistad, 308/2E
MN State Action File

The Minnesota Department of Agriculture Proposal for a Chlorpyrifos Special Registration Review

Comments Respectfully Submitted by Dow AgroSciences LLC

(Member of the Corteva Agriscience Group of Companies)

September 17, 2020

Table of Contents

Summary

Within the draft scoping document, Minnesota Department of Agriculture (MDA) repeatedly cites historical United States Environmental Protection Agency-Office of Pesticide Program (USEPA-OPP) Chlorpyrifos Human Health Risk Assessments. We ask MDA to be aware USEPA-OPP is in the final steps of updating the Agency's Human Health Risk Assessment for chlorpyrifos which is scheduled to be shared publicly soon. In addition, USEPA-OPP is scheduled to post a proposed Registration Review Interim Decision for chlorpyrifos October 2020. To keep their "Special Registration Review" current, we ask MDA to focus on the contemporary USEPA-OPP assessment of chlorpyrifos.

Our company asks regulatory authorities to work within a standardized regulatory framework relying on specified regulatory studies to establish regulatory endpoints. USEPA-OPP did not follow this traditional approach when they created their highly unusual 2016 Risk Assessment for chlorpyrifos which differed greatly from their previous chlorpyrifos assessments (e.g. 2011 and 2014).

By relying on the USEPA-OPP's chlorpyrifos assessment from 2016, MDA mischaracterizes chlorpyrifos's mammalian toxicity. In their 2016 assessment, USEPA-OPP felt the human health endpoint for chlorpyrifos should be based on (and calculated from) epidemiology data which was an unprecedented and inappropriate approach. Importantly, in 2019 USEPA signaled they may be moving away from the unusual approach they took in 2016. Looking back at a 2016 assessment to support action of chlorpyrifos, however, ignores that EPA has made no final, reviewable determinations regarding the safety of chlorpyrifos that have changed its 2006 final determination that the use of chlorpyrifos consistent with the current regulatory standard presents a reasonable certainty of no harm. EPA has itself acknowledged the tentative, non-binding nature of its recent risk assessments with respect to chlorpyrifos.

For nearly 50 years, Red blood cell acetylcholinesterase inhibition has been and remains the most sensitive mammalian toxicology endpoint associated with exposure to chlorpyrifos and should serve as the definitive human exposure regulatory endpoint.

Background

Chlorpyrifos is an organophosphorus insecticide first registered in the United States in 1965. Products containing chlorpyrifos protect more than fifty valuable U.S. food crops from destruction due to a variety of insect pests. Key crop uses include citrus fruits, corn, cotton, soybeans, sugar beets, and wheat. Chlorpyrifos has been one of the most widely used insecticides in the world, with uses approved globally. The sustained importance of chlorpyrifos for insect pest management is due to its outstanding efficacy and favorable environmental and human health characteristics.

Chlorpyrifos is highly effective in controlling a broad spectrum of both foliar-feeding and soil-dwelling insect pests, and its important role in resistance management and integrated pest management programs is widely recognized.

Chlorpyrifos exhibits moderate mammalian toxicity and is not carcinogenic, a selective reproductive or developmental toxicant, or an endocrine disruptor. Inhibition of blood cholinesterase has been used as a protective regulatory health endpoint.

Chlorpyrifos is biodegradable and has only short-to-moderate persistence in most environmental settings. In terrestrial ecosystems, chlorpyrifos rapidly dissipates from plant foliage (half-lives of <1–7 days). Soil surface half-lives are typically on the order of a few days to two weeks, whereas subsurface chlorpyrifos may demonstrate dissipation half-lives of one to two months. In aquatic ecosystems, chlorpyrifos dissipates very rapidly (half-life <24 hours) from the water column, and dissipation from sediments is like that observed for soils.

Ongoing US Regulatory Assessments - Chlorpyrifos

Throughout the draft scoping document, MDA repeatedly references historical USEPA-OPP chlorpyrifos human health risk assessments. In particular, MDA relies heavily on USEPA-OPP's November 2016 Human Health Risk Assessment to characterize the potential toxicity, potential human exposure and alleged risks associated with the use of chlorpyrifos in the US. It is important to note that the 2016 update to USEPA-OPP's chlorpyrifos human health risk assessment was highly unusual and varied greatly from their traditional approach for characterizing pesticide products including their previous chlorpyrifos assessments (e.g. 2011 and 2014).

We support MDA's priority of avoiding "Special Reviews" that are redundant to those conducted by USEPA-OPP (see page 2 of the draft scoping document). With that in mind, we ask MDA to be aware USEPA-OPP is in the process of updating their chlorpyrifos human health risk assessment. In fact, they are reaching the final steps in that process.

In the July 2019 USEPA filing with the US Court of Appeals for the 9th Circuit: "***Chlorpyrifos; Final Order Denying Objections to March 2017 Petition Denial Order***" (**Appendix I**, page 35566 of that document):

> *"EPA remains committed to expediting its registration review determination so that it is completed well in advance of the October 2022 deadline. To that end, EPA anticipates making available any updates to the human health and drinking water assessments for public availability and comment by summer of 2020.*
>
> *The Proposed Interim Decision incorporating these updated assessments is anticipated for public availability and comment by October 2020."*

In the same document (Appendix I, page 33563), the following statement suggests USEPA-OPP, in their chlorpyrifos risk assessment update may be moving in a direction on endpoint setting that is different from what they chose for their 2016 assessment:

> *"The lack of a mechanistic understanding for effects on the developing brain precludes EPA from validly or reliably assessing potential differences (and similarities) between laboratory animals and humans with respect to dose-response and temporal windows of susceptibility. In the absence of this information, EPA has no valid or reliable ways to bridge the scientific interpretation of the laboratory studies and epidemiology studies with chlorpyrifos."*

In conclusion, to prevent redundancy, MDA rightfully relies on the science reviews of USEPA-OPP to characterize the toxicity, potential exposures and risks associated with the uses of pesticide products such as chlorpyrifos. USEPA has signaled their intention to soon update their chlorpyrifos human health risk assessment and has indicated that assessment could be significantly different than their 2016 document. We ask MDA to focus their Special Review attention on USEPA-OPP's scheduled 2020 updated assessment and registration review activities for chlorpyrifos.

Moreover, taking action on chlorpyrifos based on the 2016 document ignores the fact that EPA has made no final, reviewable determinations regarding the safety of chlorpyrifos that have changed its 2006 final determination that the use of chlorpyrifos consistent with the current regulatory standard presents a reasonable certainty of no harm. See EPA, Finalization of Interim Reregistration Eligibility Decision (IREDs) and Interim Tolerance Reassessment and Risk Management Decisions (TREDs) for the Organophosphate Pesticides, and Completion of the Tolerance Reassessment and Reregistration Eligibility Process for the Organophosphate Pesticides, July 31, 2006 ("EPA has concluded, after completing its assessment of the cumulative risk associated with exposures to all of the OPs, that . . . the pesticide tolerances [for chlorpyrifos] . . . meet the safety standard under Section 408(b)(2) of the FFDCA"). This is the only final determination regarding the safety of chlorpyrifos tolerances that is currently in effect, as EPA's Registration Review of chlorpyrifos is ongoing. See New York v. EPA, 350 F. Supp. 2d 429, 435-36 (S.D.N.Y. 2004) ("[T]he issuance of a RED, whether it be one revoking, modifying, or leaving in place a tolerance, constitutes the agency's final determination, at the conclusion of a statutorily mandated review process, on the safety of the tolerance in question."), aff'd sub nom. Nat. Res. Def. Council v. Johnson, 461 F.3d 164 (2d Cir. 2006).

The EPA has never taken any final agency action subject to judicial review that departs from its 2006 final determination. To the contrary, any statements EPA made prior to its July 2019 USEPA's Final Order Denying Objections to the March 2017 Petition Denial Order (Appendix I) were part of the Agency's non-binding, deliberative process. See Appendix III for further discussion on this issue.

Chlorpyrifos Mammalian Toxicity and Human Exposure and Risk Characterization in the US

As stated earlier, the draft MDA "Special Review" scoping document cites and relies heavily on the USEPA-OPP chlorpyrifos human health risk assessment for chlorpyrifos from November 2016. It is important to recognize that the USEPA-OPP's 2016 assessment – in particular by relying on epidemiology data for regulatory endpoint setting - was vastly inconsistent with their standardized approach to characterizing human exposure and risk for pesticide products. In addition, the unprecedented approach USEPA-OPP selected for their 2016 assessment relied on

significantly different approaches and drew wildly different conclusions than their previous chlorpyrifos assessments - including USEPA-OPP's most recent final chlorpyrifos risk assessment from 2006 and updates they released in 2011 and 2014.

Dow AgroSciences prepared detailed comments in response to USEPA-OPP's 2016 risk assessment (**Appendix II**) which challenged the Agency's proposed approaches and the conclusions of their work. If MDA continues to rely on USEPA-OPP's 2016 chlorpyrifos human health risk assessment, we ask MDA to review and consider as part of their proposed "Special Registration Review" of chlorpyrifos the detailed information provided in Appendix II of this document.

In 2017, USEPA issued an order denying an administrative petition to revoke all tolerances and cancel all registrations for chlorpyrifos. EPA denied the Petition on the grounds that the scientific evidence was not sufficient to support the relief requested and required further study. In response, petitioners submitted Objections to EPA's order denying the Petition. Dow AgroSciences subsequently prepared and submitted a Response to Objections to support EPA's denial of the Petition and to clarify the scientific and factual record. This detailed, comprehensive overview of chlorpyrifos toxicity, exposure and risk is provided within this document as **Appendix III**. We ask MDA to consider this detailed information as part of their proposed "Special Registration Review" of chlorpyrifos.

RBC Acetyl Cholinesterase Inhibition is the Definitive Regulatory Endpoint for Human Exposure

A key issue raised in MDA's draft scoping document is the identification of the definitive mammalian toxicology endpoint for chlorpyrifos. Red blood cell cholinesterase inhibition (RBC ChEI) has been used historically as the relevant and sensitive regulatory marker of exposure for chlorpyrifos and subsequently as the regulatory endpoint for use in human health risk assessment. The scientific database for chlorpyrifos continues to be consistent with this position and several of USEPA's FIFRA Science Advisory Panels have also confirmed the use of RBC ChEI as the appropriate POD in regulatory decision-making. Over the past several years, investigators have explored non-cholinergic modes of action for chlorpyrifos and some have contended that

neurodevelopmental outcomes/effects are occurring below the threshold for cholinesterase inhibition (brain, RBC, or plasma cholinesterase).

In the July 2019 USEPA's Final Order Denying Objections to the March 2017 Petition Denial Order (**Appendix I**) five laboratory animal studies were referenced as under review for consideration within an assessment of potential neurodevelopmental/behavioral effects. Corteva Agriscience prepared and submitted a review of these five studies, particularly in relation to inhibition of red blood cell (RBC) acetylcholinesterase to USEPA. This review is included in this document as **Appendix IV**.

The information summarized within Appendix IV reaffirms RBC cholinesterase inhibition (ChEI) as a definitive endpoint that is protective of other potential toxicity, including neurodevelopmental/behavioral toxicity. Based on the outcomes, limitations and uncertainties associated with these five studies, reports of neurodevelopmental effects occurring in laboratory animal studies at levels below the threshold for RBC cholinesterase inhibition are not supported.

In conclusion, there are no known neurodevelopmental effects/outcomes in studies that are below the threshold associated with RBC ChEI and this endpoint continues to be protective of all toxicities, including neurodevelopmental toxicity.

References

Minnesota Department of Agriculture. July 2020, Draft Minnesota Department of Agriculture Chlorpyrifos Special Registration Review Scoping Document. https://www.mda.state.mn.us/sites/default/files/docs/2020-07/chlorspecregreview.pdf

USEPA, 2016. Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review. USEPA, Washington, DC.

Appendices

Appendix I

Commodity	Parts per million
Poultry, fat	0.02
Poultry, meat	0.1
Poultry, meat byproducts	0.3
* * * * * * *	
Rye, forage	1
Rye, grain	0.08
Rye, hay	1.5
Rye, straw	2
Sheep, fat	0.2
Sheep, meat	0.4
Sheep, meat byproducts	0.8
Sorghum, grain, forage	0.4
Sorghum, grain, grain	0.3
Sorghum, grain, stover	1
* * * * * * *	
Sunflower subgroup 20B	0.3
Teff, forage	1
Teff, grain	0.08
Teff, hay	1.5
Teff, straw	2
Teosinte, grain	0.015
* * * * * * *	
Triticale, forage	1
Triticale, grain	0.08
Triticale, hay	1.5
Triticale, straw	2
Vegetable, *brassica,* head and stem, group 5–16, except cauliflower	2
* * * * * * *	

[1] This tolerance expires on January 24, 2020.

* * * * *

[FR Doc. 2019–15648 Filed 7–23–19; 8:45 am]

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ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 180

[EPA–HQ–OPP–2007–1005; FRL–9997–06]

Chlorpyrifos; Final Order Denying Objections to March 2017 Petition Denial Order

AGENCY: Environmental Protection Agency (EPA).

ACTION: Order.

SUMMARY: In this Order, EPA denies the objections to EPA's March 29, 2017 order denying a 2007 petition from the Pesticide Action Network North America (PANNA) and the Natural Resources Defense Council (NRDC) to revoke all tolerances and cancel all registrations for the insecticide chlorpyrifos. This order is issued under section 408(g)(2)(C) of the Federal Food, Drug, and Cosmetic Act (FFDCA) and constitutes final agency action on the 2007 petition. The objections were filed by Earthjustice on behalf of 12 public interest groups, the North Coast Rivers Alliance, and the States of New York, Washington, California, Massachusetts, Maine, Maryland, and Vermont.

DATES: This Order is effective July 24, 2019.

ADDRESSES: The docket for this action, identified by docket identification (ID) number EPA–HQ–OPP–2007–1005, is available at *http://www.regulations.gov* or at the Office of Pesticide Programs Regulatory Public Docket (OPP Docket) in the Environmental Protection Agency Docket Center (EPA/DC), West William Jefferson Clinton Bldg., Rm. 3334, 1301 Constitution Ave. NW, Washington, DC 20460–0001. The Public Reading Room is open from 8:30 a.m. to 4:30 p.m., Monday through Friday, excluding legal holidays. The telephone number for the Public Reading Room is (202) 566–1744, and the telephone number for the OPP Docket is (703) 305–5805. Please review the visitor instructions and additional information about the docket available at *http://www.epa.gov/dockets.*

FOR FURTHER INFORMATION CONTACT: Pesticide Re-Evaluation Division (7508P), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave. NW, Washington, DC 20460–0001; telephone number: (703) 347–0206; email address: *OPPChlorpyrifosInquiries@epa.gov.*

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this action apply to me?

In this document, EPA denies all objections in response to a March 29, 2017 order denying the 2007 PANNA and NRDC petition requesting that EPA revoke all tolerances and cancel all pesticide product registrations for chlorpyrifos. In addition to the Petitioners, this action may be of interest to agricultural producers, food manufacturers or pesticide manufacturers, and others interested in food safety issues generally. The following list of North American Industrial Classification System (NAICS) codes is not intended to be exhaustive, but rather provides a guide to help readers determine whether this document applies to them. Potentially affected entities may include:

- Crop production (NAICS code 111), *e.g.,* agricultural workers; greenhouse, nursery, and floriculture workers; farmers.
- Animal production (NAICS code 112), *e.g.,* cattle ranchers and farmers, dairy cattle farmers, livestock farmers.
- Food manufacturing (NAICS code 311), *e.g.,* agricultural workers; farmers;

greenhouse, nursery, and floriculture workers; ranchers; pesticide applicators.

- Pesticide manufacturing (NAICS code 32532), *e.g.,* agricultural workers; commercial applicators; farmers, greenhouse, nursery, and floriculture workers; residential users.

B. What action is the agency taking?

In this order, EPA denies objections to EPA's order of March 29, 2017 (the Denial Order), in which EPA denied a 2007 petition (the Petition) from PANNA and NRDC (the Petitioners) that requested that EPA revoke all tolerances for the pesticide chlorpyrifos established under FFDCA section 408. (Ref. 1) The Petition also sought the cancellation of all chlorpyrifos pesticide product registrations under section 6 the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), 7 U.S.C. 136d.

The Petition raised the following claims regarding both EPA's 2006 FIFRA reregistration decision and active registrations of chlorpyrifos in support of the request for tolerance revocations and product cancellations:

1. EPA has ignored genetic evidence of vulnerable populations.

2. EPA has needlessly delayed a decision regarding endocrine disrupting effects.

3. EPA has ignored data regarding cancer risks.

4. EPA's 2006 cumulative risk assessment (CRA) for the organophosphates misrepresented risks and failed to apply FQPA 10X safety factor. (*Note:* For convenience's sake, the legal requirements regarding the additional safety margin for infants and children in FFDCA section 408(b)(2)(C) are referred to throughout this response as the ''FQPA 10X safety factor'' or simply the ''FQPA safety factor.'' Due to Congress' focus on both pre- and post-natal toxicity, EPA has interpreted this additional safety factor as pertaining to risks to infants and children that arise due to pre-natal exposure as well as to exposure during childhood years.)

5. EPA has over-relied on registrant data.

6. EPA has failed to properly address the exporting hazard in foreign countries from chlorpyrifos.

7. EPA has failed to quantitatively incorporate data demonstrating long-lasting effects from early life exposure to chlorpyrifos in children.

8. EPA has disregarded data demonstrating that there is no evidence of a safe level of exposure during pre-birth and early life stages.

9. EPA has failed to cite or quantitatively incorporate studies and clinical reports suggesting potential adverse effects below 10% cholinesterase inhibition.

10. EPA has failed to incorporate inhalation routes of exposure.

EPA's Denial Order denied the Petition in full (82 FR 16581). Prior to issuing that order, EPA provided the Petitioners with two interim responses on July 16, 2012 and July 15, 2014. The July 16, 2012 response denied claim 6 (export hazard) completely, and that portion of the response was a final agency action. The remainder of the July 16, 2012 response and the July 15, 2014 response expressed EPA's intention to deny six other petition claims (1–5 and 10). (*Note:* In the 2012 response, EPA did, however, inform Petitioners of its approval of label mitigation (in the form of rate reductions and spray drift buffers) to reduce bystander risks, including risks from inhalation exposure, which in effect partially granted Petition claim 10.) EPA made clear in both the 2012 and 2014 responses that, absent a request from Petitioners, EPA's denial of those six claims would not be made final until EPA finalized its response to the entire Petition. Petitioners made no such request, and EPA therefore finalized its response to those claims in the Denial Order.

The remaining Petition claims (7–9) all related to same issue: Whether the potential exists for chlorpyrifos to cause neurodevelopmental effects in children at exposure levels below EPA's existing regulatory standard (10% cholinesterase inhibition). Because these claims raised novel, highly complex scientific issues, EPA originally decided it would be appropriate to address these issues in connection with the registration review of chlorpyrifos under FIFRA section 3(g) and decided to expedite that review, intending to finalize it several years in advance of the October 1, 2022 registration review deadline. EPA decided as a policy matter that it would address the Petition claims raising these matters on a similar timeframe. Although EPA had expedited its registration review to address these issues, the Petitioners were not satisfied with EPA's progress in responding to the Petition, and they brought legal action in the Ninth Circuit Court of Appeals to compel EPA to either issue an order denying the Petition or to grant the Petition by initiating the tolerance revocation process. Following several rounds of litigation (see discussion of the litigation in Unit III. of this Order), EPA was ordered by the Ninth Circuit to issue either a tolerance revocation rule or an order denying the Petition by March 31, 2017. *In re Pesticide Action Network of North America* v. *EPA,* 840 F.3d (9th Cir. 2016). Accordingly, in compliance with the court's order, the Denial Order also finalized EPA's response on claims 7–9. As to those claims, EPA concluded that, despite several years of study, the science addressing neurodevelopmental effects remains unresolved and that further evaluation of the science during the remaining time for completion of registration review was warranted regarding whether the potential exists for adverse neurodevelopmental effects to occur from current human exposures to chlorpyrifos. EPA therefore denied the remaining Petition claims, concluding that it was not required to complete—and would not complete—the human health portion of the registration review or any associated tolerance revocation of chlorpyrifos without resolution of those issues during the ongoing FIFRA registration review of chlorpyrifos.

In June 2017, several public interest groups and states filed objections to the Denial Order pursuant to the procedures in FFDCA section 408(g)(2). Specifically, Earthjustice submitted objections on behalf of the following 12 public interest groups: Petitioners PANNA and NRDC, United Farm Workers, California Rural Legal Assistance Foundation, Farmworker Association of Florida, Farmworker Justice, GreenLatinos, Labor Council for Latin American Advancement, League of United Latin American Citizens, Learning Disabilities Association of America, National Hispanic Medical Association and Pineros y Campesinos Unidos del Noroeste. Another public interest group, the North Coast River Alliance, submitted separate objections. With respect to the states, New York, Washington, California, Massachusetts, Maine, Maryland, and Vermont submitted a joint set of objections (Ref. 2).

The objections focus on three main topics: (1) The Objectors assert that the FFDCA requires EPA apply to the FFDCA safety standard in reviewing any petition to revoke tolerances and that EPA's decision to deny the Petition failed to apply that standard; (2) The Objectors contend that the record before EPA demonstrates that chlorpyrifos results in unsafe drinking water exposures and adverse neurodevelopmental effects and that EPA must therefore issue a final rule revoking all chlorpyrifos tolerances; and (3) The Objectors claim that EPA committed procedural error in failing to respond to comments, and they specifically point to comments related to neurodevelopmental effects, inhalation risk, and Dow AgroSciences'

physiologically based pharmacokinetic model (PBPK model) used in EPA's risk assessment. Dow AgroSciences, which is now Corteva AgriScience, will be referred to as Corteva throughout the remainder of this Order.

On June 5, 2017, the same the day the Objectors were required to submit their objections to EPA, the League of United Latin American Citizens (LULAC) and the other 11 public interest Objectors represented by Earthjustice filed suit in the U.S. Court of Appeals for the 9th Circuit directly challenging the Denial Order, asserting that the court could review the order directly, even in the absence of EPA's final order under FFDCA section 408(g)(2)(C) responding to the objections they had just submitted. *LULAC, et al.* v. *Wheeler, et al.,* No. 17–71636. In their pleadings, Petitioners alternatively asked the court to issue a mandamus order compelling EPA to respond to the June 2017 objections within 60 days. On August 9, 2018, a three-judge panel of the 9th Circuit vacated the Denial Order and ordered EPA to revoke all chlorpyrifos tolerances and cancel all chlorpyrifos registrations within 60 days. *Id.,* 899 F.3d 814. EPA sought rehearing of that decision before an *en banc* panel of the 9th Circuit, a request that was granted on February 6, 2019, effectively vacating the August 9, 2018 panel decision. On April 19, 2019, the *en banc* panel granted the request for mandamus and directed EPA to respond to the objections not later than 90 days from that date. The court did not otherwise address the claims in the case.

After reviewing the objections, EPA has determined that the objections related to Petition claims regarding neurodevelopmental toxicity must be denied because the objections and the underlying Petition are not supported by valid, complete, and reliable evidence sufficient to meet the Petitioners' burden under the FFDCA, as set forth in EPA's implementing regulations. Further, for reasons stated in the Denial Order, EPA has concluded that it is also appropriate to deny the objections related to new issues raised after EPA's 2006 tolerance reassessment and reregistration of chlorpyrifos. These issues are being addressed according to the schedule for EPA's ongoing registration review of chlorpyrifos. EPA is also denying all claims related to drinking water risk and the use of the Corteva PBPK model in EPA's 2014 risk assessment and 2015 proposed rule because these claims were not made in the Petition and the objections process cannot be used to raise new issues and restart the petition process. Finally, EPA is denying the objections claiming procedural error, as EPA is not required to respond to comments made during the rulemaking process in this adjudication denying petition objections. Any response to comments will be completed in connection with EPA's final action in registration review.

C. What is the Agency's authority for taking this action?

The procedure for filing objections to EPA's final rule or order issued under FFDCA section 408(d) and EPA's authority for acting on such objections is contained in FFDCA section 408(g) (21 U.S.C. 346a(g)) and EPA's regulations at 40 CFR part 178.

II. Statutory and Regulatory Background

In this unit, EPA provides background on the relevant statutes and regulations governing the objections as well as on pertinent Agency policies and practices.

A. FFDCA and FIFRA Standards

EPA establishes maximum residue limits, or ''tolerances,'' for pesticide residues in food and feed commodities under FFDCA section 408. Without a tolerance or an exemption from the requirement of a tolerance, food containing a pesticide residue is ''adulterated'' under FFDCA section 402 and may not be legally moved in interstate commerce. FFDCA section 408 was substantially rewritten by the Food Quality Protection Act of 1996 (FQPA) (Pub. L. 104– 170, 110 Stat. 1489 (1996)), which established a detailed safety standard for pesticides and integrated EPA's regulation of pesticide food residues under the FFDCA with EPA's registration and re-evaluation of pesticides under FIFRA. The standard to establish, leave in effect, modify, or revoke a tolerance is stated in FFDCA section 408(b)(2)(A)(i). ''The Administrator may establish or leave in effect a tolerance for a pesticide chemical residue in or on a food only if the Administrator determines that the tolerance is safe.'' *Id.* ''The Administrator shall modify or revoke a tolerance if the Administrator determines it is not safe.'' *Id.* ''Safe'' is defined by FFDCA section 408(b)(2)(A)(ii) to mean that ''there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information.'' Among the factors that must be addressed in making a safety determination, FFDCA section 408(b)(2)(D) directs EPA to consider ''validity, completeness, and reliability of the available data from studies of the pesticide chemical and pesticide chemical residue.''

Risks to infants and children are given special consideration. Specifically, FFDCA section 408(b)(2)(C)(i)(II) requires that EPA assess the risk of pesticides based on ''available information concerning the special susceptibility of infants and children to the pesticide chemical residues, including neurological differences between infants and children and adults, and effects of *in utero* exposure to pesticide chemicals . . . .'' (21 U.S.C. 346a(b)(2)(C)(i)(II)). This provision also creates a presumption that EPA will use an additional safety factor for the protection of infants and children. Specifically, it directs that ''[i]n the case of threshold effects, . . . an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children.'' (21 U.S.C. 346a(b)(2)(C)). EPA is permitted to ''use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children.'' *Id.*

While the FFDCA authorizes the establishment of legal limits for pesticide residues in food, FIFRA section 3(a) requires the approval of pesticides prior to their sale and distribution and establishes a registration regime for regulating the use of pesticides. FIFRA regulates pesticide use in conjunction with its registration scheme by requiring EPA review and approval of pesticide labels and specifying that use of a pesticide inconsistent with its label is a violation of federal law. In the FQPA, Congress integrated action under the two statutes by requiring that the safety standard under the FFDCA be used as a criterion in FIFRA registration actions for pesticide uses that result in residues in or on food, (*see* FIFRA section 2(bb)), and directing that EPA coordinate, to the extent practicable, revocations of tolerances with pesticide cancellations under FIFRA. (*see* FFDCA section 408(l)(1)). FIFRA section 4 directed EPA to determine whether pesticides first registered prior to 1984 should be reregistered, including whether any associated FFDCA tolerances are safe and should be left in effect (*see* FIFRA section 4(g)(2)(E)). FFDCA section 408(q) directed EPA to complete that tolerance reassessment (which included the reassessment of all chlorpyrifos tolerances) by 2006. Following the

completion of FIFRA reregistration and tolerance reassessment, FIFRA section 3(g) requires EPA to re-evaluate pesticides under the FIFRA standard—which includes a determination whether to leave in effect existing FFDCA tolerances—every 15 years under a program known as ''registration review.'' The deadline for completing the current registration review for chlorpyrifos is October 1, 2022.

B. Procedures for Establishing, Modifying, or Revoking Tolerances

Tolerances are established, modified, or revoked by rulemaking under the unique procedural framework set forth in the FFDCA. Generally, a tolerance rulemaking is initiated by the party seeking to establish, modify, or revoke a tolerance by means of filing a petition with EPA. (*See* FFDCA section 408(d)(1)). EPA publishes in the **Federal Register** a notice of the petition filing and requests public comment. After reviewing the petition and submitted comments, FFDCA section 408(d)(4) provides that EPA may issue a final rule establishing, modifying, or revoking the tolerance; issue a proposed rule to do the same; or issue an order denying the petition.

Once EPA takes action granting or denying the petition, FFDCA section 408(g)(2) allows any party to file objections with EPA and seek an evidentiary hearing on those objections. Objections and hearing requests must be filed within 60 days after the date on which EPA issues its rule or order under FFDCA section 408(d). A party may not raise issues in objections unless they were part of the petition and an objecting party must state objections to the EPA decision and not just repeat the allegations in its petition. *Corn Growers* v. *EPA,* 613 F.3d 266 (D.C. Cir. 2010), cert. denied, 131 S. Ct. 2931 (2011). EPA's final order on the objections, issued under FFDCA section 408(g)(2)(C), is subject to judicial review. (21 U.S.C. 346a(h)(1)).

III. Chlorpyrifos Regulatory Background

Chlorpyrifos (0,0-diethyl-0–3,5,6-trichloro-2-pyridyl phosphorothioate) is a broad-spectrum, chlorinated organophosphate (OP) insecticide that has been registered for use in the United States since 1965. By pounds of active ingredient, it is the most widely used conventional insecticide in the country. Currently registered use sites include a large variety of food crops (*e.g.,* tree fruits and nuts; many types of small fruits and vegetables, including vegetable seed treatments; grain/oilseed crops; cotton), and non-food use settings (*e.g.,* ornamental and agricultural seed production; non-residential turf; industrial sites/rights of way; greenhouse and nursery production; sod farms; pulpwood production; public health; and wood protection). For some of these crops, chlorpyrifos is currently the only cost-effective choice for control of certain insect pests. In 2000, the chlorpyrifos registrants reached an agreement with EPA to voluntarily cancel all residential use products except those registered for ant and roach baits in child-resistant packaging and fire ant mound treatments (*e.g.,* 65 FR 76233 (Dec. 6, 2000); 66 FR 47481 (Sept. 12, 2001).

The OPs are a group of closely related pesticides that affect functioning of the nervous system. The OPs were included in the Agency's first priority group of pesticides to be reviewed under FQPA. In 2006, EPA completed FIFRA section 4 reregistration and FFDCA tolerance reassessment for chlorpyrifos and the OP class of pesticides and determined those tolerances were safe and should be left in effect (Ref. 3). Having completed reregistration and tolerance reassessment, EPA is required to complete the next re-evaluation of chlorpyrifos under the FIFRA section 3(g) registration review program by October 1, 2022. Given ongoing scientific developments in the study of the OPs generally, in March 2009 EPA announced its decision to prioritize the FIFRA section 3(g) registration review of chlorpyrifos by opening a public docket and releasing a preliminary work plan to complete the chlorpyrifos registration review by 2015—7 years in advance of the date required by law.

The registration review of chlorpyrifos has proven to be far more complex than originally anticipated. The OPs presented EPA with numerous novel scientific issues that the agency has taken to multiple FIFRA Scientific Advisory Panel (SAP) meetings since the completion of reregistration in 2006. (*Note:* The SAP is a federal advisory committee created by FIFRA section 25(d) and serves as EPA's primary source of peer review for significant regulatory and policy matters involving pesticides.) Many of these complex scientific issues formed the basis of the 2007 petition filed by PANNA and NRDC, specifically issues related to potential human health risks associated with volatilization and neurodevelopmental effects. During the registration review process, EPA reviews the currently available body of scientific data, including animal and epidemiology data, and the assessment of potential risks from various routes of exposure. Therefore, when EPA began the registration review for chlorpyrifos in March 2009, the Agency indicated that the Agency had decided to address the Petition on a similar timeframe to EPA's expedited registration review schedule.

Although EPA has expedited the chlorpyrifos registration review to address the novel scientific issues raised by the Petition in advance of the statutory deadline, the complexity of the issues has precluded EPA from finishing this review according to the Agency's original timeframe. The Petitioners were dissatisfied with the pace of EPA's response efforts and sued EPA in federal court on three separate occasions to compel a faster response to the Petition. As explained in Unit I. of this Order, EPA addressed 7 of the 10 claims asserted in the Petition by either denying the claim, issuing a preliminary denial or approving label mitigation to address the claims, but notwithstanding these efforts, on August 10, 2015, the court issued a mandamus order directing EPA to ''issue either a proposed or final revocation rule or a full and final response to the administrative Petition by October 31, 2015.'' *In re Pesticide Action Network of North America* v. *EPA,* 798 F.3d (9th Cir. 2015).

In response to that order, EPA issued a proposed rule to revoke all chlorpyrifos tolerances on October 30, 2015 (published in the **Federal Register** on November 6, 2015 (80 FR 69080)), based on its unfinished registration review risk assessment. EPA acknowledged it had insufficient time to complete its drinking water assessment and its review of data addressing the potential for neurodevelopmental effects.

On December 10, 2015, the Ninth Circuit issued a further order requiring EPA to complete any final rule (or petition denial) and fully respond to the Petition by December 30, 2016. On June 30, 2016, EPA sought a six-month extension to that deadline in order to allow EPA to fully consider the most recent views of the FIFRA SAP with respect to chlorpyrifos toxicology. The FIFRA SAP report was finalized and made available for EPA consideration on July 20, 2016 (Ref. 4). On August 12, 2016, the court rejected EPA's request for an extension and ordered EPA to complete its final action by March 31, 2017 (effectively granting EPA a three-month extension). On November 17, 2016, EPA published a notice of data availability (NODA) seeking public comment on both EPA's revised risk and water assessments and reopening the comment period on the proposal to revoke all chlorpyrifos tolerances (81 FR

81049). The comment period for the NODA closed on January 17, 2017.

Following the close of the comment period on the NODA, EPA issued the Denial Order on March 29, 2017, as described in Unit I. of this Order. As noted, in June 2017, EPA received objections to the Denial Order from both public interest groups and states, and some of those same organizations simultaneously filed suit in the Ninth Circuit seeking to challenge the Denial Order in advance of EPA's response to the submitted objections. That litigation is summarized in Unit I. of this Order.

IV. The Petition and EPA's Petition Response

As explained in Unit I. of this Order, PANNA and NRDC submitted the Petition in 2007, raising 10 claims in support of their request that EPA revoke all chlorpyrifos tolerances under the FFDCA and cancel all chlorpyrifos registrations under FIFRA. EPA's Denial Order denied the Petition in full. The following is a summary of EPA's response in the Denial Order to the 10 Petition claims.

A. Claim 1: Genetic Evidence of Vulnerable Populations

The Petitioners claimed that as part of EPA's 2006 reregistration and tolerance reassessment decision the Agency failed to calculate an appropriate intra-species uncertainty factor (*i.e.,* within human variability) for chlorpyrifos in both its aggregate and cumulative risk assessments (CRA). They asserted that certain data (the ''Furlong study'') addressing intra-species variability in the behavior of the detoxifying enzyme paraoxonase (PON1), indicates that the Agency should have applied an intra-species safety factor ''of at least 150X in the aggregate and cumulative assessments'' rather than the 10X factor EPA applied.

In the Denial Order, EPA explained that it carefully considered the issue of PON1 variability and determined that data addressing PON1 in isolation are not appropriate for use alone in deriving an intra-species uncertainty factor and that the issue is more appropriately handled using a PBPK model. Further, the derivation of an intra-species factor of over 150X advocated by the Petitioners is based on combining values from humanized mice with human measured values with a range from highest to lowest; the Furlong study derivation is inappropriate and inconsistent with international risk assessment practice. In addition, the 2008 FIFRA SAP did not support the PON1 data used in isolation. Finally, Petitioners' statement that the Furlong study supports an intra-species uncertainty factor of at least 150X likely overstates potential variability. EPA therefore denied this aspect of the Petition.

B. Claim 2: Endocrine Disrupting Effects

Petitioners summarized a number of studies evaluating the effects of chlorpyrifos on the endocrine system, asserting that, taken together, the studies ''suggest that chlorpyrifos may be an endocrine disrupting chemical, capable of interfering with multiple hormones controlling reproduction and neurodevelopment.''

EPA denied this claim because the Petition did not explain whether and how endocrine effects should form the basis of a decision to revoke tolerances. The basis for seeking revocation of a tolerance is a showing that the pesticide is not ''safe.'' Petitioners neither asserted that EPA should revoke tolerances because effects on the endocrine system render the tolerances unsafe, nor did Petitioners submit a factual analysis demonstrating that aggregate exposure to chlorpyrifos presents an unsafe risk to humans based on effects on the endocrine system.

EPA noted that while the cited studies provide qualitative information that exposure to chlorpyrifos may be associated with effects on the androgen and thyroid hormonal pathways, these data alone do not demonstrate that current human exposures from existing tolerances are unsafe. Further, EPA explained that in June 2015, it completed an Endocrine Disruption Screening Program weight-of-evidence conclusion for chlorpyrifos. That analysis evaluated all observed effects induced, the magnitude and pattern of responses observed across studies, taxa, and sexes, and the Agency also considered the conditions under which effects occurred, in particular whether or not endocrine-related responses occurred at dose(s) that also resulted in general systemic or overt toxicity. The Agency concluded that, based on weight-of-evidence considerations, further testing was not recommended for chlorpyrifos since there was no evidence of potential interaction with the estrogen, androgen, and thyroid pathways.

C. Claim 3: Cancer Risks

Petitioners claim that the Agency ''ignored'' a December 2004 National Institutes of Health Agricultural Health Study showing that the incidence of lung cancer has a statistically significant association with chlorpyrifos exposure. Petitioners did not otherwise explain whether and how these data support the revocation of tolerances or the cancellation of pesticide registrations. Specifically, Petitioners did not present any fact-based argument demonstrating that aggregate exposure to chlorpyrifos poses an unsafe carcinogenic risk. Accordingly, EPA denied the Petition to revoke chlorpyrifos tolerances or cancel chlorpyrifos registrations to the extent the Petition relies on claims pertaining to carcinogenicity. EPA went on to note, however, that while there is initial suggestive epidemiological evidence of an association between chlorpyrifos and lung cancer, it is reasonable to conclude chlorpyrifos is not a carcinogen in view of the lack of carcinogenicity in the rodent bioassays and the lack of a genotoxic or mutagenic potential.

D. Claim 4: CRA Misrepresents Risks, Failed To Apply FQPA 10X Safety Factor

Petitioners asserted that EPA relied on limited data and inaccurate interpretations of a specific study (the ''Zheng study'') to support its decision to remove the FQPA safety factor in the 2006 OP cumulative risk assessment (CRA). Petitioners claimed the Zheng study showed an obvious difference between juvenile and adult responses to chlorpyrifos that supported retention of the 10X safety factor for chlorpyrifos in the CRA. EPA concluded that Petitioners' assertions did not provide a sufficient basis for revoking chlorpyrifos tolerances. The Petitioners' claim that the data EPA relied upon support a different FQPA safety factor for chlorpyrifos in the CRA did not amount to a showing that chlorpyrifos tolerances are unsafe as Petitioners did not present a factual analysis demonstrating that the lack of a 10X safety factor in the CRA for chlorpyrifos poses unsafe cumulative exposures to the OPs. For this reason, EPA denied the Petitioners' request to revoke chlorpyrifos tolerances or cancel chlorpyrifos registrations on the basis of the FQPA safety factor in the CRA.

Despite the inadequacy of Petitioners' FQPA CRA safety factor claims, EPA nonetheless examined the evidence Petitioners cited regarding the Zheng study. EPA acknowledged that in that study, pups appeared to be more sensitive than adults at the tested high dose. However, at the low-dose end of the response curve, relevant for human exposures, little to no difference was observed. This result is consistent with a comparative cholinesterase study submitted by Corteva that specifically compared the dose-response relationship in juvenile and adult rats and found no basis for concluding that juveniles are more sensitive, further

supporting EPA's use of an FQPA safety factor of 1X for the AChE inhibition endpoint used in the 2006 OP CRA.

E. Claim 5: Over-Reliance on Registrant Data

Petitioners asserted that in reregistering chlorpyrifos EPA ''cherry picked'' data, ''ignoring robust, peer-reviewed data in favor of weak, industry-sponsored data to determine that chlorpyrifos could be re-registered and food tolerances be retained.'' As such, Petitioners argued that the Agency's reassessment decision is not scientifically defensible. EPA concluded that this Petition claim was not purported to be an independent basis for revoking chlorpyrifos tolerances or cancelling chlorpyrifos registrations but simply support for Petitioners' arguments in other parts of the Petition. While Petitioners claim that EPA ignored robust, peer-reviewed data in favor of weak, industry-sponsored data for the reregistration of chlorpyrifos, Petitioners did not cite to any studies other than those used to support their other claims. In general, Petitioners did not provide any studies in the Petition that EPA failed to evaluate. Since the specific studies cited by Petitioners were not associated with this claim, but rather their other claims, EPA's response to the specific studies were, therefore, addressed in its responses to Petitioners' other claims. EPA went on to explain, however, that the Agency does not ignore robust, peer-reviewed data in favor of industry-sponsored data and that EPA has a public and well-documented set of procedures that it applies to the use and significance of all data utilized to inform risk management decisions. EPA does rely on registrant-generated data submitted in response to FIFRA and FFDCA requirements, as these data are conducted and evaluated in accordance with a series of internationally harmonized and scientifically peer-reviewed study protocols designed to maintain a high standard of scientific quality and reproducibility. But EPA does not end its review there. To further inform the Agency's risk assessment, EPA is committed to the consideration of other sources of information such as data identified in the open, peer-reviewed literature and information submitted by the public as part of the regulatory evaluation of a pesticide.

F. Claim 6: EPA Failed to Properly Address the Exporting Hazard in Foreign Countries From Chlorpyrifos

In the July 16, 2012 interim Petition response, EPA issued a final denial of this claim, as it was not a claim subject to the FFDCA, which provides for an administrative objections process following the denial of a petition. EPA explained in the interim response that it lacked authority to address the risks chlorpyrifos may pose to workers in foreign countries who may not utilize worker protection equipment that the United States requires. Further, EPA noted that it has no authority to ban the export of pesticides to foreign countries regardless of whether those pesticides may be lawfully used in the United States. Accordingly, EPA denied this claim, and that denial constituted final agency action.

G. Claims 7–9: EPA Failed to Quantitatively Incorporate Data Demonstrating Long-Lasting Effects From Early Life Exposure to Chlorpyrifos in Children; EPA Disregarded Data Demonstrating That There Is no Evidence of a Safe Level of Exposure During Pre-Birth and Early Life Stages; and EPA Failed To Cite or Quantitatively Incorporate Studies and Clinical Reports Suggesting Potential Adverse Effects Below 10% Cholinesterase Inhibition.

The Petitioners asserted that human epidemiology and rodent developmental neurotoxicity data suggest that pre-natal and early life exposure to chlorpyrifos can result in long-lasting, possibly permanent damage to the nervous system and that these effects are likely occurring at exposure levels below 10% cholinesterase inhibition, EPA's existing regulatory standard for chlorpyrifos and other OPs. They assert that EPA has therefore used the wrong endpoint as a basis for regulation and that, taking into account the full spectrum of toxicity, chlorpyrifos does not meet the FFDCA safety standard or the FIFRA standard for registration.

EPA grouped these claims together because they fundamentally all raised the same issue: Whether the potential exists for chlorpyrifos to cause neurodevelopmental effects in infants and children from exposures (either to mothers during pregnancy or directly to infants and children) that are lower than those resulting in 10% cholinesterase inhibition—the basis for EPA's long-standing point of departure (POD) in regulating chlorpyrifos and other OPs. EPA noted that these claims were not challenges to EPA's 2006 reregistration decision for chlorpyrifos, but rather, new challenges to EPA's ongoing approval of chlorpyrifos under FIFRA and the FFDCA because they rely in large measure on data published after EPA completed both its 2001 chlorpyrifos Interim Reregistration Decision and the 2006 OP CRA that concluded the reregistration process for chlorpyrifos and all other OPs. As matters that largely came to light after the completion of reregistration, EPA made clear that these Petition issues are being addressed as part of the registration review of chlorpyrifos—the next round of re-evaluation under FIFRA section 3(g). The Denial Order noted that the question of OP neurodevelopmental toxicity was, and remains, an issue at the cutting edge of science, involving significant uncertainties.

During registration review, EPA conducted an in-depth analysis of the available OP and chlorpyrifos biomonitoring data and of the available epidemiologic studies from three major children's health cohort studies in the U.S., specifically from the Columbia Center for Children's Environmental Health (CCCEH), Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS), and Mt. Sinai. EPA three times, in 2008, 2012, and 2016 has presented approaches and proposals to the FIFRA SAP for evaluating this epidemiologic data exploring the possible connection between *in utero* and early childhood exposure to chlorpyrifos and adverse neurodevelopmental effects. The SAP's reports have rendered numerous recommendations for additional study and sometimes conflicting advice for how EPA should consider (or not consider) the epidemiology data in conducting EPA's registration review human health risk assessment for chlorpyrifos and served to underscore that the science on this question is not resolved and would benefit from additional inquiry. Indeed, EPA explained in the Denial Order that the comments received by EPA indicate that there are considerable areas of uncertainty with regard to what the epidemiology data show and deep disagreement over how those data should be considered in EPA's risk assessment. In August 2016, the Ninth Circuit made clear, however, that EPA was to provide a final response to the Petition by March 31, 2017, and that no more extensions would be granted—regardless of whether the science remains unsettled and irrespective of whatever options may exist for resolution of these issues during the registration review process.

While EPA acknowledged its obligation to respond to the Petition as required by the court, EPA noted that the court's order did not and could not compel EPA to complete the registration review of chlorpyrifos and the issues required for that determination in advance of the October 1, 2022 deadline

provided in FIFRA section 3(g), 7 U.S.C. 136a(g). Although past EPA Administrators had proposed to attempt to complete that review several years in advance of the statutory deadline (and respond to the Petition on the same time frame), it was not possible to fully address these registration issues earlier than the registration review period. As a result, EPA concluded that it needed to adjust the schedule for chlorpyrifos so that it could complete its review of the science addressing neurodevelopmental effects prior to making a final registration review decision whether to retain, limit, or remove chlorpyrifos from the market. Accordingly, EPA denied the Petition claims and stated its intention to complete a full and appropriate review of the neurodevelopmental data before either finalizing the proposed rule of October 30, 2015, or taking an alternative regulatory path.

EPA explained that that denial of the Petition on these grounds provided was consistent with governing law because the petition provision in FFDCA section 408(d) does not address the timing for responding to a petition, nor does it limit the extent to which EPA may coordinate or stage its petition responses with the registration review provisions of FIFRA section 3(g). Provided EPA completes registration review by October 1, 2022, Congress otherwise gave the EPA Administrator the discretion under FIFRA to determine the schedule and timing for completing the review of the over 1000 pesticide active ingredients currently subject to evaluation under FIFRA section 3(g). EPA may lawfully re-prioritize the registration review schedule developed by earlier administrations provided that decision is consistent with law and an appropriate exercise of discretion. *See Federal Communications Commission* v. *Fox Television Stations,* 129 S.Ct. 1800 (2009) (Administrative Procedure Act does not require that a policy change be justified by reasons more substantial than those required to adopt a policy in the first instance). Nothing in FIFRA section 3(g) precludes EPA from altering a previously established registration review schedule. Given the absence of a clear statutory directive, FIFRA and the FFDCA provide EPA with discretion to take into account EPA's registration review of a pesticide in determining how and when the Agency responds to FFDCA petitions to revoke tolerances. As outlined previously, given the importance of this matter and the fact that critical questions remained regarding the significance of the data addressing neurodevelopmental effects, EPA asserted that there is good reason to extend the registration review of chlorpyrifos and therefore to deny the Petition. To find otherwise would effectively give petitioners under the FFDCA the authority to re-order scheduling decisions regarding the FIFRA registration review process that Congress has vested in the Administrator.

H. Claim 10: Inhalation Exposure From Volatilization

Petitioners assert that when EPA completed its 2006 OP CRA, EPA failed to consider and incorporate significant exposures to chlorpyrifos-contaminated air that exist for some populations in communities where chlorpyrifos is applied. Petitioners assert that these exposures exceeded safe levels when considering cholinesterase inhibition as a POD and that developmental neurotoxicity may occur at even lower exposure levels than those resulting in cholinesterase inhibition.

To the extent Petitioners are asserting that human exposure to chlorpyrifos spray drift and volatilized chlorpyrifos present neurodevelopmental risks for infants and children, EPA denied this claim for the reasons stated in EPA's response to claims 7–9.

With respect to Petitioners' claim that exposures to spray drift and volatilized chlorpyrifos present a risk from cholinesterase inhibition, EPA denied the Petition for the reasons identified in EPA's Spray Drift Mitigation Decision of July 16, 2012, and EPA's interim response of July 15, 2014, addressing chlorpyrifos volatilization. Specifically, in the Spray Drift Mitigation Decision, EPA determined that the chlorpyrifos registrants' adoption of label mitigation (in the form of label use rate reductions and no-spray buffer zones) eliminated risk from cholinesterase inhibition as a result of spray drift. As for risks presented by volatilized chlorpyrifos that may occur following application, EPA's July 15, 2014 interim response to the Petition explained that vapor-phase inhalation studies for both chlorpyrifos and chlorpyrifos-oxon made clear that neither vapor-phase chlorpyrifos nor chlorpyrifos oxon presents a risk of cholinesterase inhibition.

V. Objections

The three separate sets of objections to the Denial Order filed with EPA in June 2017 raise similar concerns and can be reduced to the following three primary arguments:

- The Objectors argue that EPA's Denial Order applied the wrong legal standard. (Note: All persons filing objections will be referred to as ''Objectors.'') They assert that neither ''scientific uncertainty'' nor the October 2022 deadline for registration review under FIFRA section 3(g), nor the widespread agricultural use of chlorpyrifos, provide a basis for denying petitions to revoke. They claim that EPA has unlawfully left chlorpyrifos tolerances in place without making the safety finding required by the FFDCA.
- The Objectors assert that EPA has previously found that chlorpyrifos tolerances are unsafe and has not disavowed those findings. Specifically, they claim that EPA has found that chlorpyrifos results in unsafe drinking water exposures and results in adverse neurodevelopmental effects to children and that EPA must therefore revoke the tolerances.
- The Objectors argue that EPA's Denial Order committed a procedural error by failing to address significant concerns raised in the comments on EPA's 2014 risk assessment and 2015 proposed revocation that EPA's assessment fails to protect children. In particular, the Objectors focus on concerns raised in comments asserting that (1) EPA's use of 10% cholinesterase as a regulatory standard is not protective for effects to children's developing brains; (2) EPA has not properly accounted for effects from inhalation of chlorpyrifos from spray drift and volatilization; and (3) EPA inappropriately used the Corteva PBPK model to reduce inter- and intra-species safety factors because the model is ethically and scientifically deficient.

VI. Corteva's Comments on the Objections

Corteva, the primary registrant of chlorpyrifos products registered for use in agriculture, submitted a response to the objections on August 27, 2018, raising specific detailed scientific concerns with the objections (Ref. 4). In addition, Corteva states that there is nothing in the FFDCA suggesting that statute requires EPA to make a safety finding in order to deny a response to a petition and that the FFDCA's implementing regulations place the burden on a petitioner to prove that a pesticide is unsafe. Corteva argues that to find otherwise would lead to the result that EPA is required to renew its safety finding every time a petition is filed, irrespective of the strength and quality of the evidence cited and regardless of whether EPA is engaged in an ongoing scientific review of issues addressed in the petition through FIFRA registration review.

VII. EPA's Response to Objections

EPA's responses to the specific objections summarized in Unit V. are provided in this unit.

A. Claims Regarding the Legal Standard for Reviewing Petitions To Revoke

Before addressing the specific legal objections, EPA notes that the Objectors' concerns focus primarily on EPA's denial of Petition claims 7–10 as they relate to the potential for adverse neurodevelopmental effects to children from exposure to chlorpyrifos in food, drinking water, and from spray drift. These concerns fundamentally relate to issues EPA is evaluating in its current registration review of chlorpyrifos. EPA is in the process of completing revised risk assessments to address new data and advancements in risk assessment methodology since EPA's 2006 safety finding for chlorpyrifos as part of FIFRA section 4 reregistration and FFDCA section 408(q) tolerance reassessment to review tolerances for pesticide residues in effect (Ref. 3). The Objectors have not materially challenged EPA's denial of Petition claims that related to matters before EPA at the time of EPA's 2006 safety finding. Specifically, they have not raised objections to the denial of claims relating to the genetic evidence for human vulnerability with respect to the detoxifying enzyme paraoxonase, endocrine-related effects, or carcinogenicity (claims 1–3). Nor have Objectors challenged most aspects of EPA's conclusions in the Denial Order respecting the potential for current chlorpyrifos exposures to result in acetyl cholinesterase inhibition—the regulatory POD used in EPA's 2006 reregistration and tolerance reassessment decisions.

In sum, the objections are focused on EPA's ongoing work in FIFRA registration review to evaluate more recent information addressing the risk of adverse neurodevelopmental effects. With respect to these claims, EPA has concluded, after many years of attempting to obtain information necessary to validate this information, that the objections and the underlying petition fail to provide evidence of neurodevelopmental effects that is sufficiently valid, complete, and reliable at this time to meet the burden petitioners for revocation bear in presenting a case that tolerances are unsafe, pursuant to the standard under FFDCA section 408(b)(2). In addition, as provided in the Denial Order, EPA has concluded that it is also appropriate to deny the petition to allow EPA to complete its assessment of the potential for adverse neurodevelopmental outcomes in connection with the ongoing chlorpyrifos FIFRA registration review.

1. *Burden of coming forward with valid, complete, and reliable evidence.* In response to the Objectors' claims that EPA applied an incorrect legal standard in denying the Petition, EPA disagrees that the FFDCA requires EPA to make a new safety determination in response to every petition to revoke under FFDCA section 408(d) or that it must revoke tolerances in the absence of making a renewed safety determination in response to a petition. Petitioners cite the FFDCA safety definition and the findings EPA must make to establish a tolerance or leave a tolerance in effect when reassessing the safety of tolerance under FFDCA section 408(q) and FIFRA section 3(g). None of their arguments, however, specifically focus on the FFDCA section 408(d) petition process to modify or revoke a tolerance and EPA's implementing procedural regulations that require persons seeking tolerance revocation to come forward with evidence sufficient to support a finding that the applicable safety standard has not been met. In other words, even if one were to assume, *arguendo,* that the same safety standard applies to EPA action on a petition to revoke a tolerance as applies to the Agency's initial establishment of a tolerance, that is a separate issue from the evidentiary burden a petitioner must meet to support its position. As explained in this unit, in this case, EPA reasonably construes the FFDCA and the Agency's implementing regulations to require petitioners seeking withdrawal of a tolerance to support this request with valid, complete and reliable data that set forth why the tolerances are unsafe, a burden Petitioners here have failed to meet.

By way of background, it is important to note that while Congress addressed the requirements for petitions to establish a tolerance with considerable specificity, *see* FFDCA section 408(d)(2)(A), it by contrast expressly left the specific requirements for petitions to modify or revoke a tolerance to EPA's rulemaking discretion. Id., FFDCA section 408(d)(2)(B). In turn, EPA's long-standing regulations require petitions seeking modification or revocation of a tolerance based on ''new data'' to furnish that data in the same form required for petitions seeking to establish tolerances, to the extent applicable. 40 CFR 180.32(b) (''New data should be furnished in the form specified in 180.7(b) [pertaining to ''[p]etitions proposing tolerances''] for submitting petitions, as applicable.''). Thus, Congress expressly conferred discretion on EPA to specify the requirements for withdrawal of an existing tolerance, and EPA's long-standing regulations require a petitioner seeking revocation to meet the same standard of data reliability as a petitioner seeking to establish a tolerance.

FFDCA section 408(b)(2)(D)(i) requires that all actions of the Administrator to establish, modify, leave in effect, or revoke tolerances must consider, among other factors, ''the validity, completeness, and reliability of the available data from studies of the pesticide chemical and pesticide chemical residue.'' Consistent with this obligation, EPA regulations provide that a petitioner has a burden to provide ''reasonable grounds'' for revocation, including an assertion of facts to justify the modification or revocation of the tolerance (40 CFR 180.32(b)). Further, the regulations also make clear that persons seeking revocation have an initial evidentiary burden that must be met before the question of whether the applicable safety standard under FFDCA section 408(b)(2) is met is properly placed before EPA. *See* 40 CFR 179.91 (Party requesting revocation hearing has initial burden of going forward with evidence). This longstanding interpretation of the statute and the procedures Congress established is permissible and entitled to substantial deference. *Sebelius* v. *Auburn Reg'l Med. Ctr.,* 133 S. Ct. 817, 826–827 (2013) (citing *National Cable & Telecomm. Ass'n* v. *Brand X internet Servs.,* 545 U.S. 967, 980 (2005)). Notably, this regulation mirrors EPA's implementing FIFRA hearing regulations at 40 CFR 164.80(a), which likewise make clear that a person seeking cancellation or suspension must present the case that the standards for those actions have been met.

Recently, in *Ellis* v. *Housenger,* 252 F. Supp. 3d 800, 809 (N.D. Cal. 2017), the U.S. District for the Northern District of California interpreted those regulations, explaining that the FIFRA hearing regulations place the burden on the proponent of a regulatory action to present an affirmative case for action, and that initial burden is properly applied to petitions seeking immediate action. Similarly, before the question whether the applicable safety standard under FFDCA section 408(b)(2) is met is properly placed before the EPA, petitioners must first meet their burden of coming forward with sufficient evidence to show that pesticide tolerances to be modified or revoked are not safe.

EPA concludes that Petitioners have not met that burden. Petitioners have

not presented evidence to establish that chlorpyrifos tolerances must be revoked because of the risk of neurodevelopmental effects at levels lower than EPA's currently regulatory standard. After several years and numerous, significant efforts to evaluate the petition claims related to neurodevelopmental toxicity, including communications with study authors and researchers in an effort to obtain underlying data and validate and replicate reported results, EPA concludes that the information yet presented by Petitioners is not sufficiently valid, complete, and reliable to support abandoning the use of AChE inhibition as the critical effect for regulatory purposes under the FFDCA section 408.

Cholinesterase inhibition and the cholinergic effects (*i.e.,* the physiological or behavioral changes) caused by organophosphorous pesticides, including chlorpyrifos, have long been the endpoints that EPA and nearly every other pesticide regulatory body in the world have used in assessing potential human health hazards. EPA has regarded data showing cholinesterase inhibition in brain, red blood cell (RBC), or plasma, and data on physiological or behavioral changes as critical effects for regulatory purposes. Guideline animal toxicity studies have historically been used in support of the 10% RBC acetylcholinesterase (AChE) inhibition point of departure (POD) for chlorpyrifos in EPA risk assessments.

EPA's 2006 Registration Eligibility Decision (RED) for chlorpyrifos relied on AChE inhibition results from laboratory animals for deriving the POD. Although not acknowledged by the Petitioners and Objectors, in conducting risk assessments in support of the chlorpyrifos RED, EPA also considered the emerging new information from laboratory studies that identified potential concern for increased sensitivity and susceptibility for the young from neurodevelopmental effects unrelated to AChE inhibition. At that time, EPA did not believe those studies support a neurodevelopmental POD for quantitative risk assessment, but it did provide the support for EPA's retention of the FQPA 10X factor in the 2001 chlorpyrifos IRED (Ref. 5).

While Petitioners and Objectors are correct that EPA did not retain the FQPA 10X for chlorpyrifos in the OPs 2006 cumulative risk assessment, that assessment dealt only with the established common mechanism of toxicity for the OPs—AChE inhibition—not with potential hazards that relate to the OPs individually. Accordingly, EPA did not reduce the 10X safety factor as it relates to chlorpyrifos specifically in its 2006 tolerance reassessment and reregistration determination that chlorpyrifos tolerances are safe. To the extent the Objectors are therefore arguing that EPA must, at a minimum, retain the FQPA 10X factor for chlorpyrifos because of the potential for neurodevelopmental effects, those objections are denied as moot. EPA's most recent assessment of the chlorpyrifos tolerances that was challenged in the Petition did retain the FQPA 10X, in part because of neurodevelopmental studies.

The Petition and the objections also argue, however, that EPA should not simply retain the FQPA 10X safety factor but should revoke chlorpyrifos tolerances because of evidence showing the potential for neurodevelopmental effects to occur well below EPA's existing regulatory standard. In sum, they believe EPA should be using the results of existing epidemiologic data to set a regulatory POD for chlorpyrifos at levels that would require EPA to revoke all chlorpyrifos tolerances.

EPA has, since the issuance of the 2006 RED, consistently concluded that the available data support a conclusion of increased sensitivity of the young to the neurotoxic effects of chlorpyrifos and for the susceptibility of the developing brain to chlorpyrifos. This conclusion comes from an evaluation across multiples lines of evidence including mechanistic studies and newer *in vivo* laboratory animal studies, but particularly with the available epidemiology reports along with feedback from the 2012 and 2016 FIFRA SAP meetings. As noted, EPA has retained the FQPA 10X safety factor on these grounds. However, EPA and the FIFRA SAP have also consistently cited the lack of robustness of these data for deriving a POD for neurodevelopmental effects given (1) the absence of a clear mechanism of action for chlorpyrifos in the developing brain; (2) the dosing regimen in *in vivo* studies that differs from internationally accepted protocols; and (3) the lack of any meaningful raw data from the epidemiologic data that are the centerpiece of this area of inquiry.

The lack of a mechanistic understanding for effects on the developing brain precludes EPA from validly or reliably assessing potential differences (and similarities) between laboratory animals and humans with respect to dose-response and temporal windows of susceptibility. In the absence of this information, EPA has no valid or reliable ways to bridge the scientific interpretation of the laboratory studies and epidemiology studies with chlorpyrifos. In addition, the dosing regimen used in the *in vivo* studies means the data are not sufficiently valid, complete and reliable for regulatory purposes given the problems they present for the quantitative interpretation and extrapolation of the results. Specifically, the *in vivo* laboratory animal studies generally use fewer days of dosing that are aimed at specific periods of rodent fetal or early post-natal development compared to internationally adopted guideline studies which are intended to cover both pre- and post-gestational periods. The degree to which these shorter dosing periods coincide with comparable windows of susceptibility in human brain development is unclear. In addition, except for some studies conducted recently, most of the *in vivo* laboratory studies use doses that are higher than doses that cause 10% RBC AChE inhibition. These studies are therefore are not useful quantitatively to evaluate whether EPA's current regulatory standard is or is not sufficient to preclude the potential for neurodevelopmental effects.

Finally, and most significantly, despite numerous requests over the last decade, the authors of the epidemiologic studies that provide potentially the most relevant information regarding effects to humans have never provided the underlying data from their studies to EPA to allow EPA and others to independently verify the validity and reliability of the results reported in their published articles. EPA believes it is necessary to first replicate the statistical analyses used in the studies to ensure their accuracy. In addition, EPA wants to examine the raw data used in the analysis to ensure appropriate handling of data points and in potentially conducting alternative statistical analyses. For example, EPA would want to evaluate the elimination of certain study participants from the CCCEH study that were deemed to be outliers in order to determine whether their exclusion was proper and how it may have affected the results. The lack of publicly available raw data does not necessarily preclude EPA from reliance on such information for the purpose of risk assessment. Given the long history and internationally harmonized use of acetylcholinesterase inhibition as the point of departure for chlorpyrifos, however, EPA reasonably requires more complete information regarding the studies in the published articles to establish a POD and that threshold has not been met in this instance. Due to these limitations, EPA does not believe the Petition, or the objections make the

case for EPA to establish a POD based on neurodevelopmental effects, which remains central to the Petitioners' claims 7–9.

EPA understands that this conclusion is at odds with its revised risk assessment that it published for comment with the NODA in November 2016. By way of explanation, EPA notes that it has undertaken considerable efforts to assess the available chlorpyrifos data, including the references cited by the Petitioners in support for their claims related to neurodevelopmental effects. Specifically, in Chapter 4 and Appendices 2–4 of the 2014 human health risk assessment, EPA provides a detailed discussion of the strengths and uncertainties associated with the epidemiology studies. For example, although the studies used US-based exposure profiles in real world situations, EPA noted that the lack of data on the timing of chlorpyrifos applications was a key concern in the exposure assessment. EPA conducted a preliminary review of available literature and research on epidemiology in mothers and children following exposures chlorpyrifos and other OPs, laboratory studies on animal behavior and cognition, AChE inhibition, and mechanisms of action, and took it to the SAP in 2008.

The CCCEH study used concentrations of pesticides (including chlorpyrifos) in umbilical cord blood as a measure of exposure, while two other birth cohorts used urinary biomarkers in the mothers to estimate pesticide exposure. In 2012, the EPA convened another meeting of the FIFRA SAP to review the latest experimental data related to AChE inhibition, cholinergic and non-cholinergic adverse outcomes, including neurodevelopmental studies on behavior and cognition effects. The EPA also performed an in-depth analysis of the available chlorpyrifos biomonitoring data and of the available epidemiologic studies from three major children's health cohort studies in the U.S., including those from the CCCEH, Mt. Sinai, and CHAMACOS. The EPA explored plausible hypotheses on mode of actions/adverse outcome pathways (MOAs/AOPs) leading to neurodevelopmental outcomes seen in the biomonitoring and epidemiology studies.

EPA convened another meeting of the FIFRA SAP in April 2016, which was unique in focus compared to the previous meetings in that EPA explicitly proposed using information directly from the CCCEH published articles for deriving the POD. The 2016 SAP did not support the ''direct use'' of the cord blood and working memory data for deriving the regulatory endpoint for several reasons, among them, the lack of raw data from the epidemiology study (Ref. 4).

This feedback is consistent with concerns raised in public comments EPA received on the use of the epidemiology data throughout the course of registration review from the grower community, pesticide registrants, and the U.S. Department of Agriculture. The final FIFRA SAP report provides a detailed account of the concerns associated with the Agency's April 2016 proposed approach to selecting the point of departure (POD) and its use in quantitative risk assessment. Specifically, the SAP report noted that ''[t] he majority of the panel stated that using cord concentrations for derivation of the POD could not be justified by any sound scientific evaluation. The Panel was conflicted with respect to the importance of a 2% change in working memory.'' *Id.* at 19. The Panel went on to note that ''the Agency's inability to confidently estimate previous exposure patterns and/or intensity hinders the use of cord blood at delivery as an anchor from which to extrapolate back to a more toxicologically meaningful internal exposure metric.'' *Id.* at 42. The SAP also noted the insufficient information about timing of chlorpyrifos applications in relation to cord blood concentrations at the time of birth, as well as uncertainties about the prenatal window(s) of exposure linked to reported effects.

EPA acknowledges that the 2012 and 2016 SAPs note effects in the epidemiology and experimental studies below 10% AChE inhibition. In addition, both the 2008 and 2012 SAP commented on the strengths of the CCCEH epidemiologic studies and the value of the information they provide. However, despite these strengths, both the 2008 and 2012 Panels recommended that AChE inhibition remain as the source of data for the PODs. The 2016 SAP expressed significant reservations about the proposed approach to use the cord blood as the source of data for the POD. It noted the incompleteness of the information, including the lack of raw data, reproducibility of analytical blood data, and knowledge about chlorpyrifos application timing relative to pregnancy. EPA has evaluated the SAP's concerns, as well as public comments received on the 2016 updated human health risk assessment echoed a number of the SAP's concern regarding use of the CCCEH study. Based on the uncertainties identified by the 2016 SAP, the published articles from CCCEH are not complete for deriving a POD. EPA acknowledges this conclusion differs from the position supported in the 2016 revised human health risk assessment, but EPA believes the shortcomings of the data identified raise issues of validity, completeness and reliability under the FFDCA that direct against using the data for risk assessment at this time. As stated in the Denial Order, EPA intends to continue its exploration of the uncertainty around using neurodevelopmental effects to establish a POD as it works to complete registration review, including renewed efforts to obtain the raw data from the epidemiologic studies that are the central to consideration of potential neurodevelopmental effects.

Notably, EPA has made requests to CCCEH, CHAMACOS, and Mt. Sinai to obtain the raw data, and visited Columbia University in an attempt to better understand their study results and what raw data exist. EPA also requested the original CCCEH study protocol to determine whether its specific questions regarding exposure timing could be addressed with the raw data. EPA was informed the CCCEH protocol was not available, and EPA did not receive the raw data from any of those research institutions. Columbia made a public commitment to ''share all data gathered,'' however, to date, CCCEH has not provided EPA with the data, citing subject privacy concerns. In 2018, EPA explored options for blinding the data to eliminate this concern. However, through these conversations, CCCEH indicated there is no effective way to remedy this issue, citing that since the cohort is from a very small geographic area, subject identification would still be possible, and therefore, was still of concern.

In addition, EPA actively sought clarification on the kinds of residential application methods of chlorpyrifos used in New York City (NYC) during the time the CCCEH study was conducted (1998–2000) in order to provide additional context to the results of the CCCEH study conclusions. Through a series of email and telephone conversations with NYC pest control officials in 2016, EPA consistently heard that chlorpyrifos was typically applied as a crack and crevice application between 1998 and 2000. Unfortunately, EPA has no way to verify that this use pattern aligns with the exposures of participants in the CCCEH study and would not be able to corroborate the correlation between crack and crevice application and the observed neurodevelopmental effects.

As indicated, EPA has undertaken considerable efforts to assess the CCCEH

study, including submitting EPA's evaluation of the CCCEH study to multiple SAPs. Given that CCCEH has not shared the raw data or the results of their exploratory analyses, EPA cannot validate or confirm the data analysis performed, the degree to which the statistical methods employed were appropriate, or the extent to which (reasonable or minor) changes in assumptions may have changed any final results or conclusions. EPA has been unable to conduct its own evaluation of the study conclusions utilizing the raw data nor has EPA has been able to address the issues identified by the 2016 SAP. While EPA has retained the FQPA 10x safety factor in order to address this potential uncertainty, given the shortcomings to date of the published epidemiology data, EPA does not have sufficiently complete information to currently support using the epidemiology studies as the POD in place of AChE inhibition as the POD.

In conclusion, the epidemiologic studies are central to the Petitioner's claims regarding neurodevelopmental effects, yet the Petitioners and Objectors rely only on summaries in publications to present their case. Petitioners have not presented the raw data from the epidemiology studies for consideration of their claims. EPA has likewise been unable to obtain this critical information, though the FIFRA SAP and commenters have raised many questions about it. So, EPA has not been able to verify the conclusions of the epidemiology studies due to this lack of raw data. Further, the lack of a clear mechanism of action and the lack of an internationally accepted dosing regimen in the *in vivo* data also preclude EPA from determining the relevance of the limited animal data addressing the potential for neurodevelopmental effects. The Petitioners have therefore failed to meet their initial burden of providing sufficiently valid, complete, and reliable evidence that neurodevelopmental effects may be occuring at levels below EPA's current regulatory standard and no information submitted with the objections addresses this shortcoming of the Petition.

2. *Reconciling FFDCA petitions to revoke and FIFRA Registration Review.* EPA also continues to conclude that denial is appropriate for claims related to matters that are the subject of registration review, specifically for chlorpyrifos, claims related to neurodevelopmental toxicity. In this case, the data deficiencies in the Petition related to neurodevelopmental toxicity that EPA is currently studying in a more up-to-date, thorough and methodical fashion in conjunction with the statutorily prescribed FIFRA re-registration process. In this context, it is particularly appropriate for EPA to take into account the substantive work that it is conducting under FIFRA in reaching its decision on the Petition.

As EPA explained in the Denial Order, to reconcile the FFDCA petition procedures with the FIFRA registration review provisions that require EPA to conduct periodic reviews of all pesticides, EPA must be able to take account of the FIFRA registration review schedule for a pesticide in determining how and when to respond to an FFDCA petition that raises issues that are also the subject of a current registration review. As noted, the Denial Order fully responded to Petitioners' claims that address the substance of EPA's 2006 safety finding, and Petitioners and the other Objectors could have chosen to challenge and litigate that determination through the petition and judicial review provisions of the FFDCA, had they wished. The objections, however, do not for the most part go to the substance of EPA's 2006 safety finding. Those claims have largely been abandoned and instead the objections now focus only on compelling EPA to resolve on a petitioner-dictated schedule new issues regarding the potential for neurodevelopmental toxicity that are part of an ongoing evaluation in registration review in advance of the statutory deadline (October 1, 2022) provided by Congress in FIFRA section 3(g) for completing that assessment. To that end, Objectors argue that the fact Congress established a 2022 deadline for registration review is no license for EPA to delay its response to an FFDCA petition and that EPA is in fact prohibited from relying on registration review as a basis for determining how to complete other reviews of a pesticide. Specifically, they cite to language in FIFRA section 3(g)(1)(C) that states that ''[n]othing in this subsection shall prohibit the Administrator from undertaking any other review of a pesticide under this chapter.'' Objectors have overlooked the critical language at the end of this passage (''under this chapter'') that by its terms only speaks to how EPA should reconcile registration review with other reviews under FIFRA. The language does not address reviews under the FFDCA, much less prohibit EPA from reconciling its responses to FFDCA petitions with the timeframe for registration review under FIFRA. The Objectors also do not point to any language in the FFDCA prohibiting the reconciliation of a response to a petition to revoke tolerances with the registration review schedule for reviewing the pesticide—which includes a determination whether to leave existing tolerances in effect. The 15-year registration review interval reflects Congress's effort to balance the need for EPA to assure that pesticides meet the FFDCA and FIFRA standards, while at the same time recognizing that completing scientific evaluations for over 1000 active ingredients is both time-consuming and resource-intensive. During a registration review, EPA is required to ''assess changes since a pesticide's last [registration] review,'' including new risk assessment methods, new studies and new data on pesticides. 40 CFR 155.53(a). This is precisely the assessment EPA is in the process of undertaking in the chlorpyrifos registration review with respect to the Petition claims addressing new information on the potential for adverse neurodevelopmental effects. If, as Petitioners and Objectors argue, EPA were required to truncate its ongoing registration review process to make a new FFDCA safety finding every time it received a petition to modify or revoke tolerances, petitioners would effectively have the authority to re-order the Administrator's scheduling of registration review decisions under FIFRA and dictate the extent of inquiry EPA may put to a matter before reaching a resolution. EPA continues to believe that with the passage of FIFRA section 3(g) and the 15-year review cycle created by that provision, Congress directed the Administrator, not FFDCA petitioners, to determine the appropriate timing and process for completing the review of dietary risk within that 15-year review period. EPA therefore concludes that it is also appropriate to deny the objections and the underlying petition to the extent they seek to compel EPA's consideration of neurodevelopmental toxicity issues raised during the course of the current registration review in advance of the schedule provided by Congress under FIFRA section 3(g).

As described previously, EPA has compelling reasons to follow its regulatory process through registration review. Specifically, EPA is working to update a number of assessments that will result in a more complete, accurate assessment of the risks of chlorpyrifos than if EPA were compelled to truncate that review now. The key components of EPA's updates to its analysis are (1) Review of five new laboratory animal studies for consideration in the updated human health risk assessment, and (2) Incorporating refined use information

into the 2016 updated drinking water assessment.

With respect to the animal data, in 2018, the California Department of Pesticide Regulation (CDPR) proposed to adopt a regulation designating chlorpyrifos as a toxic air contaminant (TAC) in California. As part of this determination, CDPR developed its ''Final Toxic Air Contaminant Evaluation of Chlorpyrifos Risk Characterization of Spray Drift, Dietary, and Aggregate Exposures to Residential Bystanders.'' The CDPR risk characterization document cites five new laboratory animal studies not previously reviewed by EPA (Gomez-Gimenez et al., 2017, 2018; Silva et al., 2017; Lee et al., 2015; Carr et al., 2017). It is appropriate for EPA to review these five new studies in order to complete EPA's evaluation of potential neurodevelopmental effects. CDPR is using these studies as the main source of information for their new POD for acute oral exposure, so it is prudent for EPA to evaluate the data's quality and whether it provides the strong support for the conclusion that effects on the developing brain may occur below a dose eliciting 10% AChE inhibition that would be used to establish a new POD for the EPA's risk assessment. EPA is conducting its review in accordance with OPP's Guidance for Considering and Using Open Literature Toxicity Studies to Support Human Health Risk Assessment. It has contacted the primary investigators associated with the new animal studies in July–August 2018, and received the raw data associated with one of these studies.

As for EPA's drinking water assessment, the Agency identified certain uses, application rates, and practices described in the current chlorpyrifos labels that are not actually being used in the field and are contributing to an over-estimate of potential drinking water concentrations. EPA has requested additional information from the registrants to confirm the accuracy of these assumptions and anticipates including these updates in the Proposed Interim Decision.

To be clear, EPA remains committed to expediting its registration review determination so that it is completed well in advance of the October 2022 deadline. To that end, EPA anticipates making available any updates to the human health and drinking water assessments for public availability and comment by summer of 2020. Updates will also include EPA's response to public comments from the previous comment periods. In addition, EPA has been engaged in discussions with the chlorpyrifos registrants that could result in further use limitations affecting the outcome of EPA's assessment. The Proposed Interim Decision incorporating these updated assessments is anticipated for public availability and comment by October 2020. If EPA were compelled to act in advance of these registration review activities, none of these assessments would be available to inform that review. For example, OPP is pursuing the use of surface water monitoring data to confidently estimate pesticide concentrations in surface water that may be sourced by community water systems. A meeting of the FIFRA Scientific Advisory Panel is planned for obtaining expert feedback on tools and methodologies currently in development for using surface water monitoring data quantitatively in drinking water assessments. While the focus of the SAP is not specific to chlorpyrifos, the EPA will consider any recommendations from the SAP that are appropriate for inclusion in the chlorpyrifos drinking water assessment.

B. Objections Asserting That EPA Has Found Chlorpyrifos To Be Unsafe

The Objectors argue that EPA not only failed to make a safety finding in denying the Petition, but that it has never disavowed previous EPA findings that it could not conclude chlorpyrifos is safe with respect to both the potential for adverse neurodevelopmental effects and harmful drinking water exposures. In particular, the objections point to various statements in EPA risk assessments and in EPA's 2015 proposed tolerance revocation action asserting that EPA is unable to conclude that chlorpyrifos tolerances are safe.

Contrary to these assertions, as noted by Corteva in its response to the objections, EPA has not made any findings that chlorpyrifos tolerances are not safe. In fact, EPA's last final action with respect to the safety of chlorpyrifos tolerances was its determination in 2006 that chlorpyrifos and the other pesticides in the organophosphate class meet the FFDCA safety standard in connection with FIFRA section 4 reregistration and FFDCA section 408(q) tolerance reassessment. This is the only regulatory finding currently in effect for chlorpyrifos as EPA has taken no final action on the proposed rule it published in 2015 to comply with the Ninth Circuit mandamus order in the *PANNA* v. *EPA* decision. Proposed rules are just that—proposals; they do not bind federal agencies. Indeed, EPA made clear it was issuing the proposal because of the court order, without having resolved many of the issues critical to EPA's FFDCA determination and without having fully considered comments previously submitted to the Agency (69 FR 69079, 69081–83). Similarly, risk assessments that underly proposed rules are not final agency actions and likewise are not binding.

At this stage, EPA may choose to finalize, modify or withdraw the proposal based on the comments received and EPA's evaluation following its review of the comments. Until such time, EPA's statements in the proposed rule are not binding pronouncements with respect to EPA's decision whether to grant or deny the Petition. See, *e.g., Northwest Coalition for Alternatives to Pesticides* v. *EPA,* 544 F.3d 1043, 1051 (9th Cir. 2008) (''as long as agencies follow the proper administrative procedures, they have the authority to change their minds before issuing a final order''); *Public Citizen Health Research Grp.* v. *FDA,* 740 F.2d 21 (D.C. Cir. 1984) (''Neither the substance of the decision to require further study nor the circumstances leading to the decision . . . suffice, however, to permit us to leapfrog back over the Secretary's decision . . . hold the agency to its preliminary decision to promulgate a labeling requirement. In connection with the registration review of chlorpyrifos, which EPA expects to complete in advance of the October 1, 2022 statutory deadline, EPA will make a determination regarding the safety of chlorpyrifos and will either finalize, modify or withdraw the proposal at that time.

With respect to objections related to drinking water, as explained in Unit II., a party may not raise issues in objections unless they were part of the petition. *Corn Growers* v. *EPA,* 613 F.3d 266 (D.C. Cir. 2010), cert. denied, 131 S. Ct. 2931 (2011). The Petition did not identify drinking water exposure as a basis for seeking tolerance revocation, and the Objectors cannot therefore raise that concern as a basis for challenging EPA's denial of the Petition. The mere fact that EPA is considering the potential impact of chlorpyrifos exposures in drinking water in the Agency's FIFRA section 3(g) registration review does not somehow provide Petitioners and Objectors with a vehicle for introducing that topic in the objections process on the Petition denial. And the objections phase of the petition process does not provide Petitioners a means to effectively start the petition process over again by raising issues that were not originally raised in the 2007 petition to revoke. Accordingly, EPA denies all objections regarding drinking water exposures. To be clear, however, EPA is continuing its

FIFRA section 3(g) registration review and to complete its evaluation of drinking water exposures to chlorpyrifos. EPA will address these issues in its upcoming registration review decision.

C. Objections Asserting That the Denial Order Failed To Respond to Significant Concerns Raised in Comments

The Objectors claim that EPA has committed procedural error in failing to respond to certain comments raised in comments to EPA's 2014 Revised Human Health Risk Assessment and the 2015 proposed revocation. The Objectors appear to assert that in the absence of any comment response document in the record, EPA has violated the requirements of section 553(c) of the Administrative Procedure Act (APA) which requires agencies to give consideration to relevant matter submitted during the comment period on proposed rules. While these objections correctly recite the requirements of the APA rulemaking provisions, the requirement to respond to comments on proposed rules applies to the ''rules adopted'' by agencies—*i.e.,* final rules—and EPA has neither finalized nor withdrawn the 2015 proposed revocation rule. Further, the FFDCA does not require EPA to respond to rulemaking comments in issuing petition denial orders under FFDCA section 408(d)(4). In connection with EPA's completion of the FIFRA section 3(g) registration review of chlorpyrifos, EPA will either finalize or withdraw the proposed rule and address significant comments on the proposal at that time. But EPA has no obligation to respond to rulemaking comments in denying the Petition or responding to objections, both of which are adjudicatory actions that are not part of the rulemaking process.

In addition to raising procedural error, Objectors appear to adopt as their own substantive objections some of the comments on the proposed rule and risk assessment. Specifically, they focus on comments asserting that (1) EPA's use of 10% cholinesterase as a regulatory standard is not protective for effects to children's developing brains; (2) EPA inappropriately used Corteva's PBPK model, which is ethically and scientifically deficient, to reduce inter and intra-species safety factors; and (3) EPA has not properly accounted for effects from inhalation of chlorpyrifos from spray drift and volatilization.

The comments adopted by the Objectors regarding effects on the developing brain mirror the claims raised in the Petition regarding the potential for adverse neurodevelopmental effects. Accordingly, EPA restates its response provided in Unit VII.A.1. that the Petition and the objections fail to meet burden of presenting evidence sufficiently valid, complete and reliable to demonstrate that chlorpyrifos results in neurodevelopmental effects that render its tolerances not safe.

With respect to EPA's use of the Corteva PBPK model, these claims, as with claims respecting drinking water, were not raised in the Petition and cannot be raised for the first time in the objections phase of the petition process. Further, the Objections appear to oppose EPA's use of the PBPK model in conducting the assessment underlying EPA's 2014 and 2016 risk assessments and 2015 proposed tolerance revocation and do not appear to address EPA's Petition denial. This objection therefore does not appear to be relevant to the Denial Order. For these reasons, this objection is also denied.

Regarding the objections related to inhalation risk, Objectors raise three distinct issues from the public comments that relate to EPA's completed inhalation exposure assessment addressing the potential for bystanders to experience cholinesterase inhibition from exposure to spray drift at the time of application and volatilized chlorpyrifos following application. First, the Objectors dispute EPA' s legal authority not to consider in its risk assessment exposures to chlorpyrifos from illegal spraying prohibited by product labeling. Second, the Objectors assert that the Denial Order inappropriately relied on two recent Corteva studies on the effects of chlorpyrifos in its vapor phase to conclude that volatilized chlorpyrifos presents no risk of cholinesterase inhibition. Third, the Objectors assert that documented poisoning incidents demonstrate that the no-spray buffer-zones that EPA approved on product labeling in 2012 are inadequate to address harm from spray drift. Objectors point specifically to a May 2017 poisoning incident in Kern County, California, involving a total of 50 people who were either harmed or put at risk, as evidence for their concern.

In response, EPA believes it is lawful and appropriate for it to consider federally enforceable chlorpyrifos product labeling restrictions in assessing the extent of bystander risk from spray drift under both the FFDCA and FIFRA. Under FIFRA, pesticide labeling use instructions are enforceable limits on the use of the product that serve as the basis for EPA's evaluation of potential risks. Indeed, in registering pesticides, FIFRA section 3(c)(5) directs EPA to register pesticides when, among other things, a pesticide ''will perform its intended function without unreasonable effects on the environment'' and ''when used in accordance with widespread and commonly recognized practice it will not generally cause unreasonable adverse effects on the environment.'' These directives functionally instruct EPA to consider the intended, widespread and commonly recognized use of a pesticide as set forth on proposed product labeling in determining whether the pesticide will cause unreasonable adverse on the environment. While these provisions do not serve as a bar to EPA considering the impacts from unlawful misuse, unless such misuse is a widespread or commonly recognized practice, it does not provide a basis for regulatory action under FIFRA or a basis for determining that current tolerance levels are unsafe. Rather, misuse is first and foremost a matter for enforcement under FIFRA. It should also be noted that because chlorpyrifos is a restricted use pesticide, applicators must have specific training meant, in part, to assure proper pesticide application. When these restrictions are followed, exposures are significantly limited. To be clear, while drift is minimized when applicators follow label directions, EPA does assume that some residues may settle off-target, and that there may be dermal and incidental oral exposure from contacting residential turf adjacent to treated fields. To address the potential for cholinesterase inhibition from these exposures, EPA assessed the risk from these exposures and establishes appropriate distances between such locations and the site of application. Accordingly, following EPA's assessment of spray drift in 2012, the chlorpyrifos registrants agreed to place additional limitations on use to include use rate reductions and spray drift buffers that are sufficient to eliminate a risk of cholinesterase inhibition from lawful use.

With respect to the objections concerning volatility and the potential for cholinesterase inhibition, EPA has not changed its position set forth in the Denial Order and does not believe it is disregarding the potential for volatilization exposures. Exposure to low levels of vapor-phase chlorpyrifos following application near treated fields is possible. After the Agency's 2011 preliminary risk assessment, Corteva submitted toxicity data that measured cholinesterase inhibition resulting from acute exposure to vapors of chlorpyrifos and its oxon rather than exposure to

aerosols of these compounds as was done for previous assessments. Since inhalation exposure to bystanders will be only to vapor phase chlorpyrifos rather than aerosols due to spray drift restrictions, use of these data to assess inhalation risk of cholinesterase inhibition to bystanders is appropriate. In these vapor-phase toxicity studies, test animals were exposed in atmospheres containing saturation concentrations of chlorpyrifos and its oxon, the maximum potential level of the compounds in air. No cholinesterase inhibition was observed, and the studies were determined to have been conducted properly using saturation concentrations of the compounds and controls appropriate for these types of studies, *i.e.,* animals receiving no pesticide exposure, as further explained in ''*Chlorpyrifos: Reevaluation of the Potential Risks from Volatilization in Consideration of Chlorpyrifos Parent and Oxon Vapor Inhalation Toxicity Studies, W. Britton, W. Irwin, 6/25/14.*''

EPA has also done a comprehensive review of chlorpyrifos incidents and found that most were due to accidents and misuse as specified in EPA's most recent final incident review ''*Chlorpyrifos: Tier II Incident Report, S. Recore and K. Oo, 7/27/11.*'' The agency is aware of the referenced Kern County chlorpyrifos incident that occurred in 2017 in which the pesticide appears to have been applied in a manner in which direct drift onto bystanders occurred, a case of misuse. Spray drift buffers address exposure to bystanders when chlorpyrifos is applied as required by the pesticide label. In addition, it should be noted that EPA's 2000 cancellation of homeowner products and many indoor and outdoor non-residential uses (*e.g.,* schools and parks where children may be exposed) has led, according to data from 2002–2010, to a 95% decrease in the number of incidents reported in residential areas. In sum, EPA does not believe available incident data suggests that there exists a widespread and commonly recognized practice of misusing chlorpyrifos and EPA therefore believes it is appropriate to use the enforceable label instructions as the basis for evaluating the potential for inhalation exposure from spray drift and volatilization.

VIII. Regulatory Assessment Requirements

As indicated previously, this action announces the Agency's order denying objections filed under FFDCA section 408. As such, this action is an adjudication and not a rule. The regulatory assessment requirements imposed on rulemaking do not, therefore, apply to this action.

IX. Submission to Congress and the Comptroller General

The Congressional Review Act, 5 U.S.C. 801 *et seq.,* does not apply because this action is not a rule for purposes of 5 U.S.C. 804(3).

X. References

The following is a listing of the documents that are specifically referenced in this document. The docket includes these documents and other information considered by EPA, including documents that are referenced within the documents that are included in the docket, even if the referenced document is not physically located in the docket. For assistance in locating these other documents, please consult the person listed under **FOR FURTHER INFORMATION CONTACT**.

1. The Petition from NRDC and PANNA and EPA's various responses to it are available in docket number EPA–HQ–OPP–2007–1005 available at *http://www.regulations.gov.*
2. The objections submitted on the Petition Denial are available in docket number EPA–HQ–OPP–2007–1005 available at *http://www.regulations.gov.*
3. For additional information on the organophosphate cumulative risk assessment, see *http://www.epa.gov/pesticides/cumulative/2006-op/op_cra_main.pdf.*
4. FIFRA Scientific Advisory Panel (2016). ''Chlorpyrifos: Analysis of Biomonitoring Data''. Available at: *https://www.epa.gov/sap/meeting-materials-april-19-21-2016-scientific-advisory-panel.*
5. For additional information on the 2000 chlorpyrifos IRED and 2006 chlorpyrifos RED, see *https://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/red_PC-059101_1-Jul-06.pdf.*
6. FIFRA Scientific Advisory Panel (2008). ''Scientific Issues Associated with Chlorpyrifos and PON1''. Available in docket number EPA–HQ–OPP–2008–0274 available at *http://www.regulations.gov.*
7. EPA, 2012. ''Guidance for Considering and Using Open Literature Toxicity Studies to Support Human Health Risk Assessment'' as well as it's ''Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment.'' Available at *https://www.epa.gov/sites/production/files/2015-07/documents/lit-studies.pdf.*
8. EPA, 2016. Record of Correspondence. Available in docket number EPA–HQ–OPP–2015–0653.

List of Subjects in 40 CFR Part 180

Environmental protection, Administrative practice and procedure, Agricultural commodities, Pesticides and pests, Reporting and recordkeeping requirements.

Dated: July 18, 2019.

Alexandra Dapolito Dunn,

Assistant Administrator, Office of Chemical Safety and Pollution Prevention.

[FR Doc. 2019–15649 Filed 7–23–19; 8:45 am]

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DEPARTMENT OF COMMERCE

National Oceanic and Atmospheric Administration

50 CFR Part 300

[Docket No. 190325272–9537–02]

RIN 0648–XP002

Western and Central Pacific Fisheries for Highly Migratory Species; 2019 Bigeye Tuna Longline Fishery Closure

AGENCY: National Marine Fisheries Service (NMFS), National Oceanic and Atmospheric Administration (NOAA), Commerce.

ACTION: Temporary rule; fishery closure.

SUMMARY: NMFS is closing the U.S. pelagic longline fishery for bigeye tuna in the western and central Pacific Ocean because the fishery has reached the 2019 catch limit. This action is necessary to ensure compliance with NMFS regulations that implement decisions of the Western and Central Pacific Fisheries Commission (WCPFC).

DATES: Effective 12:01 a.m. local time July 27, 2019, through December 31, 2019.

ADDRESSES: NMFS prepared a plain language guide and frequently asked questions that explain how to comply with this rule; both are available at *https://www.regulations.gov/docket?D=NOAA-NMFS-2019-0085.*

FOR FURTHER INFORMATION CONTACT: Rebecca Walker, NMFS Pacific Islands Region, 808–725–5184.

SUPPLEMENTARY INFORMATION: Pelagic longline fishing in the western and central Pacific Ocean is managed, in part, under the Western and Central Pacific Fisheries Convention Implementation Act (Act). Regulations governing fishing by U.S. vessels in accordance with the Act appear at 50 CFR part 300, subpart O.

NMFS established a calendar year 2019 limit of 3,554 metric tons (t) of bigeye tuna (*Thunnus obesus*) that may be caught and retained in the U.S. pelagic longline fishery in the area of application of the Convention on the Conservation and Management of Highly Migratory Fish Stocks in the

Appendix II

STUDY TITLE:

Public Comments:
Chlorpyrifos Revised Human Health Risk Assessment for Registration Review
(EPA's Office of Pesticide Programs, November 3, 2016)

DATA REQUIREMENT:

Not Applicable

AUTHORS:

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STUDY COMPLETION DATE:

January 16, 2017

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CA FL VA

PROJECT IDENTIFICATION:

DAS–009-16

STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS

Compound: **Chlorpyrifos**

Title: **Public Comments: Chlorpyrifos Revised Human Health Risk Assessment for Registration Review (EPA's Office of Pesticide Programs, November 3, 2016)**

No claim of confidentiality is made for any information contained in this study on the basis of its falling within the scope of FIFRA §10(d)(1)(A), (B), or (C)*.

Company: Dow AgroSciences, LLC

Company Agent 

Jan-17-2017
(Date)

*In the United States, the above statement supersedes all other statements of confidentiality that may occur elsewhere in this report.

THESE DATA MAY BE CONSIDERED CONFIDENTIAL IN COUNTRIES OUTSIDE THE UNITED STATES.

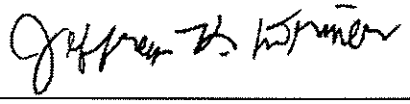
GOOD LABORATORY PRACTICES STATEMENT

Compound: **Chlorpyrifos**

Title: **Public Comments: Chlorpyrifos Revised Human Health Risk Assessment for Registration Review (EPA's Office of Pesticide Programs, November 3, 2016)**

This study is not subject to Good Laboratory Practice Standards (GLP). The present report primarily contains descriptions and discussions not specifically reviewed or audited in a GLP context.

Study Author:



January 16, 2017

Jeffrey Driver, Dr.P.H., D.A.B.T., M.T., C.L.S.
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Sponsored by:

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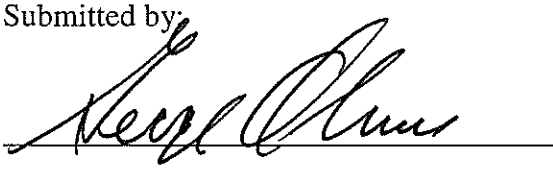
(Date)

Submitted by:



Jan-17-2017

(Date)

Table of Contents

Public Comments:

Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review (EPA's Office of Pesticide Programs, November 3, 2016)

I. SUMMARY

U.S. EPA's most recent Revised Human Health Risk Assessment (RHHRA) for chlorpyrifos dated November 3, 2016 represents a radical departure from past HHRAs for chlorpyrifos specifically, and for most pesticides in general. This has resulted in areas of concern regarding the overall methodology employed by EPA specifically relating to the accuracy, precision, representativeness, and reliability of deriving a Point of Departure (PoD) for post-application chlorpyrifos exposure following alleged crack and crevice (C&C) use. The following summary comments identify key concerns about the 2016 RHHRA for chlorpyrifos.

- EPA is assuming that the neurodevelopmental effects allegedly observed in the Columbia Center for Children's Environmental Health (CCCEH) study were due to very low chlorpyrifos exposures (well below EPA benchmarks for 10% inhibition of red blood cell cholinesterase inhibition), specifically following C&C application. There are numerous problems with this assumption.
  - From an epidemiologic perspective, the weight-of-evidence has not been considered. There are *more cohorts* of individuals tested for association of organophosphate (OP) exposure associated *with a lack of neurodevelopmental problems* than there are cohorts where there is a positive association.
  - There were *many other pesticides and potent toxicants in the environment of the women in the CCCEH* study than were quantitatively tested, and the CCCEH study is the only cohort that specifically examined chlorpyrifos.
  - There is *no definitive evidence that chlorpyrifos was applied by C&C in any of the residences of the CCCEH cohort*, and many study subjects changed residences frequently during the study.
  - *C&C exposure represents a small fraction of the total aggregate sources of exposure* that the CCCEH cohort (and the US population) experienced including dietary, water and public health sources, which have been demonstrated to be risk-manageable within the Food Quality Protection Act "risk cup" (i.e., can be managed to present reasonable certainty of no harm), when based on the widely accepted human health standard (PoD) related to cholinesterase inhibition. Thus, *a fundamental deficiency exists, i.e., C&C dose reconstruction should not be used to establish a route-specific PoD, especially*

given the deficiencies associated with the CCCEH cohort data. If anything, the dose reconstruction should be an aggregate metric, estimated across the relevant time domain (duration and frequency), routes and potential pathways/sources (food, water, indoor residential, including C&C and other product uses such as public health vector control, etc.). Further, *the observed effects in the CCCEH study cannot have been primarily due to C&C post-application exposure to chlorpyrifos since there were members of the cohort that received C&C applications without the claimed health effects and the entire cohort could have had exposures through diet and water which would be higher than through the added C&C exposure. Thus, the allegedly observed neurodevelopmental effect cannot be related to chlorpyrifos exposure, as the CCCEH cohort was not exposed to more chlorpyrifos than the general population.*

- EPA has not cited any of the biomonitoring data from the published literature including the CCCEH cohort itself and persons that are known to have been exposed following C&C application of chlorpyrifos in their homes, nor have they compared their estimates to the measurements made in the published data. None of the information from the CCCEH study was obtained under conditions of Good Laboratory Practices (GLP).
  - *The published literature reveals that the CCCEH cohort had chlorpyrifos exposure that was approximately 3-fold less than women in the US population* (NHANES; see Table 1) sampled at approximately the same time, i.e., the aggregate exposure, as measured via urinary biomonitoring, which includes all sources of chlorpyrifos, was less in the CCCEH cohort than in the general population.
- EPA estimated blood levels of chlorpyrifos as a PoD and estimated blood levels for each exposure pathway and scenario. *It is unclear why EPA decided to derive blood levels as the basis for PoD, since the blood levels reported for the CCCEH cohort are not reliable according to the Scientific Advisory Panel (SAP).*
  - The blood levels that EPA derived for just the C&C exposure were more than 3 orders of magnitude larger than the values reported for the CCCEH cohort.
  - *Blood levels are very sensitive to time of sampling relative to time of last exposure, and are not a reliable biomarker for comparison of exposure.*
  - *EPA did not estimate aggregate dosages or aggregate blood levels, even though a single source or pathway of exposure to chlorpyrifos is inconceivable.*
  - Representative *aggregate urine biomonitoring samples of both the CCCEH cohort at various times during pregnancy and the US population during the period of time in question are available for comparison*, but that comparison was not made by EPA.

II. INTRODUCTION

The following comments represent both general and specific issues regarding the U.S. Environmental Protection Agency's (EPA's) most recent Revised Human Health Risk Assessment (RHHRA) for chlorpyrifos dated November 3, 2016. In this assessment, the EPA derived a human blood level that they intend to represent as the 30-day time-weighted average (TWA) blood concentration of chlorpyrifos for women age 13-49 living in residences treated by crack and crevice (C&C) application. As the basis of the blood level estimation methodology, EPA utilized the 2012 Standard Operating Procedures for Residential Exposure (SOPs), and input those values into a Physiologically Based Pharmacokinetic (PBPK) model. The SOP C&C scenario calculations include simplistic (conservative) representations of temporal exposure factors such as dermal contact rate with (and access to) residues on treated surfaces, clothing configuration, exposure duration, etc. The PBPK model was used to provide estimates of daily blood levels, and then the TWA blood concentration over 30 days following C&C application was calculated. This 30-day TWA blood level was then used as the PoD against which all other estimates of exposure (residential, bystander and occupational) were evaluated. The PBPK methodology is commendable, but the utility of the epidemiology data from the CCCEH has not been properly reviewed for purposes of risk assessment, especially when the raw data are unavailable. Thus, many unanswered questions and deficiencies result and pose serious concern. While the use of PBPK modeling is recommended for estimating blood and tissue concentrations, the use of the C&C scenario as the sole exposure source responsible for alleged effects observed in the CCCEH study raises questions regarding the appropriateness, precision, representativeness, and reliability, specifically in the context of deriving a PoD. Most importantly, it is unclear why there is a need to derive an estimate of blood level, as there is no confidence in the levels reported by Rauh et al. (2011), and there are significant concerns and deficiencies associated with the epidemiological data that are being considered as the basis for an effect level.

III. DEFICIENCIES ASSOCIATED WITH EPIDEMIOLOGY STUDIES AS THE BASIS FOR A POINT OF DEPATURE

There are significant scientific merit-based questions as to whether the specific published epidemiological study should be used as the basis for developing a PoD to inform quantitative risk analyses, or any subsequent risk management decision-making. As noted by the EPA's Scientific Advisory Panel (SAP)[1]:

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> "The uncertainty in the timing of the biomarker measurements related to developmental susceptibility (e.g., cord blood measures of chlorpyrifos at the time of birth may be associated with neurodevelopmental health outcomes, but may not be causal). Exposures during other periods of fetal development that might be more causally related to measured health outcomes were not measured, and there is the inability to determine the true magnitude of the exposure. In addition, there is a lack of dose dependence for the adverse biological outcome (IQ, working memory). These are key issues in the fields of toxicology and pharmacology.
>
> There is a lack of biological plausibility or animal evidence for how picomolar (pM) cord blood levels of >6.17 pg/g chlorpyrifos (>17.6 pM based on the CCCEH analytical results) can alter working memory and produce neurodevelopmental impairment. The mechanisms for how such potent effects can be produced at these concentrations in vivo are not known and have not been previously described. By comparison, the most potent selective anti-AChE drugs in current clinical use to treat deficits in working memory are known to directly engage brain AChE with inhibitory constants (IC50's) in the range of 20,000 pM (physostigmine) to 600,000 pM (tacrine). In this regard, CPFO, the active metabolite of chlorpyrifos, has an IC50 towards AChE of ~10,000 pM. One is left to speculate on one or more causative mechanisms having potencies more than 1,000 to 30,000-fold lower than cholinergic drugs known to alter working memory in patients. These estimates are conservative, since they assume chlorpyrifos levels in cord blood will directly reflect CPFO levels in the developing brain, an assumption that is currently unproven given the challenges in directly measuring the active metabolite CPFO in any tissue after exposure."

[1] Transmittal of Meeting Minutes of the April 19-21, 2016 FIFRA SAP Meeting Held to Consider and Review Scientific Issues Associated with "Chlorpyrifos: Analysis of Biomonitoring Data." EPA Memorandum. July 20, 2016.

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"Because many uncertainties cannot be clarified, the majority of the Panel does not have confidence that the Columbia Center for Children's Environmental Health (CCCEH) cord blood data on chlorpyrifos concentrations can accurately be used in quantitative risk assessment to determine a Point of Departure (PoD). A major source of uncertainty for the Panel was the lack of verification and replication of the analytical chemistry results that reported very low levels of chlorpyrifos (pg/g). Imputing quantitative values when the concentration of analyte falls below the level of detection (LOD) was a particular concern, especially given that a large fraction of cord blood samples included in the analyses presented with levels below LOD."

EPA (2016) states that "The epidemiology studies reviewed in the 2012/2014 and 2015 literature reviews represent different investigators, locations, points in time, exposure assessment procedures, and outcome measurements. Despite differences in study design, with the exception of two negative studies in the 2015 literature review (Guodong et al., 2012; Oulhote and Bouchard, 2013) and the results from the more recent Engel et al. (2015) study, all other study authors have identified associations with neurodevelopmental outcomes associated with OP exposure; these conclusions were across four cohorts and twelve study citations." This statement is a misrepresentation of the facts. The Engel et al. (2015) study pooled the data from the four 4 "positive" study cohorts and identified no adverse association. Only one cohort, the CCCEH, specifically studied chlorpyrifos, and although EPA (2016) acknowledges that there are three cohorts that did not demonstrate adverse neurodevelopmental effects, it failed to acknowledge other recent citations from the US (Yolton et al., 2013), and France (Cartier et al., 2016) that do not support adverse neurodevelopmental outcomes associated with OP exposure. Consequently, the epidemiology is not at all persuasive as to association of adverse neurodevelopment due to OPs in general or chlorpyrifos in particular. All of the positive studies rely upon dose quantitation methods that are faulty, i.e., either non-specific and/or unreliable (Krieger et al., 2012) and generally taken only once during gestation or at delivery. As shown in Figure 1 of the Agency RHHRA document (EPA Office of Pesticide Programs, November 3, 2016), timing of blood sampling will be important. Thus, there appears to be no compelling epidemiologic "weight of evidence" to conclude that chlorpyrifos, specifically, or OPs in general are responsible for adverse neurodevelopmental outcomes in humans.

It is also important to recognize that the PoD derived by EPA (2016) [0.004 μg/L or ~4 ng/g] is more than 1000-fold greater than the average maternal blood levels "measured" in the CCCEH study (Rauh et al., 2011; Figure 1A range 0-25 pg/g)[2]. Thus, despite "refining" the estimated PoD,

[2] It should be noted that much of the measurement data from the CCCEH are below quantitation limits reported by the analytical laboratory.

EPA's value is disproportionately high compared to the "measured" values from the CCCEH study. This indicates inconsistency between modeled estimates and measurements, demonstrates deficiencies in the PoD derivation, and emphasizes the importance of the SAP's comments regarding a lack of dose dependence for the adverse biological outcome (IQ, working memory), key toxicological considerations, and the lack of biological plausibility or animal evidence for how observed maternal and cord blood levels can alter working memory and produce neurodevelopmental impairment.

As EPA (2016) noted, the SAP specifically stated that PBPK modelling "is a valuable tool to interpret the biomonitoring data in circumstances where multiple routes of exposure occur and when based on best available information as inputs (RHHRA at 10)." For chlorpyrifos, there have been no valid biomonitoring data cited by EPA for the purpose of comparison with the C&C exposure estimate or the PBPK model results. Rather, EPA (2016) has utilized various models (some validated with biomonitoring, and some not) for dietary, water, drift, and residential exposure to estimate blood levels using PBPK. EPA (2016) has stated that "The CCCEH study primarily tested for the presence of chlorpyrifos in cord blood, and therefore remains the most relevant for the purposes of chlorpyrifos risk assessment." However, the SAP completely discounted those data because of "...the lack of verification and replication of the analytical chemistry results that reported very low levels of chlorpyrifos (pg/g); and the lack of raw data available for independent evaluation" (EPA, 2016).

Additionally, EPA (2016) states "In situations where the agency selects a PoD from a study where a NOAEL has not been identified, the EPA generally will retain the FQPA SF of 10X to account for the uncertainty in using a LOAEL." However, the "average" value in the CCCEH study very conservatively reflects the central point in a distribution (where 3/4ths of the data fall in the range of 0 to 6 pg/g for blood concentration of chlorpyrifos) that spans a range of 0 to 25 pg/g (Rauh et al., 2011; Figure 1A). Because there were no "controls" in this cohort, it is not possible to establish a no effect exposure, although it would seem logical that at a blood level of zero, there should be no effect. At the same time, since the IQ is expressed on a log scale, there is no way to make a linear relationship with dose or to derive an uncertainty factor.

IV. DEFICIENCIES ASSOCIATED WITH TEMPORAL EXPOSURE AND ABSORBED DOSE MODELING

EPA SAP members noted that PBPK modeling is a valuable tool to interpret the biomonitoring data in circumstances where multiple routes of exposure occur and when based on best available information as inputs. However, panel members were not in consensus as to the level of agreement between the Agency's exposure characterization of the CCCEH and the blood measurements from the study. While, overall, the Panel found that the general scenarios provided for PBPK modeling are reasonable (drinking water, food, residential), the Panel found several sources of uncertainty in the estimates of internal blood levels and their relationship to the CCCEH cohort results. Some Panel members thought the quality of the CCCEH data is hard to assess when raw analytical data have not been made available, and the study has not been reproduced.

The methodology EPA employed most recently to evaluate risk of exposure to chlorpyrifos is a radical departure from anything that EPA has utilized in the past. For example, while EPA's methodology for evaluating exposure in the past has systematically tended to be "conservative" and typically overestimated absorbed dosage by several-fold to several orders of magnitude (see Cochran and Ross, 2016 for examples of such bias), the current estimates of crack and crevice (C&C) post-application residential exposure appear to be not only low relative to any past estimates, but also low by any actual measures of chlorpyrifos population-based exposure. For example, it is not coincidental that EPA (2016) estimated post-application residential exposure (approximately 7 μg/kg; see "Dermal Dose" in Table 5.3.2 of EPA 2016) that is orders of magnitude lower than the value they derived in 2000 for adult females. While actual measures of young children's exposure to chlorpyrifos were available in 2000, and there were no federal regulations precluding this use of these human subject data at that time, they were not used in preference to the completely theoretical (and inaccurately high) estimated exposure values EPA put forth at that time. In the current assessment, those "day-following-application" estimated dosages are LOWER than the actual 3,5,6-trichloropyridinol (TCPy) population-based biomonitoring measurements (see Table 1 below). It is noteworthy that the TCPy urinary biomonitoring measurements (which were post-indoor product use cancellation) presented in Whyatt et al. (2009) are LOWER than NHANES measurements for adult females during the time period following cancellation of some or all indoor uses, i.e., using Equation [1] in Appendix A, the 50th percentile for the pre-natal urine collection intervals with values >LOD is 0.547 μg/L TCPy which equates to 0.019 to 0.028 μg/kg-d chlorpyrifos using a correction factor (see Appendix) of 1 (Krieger et al., 2001) or 0.7 (Byrne et al., 1998), respectively. To put these numbers into perspective, the measured chlorpyrifos exposures in the CCCEH cohort (using TCPy based exposure estimates) are approximately 10-fold lower than EPA's dermal dose of 7 μg/kg on the

day of application adjusted for 3% dermal absorption (Nolan et al., 1984) corresponding to an absorbed dose of 0.21 μg/kg.

Table 1: Aggregate, chronic non-occupational estimates of exposure to chlorpyrifos for the general public from biomonitoring data and EPA Standard Operating Procedures.

Population Subgroup	USEPA 2000 (μg/kg-d)	NHANES[b] (μg/kg-d)	DAS (μg/kg-d)	USEPA 2016 (μg/kg-d)
1995 residential uses (broadcast and crack and crevice etc. available)				
		1995 data[d]		
Adult males, (481)	11.4	0.19	-	NA
Adult females, (405)	10.9	0.19	-	0.075 (diet)
Infants, 0-1yr, (39)	32.1	-	0.24±0.21[c]	0.186 (diet)
Children, 1-6 yr, (376)	16.1	-	0.49±0.48[c]	0.242 (diet)
1997 broadcast and total release/aerosol foggers cancelled; crack and crevice still allowed				
		1999 data		
Adult males, (972)		0.096	0.049[e]	
Adult females, (1022)		0.076		
2000 residential uses cancelled (home, lawn, crack and crevice). Stop sale December 2001				
		2002 data		
Adult males, (1416)		0.135		
Adult females, (1596)		0.082		
		2008 data		
Adult males, (1293)		0.086		
Adult females (1295)		0.065		

a USEPA estimate of aggregate exposure using standard defaults and based on passive dosimetry for combined indoor, outdoor, and dietary exposures (USEPA, 2000a,b).

b Center for Disease Control's National Health and Nutrition Examination Survey biological monitoring data (Hill *et al.*, 1995). Average (avg.) value. Number of subjects listed in parentheses.

c Dow AgroSciences biological monitoring survey of children (0–6 years) in North and South Carolina exposed during termiticide treatment of homes (Iachan *et al.*, 1999). Number of subjects listed in parentheses.

d 50th percentile of NHANES data, assuming a body wt of 70 kg.

e Byrne et al., 1998.

No clear explanation was provided as to why EPA (2016) chose to derive a TWA rather than an acute estimate of exposure as the PoD. EPA (2016) noted "Given that the window(s) of susceptibility are currently not known for the observed neurodevelopmental effects, and the deficiencies associated with quantitatively interpreting the CCCEH cord blood data, the SAP recommended that the agency use a time weighted average (TWA) blood concentration of chlorpyrifos for the CCCEH study cohort as the PoD for risk assessment." However, the SAP specifically recommended against using the actual CCCEH blood data for numerous reasons. This, also, is a departure from past actions in that the evaluation of neurotoxicity that utilized cholinesterase inhibition as an endpoint was based on acute, and not chronic exposure. Again, the manifold *theoretical* mechanisms of action possibilities that EPA (2016) has cited result from acute

(peak) blood levels and not chronic TWA levels. Further, per EPA (2016) "...the SAP stated that, given the absence of a key window of exposure for the effects shown in the CCCEH study, the EPA should use estimated peak blood concentrations or TWA blood concentrations within the prenatal period as the PoD...". Note the very different implication of this sentence compared to the one cited at the beginning of this paragraph. Apparently, EPA has chosen to ignore the advice of the SAP to use peak blood concentrations.

Moreover, because dietary exposure occurs daily (and not on a geometrically reduced level each day as assumed by EPA for post-application C&C exposure), it is the estimated dietary exposure that exceeds both measured (multiple C&C biomonitoring studies) and estimated aggregate dosages from the CCCEH cohort. NHANES (Reiss 2013) biomonitoring of the general populace is concordant with EPA's DEEM dietary exposure modeling, and theoretically should be included as the exposure basis for derivation of an internal dose or blood level of chlorpyrifos (CPF). Currently, EPA (2016) is assuming that the primary exposure to the CCCEH cohort was derived from the dermal route as the result of post application exposure to possible C&C applications of chlorpyrifos. However, as discussed below, a true comparison of dose from post-application C&C exposure and dietary exposure reveals that the dietary exposure exceeds the C&C exposure (Hore et al., 2006). To emphasize this point, one only needs to examine the biomonitoring data from NHANES summarized in Table 1. The difference between adult female exposures before all chlorpyrifos use indoors was cancelled and after is 2 to 3-fold. Remembering that prior to cancellation of foggers in 1997, indoor broadcast use was common (both from residential users and professional applicators), and that with the year 1999-2000 that C&C applications could have been made by professional applicators (albeit the CCCEH cohort does not have documented chlorpyrifos-based applications), there is much less than a 2-fold difference between before and after cancellation of the remaining residential uses, meaning that based on measured TCPy in 1999-2000 vs. 2007-2008 the C&C use could have constituted approximately 20% of the dose derived from aggregate dietary and water sources at the time of the CCCEH study. To consider post-application exposure to C&C application of chlorpyrifos in isolation is not consistent with the aggregate exposure to dietary and food sources that are even greater than C&C exposures.

While ignoring other sources of exposure is troubling, EPA's inputs for estimating C&C exposure discussed on page 16 (EPA, 2016) also seem to be arbitrary. The assumption of 10% dissipation of surface residues per day for chlorpyrifos may be exaggerated. There are very few studies that have examined dissipation for more than a few days, and many dissipation curves are biphasic, i.e., very rapid decline in the first 24 hr, with a slower dissipation beyond that time (Whitmyre et al., 2004). One example of this is that a random sample of US houses in 2005-2006 found detectable surface residues in >76% of all homes tested, years after the last indoor use of chlorpyrifos (Stout et al., 2009). Another example is the actual measurements of transferable residue using a CA roller (Figure 1 of Krieger et al., 2001), where the dissipation is clearly biphasic

declining 8.8-fold in the first 4 days, and only 2-fold from day 4 to 9. EPA's assumed dissipation rate also does not account for an effect of multiple applications. Although this effect has not been examined for indoor use, it is well-known that outdoor use produces increased half-lives with sequential applications, and is one reason the EPA guidelines call for DFR studies to be conducted after the maximum number of seasonal applications are made. Because of these factors, coupled with lack of records about whether chlorpyrifos was even used in the CCCEH residences during their occupancy, there are significant deficiencies and resulting weaknesses regarding EPA's derivation of a PoD from C&C use.

Another EPA assumption is that pregnant women spent 2 hr/day every day on hard surfaces involving extensive and intense dermal contact. This also seems unlikely. The justification for this assumption was that the hard surface scenario resulted in the highest estimated exposures (EPA, 2016). For a 2 hr exposure on a hard surface to exceed an 8 hr exposure on carpet, the transferable residue must be more than 4 times greater on hard than soft surfaces. This would be unusual, because a modified CA roller (the recognized standard transferable residue method for regulatory purposes) tends to transfer less from a hard than soft surface. Examination of the source of the hard surface transferability data in the SOPs (Appendix D) reveals that the majority of the transfer data were produced by Camann et al. (1996) and consisted of hand press data. Such data are NOT comparable to roller transferability, which is used with the Transfer Coefficient for estimating whole body exposure to hard or soft surfaces. Further, all women were assumed to take a shower daily immediately following contact with the hard surface over a 30-day interval as postulated by EPA. However, the bathing frequency, timing, and cultural history of the cohort of interest are unknown. EPA's assumptions likely underestimated actual total or aggregate exposures and therefore, resulted in a PoD that is likely unrealistically low.

For the C&C scenario, EPA (2016) only considered inhalation exposure for a 2 hr period and dermal exposures for the remaining 30 days. No other exposures were included, resulting in a gross under-estimate of internal dose. The Agency estimated an external dermal dose of 7.1 μg/kg (shown in Table 5.3.2), and allegedly derived an estimate of absorbed dosage for the C&C scenario by assuming a 50% body surface area was exposed to CPF, exposed women showered 2 hr after dermal contact began on each day, and dose available to be absorbed dropped 10% each day, resulting in the CPF profile in blood as shown in Figure 1 of their document. The internal dose that resulted in the blood data depicted in EPA Figure 1 is 0.012 μg/kg for the first 24 hr. Total absorption over the 30 days of exposure is 0.087 μg/kg, or an average of 0.0027 μg/kg/day.[3] As noted previously, this is several orders of magnitude lower than the estimated multi-route exposures in EPA (2000), and others, see Table 1.

[3] The Agency did not report the absorbed dose; thus, the .m script was used to re-create Figure 1 and the absorbed dose that it represents.

It is noteworthy that there are multiple studies conducted using biomonitoring following crack and crevice application including Byrne et al. (1998), Krieger et al. (2001), and Hore et al. (2006) (see Appendix A), and estimated mean absorbed chlorpyrifos dose based on metabolite (TCPy) levels in the urine (Table 2). The estimated total internal doses pre-exposure were 0.408 μg/kg/day in adults or 0.3 μg/kg/day in the female populations in Byrne et al. (1998) and Krieger et al., (2001), respectively. Post application, increases were greater in the study of Krieger et al. (2001) than Byrne et al. (1998). Both studies monitored TCPy in urine for 10-11 days post exposure. Over that period, Byrne et al. (1998) reported C&C internal dose of 0.002-0.09 μg/kg/day, which indicates the EPA assumptions of just this dose route are consistent with biomonitoring data. However, when Byrne et al. report these values, they must subtract them from pre-exposure biomonitoring values. The total daily exposure in these same volunteers is 0.46 ± 0.30 μg/kg/day (range 0.2-0.88 μg/kg/day), and is approximately 100-fold (0.46/0.006) greater than our estimate of the Agency-generated dose for C&C exposure alone (i.e., 0.006 μg/kg/day). Similarly, Hore et al. (2006) reported TCPy averages in urine of 6.8 μg/L in a post-application exposure study. Using a simple molecular weight conversion, this equates to an average of ~12 μg/L CPF, and using eq. 1 in the Appendix, results in an estimated internal dose of 0.32 μg/kg/day. As pointed out in Hore et al. (2006), the TCPy measured in urine is likely resulting primarily from exposures from food, which shows the Agency body burden estimates are only considering a minor fraction of exposure. The Agency has previously (in 2000) estimated total exposures in adult females of 10.9 μg/kg/day (See Table 1), > 3000x higher than the absorbed dermal dose in their C&C exposure scenario. The fundamental issue remains, that dose reconstruction should not be used to establish a route-specific PoD, especially given the deficiencies associated with the CCCEH cohort data. If anything, the dose reconstruction should be an aggregate across all routes and potential pathways/sources (food, water, indoor residential, including C&C and other product uses including public health vector control, etc.).

Table 2. Comparison of C&C Dose Estimates.

Study	Pre-C&C Treatment (µg/kg/day)	C&C Treatment Only (µg/kg/day)	Aggregate (µg/kg/day)	Notes
Agency Estimate: EPA, 2016	NA	0.006[a]	Unknown	75 kg women
Byrne et al., 1998[b]	0.11-0.87	0.002-0.09	0.46 ± 0.30; (0.2-0.88)[c]	household
Hore et al., 2006 [b]	NA	NA	0.32	children
Hore et al., 2006[d]	0.04-1.6	<0.0-0.92	0.17-1.4	children
Krieger et al., 2001[b]	0.3-2.1	NA	0.8-5.3	household

[a]This is an estimate using the Agency scenario and PBPK model for 10 days to be consistent with Bryne et al. and Hore et al., who monitored TCPy in urine for 10-11 days post C&C. The value reported in the text, 0.0027 µg/kg/day is over the entire 30-day exposure.
[b] These values are based on urinary elimination of TCPy.
[c] Mean +/- standard deviation; range.
[d] Averages for Days 1-5. Note on average over the first 5 days, peak aggregate is lower than pre-treatment maximum.
NA- not available

We appreciate EPA (2016) candor and interest that a "combination of inputs used to estimate exposures is expected to reasonably approximate exposures to these women resulting in reasonable risk assessment PODs"; however, it is difficult to conclude that the values estimated in the 2016 assessment are any more likely to be correct than they were in the year 2000, although for different reasons. Part of the problem is that EPA has used a number of models, and provided limited dose route/pathway comparison, i.e., there is a general lack of transparency. For example, if one assumes a 10% decline in dermal exposure per day as EPA did, and calculates the average absorbed dose over a 30-day interval from post-application exposure to C&C application, the EPA estimated total absorption[4] is 0.087 µg/kg, and the 30 day TWA is 0.0027 µg/kg/day, which is less than the 21 day dietary exposure average estimated by EPA (2016). This reveals the innate inaccuracy of utilizing the C&C dose as the basis for derivation of a POD. ***Simply put, the entire premise that C&C exposure alone can be associated with an effect is false as there are contributions from other, larger sources of exposure.*** From an aggregate exposure perspective, the women in the CCCEH study were not exposed to chlorpyrifos at a dose any different from the general population. In fact urinary biomonitoring revealed that the CCCEH cohort had on average 3-fold less exposure than the general female population in the US. ***Thus, the allegedly observed neurodevelopmental effect cannot be related to chlorpyrifos exposure, as the CCCEH cohort was not exposed to more***

[4] The Agency did not report the absorbed dose; EPA's .m script was used to re-create Figure 1 and the absorbed dose that it represents.

chlorpyrifos than the general population. The calculated day of application dermal absorbed dose is less than the steady state food-only exposure (0.075 μg/kg) shown in Table 6.2 (EPA, 2016). Further, the cohorts that have a positive association with adverse neurodevelopmental outcomes that EPA (2016) have cited as corroborating evidence have also been tested for other chemically-related exposure associations, and there are much greater odds ratios for association of adverse neurodevelopmental effects with exposure to DDT (Gaspar et al., 2015) or flame retardants (Eskenazi et al., 2013) than with chlorpyrifos, specifically, or OPs in general raising the question of the validity of attributing effects to one specific chemical or class of chemicals.

Moreover, some of EPA (2016) assumptions and justifications are not well-explained. For example, it is unclear why 21 days (Table 5.3.3.2) was used as the averaging time for PBPK for all routes, pathways and types of exposure, but the "normalizing" exposure (post-application exposure to crack and crevice use) was calculated as a 30-day average. EPA (2016) also did not justify why they assumed "All residential exposures were set to be continuous for 21 days." For example, exposure from drift following agriculture or public health use on a single day would be improbable, but exposure to drift every day for 21 days is impossible. The same can be said for every non-dietary residential exposure scenario. While EPA (2016) tried to make occupational exposure more consistent with reality, it too is a gross overestimate. EPA states "This worker is exposed to chlorpyrifos either via inhalation or skin for 8 hours/day, 5 days/week, for a total of 21 days." Whether a pesticide handler or reentry worker, an individual is highly unlikely to be exposed to upper bound levels of chlorpyrifos for 3 consecutive work weeks due to competing pesticide use, rate of decay on foliage (for reentry workers), and a host of other mitigating factors (Cochran and Ross, 2016).

The nuances of the methods to estimate doses that EPA (2016) used are evidenced in the huge differences in PoD for various routes and rates of exposure. If it is true that the dermal dose results in a much smaller PoD, chlorpyrifos oxon is apparently considered inactive since the dermal route bypasses first pass bioactivation; this is at odds with any known mechanism of action for chlorpyrifos. However, as noted previously, it is entirely unclear why there is a need to derive an estimate of blood level, as there is no confidence in the levels reported by Rauh et al. (2011), and a comparison of dosages would be much more transparent, easier to understand, and consistent with EPA's past regulatory action on not only chlorpyrifos, but also virtually every other pesticide they have regulated. Again, we applaud the use of the PBPK model to extrapolate to lower doses than can be observed in laboratory settings, but it is important to recognize sources of inaccuracy (e.g., changes in kinetics, sinks, metabolic routes that were not recognized at higher dosages), particularly in the context of establishing a PoD. Moreover, there is no tangible benefit to deriving blood levels as PoD once it becomes apparent that the best estimates of blood level derived from a validated PBPK model are more than 3 orders of magnitude greater than the "measured" values described by Rauh et al. (2011). Additionally, blood levels of chlorpyrifos are not routinely

measured in humans, i.e., they are not diagnostic. Blood levels are also more sensitive to time of last exposure than either urinary metabolites or cholinesterase levels. Further, blood levels of chlorpyrifos cannot be related to comparable measures with other OPs, and finally, blood levels cannot be used as the basis for cumulative exposure to OPs.

V. CONCLUSIONS

In summary, major conclusions are as follows:

1) Epidemiologic association of exposure to chlorpyrifos and/or OPs in general is not consistent and should not be used as the basis for estimating a Point of Departure, because the proposed PoD is biologically (toxicologically) implausible. Further, EPA's estimates of blood levels from C&C post-application exposure alone are more than 1000-fold greater than those "measured" in the CCCEH study. This indicates inconsistency between modeled estimates and measurements, demonstrates deficiencies in the PoD derivation, and emphasizes the importance of the SAP's comments regarding a lack of dose dependence for the adverse biological outcome (IQ, working memory), key toxicological considerations, and the lack of biological plausibility or animal evidence for how observed maternal and cord blood levels can alter working memory and produce neurodevelopmental impairment.
2) The observed effects in the CCCEH study cannot have been primarily due to C&C post-application exposure to chlorpyrifos since there were members of the cohort that received C&C applications without the claimed health effects and the entire cohort could have had exposures through dietary and water which would be higher than through any potential C&C exposure. Further, the urinary biomonitoring conducted specifically with the CCCEH cohort at multiple times during pregnancy reveals less exposure than in adult women across the US. Thus, the allegedly observed neurodevelopmental effects cannot be related to chlorpyrifos exposure, as the CCCEH cohort was not exposed to more chlorpyrifos than the general population, particularly since there were members of the cohort that apparently received C&C applications.

These conclusions create significant deficiencies regarding the proposed PoD and indicate further revisions and quantitative analyses are necessary by EPA and stakeholders, and additional external peer review is highly recommended.

VI. REFERENCES

Byrne SL, Shurdut BA, Saunders DG. (1998). Potential Chlorpyrifos Exposure to Residents Following Standard Crack-and-Crevice Treatment. Environmental Health Perspectives 106:725–731.

Cartier C, Warembourg C, Le Maner-Idrissi G, Lacroix A, Rouget F, Monfort C, Limon G, Durand G, Saint-Amour D, Cordier S, Chevrier C. (2016). Organophosphate Insecticide Metabolites in Prenatal and Childhood Urine Samples and Intelligence Scores at 6 Years of Age: Results from the Mother-Child PELAGIE Cohort (France). Environ Health Perspect. 124:674-680. doi: 10.1289/ehp.1409472.

Camann, D.; Harding, H.; Geno, P.; and Agrawl S. (1996). Comparison of Methods to Determine Dislodgeable Residue Transfer from Floors (EPA/600/R96/089). United States Environmental Protection Agency, Research Triangle Park, NC.

Cochran, R.C. and Ross, J.H. (2016). A Method for Quantitative Risk Appraisal for Pesticide Risk Assessments. J. Toxicol. Environ. Health A. DOI: 10.1080/15287394.2016.1224747.

EPA (U.S. Environmental Protection Agency). (2000). Human Health Risk Assessment: Chlorpyrifos. Smegal. D.C. June 8, 2000. Office of Pesticide Programs, Health Effects Division. Washington D.C.

EPA (U.S. Environmental Protection Agency). (2016). Revised Human Health Risk Assessment for Registration Review. (EPA's Office of Pesticide Programs, November 3, 2016; DP Barcode: D436317).

Eskenazi B, Chevrier J, Rauch SA, Kogut K, Harley KG, Johnson C, Trujillo C, Sjödin A, Bradman A. (2013). In utero and childhood polybrominated diphenyl ether (PBDE) exposures and neurodevelopment in the CHAMACOS study. Environ Health Perspect. 121:257-262.

Gaspar FW, Harley KG, Kogut K, Chevrier J, Mora AM, Sjödin A, Eskenazi B. (2015). Prenatal DDT and DDE exposure and child IQ in the CHAMACOS cohort. Environ Int. 85:206-212.

Hore P, Zartarian V, Xue J, Ozkaynak H, Wang SW, Yang YC, Chu PL, Sheldon L, Robson M, Needham L, Barr D, Freeman N, Georgopoulos P, Lioy PJ. (2006). Children's residential exposure to chlorpyrifos: application of CPPAES field measurements of chlorpyrifos and TCPy within MENTOR/SHEDS-Pesticides model. Sci Total Environ. 366:525-537.

Iachan, R., Nishioka, M. and Van Dyck, K. et al. (1999). TCP Biomonitoring Study: Lab Project Number: GH-C 4946. Unpublished study prepared by Battelle Centers for Public Health Research and Evaluation. 138 p. MRID # 44889501.

Krieger, R.I., Bernard, C.E., Dinoff, T.M., Ross, J.H. and Williams, R.L. (2001). Biomonitoring of persons exposed to insecticides used in residences. Ann. Occup. Hygiene, 45 (Suppl 1): 143-153.

Krieger, R.I., Chen, L., Ginevan, M., Watkins, D., Cochran, R.C., Driver, J.H., and Ross, J.H. (2012). Implications of estimates of residential organophosphate exposure from dialkylphosphates (DAPs) and their relevance to risk. Regul. Toxicol. Pharmacol. 64:263–266.

Rauh V, Arunajadai S, Horton M, Perera F, Hoepner L, Barr DB, Whyatt R, (2011). Seven-year neurodevelopmental scores and prenatal exposure to chlorpyrifos, a common agricultural pesticide. Environ Health Perspect. 119:1196–1201.

Reiss, R. (2013). Estimation of Chlorpyrifos Population Exposure from NHANES Biomonitoring Data. PROJECT I.D.: 1303719.000 3757. REPORT DATE: October 17, 2013. SPONSOR: Dow AgroSciences, 9330 Zionsville Rd., Indianapolis, IN 4626.

Stout, D.M. and M.A. Mason. (2003). The distribution of chlorpyrifos following a crack and crevice type application in the US EPA Indoor Air Quality Research House. Atmos. Environ. 37: 5539-5549.

Stout, D.M. and K.D. Bradham, P.P. Egeghy, P.A. Jones, C.W. Croghan, P.A. Ashley, E. Pinzer, W. Friedman, M.C. Brinkman, M.G. Nishioka and D.C. Cox. (2009). American healthy homes survey: a national study of residential pesticides measured from floor wipes. Environ Sci. Technol 43: 4294-4300.

Whitmyre, G.K., J.H. Ross, C. Lunchick, B. Volger, and S. Singer (2004). Biphasic dissipation kinetics for dislodgeable foliar residues in estimating postapplication occupational exposures to endosulfan. Arch. Environ. Contam. Toxicol. 46:17-23.

Whyatt, R.M., R. Garfinkel, L.A. Hoepner, H. Andrews, D. Holmes, M.K. Williams, A. Reyes, D. Diaz, F.P. Perera, D.E. Camann and D.B. Barr. (2009). A Biomarker Validation Study of Prenatal Chlorpyrifos Exposure within an Inner-City Cohort during Pregnancy. Environmental Health Perspectives. 117:559-567.

Wilson, N. K., Chuang, J. C., Lyu, C., Menton, R., and Morgan, M. K. (2003). Aggregate exposures of nine preschool children to persistent organic pollutants at day care and at home. J. Expos. Anal. Environ. Epidemiol. 13:187–202

Yolton K, Xu Y, Sucharew H, Succop P, Altaye M, Popelar A, Montesano MA, Calafat AM, Khoury JC. (2013). Impact of low-level gestational exposure to organophosphate pesticides on neurobehavior in early infancy: a prospective study. Environ Health. 12(1):79. doi: 10.1186/1476-069X-12-79.

VI. APPENDIX A: CHLORPYRIFOS BIOMONITORING AS A VALIDATION OF EXPOSURE ESTIMATES

Residential (Scenario-Specific) Data

Three key studies are summarized below. The first was a doctoral dissertation research project by Dr. Paromita Hore, i.e., Hore (2003) and Hore et al. (2006). As part of this research program, environmental and biological measurements of chlorpyrifos were made in ten residential homes involving 2 to 5 year-old children. Measurements included indoor air, indoor surfaces, gauze pads, plush toys, hand rinse/wipes, and urine samples. This research demonstrated the very low potential for measurable absorbed doses associated with reentry exposures following a crack and crevice treatment, and the corresponding low residential media (air, surfaces) levels.

In the second study, Byrne et al. (1998) had a professional applicator treat three homes via crack and crevice and spot spray with Dursban Pro diluted to 0.5%. Doors and windows remained closed most of the time, and air handling was turned off except during the night in one house. Two adults in each house collected their urine specimens 24 hours before and for 11 days after treatment. Additionally, room air was sampled at two heights and surface residues remote from the application site were measured using a drag sled to determine dislodgeable residues. Also, deposition pads were placed in rooms away from application sites to determine the amount of chlorpyrifos that redistributed to the interior of the rooms.

In the third study, Krieger et al. (2001) describe a home treated with Dursban Pro at 0.25% by crack and crevice application in which a family of five individuals (one adult, three teenage children, and a toddler) were biomonitored. Urine specimens were collected prior to application and daily for five days post application and at irregular intervals thereafter. No environmental monitoring (air/surface) samples were collected in the residence. Daily dosage was estimated and normalized to creatinine excretion.

The results of these three studies are summarized in Table A1 below. The total daily absorbed dose levels across these three studies ranged from 0.0 to 4.8 μg/kg/day. This level of exposure (or internal dose) is also consistent with studies conducted by EPA's Office of Research and Development (ORD). In one of these studies, EPA's ORD reconstructed dose estimates for a cohort of children which they believed to be highly exposed relative to the general population (Rigas et al., 2001). In this study, biomonitoring of 15 children (ages 3 to 12) that commenced 1-3 days following a non-broadcast (crack and crevice) treatment showed chlorpyrifos dose (internal, absorbed) levels in the range of 0.36 to 4.01 μg/kg/day (Rigas et al., 2001). In another EPA ORD study involving environmental measurements in a research house following a crack and crevice application (Stout and Mason, 2003), the average (mean) chlorpyrifos dose estimate for children (ages 3 and 6 yrs) on the day of application was 3.3 μg/kg/day; the median post-application dose estimate was 2.1 μg/kg/day. Adult dose levels (normalized to body weight) are consistently significantly lower than those for children.

Table A1: Summary of Chlorpyrifos Post-Application Human Exposure Monitoring Studies Following Indoor Residential Crack & Crevice Treatments.

Study[a]	Number of Replicates	Chlorpyrifos Applied (g/m^2)[b]	Air Conc. ($\mu g/m^3$)[c]	Surface Conc.[d] (ng/cm^2)	Time in House (hr/d)	Internal Dosage ($\mu g/kg/day$)[e]
Byrne, 1998	6[f]	0.026-0.037	0.76-2.3	3.2-8.7	12+	0.049±0.042 (0.009-0.09)[j]
Krieger, 2001	5[g]	0.042	NA[i]	NA	14-24	1.3±1.1 (0.4-3.2)[k]
Hore, 2003; Hore, 2006	7[h]	0.002-0.022	0.032-0.82	8.5-10	21±2	0.002±0.50 (0-0.92)[l]
Summary[m]	18	0.002-0.042	0.032-2.3	3.2-10	>16	0.002-3.2

[a] First author, year of published results.
[b] Grams of chlorpyrifos applied divided by the surface area of the house.
[c] Peak air concentration reported.
[d] Peak surface concentration reported (re-deposited based on denim deposition samplers or isopropanol wipes; dislodgeable residues were <0.2 ng/cm^2 in Byrne, and 0.1-25 ng/cm^2 in Hore).
[e] Mean ± Standard Deviation (Range of values); after subtracting pre-exposure values.
[f] No children (all adults).
[g] Four children, one adult.
[h] All replicates were children age 2-4 yrs. Only seven replicates from houses with verified treatment levels were included.
[i] NA = not measured or not available.
[j] Pre-treatment exposure = 0.11-0.87 µg/kg; dose estimates for children ranged from 0.26 and 2.10 µg/kg.
[k] Pre-treatment exposure = 0.3-2.1 µg/kg.
[l] Pre-treatment exposure = 0.04-1.6 µg/kg (see Table 6, Hore 2006); creatinine-adjusted dose range was 0.04 – 4.8 µg/kg. Days 1-5 post exposure was assessed, by day 5, the average increase in apparent CPF body burden following exposure was -0.32 ± 0.18 µg/kg/day. Samples deemed too dilute by the researchers were not included.
[m] Three replicates from Hore (2003) were excluded because application rates were below normal.

Population Based Data

Chlorpyrifos (CPF) is metabolized in the body to 3,5,6-trichloropyridinol (TCPy) and 3 dialkylphosphate metabolites. TCPy has been monitored in a number of human populations over the past 30 years, and the rate and route of excretion are well known (Nolan et al., 1984; Timchalk et al., 2007). In addition to periodic biomonitoring conducted by the Centers for Disease Control and Prevention (CDC) for ages 6 to >60 years, there are a number of other studies conducted with young children (see Table A2). Although biomonitoring with TCPy tends to overestimate absorbed dosage because it is a metabolite of other molecules, TCPy forms spontaneously in and on food, water, surfaces a person might contact, and has appreciable volatility so it can be inhaled (Morgan et al., 2005; Wilson et al., 2003), it nevertheless provides an upper bound estimate for exposure to CPF. As an alternative measure of estimating absorbed dose, TCPy biomonitoring allows comparison of aggregate absorbed dose estimates from models such as those used by EPA (2012). Summarized in Table A2 are *some* of the biomonitoring studies conducted with groups of >10 individuals. Equation [1] presents the method of estimating CPF dosage from urinary biomonitoring of TCPy:

$$\textit{Dosage } (\mu g/kg) = (\textit{TCPy } \mu g/L \times \textit{L urine/day}) \times (\textit{MW CPF/MW TCPy})/(0.7 \times kg) \qquad [1]$$

Where:
Dosage = the absorbed dosage of CPF;
TCPy μg/L = micrograms of the chlorpyrifos metabolite 3,5,6-trichloropyridinol (TCPy) per liter of urine;
L urine/day = 1.4 for adults; 0.8 for age 6-11;
MW CP/MW TCPy = molecular weight of chlorpyrifos (350.6)/molecular weight of TCPy (198);
0.7 = molar fraction of an absorbed dose of chlorpyrifos excreted as TCPy in urine (note: Krieger et al., 2001 use an alternative value of 1); and
kg = body weight in kilograms.

Table A2: Summary of Biomonitoring for Chlorpyrifos Based on Urinary TCPy Using Equation [1]. (not adjusted for directly ingested TCP).

Citation	Age	Number	Type of Application	Mean (µg/kg)
Iachan et al., 1999	0-1	39	termiticide	0.24±0.21
Iachan et al., 1999`	1-6	376	termiticide	0.49±0.48
Morgan et al., 2005	1.7-5.5	128	unknown	0.43[a]
Alexander et al., 2006	4-11	23	farm	1.2
Hore et al., 2006	children	7	crack & crevice	0.62
Rigas et al., 2001	children	15	residential	1.6
CDC 1999-2000[b]	6-11	481	unknown	0.182
CDC 2001-2002	6-11	573	unknown	0.169
CDC 2007-2008	6-11	385	unknown	0.109
CDC 1999-2000	12-59	1513	unknown	0.103
CDC 2001-2002	12-59	1936	unknown	0.112
CDC 2007-2008	12-59	1570	unknown	0.072

[a] Assumed that the arithmetic mean excretion of TCPy (167.7 ng/kg/d) was solely attributable to CPF. Morgan et al. (2005) estimated the actual CPF exposure from food, surfaces and air as 0.008 µg/kg/d.

[b] Geometric mean for all CDC data.

Note that with the CDC data, there is a noticeable drop from the years 1999-2000 (when CPF was last sold for residential use), and subsequent years. This differential is likely attributable to the reduction and subsequent elimination of residential use, although the less than 2-fold reduction does not comport with the un-validated modeling estimates that attributed much larger dosages to residential use.

Data from Table A2 shows that for the age group of 1-6 (summarizing results from over 500 individuals), the dosage from biomonitoring is an average of 0.49 and 0.43 = 0.46 µg/kg/d. The average dosage from 5,019 persons is 0.096 µg/kg/d. In summary, biomonitoring data are the most appropriate values for comparison modeled (estimated) aggregate absorbed dosage (sum of all routes and pathways).

REFERENCES

Alexander, B.H., C.J. Burns, M.J. Bartels, J.F. Acquavella, J.S. Mandel, C. Gustin and B.A. Baker. (2006). Chlorpyrifos exposure in farm families: Results from the farm family exposure study. Journal of Exposure Science and Environmental Epidemiology (2006) 16, 447–456. doi:10.1038/sj.jes.7500475.

Byrne, S.L., Shurdut, B.A., and Saunders, D.G. (1998). Potential chlorpyrifos exposure to residents following standard and C&C treatment. Environ. Health Persp. 106:725-731.

Hore, P. (2003). Pesticide accumulation patterns for child accessible surfaces and objects and urinary metabolite excretion by children for two-weeks after a professional crack-and-crevice application. Dissertation for Doctor of Philosophy, Rutgers State University, New Jersey.

Hore P, Zartarian V, Xue J, Ozkaynak H, Wang SW, Yang YC, Chu PL, Sheldon L, Robson M, Needham L, Barr D, Freeman N, Georgopoulos P, Lioy PJ. (2006). Children's residential exposure to chlorpyrifos: application of CPPAES field measurements of chlorpyrifos and TCPy within MENTOR/SHEDS-Pesticides model. Sci Total Environ. 366(2-3):525-37.

Iachan, R., Nishioka, M. and Van Dyck, K. et al. (1999). TCP Biomonitoring Study: Lab Project Number: GH-C 4946. Unpublished study prepared by Battelle Centers for Public Health Research and Evaluation. 138 p. MRID # 44889501.

Krieger, R.I., Bernard, C.E., Dinoff, T.M., Ross, J.H. and Williams, R.L. (2001). Biomonitoring of persons exposed to insecticides used in residences. Ann. Occup. Hygiene, 45 (Suppl 1):143-153.

Krieger RI, Bernard CE, Dinoff TM, Fell L, Osimitz TG, Ross JH, Ongsinthusak T. (2000). Biomonitoring and whole body cotton dosimetry to estimate potential human dermal exposure to semivolatile chemicals. J Expo Anal Environ Epidemiol. 10(1):50-57.

Morgan MK, Sheldon LS, Croghan CW, Jones PA, Robertson GL, Chuang JC, Wilson NK, Lyu CW. (2005). Exposures of preschool children to chlorpyrifos and its degradation product 3,5,6-trichloro-2-pyridinol in their everyday environments. J Expo Anal Environ Epidemiol. 15(4):297-309.

Scher DP, Alexander BH, Adgate JL, Eberly LE, Mandel JS, Acquavella JF, Bartels MJ, Brzak KA. (2007). Agreement of pesticide biomarkers between morning void and 24-h urine samples from farmers and their children. J Expo Sci Environ Epidemiol. 17(4):350-357.

Freeman NC, Hore P, Black K, Jimenez M, Sheldon L, Tulve N, Lioy PJ. (2005). Contributions of children's activities to pesticide hand loadings following residential pesticide application. J Expo Anal Environ Epidemiol. 15(1):81-88.

Appendix III

Dow AgroSciences LLC's Response to Objections to EPA's Denial of Petition to Revoke All Tolerances and Cancel All Registrations for Chlorpyrifos

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TABLE OF CONTENTS

I. INTRODUCTION

On March 29, 2017, the U.S. Environmental Protection Agency ("EPA" or the "Agency") issued an order denying an administrative petition (the "Petition") to revoke all tolerances and cancel all registrations for chlorpyrifos. EPA denied the Petition on the grounds that the scientific evidence was not sufficient to support the relief requested and required further study.

On June 5, 2017, Pesticide Action Network ("PAN")/Natural Resources Defense Council ("NRDC") *et al.* and the Attorneys General of the States of New York, Washington, California, Massachusetts, Maine, Maryland, and Vermont (individually "Petitioners" and collectively the "States"), and others, submitted objections to EPA's order denying the Petition (collectively the "Objections").[1] Dow AgroSciences LLC ("DAS") submits this Response to Objections in support of EPA's denial of the Petition and to clarify the scientific and factual record.

As set forth herein, EPA's Order correctly denied the Petition because there is an extensive and complete set of animal toxicology data that supports the current regulatory standard for chlorpyrifos. EPA's Order correctly recognized that its recent assessments and proposals with respect to chlorpyrifos were part of its non-binding agency deliberations and were based on inconclusive science that is not sufficient to support a change in the current regulatory standard for chlorpyrifos. The epidemiology and other studies advocated by the Petitioners are not reliable, consistent in their findings, nor valid for purposes of regulatory decision-making, and the Objections to the Order are otherwise meritless.

II. EXECUTIVE SUMMARY

For nearly fifty years, EPA has set a Point of Departure ("PoD") for chlorpyrifos based on cholinesterase inhibition.[2] This conservative and health-protective endpoint remains the gold standard used by regulatory bodies around the world, including the European Food Safety Authority ("EFSA") and the World Health Organization ("WHO"). Indeed, just over a year ago,

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[1] The District of Columbia joined in the States' objections on August 17, 2017.

[2] For chlorpyrifos, acetylcholinesterase ("AChE") inhibition ("ChEI") is the mode/mechanism of action for effects to the mammalian system. EPA regulates on a particular type of AChE which is Red Blood Cell Acetylcholinesterase ("RBC AChE") inhibition, or simply Red Blood Cell cholinesterase inhibition ("RBC ChEI"). RBC ChEI is not an adverse effect in itself, but a marker of exposure and a conservative and protective endpoint that occurs well below levels required to inhibit other types of AChE that could be considered an adverse health effect.

Australia concluded that "cholinesterase inhibition remains the most sensitive and relevant adverse effect caused by chlorpyrifos and is therefore the most appropriate endpoint for the establishment of health based guidance values used to protect the entire population including pregnant women, infants and children." Australian Pesticides and Veterinary Medicines Authority ("APVMA"), Reconsideration of Chlorpyrifos: Supplementary Toxicology Assessment Report at 1 (Apr. 2017) ("APVMA, Reconsideration of Chlorpyrifos"). Moreover, several Federal Insecticide, Fungicide, and Rodenticide Act ("FIFRA") Scientific Advisory Panels ("SAPs") convened by EPA over the past eight years have expressed confidence in RBC ChEI as the appropriate regulatory standard.

In 2006, EPA completed reregistration of chlorpyrifos under FIFRA and the Federal Food, Drug, and Cosmetic Act ("FFDCA") and reauthorized all existing agricultural uses for chlorpyrifos, relying on cholinesterase inhibition for the regulatory standard. This final decision and regulatory standard has been in effect ever since.

The current regulatory standard is supported by over fifty years of robust animal toxicological data generated during the statutorily mandated registration and reregistration review processes for chlorpyrifos. As discussed *infra,* Section V.A, EPA's 2011 Preliminary Human Health Risk Assessment ("PHHRA") stated that "[t]he toxicological database for chlorpyrifos is extensive and is adequate to support the registration review." EPA, Chlorpyrifos Preliminary Human Health Risk Assessment for Registration Review at 22 (June 30, 2011). EPA addressed the Food Quality Protection Act's ("FQPA") safety factor provision by relying on a robust set of animal toxicological data that accounted for children's susceptibility to set a safety factor of 1X in the Agency's 2006 cumulative risk assessment ("CRA") for organophosphate pesticides. *See* July 16, 2012 Letter from Steve Bradbury to PAN/NRDC ("2012 Bradbury Letter") at 20 ("Therefore, the Agency remains confident in the FQPA safety factor of 1X used in the cumulative risk assessment for chlorpyrifos.").

Contrary to Petitioners' claim, there is no credible, growing body of animal toxicology evidence corroborating the epidemiology studies claiming neurodevelopmental effects at exposure levels below the current regulatory standard. As detailed in DAS's prior comments and the attached Appendix A, animal toxicology studies examined by EPA and the California Department of Pesticide Regulation ("DPR") in their recent literature reviews and advanced by Petitioners and others as showing adverse neurodevelopmental outcomes suffer from significant

limitations, undermining the validity of their findings. For example, these studies employed doses at or above those known to result in 10% RBC ChEI or failed to measure cholinesterase inhibition at all, reported inconsistent findings, and/or had significant design flaws.

In addition, neither *in vitro* studies (*i.e.*, those studies conducted outside a living organism such as in a test tube or cell culture dish) nor epidemiology studies cited in the Petitioners' Objections create uncertainty with respect to the regulatory standard, nor are they reliable enough to undermine the robust animal toxicological data. *See* Sections V.A, V.B, *infra.* While EPA has considered certain *in vitro* studies in the past regarding purported neurodevelopmental effects below the current regulatory standard, these *in vitro* studies have not been validated in *in vivo* studies (*i.e.*, studies conducted in a living organism such as a laboratory animal) and are not based on conditions of real-world human exposure, and thus lack meaningful relevance to human risk assessment. EPA itself has recognized that *in vitro* studies must be considered with great caution, and in the absence of appropriate validation that *in vitro* methodologies and/or findings are relevant to *in vivo* outcomes, *in vitro* findings alone are not sufficient to infer potential human health risks.

As discussed in Section VI, *infra,* the Columbia, CHAMACOS, and Mt. Sinai epidemiology studies that have been cited as showing a link between chlorpyrifos exposure and neurodevelopmental effects have shown only questionable and inconsistent statistical associations, not causation. The Columbia study, in particular, has served as the centerpiece of Petitioners' claim that neurodevelopmental effects are associated with exposures below the current regulatory standard. But EPA's own SAP has cited weaknesses in the Columbia and other epidemiology studies, questioned their scientific validity and reliability on several occasions, and—as recently as 2016—rejected the use of these studies to support a proposed new regulatory endpoint. Numerous commenters, including the U.S. Department of Agriculture, have consistently criticized the reliability of the Columbia study for use in regulatory decision-making. *In addition, a very recent analysis of Columbia study data by Toxicology Excellence for Risk Assessment ("TERA") raised a number of additional, significant concerns about the reliability of the Columbia study's conclusions. See* Appendix B. The bottom line, as discussed herein, is that the Columbia study relies on spot samples of questionable analytic merit, and has served as the very weak underpinning for every related publication that has followed.

Moreover, the neurodevelopmental outcomes in the epidemiology studies advanced by Petitioners have been over-generalized across studies. The specific results are not replicated in other studies, undermining the claim of a link between neurodevelopment effects and chlorpyrifos exposures. In fact, consideration of the findings *in total across* these studies, does not support and even counters such a claim. Indeed, as time has passed, more epidemiology studies have been conducted studying chlorpyrifos. The results of these studies show no consistent, clear evidence of any associations between prenatal or childhood exposure to chlorpyrifos at levels below the current regulatory standard and adverse neurodevelopmental effects, further undermining the reliability of the Columbia, CHAMACOS, and Mt. Sinai studies.

Also, many factors can influence childhood development—both for better or worse—and could also be correlated with the effects reported. Most of these factors were unmeasured in the epidemiology studies, but are important in understanding the underlying factors of childhood development. These alternate explanations need to be fully considered and accounted for when attempting to establish any causation.

Moreover, as discussed *infra* in Section V.C, no reliable, science-based alternative mode of action associated with putative neurodevelopmental/behavioral effects has been identified at exposure levels below those that would trigger cholinesterase inhibition. And, as EPA's SAP stated in 2016, "there does not appear to be biological plausibility" for effects from chlorpyrifos exposures that are below the level that would trigger cholinesterase inhibition. EPA, Transmittal of Meeting Minutes of the April 19–21, 2016 FIFRA SAP Meeting Held to Consider and Review Scientific Issues Associated with "Chlorpyrifos: Analysis of Biomonitoring Data" ("2016 SAP Minutes") at 41 (July 20, 2016).

As further discussed *infra*, Section VII.A, the FQPA and the FFDCA are guided by two fundamental threshold principles: first, they are not statutes based on the precautionary principle, under which all doubt must be exhausted before a crop protection product may be registered. Rather, the food safety standard under the FFDCA and the FQPA is based on reasonable certainty of no harm. Second, the Agency must have valid, reliable data in order to make regulatory decisions, including to set a safety factor. Here, there are no valid, reliable data to call into question the current regulatory standard for chlorpyrifos.

As discussed *infra* in Section VIII.A, Petitioners and the States' Objections are replete with misstatements and false assertions. The Objections misrepresent the scientific and

regulatory history for chlorpyrifos. Petitioners represent that the lack of safety for chlorpyrifos is uncontroverted when, in fact, substantial valid and reliable science exists to support the safety of this product under FQPA's reasonable certainty of no harm standard. Petitioners assert that the Agency has made conclusive scientific findings that chlorpyrifos is unsafe at the current regulatory standard, but fail to acknowledge that EPA has not changed its 2006 final determination that chlorpyrifos is safe at the current regulatory standard. As further discussed *infra,* Section VIII.A, all of EPA's subsequent statements about chlorpyrifos, made before the Agency considered a multitude of science-based comments, were simply part of the Agency's non-binding deliberative process. EPA's Order denying the Petition, made after the Agency's consideration of relevant science-based comments, expresses confidence that the current regulatory standard is protective of human health, consistent with recent findings in the European Union and Australia. Therefore, all claims that EPA found current potential exposures exceed acceptable risk from all possible sources, including food and water, are inaccurate.

While Petitioners suggest that chlorpyrifos poses a volatilization risk at the current regulatory standard, they present no new evidence in support. As more fully discussed *infra,* Section VIII.B, EPA's 2014 Revised Human Health Risk Assessment stated that "there is no anticipated risk[] of concern from exposure to the volatilization of either chlorpyrifos or chlorpyrifos oxon." Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review ("2014 RHHRA") at 84 (Dec. 29, 2014).

Petitioners' Objections also rely on a declaration by Dr. Philip Landrigan. But, as discussed in Section VIII.D, that declaration is rife with errors and incorrect assumptions. In addition, Dr. Landrigan asserts that exposure to organophosphate pesticides has led to a loss of IQ points in children, citing an article by Dr. David Bellinger in support of this assertion. As discussed *infra,* Section VIII.D, Dr. Bellinger's article fails to undertake a systematic review of the epidemiology studies underlying its conclusions, and makes assumptions that are not scientifically justified. There is no credible evidence to suggest that chlorpyrifos exposure has led to a loss of IQ points in children.

Moreover, Petitioners' Objections wrongly assert that EPA has found unsafe drinking water contamination from chlorpyrifos. As discussed *infra,* Section VIII.E, and in DAS's prior comments, the Agency has not made any final determinations with respect to drinking water.

EPA's drinking water assessment is still largely a screening-level assessment and not yet sufficiently refined or complete for purposes of human health risk assessment.

Finally, while Petitioners and the States assert that the Petition shifts the burden to the registrant or EPA to prove that chlorpyrifos is safe, neither the FFDCA nor the FQPA state that a petition to revoke already established tolerances shifts the burden of proving safety to the Agency or the registrant. In addition, the Objections cite no compelling authority for the argument that the Petition cannot be denied unless and until EPA affirmatively makes a new "safety" determination under the FFDCA.

III. REGULATORY HISTORY

In 2006, EPA completed its statutorily mandated reregistration of chlorpyrifos under FIFRA and the FFDCA. In a final decision that is still in effect, EPA reauthorized all existing agricultural uses for chlorpyrifos. EPA, Reregistration Eligibility Decision ("RED") for Chlorpyrifos (2006). In particular, pursuant to Section 408(b)(2) of the FFDCA, as amended by the FQPA, EPA determined that chlorpyrifos food tolerances (allowed pesticide residue limits) are "safe," meaning there is "a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue." 21 U.S.C. § 346a(b)(2)(A)(ii). Importantly, EPA's cumulative risk assessment in support of reregistration set an FQPA safety factor of 1X for the AChE inhibition endpoint for organophosphate pesticides ("OP"), including chlorpyrifos.

In 2007, PAN/NRDC filed the Petition with the Agency, seeking revocation of all chlorpyrifos tolerances and cancellation of all EPA registrations for products containing chlorpyrifos. The Petition was based, in significant part, on a taxpayer-funded epidemiology study conducted by researchers at Columbia University (the "Columbia study"), first published in 2002. The Columbia study claimed an association between *de minimis* amounts of chlorpyrifos allegedly found in the umbilical cord blood of a group of mothers almost twenty years ago with neurodevelopmental effects in their children later in life.

In response to the Petition, EPA accelerated the human health risk assessment process initiated as part of the Registration Review of chlorpyrifos. Under FIFRA, Registration Review is a periodic reassessment EPA is required to complete for all pesticide registrations, 7 U.S.C. § 136a(g). During Registration Review, which is still ongoing, EPA conducted multiple risk assessments, which were released for comment but are not final Agency conclusions. EPA also

convened several sessions of its FIFRA SAP, an independent advisory committee of scientific experts, *see* 7 U.S.C. § 136w(d)(1), to evaluate several scientific issues relating to chlorpyrifos, including the Columbia study. The SAP expressed significant concerns about the quantitative use of the Columbia study in risk assessment, among other issues. *See, e.g.*, EPA, Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting held April 10–12, 2012 on "Chlorpyrifos Health Effects" ("2012 SAP Minutes") at 19 (July 11, 2012) ("[T]he Panel largely concurs with EPA that the data generated from [the epidemiology] studies alone are not adequate enough to obtain a point of departure (POD) for the purposes of quantitative risk assessment."); *see also* EPA, Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting Held September 16–18, 2008 on the Agency's Evaluation of the Toxicity Profile of Chlorpyrifos at 12 ("2008 SAP Minutes") at 46 (Dec.17, 2008) ("The Panel agreed with the Agency that there were limitations in the [Columbia Study and two additional] epidemiological studies that precluded them from being used to directly derive the PoD or the uncertainty factor.").

In 2012, EPA issued a denial as to six of the ten claims raised in the Petition. EPA notified Petitioners that it would not issue a final denial as to those claims unless requested, and Petitioners made no such request. Instead, Petitioners sought mandamus relief in the U.S. Court of Appeals for the Ninth Circuit because they believed the process was taking too long. The Ninth Circuit denied Petitioners' original mandamus petition, finding no unreasonable delay by EPA. *In re Pesticide Action Network N. Am.*, 532 F. App'x 649, 651 (9th Cir. 2013). Petitioners then filed a new mandamus action with the Ninth Circuit in September 2014, asking the court to force EPA to make a decision on the Petition. *In re Pesticide Action Network N. Am.*, No. 14-72794 ("*PANNA II*") (9th Cir. Sept. 10, 2014).

From 2007 until 2015, EPA gave every indication that it intended to deny the Petition. As recently as March 2015, EPA informed both the Petitioners and the Ninth Circuit that it planned to deny the Petition, having determined, based on the results of its 2014 RHHRA, that the claims raised in the Petition did not provide a basis to revoke all chlorpyrifos tolerances and cancel all chlorpyrifos registrations. *See* Status Rep., *In re Pesticide Action Network N. Am.*, No. 14-72794, at 2 (9th Cir. Mar. 31, 2015), ECF No. 14. Specifically, EPA's March 26, 2015, letter to Petitioners advised Petitioners that it "does not believe the claims raised in your petition establish a basis to revoke all chlorpyrifos tolerances and cancel all chlorpyrifos registrations." *Id.*, Attach. 1 at 3. EPA explained, among other things, that the scientific evidence was

"insufficient" to depart from the 10% red blood cell acetylcholinesterase inhibition regulatory standard upon which EPA's 2006 safety determination was based. Id.

EPA then changed course, not due to any newfound concern related to the Petition, but based on purported drinking water exposure concerns the Agency was working to address that were raised from hypothetical modeling assessments. EPA advised the Ninth Circuit in the mandamus action in June 2015 that it intended to grant the Petition. *Id.*, Status Rep. at 1-2 (June 30, 2015), ECF No. 20. On August 10, 2015, the Ninth Circuit issued a mandamus order compelling EPA to "issue *either* a proposed or final revocation rule *or* a full and final response to the administrative petition by October 31, 2015." *Id.*, Op. at 12, ECF No. 23 (emphasis added).

On October 28, 2015, EPA issued a proposed rule to revoke all chlorpyrifos tolerances, this time based on the Columbia study and also on an initial, screening-level drinking water assessment, which EPA said it needed to further refine. Chlorpyrifos; Tolerance Revocations, 80 Fed. Reg. 69,080 (Nov. 6, 2015) (the "Proposed Rule"). EPA issued the Proposed Rule to comply with the Ninth Circuit's deadline, though it had not yet completed a full, refined drinking water assessment or had sufficient time to address a multitude of comments regarding the 2014 RHHRA, including the registrant's. As a result, EPA stated that it "may update this action with new or modified analyses as EPA completes additional work" and expressed its intent to allow the public to comment on that work prior to issuing a final rule. *Id.* at 69,083. Following issuance of the Proposed Rule, the Ninth Circuit extended the deadline for EPA to act on the Petition until December 30, 2016, and later extended the deadline until March 31, 2017. *In re Pesticide Action Network N. Am.*, No. 14-72794, ECF Nos. 29, 51.

Clearly not yet content with the scientific basis for its Proposed Rule, in April 2016, EPA convened the SAP to review a novel, unprecedented proposal developed by the Agency after issuance of the Proposed Rule that would base a new regulatory standard for chlorpyrifos directly on cord blood concentrations reported in the Columbia study. Echoing criticisms raised at SAP meetings, the 2016 SAP cited numerous deficiencies in the study and expressed concerns about reliance on the study in the absence of the underlying raw data, which Columbia researchers have steadfastly refused to provide, despite EPA's repeated requests—as recently as January 2018. *See* Chlorpyrifos: EPA's Seven Year Quest for Columbia's Raw Data, https://www.epa.gov/ingredients-used-pesticide-products/chlorpyrifos-epas-seven-year-quest-

columbias-raw-data. The SAP rejected EPA's proposal for a new regulatory standard, deeming the cord blood results from the study unreliable and insufficient for use in setting a point of departure. *See* 2016 SAP Minutes at 25 ("[T]he majority of the Panel considers the Agency's use of the results from a single longitudinal study to make a decision with immense ramifications based on the use of cord blood measures of chlorpyrifos as a [point of departure] for risk assessment as *premature and possibly inappropriate*.") (emphasis added).

Notwithstanding the SAP's admonition against using the Columbia study cord blood results for regulatory purposes, and still plainly not satisfied with the status of its scientific analysis, in November 2016, EPA proposed yet another, completely new regulatory standard that was also based principally on the Columbia study's conclusions, and thus the cord blood results the SAP rejected. *See* EPA, Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review (Nov. 3, 2016) ("2016 RHHRA"). EPA did not convene the SAP to review this novel approach, which was severely criticized by public commenters, including the U.S. Department of Agriculture ("USDA") under the prior Administration, and other commenters. For example, in its comments on EPA's November 2016 proposal, USDA stated:

> [EPA's] latest risk assessment is still based on just the single, not replicated, and unconfirmed [Columbia] study. Many weaknesses inherent in the study have been identified by the SAP and others, which undermine its suitability for determining a point of departure. These weaknesses remain unaddressed in EPA's latest risk assessment. This cannot be the type of "sound, high quality science" the writers of EPA's Scientific Integrity Policy envisioned as the "backbone of the EPA's decision-making." USDA has grave concerns that ambiguous response data from a single, inconclusive study are being combined with a mere *guess* as to dose levels, and the result is being used to underpin a regulatory decision about a pesticide chemical that is vital to U.S. agriculture, and whose removal from the market would have a major economic impact on growers and consumers.

USDA Comments on the Risk Assessment Underlying the Reopened Proposed Rule "Chlorpyrifos; Tolerance Revocations; Notice of Data Availability and Request for Comment" (Docket ID EPA-HQ-OPP-2015-0653-0648), at 2 (Jan. 17, 2017).

On March 29, 2017, following a review of comments submitted on the Proposed Rule and 2016 RHHRA, EPA issued its Order denying the Petition. Chlorpyrifos; Order Denying PANNA and NRDC's Petition To Revoke Tolerances, 82 Fed. Reg. 16,581 (Apr. 5, 2017) (the "Order" or "EPA Order"). EPA acknowledged that it had "three times presented *approaches and*

proposals" to the SAP for evaluating the epidemiologic evidence of chlorpyrifos exposure and neurodevelopmental effects. *Id.* at 16,590 (emphasis added). But, EPA stated:

> The SAP's reports have rendered numerous recommendations for additional study and sometimes conflicting advice for how EPA should consider (or not consider) the epidemiology data in conducting EPA's registration review human health risk assessment for chlorpyrifos. While industry and public interest groups on both sides of this issue can debate what the recommendations mean and which recommendations should be followed, one thing should be clear to all persons following this issue: *the science on this [issue] is not resolved* and would likely benefit from additional inquiry.

Id. (emphasis added).

In its March 29th Order, EPA stated that it had examined the evidence cited by Petitioners and concluded that it failed to show that chlorpyrifos is not safe. *Id.* at 16,587, 16,588. EPA also stated in its Order that animal toxicology data "support the FQPA safety factor of 1X for the AChE inhibition endpoint used in the 2006" cumulative risk assessment for organophosphate pesticides, including chlorpyrifos. *Id.* at 16,589. EPA expressed confidence in AChE inhibition as the appropriate regulatory endpoint. *Id.* With respect to epidemiology studies claiming an association between chlorpyrifos exposure at levels below the current regulatory standard and neurodevelopmental effects, EPA said that the studies were inconclusive and required further scientific review. *Id.* Thus, EPA denied the remaining Petition claims and issued a full and final denial of the Petition. *See id.* at 16,583 ("In this order EPA is denying the Petition in full.").

Importantly, in its Order, EPA stated that its decision "[f]ollow[ed] a review of comments on both the November 2015 [Proposed Rule] and the November 2016 [RHHRA]." *Id.* This is the first time EPA indicated that it had reviewed comments from interested stakeholders like growers, grower groups, the primary registrants, and USDA addressing the possible revocation of tolerances for chlorpyrifos.[3]

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[3] For ease of reference, DAS's prior comments are as follows, and are incorporated by reference: (1) Dow AgroSciences LLC's Response to EPA's Revised Human Health Risk Assessment for Chlorpyrifos Registration Review dated April 29, 2015, EPA-HQ-OPP-2015-0653-0214 (hereafter referred to as "DAS Response to RHHRA"); (2) Dow AgroSciences' Response to EPA's: Chlorpyrifos; Tolerance Revocations; Proposed Rule and EPA Analysis of the Small Business Impacts of Revoking Chlorpyrifos Food Tolerances, dated January 4, 2016, EPA-HQ-OPP-2015-0653-0386 (including all references and appendices therein) (hereafter referred to as

Soon after the Order was issued, PAN/NRDC filed a motion with the Ninth Circuit for "further mandamus relief," challenging the Administrator's alleged failure to make "new safety findings" supporting his denial of the administrative petition. *PANNA II*, at 3, ECF No. 55. The Ninth Circuit denied the motion on the ground that EPA had complied with the Court's orders by issuing a "final response to the petition." *Id.* at 4, ECF No. 65. The Ninth Circuit instructed PAN/NRDC that the administrative objections process under the FFDCA was the pathway to obtaining judicial review. *Id.* (citing 21 U.S.C. §§ 346a(g)(2), (h)(1); 40 C.F.R. §§ 178.65, 180.30(b)).

On June 5, 2017, Petitioners and the States filed objections, challenging the EPA Order on what they allege are purely legal grounds. In particular, Petitioners and the States assert that there is "overwhelming" scientific evidence that chlorpyrifos is unsafe at the current regulatory

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"DAS Response to Proposed Rule"); (3) Burns, C. 2015, Comments on EPA's Literature Review on Neurodevelopment Effects & FQPA Safety Factor Determination for the Organophosphate Pesticides, dated December 22, 2015 (document posted in docket EPA-HQ-OPP-2010-0119), submitted by G. Oliver, Dow AgroSciences LLC, EPA-HQ-OPP-2015-0653-0230 (hereafter referred to as "DAS Comments Regarding Epidemiology"); (4) DAS (Dow AgroSciences) Legal and Policy Comments in Response to EPA's Proposed Rule to Revoke Tolerances for Chlorpyrifos, dated January 5, 2016, EPA-HQ-OPP-2015-0653-0266 (hereafter referred to as "DAS Legal Comments Regarding Proposed Rule to Revoke Tolerances for Chlorpyrifos"); (5) Dow AgroSciences LLC's Response to EPA's Chlorpyrifos-Methyl: Human Health Draft Risk Assessment (DRA) for Registration Review, dated September 15, 2015, EPA-HQ-OPP-2010-0119-0044 (hereafter referred to as "DAS Response to EPA's Draft Risk Assessment for Chlorpyrifos-Methyl"); (6) DAS Legal and Policy Comments in Response to (i) EPA's Literature Review on Neurodevelopment Effects & FQPA Safety Factor Determination for Organophosphate Pesticides and (ii) EPA's Chlorpyrifos-Methyl: Human Health Draft Risk Assessment for Registration Review, dated February 19, 2016, EPA-HQ-OPP-2010-0119-0033 (hereafter "DAS Literature Review Comments"); (7) Dow AgroSciences LLC's Comments on 2016 Notice of Data Availability, Revised Human Health Risk Assessment and Refined Drinking Water Assessment for Chlorpyrifos, dated January 17, 2017, EPA-HQ-OPP-2015-0653-0651 (hereafter "DAS Comments on 2016 RHHRA"); (8) C. Burns. 2017. Dow AgroSciences LLC Comments on EPA's Response to Comments for Public Comments Related to Applying the FQPA 10X Safety Factor for the Organophosphate Pesticides (document dated December 29, 2016, EPA-HQ-OPP-2008-0316-0071). Submitted by G. Oliver to docket EPA-HQ-OPP-2010-0119; and (9) DAS (Dow AgroSciences). 2017. DAS Legal and Policy Comments in Response to (i) Response to Comments for Public Comments Related to Applying the FQPA 10X Safety Factor for the Organophosphate Pesticides; (ii) Organophosphates: Response to Occupational and Residential Exposure-Related Comments on the Preliminary Organophosphate Human Health Risk Assessments; and (iii) Response to Dietary-Related Comments on the Preliminary Organophosphate Human Health Risk Assessments. Dated July 24, 2017 (EPA docket: EPA-HQ-OPP-2010-0119).

standard, that EPA had previously made a finding that chlorpyrifos was unsafe, and that the burden was on EPA to make a new safety determination when denying the administrative petition to revoke tolerances. As outlined further in this Response, DAS disagrees with all of these assertions on a factual, scientific, and legal basis.

DAS submits this Response to Objections to correct the many false and inaccurate representations about chlorpyrifos and its regulatory history that are set forth in the Objections. Moreover, as set forth herein, and in the multitude of comments to the docket from DAS and other stakeholders, a robust set of reliable toxicology data support EPA's current regulatory standard for chlorpyrifos. Epidemiology and other studies that the Objections assert demonstrate otherwise are unreliable and invalid for purposes of regulatory decision-making, and must not be relied on to take such a draconian and significant regulatory action like a tolerance revocation.

IV. CHLORPYRIFOS IS CRITICAL TO GROWERS.

A. Chlorpyrifos Is an Essential Agricultural Crop Protection Tool.

Chlorpyrifos is an organophosphorus insecticide first registered in the United States in 1965. Chlorpyrifos currently protects more than fifty valuable U.S. food crops from destruction due to a variety of insect pests. Key crop uses include citrus fruits, corn, cotton, soybeans, sugarbeets, and wheat. Chlorpyrifos is one of the most widely used insecticides in the world, with approved uses in approximately 100 countries. The sustained importance of chlorpyrifos for global insect pest management is due to its outstanding efficacy and favorable environmental and human health characteristics. In situations of a sudden outbreak of a new pest, growers often go to chlorpyrifos as a proven tool for control and to prevent widespread yield loss.

Chlorpyrifos exhibits moderate mammalian toxicity (WHO Hazard Class II) and is not carcinogenic, a selective reproductive or developmental toxicant, or an endocrine disruptor. EPA has used inhibition of blood cholinesterase as a protective regulatory health endpoint, PoD, for risk assessment for over forty-five years.

Chlorpyrifos is biodegradable and has only short-to-moderate persistence in most environmental settings. In terrestrial ecosystems, chlorpyrifos rapidly dissipates from plant foliage (half-lives of <1–7 days). Soil surface half-lives are typically on the order of a few days to two weeks, whereas subsurface chlorpyrifos may demonstrate dissipation half-lives of one to

two months. In aquatic ecosystems, chlorpyrifos dissipates very rapidly (half-life <24 hours) from the water column, and dissipation from sediments is similar to that observed for soils.

A study of the benefits of chlorpyrifos to U.S. growers was submitted to the chlorpyrifos tolerance revocations docket in 2016 (Nelson, J.E., Schneider, L.L. *Use and Benefits of Chlorpyrifos in Agriculture*. Submitted to docket EPA-HQ-2015-0653 (January 2016)). Twenty-three hundred (2,300) U.S. growers, many of them representing family farms, have expressed their need for chlorpyrifos on the critical crops of corn, soybean, wheat, cotton, alfalfa, and sugar beets, along with multiple other crops through petitions submitted to the docket. In addition, multiple grower groups and many individual growers have provided comments throughout the various EPA public comment periods expressing the need for chlorpyrifos.

B. Loss of Chlorpyrifos Uses Would Have Significant Negative Impacts on Trade.

Chlorpyrifos is highly effective in controlling a broad spectrum of both foliar-feeding and soil-dwelling insect pests, and its important role in resistance management and integrated pest management ("IPM") programs is widely recognized. The widespread international registration approvals for chlorpyrifos and establishment by the Codex Alimentarius Commission of more than fifty international maximum residue limits ("MRLs") for chlorpyrifos residues on food crop commodities have facilitated global free trade of treated crops. Revocation of U.S. tolerances would create a significant regulatory gap for U.S. food import standards and result in a state of regulatory disharmonization between the United States and the other 165 member countries of Codex. Indeed, EPA has never fully assessed the potential impact of the loss of use of chlorpyrifos.

Revoking chlorpyrifos tolerances would also significantly disrupt the pest management practices used in the production of certain import crops, impair long-standing trade relationships, and create a new set of winners and losers as market participants adapt to regulatory changes. Revocation of tolerances would have a significant impact on trade particularly with regard to developing countries that rely on exports of agricultural commodities to the United States. Nelson, J.E., Schneider, L.L. *The Impact of Revoking Chlorpyrifos Tolerances (MRLs) on U.S. Agricultural Imports from Key Food Exporting Countries*. Docket: EPA-HQ-OPP-2015-0653-0526 (Jan. 2017). Numerous foreign trade and government groups also commented on the need for these tolerances during the various EPA public comment periods.

Nelson and Schneider assessed chlorpyrifos use on key crops exported to the United States from several important trading partners, including Brazil, Canada, Costa Rica, Israel, Mexico, Morocco, South Africa, and Spain. They reported that revoking chlorpyrifos tolerances would potentially have a significant economic impact on consumers and food chain members in the United States, as well as on the exporting countries:

> From the export partners' perspective, . . . citrus fruit and essential oils of citrus (Mexico), wine (Italy), soybeans (Brazil), essential oils of citrus (Israel, South Africa, Spain), sorghum (Mexico), and sugar (Costa Rica) are the exports most impacted by revoking chlorpyrifos' tolerances because of the large proportion of each commodity exported from these countries to the U.S. and the large crop area treated with chlorpyrifos.

Id. at 4–5.

V. SCIENTIFIC FRAMEWORK: The Current Regulatory Standard for Chlorpyrifos is Based on Decades of Solid Science.

A. EPA Has a Robust and Complete Set of Animal Toxicology Data that Supports its Current Safety Determination; Recent Experimental Toxicology Studies Reviewed by EPA and the California DPR Do Not Support Any Changes to that Standard.

As discussed in DAS's prior comments, over fifty years of robust animal toxicology data conducted during the registration and reregistration review process for chlorpyrifos show that chlorpyrifos meets the EPA standard for safety. *See* Declaration of Dr. Jennifer Seed ("Seed Decl."), Attach. A, ¶ 12 ("For many years, a complete and reliable animal toxicology data set, including reliable developmental neurotoxicity data, have supported the current regulatory standard for chlorpyrifos."). Further, "the animal toxicology data set for chlorpyrifos is complete and reliable and demonstrates (i) a well-established mode of action (AChE inhibition) and (ii) that there is no hazard identified to date that EPA has not accounted for under the current regulatory standard with respect to children's susceptibility." *Id.* ¶ 13.

EPA confirmed the reliability of the toxicological database for chlorpyrifos in its 2011 Preliminary Human Health Risk Assessment for chlorpyrifos, in which it stated that "[t]he toxicological database for chlorpyrifos is extensive and is adequate to support the registration review." PHHRA at 22. The Agency observed that "[t]he toxicity database includes the standard battery of guideline studies as well as special studies conducted by the registrant." *Id.* at 36. The Agency also stated that the available data showed "that cholinesterase inhibition

(ChEI) provides the most sensitive dose-response information for deriving points of departure for chlorpyrifos." *Id.* at 7. The Agency went on to describe the extensive scope of animal studies supporting chlorpyrifos:

> [the] studies consider different durations of exposure (acute, short-, intermediate-term and chronic) and relevant routes of exposure (oral, dermal, and inhalation), different laboratory animal species, reproductive and developmental toxicity, neurotoxicity, developmental neurotoxicity (DNT), new acute and repeat dose comparative cholinesterase assays (CCA) for both chlorpyrifos and chlorpyrifos oxon, a special acute inhalation toxicity study and a required immunotoxicity study.

Id. at 36.

Use of this endpoint was also confirmed as recently as 2014 by the EFSA and the APVMA, and also remains the gold standard and point of departure used by the World Health Organization and virtually all major global regulatory authorities. *See, e.g.,* APVMA, Reconsideration of Chlorpyrifos at 1 ("[C]holinesterase inhibition remains the most sensitive and relevant adverse effect caused by chlorpyrifos and is therefore the most appropriate endpoint for the establishment of health based guidance values used to protect the entire population including pregnant women, infants and children."); EFSA Scientific Panel on Plant Protection Products and their Residues, Minutes of the 70th Plenary Meeting Held on 08-09 October 2014, Parma (Italy) ("PPR Panel Minutes") at 9 ("Considering the available studies, cholinesterase inhibition was considered the most sensitive endpoint on which reference values should be based."); World Health Organization, Chlorpyrifos in Drinking-Water, Background document for development of WHO Guidelines for Drinking-water Quality at 3 (2004) ("In long-term studies, inhibition of cholinesterase activity was again the main toxicological finding in all species.").

The 2014 RHHRA also confirmed that AChE inhibition is an appropriate regulatory endpoint: "AChE inhibition remains the most robust quantitative dose response data and thus continues to be the critical effect for the quantitative risk assessment." 2014 RHHRA at 24. The Agency also described the strength of the animal toxicological data:

> There are many chlorpyrifos studies evaluating AChE inhibition in red blood cell (RBC) or brain in multiple lifestages (gestational, fetal, post-natal, and non-pregnant adult), multiple species (rat, mouse, rabbit, dog, human), methods of oral administration (oral gavage with corn oil, dietary, gavage via milk) and routes of exposure (oral, dermal, inhalation via vapor and via aerosol). In addition, chlorpyrifos is unique in the availability of ChE data from peripheral tissues in some studies (e.g., heart, lung, liver). There are also literature studies comparing the *in vitro* ChE response to a variety of tissues (Chambers, 2013) which show

> similar sensitivity and intrinsic activity. Across the database, brain AChE tends to be less sensitive than RBC AChE or peripheral ChE. In oral studies, RBC AChE inhibition is generally similar in response to peripheral tissues. *Thus, the in vitro data and oral studies combined supports the continued use of RBC AChE inhibition as the critical effect for quantitative dose-response assessment.*

Id. (emphasis added).

Petitioners claim that a growing body of animal toxicology data supports epidemiology studies claiming associations between chlorpyrifos exposure at levels below the current regulatory standard and neurodevelopmental effects. DAS has detailed the flaws and limitations in these animal studies in prior comments to EPA[4]; it is indefensible for EPA to use these studies as a basis for the significant regulatory action requested by Petitioners. As further summarized in the attached Appendix A, other animal toxicology studies more recently considered by EPA and the California Department of Pesticide Regulation are not viable or reliable for use in science-based decision-making due to deficiencies and limitations in their study design—including, in many studies, use of a single dose, use of doses that exceed those known to cause cholinesterase inhibition, use of subcutaneous injection as the route of exposure, use of dimethyl sulfoxide ("DMSO") as a vehicle, and/or failure to measure cholinesterase inhibition.

B. *In Vitro* Studies Do Not Create Uncertainty With Respect to the Current Regulatory Standard for Chlorpyrifos.

"EPA has long relied on *in vivo* 'apical' endpoints as the primary bases for the regulation of chemicals. These apical endpoints are empirically identified outcomes in intact animals exposed to the chemical at issue." Declaration by Dr. James Bus ("Bus Decl."), Attach. B, ¶ 11. In contrast, *in vitro* study outcomes are typically not regarded as apical endpoints because *in vitro* studies look at effects on only a group of cells or isolated organs in a test tube. *Id.* "Effects observed only in cells or isolated organs in a test tube do not reflect the overall complex biological functions of the intact organism that ultimately determine the end toxicological effect, and do not account for the full range of homeostatic and protective mechanisms that occur in an

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[4] *See, e.g.,* Dow AgroSciences LLC's Response to EPA's [RHHRA] for Chlorpyrifos Registration Review, EPA Dkt. EPA-HQ-OPP-2008-0850-0845, at 57–64 (Apr. 2015); Dow AgroSciences LLC's Comments on 2016 [NODA/RHHRA] and Refined Drinking Water Assessment for Chlorpyrifos, EPA Dkt. EPA-HQ-OPP-2015-0653-0651, at 33 and Appendix D (Jan. 2017); *see also* Dow AgroSciences LLC's Amicus Brief in Support of EPA, *League of United Latin Am. Citizens, et al. v. Wheeler*, No. 17-71636, ECF No. 72-2, at 20–23 (9th Cir. Mar. 15, 2018).

in vivo animal." *Id.* "While the Agency may consider both *in vitro* and *in vivo* studies in its risk assessments, *in vitro* studies present numerous challenges that make them much less reliable for human health assessments than *in vivo* studies." *Id.* ¶ 10.

In the past, EPA has referred to *in vitro* studies of chlorpyrifos by Howard *et al.* (2005), Schuh *et al.* (2002), and Yang *et al.* (2008) and "suggested that these studies . . . create some additional 'uncertainty' concern regarding conclusions from high quality *in vivo* studies that indicate developmental neurotoxicity is observed only under conditions sufficient to cause maternal and fetal/pup AChE inhibition. [However, such] an additional uncertainty concern is not warranted by an examination of the whole animal, developmental neurotoxicity data." *Id.* ¶ 18. A review of the *in vitro* studies shows that "[t]here is no scientific basis for the Agency to infer uncertainty from *in vitro* data reporting neuronal cell effects at sub-AChE-inhibiting test concentrations [because] those effects have not been affirmed in a robust set of animal toxicological data supporting the current regulatory standard (*e.g.*, Maurissen *et al.*, 2000, Mattsson *et al.*, 2000)." *Id.* ¶ 20.

Further, "[f]or *in vitro* studies to be relevant for risk assessment, the test concentrations in the test tube or laboratory dish must have interpretable and meaningful relevance to human exposures." *Id.* ¶ 10. "Frequently, concentrations at which positive responses are observed *in vitro* are far removed from real-world human exposure conditions, thus rendering reliance on these *in vitro* studies inappropriate for risk assessment." *Id.* Thus, if it cannot be proven that the *in vitro* endpoints are relevant to apical *in vivo* outcomes, *in vitro* findings alone are not sufficient as a basis for assessment of potential human health risks. *Id.* ¶ 12. EPA has recognized that *in vitro* studies must be considered with great caution. *Id.* ¶ 14 (citing *EPA, Human Exposure Estimates and Oral Equivalents of In Vitro Bioactivity for Prioritizing, Monitoring and Testing of Environmental Chemicals* (2010)).

EPA has clearly delineated its expectation that *in vitro* findings be relevant to apical *in vivo* outcomes in its "Endocrine Disruptor Screening Program (EDSP) guidance[,] in which a two-tiered testing approach has been implemented (EPA, 2009)." *Id.* This Program "requires that the mostly *in vitro* tier 1 screening-level tests be validated against apical *in vivo* responses. In other words, the EDSP requires that positive findings in *in vitro* tier 1 must be directly correlated with adverse outcomes in *in vivo* apical tier 2 tests *before* such *in vitro* tests can be used as screening-level indicators of potential toxicological hazards." *Id.* ¶ 12 (emphasis added).

"Thus, relying on *in vitro* studies conducted at the test tube or lab dish scale alone are not sufficient to supplant a failure to identify corresponding apical responses in more robust and high-quality *in vivo* studies. To do otherwise would undermine EPA's long-held reliance on whole animal studies to determine apical endpoints and the dose-response thereof as most appropriate for the purpose of risk assessment." *Id.*

Moreover, numerous conditions used in the *in vitro* studies considered by EPA and others call into question reliance on these experimental data for regulatory decision-making. For example, Howard (2005) and Yang (2008) used DMSO as a carrier solvent for the chlorpyrifos or chlorpyrifos oxon test material. The concentration of DMSO could have a substantial impact on many of the measured results. Cavaletti *et al.* have shown that intraperitoneal administration of dilute solutions of DMSO can have a significant impact on the nervous system. Cavaletti *et al.* (2000), *Effect on the Peripheral Nervous System of Systemically Administered Dimethylsulfoxide in the Rat: a Neurophysiological and Pathological Study*. Toxicol. Ltrs. 118: 103-07. They caution researchers that "[t]he neurophysiological and pathological changes observed in our study are severe enough to merit careful consideration in the course of experimental studies involving DMSO as a solvent for drugs which are under evaluation for their potential neurotoxicity." *Id.* at 103. Other authors have shown that DMSO used as a dose vehicle can also enhance the clinical symptoms of organophosphates. Ballough *et al.* (2008), *Brain Damage from Soman-Induced Seizures is Greatly Exacerbated by Dimethyl Sulfoxide (DMSO): Modest Neuroprotection by 2-aminoethyl diphenylborinate (2-APB), a Transient Receptor Potential Channel Inhibitor and Inositol 1,4,5-triphosphate Receptor Antagonist*, J. Med. CBR Def 6: 1-20; Carr *et al.* (2008), *Effect of Different Administration Paradigms on Cholinesterase Inhibition Following Repeated Chlorpyrifos Exposure in Late Preweanling Rats*. Toxicol. Sci. 106: 186-92. Further, "[a]lthough the Howard *et al.* (2005) and Yang *et al.* (2008) studies diluted the 100% DMSO stock solutions by 1:1000 for final cell culture, this dilution approximates the DMSO dose (1 ml/kg = 1 ml/1000 ml) that is neurotoxic *in vivo*." Bus Decl. ¶ 22.

The 2012 SAP echoed these concerns about the use of DMSO: "in keeping with the 2008 SAP, this Panel expresses concern about the use of Dimethyl Sulfoxide (DMSO) as a vehicle because of its intrinsic toxicity, its potential influence on absorption and interaction with chlorpyrifos, and the impact of this interaction on the developing organism." 2012 SAP Minutes

at 12. The Agency recognized in its charge question to the 2012 SAP that it should exercise caution in making connections between possible effects observed in the above-referenced *in vitro* studies and effects *in vivo*: "Some of these comparisons must be considered with caution since the amount of change in the *in vitro* systems required to elicit an adverse effect *in vivo* is unknown. Moreover, extrapolation from *in vitro* perturbations to *in vivo* effects has not been established. . . ." 2012 SAP Minutes at 13. The SAP agreed with the Agency's concerns:

> The Panel concurs with the Agency that caution should be applied in interpreting the *in-vivo* significance of the changes observed across the various *in vitro* studies. Several uncertainties and limitations are associated with the translation of *in vitro* study results to *in vivo* effects. The inherent complexity of the nervous system presents significant challenges to accomplishing this translation. An additional example of uncertainty is that cells that are isolated in culture within an *in vitro* experiment may be affected differently than they would if they were within their *in vivo* environment.

Id. at 14.

At least one court has also noted the limitations of relying on *in vitro* studies. In *In re Ephedra Prods. Liab. Litig.*, 393 F. Supp. 2d 181, 194 (S.D.N.Y. 2005), the court observed that "the gaps between [*in vitro*] data and definitive evidence of causality are real and subject to challenge before the jury[.]"). Other scientists have echoed these concerns: the "weakness of [*in vitro*] studies is the uncertainty that the effects observed at cell level would occur in the 'real world' of the complex living organism." Huber *et al.* (2011), *Organic Food and Impact on Human Health: Assessing the Status Quo and Prospects of Research*, Wageningen J. of Life Sci. 58: 103-09, at 105.

In sum, the *in vitro* studies cited by EPA and others in the past do not create uncertainty with respect to the current regulatory standard for chlorpyrifos.

C. There Is No Reliable Science to Support a Mode of Action Other Than Cholinesterase Inhibition.

Over the last several years, significant attention has focused on whether non-cholinergic modes of action exist for chlorpyrifos and, if they do, whether they may be operating at dose levels below which cholinesterase inhibition occurs. But no such non-cholinergic mode(s) of action has been observed in the significant number of Guideline studies (covering many endpoints that would detect impacts on development or neurodevelopment) that have been conducted over more than forty years as part of EPA's registration and reregistration processes for chlorpyrifos.

Many of the studies that have purportedly shown non-cholinergic effects associated with neurodevelopmental effects were not designed for regulatory decision-making or risk assessment purposes. In addition, specific hypotheses evaluating potential non-cholinergic mode(s) of action have not been adequately proposed, tested, or validated in appropriate animal models. Both EPA and its SAP have concluded, upon review of the scientific literature, that there are insufficient data to support a potential non-cholinergic mode(s) of action for chlorpyrifos. For example, when asked about a possible non-cholinergic mode of action for chlorpyrifos, the 2008 FIFRA SAP stated that

> [t]here was a consensus of the Panel that available data were inadequate to support a weight of evidence evaluation for non-cholinergic mode(s) of action for the behavioral alterations following gestational and early postnatal exposure to chlorpyrifos that persisted into adulthood. The Panel agreed that the available information does not allow for behavioral endpoints to be considered as a point of departure and recommended, based upon currently available data, that cholinesterase inhibition be used as the PoD.

2008 SAP Minutes at 28. *See also id.* at 56 ("[T]here is a clear lack of identifiable key events for mode of actions not related to AChE inhibition.").

D. Reliance on Prior EPA Dose Reconstruction for Exposure Assessment Does Not Lead to Reliable Results.

In its 2014 RHHRA, the Agency suggested that it could make up for the lack of raw data underlying the Columbia study by conducting a dose reconstruction, which "showed that using high end exposure assumptions . . . peak RBC AChE inhibition was predicted to be only 0.45%" (thus supporting a 10X safety factor). EPA, Response to Comments for Public Comments Related to Applying the FQPA 10X Safety Factor for the Organophosphate Pesticides at 19, published May 25, 2017 in docket: EPA-HQ-OPP-2010-0119-0055 ("Response to Comments").

The dose reconstruction was based in large part on hearsay and questionnaires that did not assess which particular pesticide study participants had been exposed to. The results of the dose reconstruction are therefore unreliable—"[a] tenuous, opaque dose reconstruction based on questionnaires presented to study participants, which EPA recognized as having limitations and which did not undergo peer review, cannot support the conclusion that using high end exposure assumptions results in peak RBC AChE inhibition of only 0.45%. The dose reconstruction simply does not provide data that are reliable or valid." Declaration of Dr. Jeffrey Driver ("Driver Decl."), Attach. C, ¶ 21.

In its 2016 RHHRA, EPA reviewed the registered home uses that would have been available to the Columbia study cohort to develop a new PoD for risk assessment from internal concentrations of chlorpyrifos. 2016 RHHRA at 14. EPA then conducted interviews with technical pest advisors responsible for overseeing New York City's housing authority and "determined" that crack and crevice use was the predominant type of application method used at the time of the Columbia study nearly two decades ago. *Id.* at 14–15. However, "there is no definitive evidence that chlorpyrifos was applied by indoor crack and crevice application methods in any of the residences of the Columbia cohort, and many study subjects changed residences frequently during the study." *Id.* ¶ 22. Therefore, crack and crevice dose reconstruction "should not be used to establish a route-specific PoD, especially given the deficiencies associated with the Columbia cohort data." *Id.* ¶ 23.

Further, the underlying premise that the effects purportedly observed and claimed to be linked to chlorpyrifos exposures from these crack and crevice treatments is unfounded since "there were members of the cohort that received crack and crevice applications without the claimed health effects, and the entire cohort could have had exposures through diet and water, which would be higher than through the added crack and crevice exposure." *Id.* ¶ 23. *See also* DAS Comments on 2016 RHHRA at 35-41; Driver *et al.*, Public Comments: Chlorpyrifos Revised Human Health Risk Assessment for Registration Review (EPA's Office of Pesticide Programs, November 3, 2016) (EPA-HQ-OPP-2015-0653-0647) (Jan. 16, 2017).

VI. EPIDEMIOLOGICAL STUDIES ARE NOT RELIABLE ENOUGH FOR REGULATORY DECISION-MAKING AND SHOULD NOT IMPACT THE CURRENT REGULATORY STANDARD.

Petitioners urge that the Columbia, Mt. Sinai, and CHAMACOS studies show that chlorpyrifos is not safe at the current regulatory standard. But the conclusions in the Columbia study are based on unreliable blood test results (as well as multiple additional deficiencies), and a new analysis of some data from a Columbia study publication raises additional significant questions about the scientific validity of the study's conclusions. Moreover, the Mt. Sinai, CHAMACOS, and other epidemiology studies are inconsistent and do not support the published conclusions in the Columbia study.

A. The Cord Blood Measurements in the Columbia Study Are Not Valid or Reliable, and Any Published Conclusions Drawn from Those Measurements are Therefore Not Valid or Reliable for Regulatory Decision-Making.

i. The 2008 and 2016 SAP Heavily Criticized the Validity and Reliability of the Columbia Study's Cord Blood Measurements.

The 2008 and 2016 SAP raised numerous doubts about the reliability and validity of the cord blood data that form the basis of the conclusions drawn in the study, both as to the reliability and accuracy of the analytical methodology used to derive results, and as to whether the results represent an accurate picture of exposure. *See, e.g.,* Transcript of April 2016 SAP Meeting ("2016 SAP Tr.") at 89 ("I disagree with the validity of the cord blood data, really."); *id.* at 501 ("But you know, I personally don't really think that cord blood is usable as an exposure assessment for anyone here, really."); *id.* at 768 ("[T]here are a lot of uncertainties in the data . . . I don't think the data are very strong."). The 2016 SAP expressed concerns with, among other issues, the Columbia researchers' arbitrary assignment of values for over 40% of the children in the Columbia study who had chlorpyrifos levels that were below the level of detection[5] and use of a surrogate measurement for 12% of children for whom they lacked any chlorpyrifos measurements at all; the use of a single point in time measurement to estimate exposure; and the lack of biological plausibility for how the extremely low levels of chlorpyrifos reported in the study could produce the effects claimed. These levels in the pg/g range are several-fold lower than the current regulatory endpoint. Specifically, the 2016 SAP said that:

- "A major source of uncertainty for the Panel was the lack of verification and replication of the analytical chemistry results that reported very low levels of chlorpyrifos (pg/g). Imputing quantitative values when the concentration of analyte falls below the level of detection (LOD) was a particular concern, especially given that a large fraction of cord blood samples included in the analyses presented with levels below LOD." 2016 SAP Minutes at 18; *see also id.* at 41 ("[T]he use of means with large standard deviations that extend below the level of detection that are included in the analysis . . . further decreases the value and increases uncertainties associated with the raw data that cannot and has not been independently reviewed or verified.").

[5] *See* Rauh *et al.*, *Seven-Year Neurodevelopmental Scores and Prenatal Exposure to Chlorpyrifos, a Common Agricultural Pesticide*, 119 Environ Health Persp 1196, 1198 (2011) (stating that cord blood measurements for 43% of the Columbia cohort fell below the limit of detection).

- "The Panel is not aware of any scientific evidence where pg/g levels in the blood would lead to deleterious neurotoxicological effects in a mammalian system." *Id.* at 22–23.
- "The assumption that the impaired working memory and lower IQ measures observed are caused primarily by a single insecticide (chlorpyrifos) and predicted by the blood levels at time of delivery is not supported by the scientific weight of evidence." *Id.* at 23.
- "Some Panel members stated that the reliance on single cord blood measurements from only one study (i.e., the CCCEH study) as a primary basis for a highly impactful regulatory decision goes against standard practices of science in the fields of toxicology and pharmacology." *Id.* at 42.
- Noting the majority view that there is a "lack of biological plausibility for how low cord blood (low parts per trillion) concentrations of chlorpyrifos can alter working memory and produce neurodevelopmental impairment." *Id.* at 25-26.
- "And a single study, single point in time, questionable, extremely low values, no biological plausibility – there's nothing I'm aware of in the literature that would suggest[,] you know, [picomolar] levels cause some significant neuronal change that could underlie a prefrontal cortex-based memory task." 2016 SAP Tr. at 628.
- "Well if [the chlorpyrifos measurements in the cord blood samples are] below the level of detection for that study then that, in my mind raises an issue with the validity of that study." *Id.* at 663.

As one Panel member aptly stated, the Columbia Study "is plagued by issues that diminish the enthusiasm for this study." *Id.* at 622.

Moreover, the 2016 SAP made several statements that undermine any contention that there are purported effects at exposures below the current regulatory standard. For example, the 2016 SAP Minutes state that "*[W]ithout any evidence in the animal literature or elsewhere of a mechanism of action that could explain how pg/g levels in blood could impair IQ and/or working memory, there does not appear to be biological plausibility.*" 2016 SAP Minutes at 40–41 (emphasis added). The 2016 SAP also pointed out that effects at these extremely low levels are rarely seen even with the most potent acetylcholinesterase-inhibiting drugs:

> There is a lack of biological plausibility or animal evidence for how picomolar (pM; 10-12M) cord blood levels of >6.17 pg/g chlorpyrifos (>17.6 pM based on the CCCEH analytical results) can alter working memory and produce neurodevelopmental impairment. The mechanisms for how such potent effects can be produced at these concentrations *in vivo* are not known and have not been previously described. By comparison, the most potent selective anti-AChE drugs in current clinical use to treat deficits in working memory are known to directly

> engage brain AChE with inhibitory constants (IC_{50}'s) in the range of 20,000 pM (physostigmine) to 600,000 pM (tacrine). In this regard, CPFO, the active metabolite of chlorpyrifos, has an IC_{50} towards AChE of ~10,000 pM. One is left to speculate on one or more causative mechanisms having potencies more than 1,000-30,000 fold lower than cholinergic drugs known to alter working memory in patients. These estimates are conservative, since they assume chlorpyrifos levels in cord blood will directly reflect CPFO levels in the developing brain, an assumption that is currently unproven given the challenges in directly measuring the active metabolite CPFO in any tissue after exposure.

Id. at 54.

The 2008 SAP also expressed similar concerns about the cord blood measurements. *See, e.g.,* 2008 SAP Minutes at 34 ("[T]he single measurement of cord blood chlorpyrifos may not be representative of the total exposure during pregnancy, but only reflects exposure [that] happened in the few days before delivery."); *id.* at 45 ("One of the key limitations of the epidemiological studies is that the exposure data were collected at single time point and lack information on the long-term exposure level and duration.").

In sum, the 2008 and 2016 SAP identified a number of deficiencies and limitations in the Columbia study, including as to the validity and reliability of the reported test results. These deficiencies and limitations have been further discussed in detail in DAS's prior comments. *See, e.g.,* DAS Comments on 2016 RHHRA § IV and App'x B; DAS Comments on 2014 Revised Human Health Risk Assessment § 4.2.2; Dow AgroSciences Additional Comments for the EPA's FIFRA Scientific Advisory Panel (SAP): Chlorpyrifos: Analysis of Biomonitoring Data (April 19–21) (April 15, 2016), Docket EPA-HQ-OPP-2016-0062).

Moreover, EPA's 2016 Updated Literature Review of epidemiology studies recognizes numerous deficiencies in the Columbia study. *See* EPA, Updated Literature Review on Neurodevelopment Effects & FQPA Safety Factor Determination for the Organophosphate Pesticides, published May 25, 2017 in docket: EPA-HQ-OPP-2010-0119-0060 ("Updated Literature Review") at 49–62. For example, the Updated Literature Review states that a weakness of the Columbia study is the fact that "[t]he use of a single snapshot of prenatal chlorpyrifos exposure may not be an accurate surrogate for full prenatal exposure levels." *Id.* at 59; *see also id.* at 54 (criticizing "[r]eliance on a single exposure level (prenatal/cord blood.)"). *See also* Declaration by Dr. Carol Burns ("Burns Decl."), Attach. D, ¶ 13 ("It is fundamentally flawed to use a single biological sample of a short-lived chemical to infer the level of past exposure. . . . Researchers have cautioned against relying upon a single sample to estimate long

term exposure (Morgan *et al.* 2016, LaKind and Naiman 2015, Spaan *et al.* 2015, Aylward *et al.* 2014). Exposure assessments based upon a 'single sample without considering error' are considered to be of low utility (LaKind *et al.* 2014)."); *id.* ¶ 11 ("[T]he Columbia and Mt. Sinai studies relied upon a single biological sample collected at delivery. Due to the short half-life of chlorpyrifos in the body, the concentration of chlorpyrifos or the metabolite are not a valid estimate of the exposure levels throughout the prenatal period."). The Updated Literature Review also observes that "[d]ue to the pervasive, non-specific nature of neurological effects, it is difficult to attribute causality." Updated Literature Review at 54–55. Finally, the Updated Literature Review states that one of the Columbia study publications "only included participants recruited in the post-cancellation period" and "the large number of observations below the level of detection receiving equal rank. . . may be problematic." *Id.* at 62.

A study with so many limitations and deficiencies is not only inappropriate as the basis for a point of departure, it should also not be used *for any purpose* in regulatory decision-making, including as support for setting an FQPA 10X safety factor or to suggest uncertainty with respect to the current regulatory standard. The Columbia study simply does not meet the statutory test for validity and reliability, by any measure.

ii. The Columbia Study's Conclusions Are Not Valid or Reliable Because they are Primarily Based on the Deficient Cord Blood Measurements.

Of critical importance, the Columbia study's conclusions are primarily based on cord blood measurements. Driver Decl. ¶ 17. Specifically:

- "[T]he conclusions set forth in the published articles for the Columbia study are predicated on a presumed dose-response related to cord blood level measurements of chlorpyrifos and neurodevelopmental outcome indicators." *Id.* ¶ 16.

- For example, the Columbia study investigators reported that "higher prenatal [chlorpyrifos] exposure, as measured in umbilical cord blood plasma, was associated with decreases in cognitive functioning on two different WISC-IV indices, in a sample of urban minority children at 7 years of age." Rauh *et al.* (2011), *Seven-Year Neurodevelopmental Scores and Prenatal Exposure to Chlorpyrifos, a Common Agricultural Pesticide,* 119 Environ Health Persp at 1200.

- "Using a different biomarker of exposure (the parent compound of [chlorpyrifos] in umbilical cord plasma), we have previously reported (in the same cohort as the present study) significant associations between prenatal exposure to [chlorpyrifos] (> 6.17 pg/g) and reduced birth weight and birth length (Whyatt *et al.* 2004), increased risk of small size for gestational age (Rauh V, Whyatt R, Perera F, unpublished data),

increased risk of mental and motor delay (< 80 points) and 3.5- to 6-point adjusted mean decrements on the 3-year Bayley Scales of Infant Development (Rauh *et al.* 2006), and evidence of increased problems related to attention, attention deficit hyperactivity disorder, and pervasive developmental disorder as measured by the Child Behavior Checklist at 2–3 years." *Id.* at 1196.

Similarly, the published Columbia study articles rely on the cord blood test results to reach associational conclusions with respect to the following:

- "Highly exposed children ([those with] chlorpyrifos [cord blood] levels of >6.17 pg/g plasma) scored, on average, 6.5 points lower on the Bayley Psychomotor Development Index and 3.3 points lower on the Bayley Mental Development Index at 3 years of age compared with those with lower levels of exposure." Rauh *et al.* (2006), *Impact of Prenatal Chlorpyrifos Exposure on Neurodevelopment in the First 3 Years of Life Among Inner-City Children*, Pediatrics at 1, 10.

- "The high chlorpyrifos exposure group includes those with cord blood chlorpyrifos levels >6.17 pg/g, and the low group includes all those with lower levels." *Id.* at 19.

- "[B]irth weight decreased by 42.6 g (95% CI, –81.8 to –3.8, p = 0.03), and birth length decreased by 0.24 cm (95% CI, –0.47 to –0.01, p = 0.04) for each log unit increase in cord plasma chlorpyrifos levels." Whyatt *et al.* (2004), *Prenatal Insecticide Exposures and Birth Weight and Length among an Urban Minority Cohort,* 112 Environ Health Persp 1125, 1128–29.

- "Spearman's rank correlation coefficients were used to examine associations between pesticide levels in paired maternal and newborn blood samples." Whyatt *et al.*, *Biomarkers in assessing residential insecticide exposures during pregnancy and effects on fetal growth*, Toxicol. Appl. Pharmacol. 206: 246-254 at 248 (2005).

- "[A] highly significant inverse association between umbilical cord chlorpyrifos levels and both birth weight and birth length among infants in the current cohort born prior to U.S. EPA regulatory actions to phase out residential uses of the insecticide" was reported. *Id.* at 252.

- "[P]rior research has shown significant associations between chlorpyrifos concentrations in umbilical cord blood, and newborn birth weight and length (Whyatt *et al.* 2004) and child mental and motor development at age 36 months (Rauh *et al.* 2006)." Whyatt *et al.* (2009), *A Biomarker Validation Study of Prenatal Chlorpyrifos Exposure within an Inner-City Cohort during Pregnancy,* 117 Environ Health Persp 559, 565.

As discussed above, "these conclusions in the published articles for the Columbia study are invalid and unsupported because they are directly based on blood test results which are unreliable and invalid." Driver Decl. ¶ 18. For example, "[b]asing conclusions on a once-in-

time cord blood measurement is simply not scientifically justified because a once-in-time measurement is not representative of long-term exposure." *Id.* ¶ 14. Thus, "the unreliability and invalidity of the blood tests raises serious concerns about the accuracy of the classification of the blood test results into high (above 6.17 pg/g) and low (below 6.17 pg/g) exposure groups which, in turn, raises serious doubt about the claimed correlation between exposure groups and effects." *Id.* ¶ 17. Further, "[s]ince the blood test results for the Columbia cohort are not representative of true exposure, the threshold blood level (6.17 pg/g) above which effects are assigned to chlorpyrifos is meaningless." *Id.* In addition, "blood levels are very sensitive to time of sampling relative to time of last exposure (which is unknown), and are not a reliable biomarker for comparison of exposure in the individual." *Id.* In sum, "[b]ecause the Columbia study blood test results are not valid and reliable, the conclusions reached by the published studies based on the blood test results are not valid and reliable, especially for regulatory action." *Id.* ¶ 15.

iii. A New Analysis of Data from a Columbia Study Publication Casts Further Doubt on Columbia Study's Findings.

One of the most cited publications resulting from the Columbia study is Rauh *et al.* (2011). However, a recent analysis of data from the Rauh *et al.* (2011) publication conducted by TERA, attached as Appendix B, raises a number of scientific concerns about the reliability of the Columbia study's data and validity of the Columbia study's conclusions, similar to those raised by prior SAPs and numerous public commenters. Chief among those concerns is that, based on TERA's analysis of data that could be derived from figures and text of the Rauh *et al.* (2011) published article, certain data were missing and/or, because of the way they were graphically represented or plotted, may have impacted the trends observed and thus the conclusions drawn. For example, the TERA analysis found:

> Rauh et al. (2011) reported evidence of deficits in Working Memory Index and Full-Scale IQ in children at 7 years old as a function of prenatal CPF exposure. Although these data have not been made available, we were able to extract them in part through an analysis of Figures 1A and 1E of Rauh et al. (2011). This analysis uncovered a surprising fact. Data from approximately 35% of the 265 children described in the text of Rauh et al. (2011) were missing from Figure 1A; approximately 15% of these data were missing from Figure 1E. Although some of the missing data are possibly due to overlay of data points not observable in these published figures, such overlay cannot reasonably account for the extent of these missing data. Further, CCCEH correspondence to EPA admits that data of the four highest exposed children from Rauh et al. (2011) were removed from these figures because at least one data point "drastically impacts inference," *suggesting that the*

> *statistical significance of these findings may have changed had these data been included.*
>
> The data extracted from the figures were analyzed in a number of ways, including a plot of data as response versus log dose, a typical toxicological and risk assessment approach. In contrast to Rauh et al. (2011), our analysis does not suggest any evidence of an effect on Full-Scale IQ (Figure 1E). We also find less of a negative association (reduction) in Working Memory Index (Figure 1A).

Appendix B at 13 (emphasis added). The TERA report's findings continue to demonstrate that there are significant scientific issues regarding the Columbia study's conclusions casting doubt on its suitability for use in regulatory decision-making, thus supporting EPA's Order denying the Petition.

iv. EPA Recently Recognized the Shortcomings of Epidemiology Studies in the Case of Fluoride.

EPA recognized that a single epidemiology study could not overcome robust animal toxicological data in its recent action denying a petition to prohibit the addition of fluoride to drinking water. *See* Fluoride Chemicals in Drinking Water; TSCA Section 21 Petition; Reasons for Agency Response, 82 Fed. Reg. 11,878 (Feb. 27, 2017). In denying the fluoride petition, EPA determined that the epidemiology studies urged in support of the petition had "significant limitations," including issues with study quality, uncontrolled confounders, and the lack of a dose-response relationship, such that the collective weight of evidence did not support granting the petition. For example, EPA stated that:

> [m]any of the human studies cited in the petition are cross-sectional in design, . . . are affected by antecedent-consequent bias . . . [and] are rarely suitable for the development of a dose-response relationship for risk assessment. . . . In epidemiology, studies using cross-sectional data are most often used to generate hypotheses that need to be further studied to determine whether a 'true' association is present. " 82 Fed. Reg. at 11,882, 11,884. Importantly, the Agency stated that a "*single epidemiological study* is not sufficient to 'corroborate' neurotoxic health effects, as stated in the petition." *Id.* at 11,884 (emphasis added). Finally, EPA observed that cross-sectional studies are "most useful for developing hypotheses about possible causal relationships between an exposure and a health effect, but are *rarely suitable for the development of a dose-response relationship for risk assessment.*

Id. at 11,882 (emphasis added).

B. The Absence of the Raw Data Underlying the Epidemiology Studies Precludes Reliance on These Studies to Change the Current Regulatory Standard.

Principles of sound science dictate that the Agency must have access to all the raw data underlying the epidemiology studies before relying on them to make a regulatory decision. "Accessibility to the raw data would also further an evaluation of the exposure and health groupings, which may not be included in the peer review publications. . . . [T]his would permit an assessment of the reliability of the findings." Burns Decl. ¶ 25. Indeed, "[t]he lack of full accessibility to data and analytical results is a threat to scientifically-valid public health decision making." *Id.* ¶ 24. Moreover, "[a] systematic review of the published data is incomplete without having the complete analytical results to address more complex relationships that are not disclosed in the scientific epidemiology publications." *Id.* In addition, "[t]ransparency of the full scope of exposure data and outcomes, including those that show no effects, for the Columbia, Mt. Sinai and CHAMACOS studies, for example, would permit improved comparisons across studies." *Id.* ¶ 25.

But principles of sound science were not followed with respect to the epidemiology data. As set forth in the following chronology, and summarized on EPA's website, Chlorpyrifos: EPA's Seven Year Quest for Columbia's Raw Data, available at https://www.epa.gov/ingredients-used-pesticide-products/chlorpyrifos-epas-seven-year-quest-columbias-raw-data, EPA repeatedly recognized the need for the raw data and requested the raw data from the Columbia researchers, but did not receive any meaningful raw data in response to its requests:

- January 25, 2013: Letter from Steve Bradbury at EPA to PAN/NRDC, stating that "[i]n order to complete both the dose reconstruction and analyses on other chemical exposures, however, we will need to analyze the original data ('raw data') from the Columbia University study to better understand the exposure to chlorpyrifos and other chemicals. To date, the study authors have declined our request to provide [the raw data] to us, but we are continuing to discuss our need for evaluating these data with the study authors and we are hopeful that a resolution can be reached." Jan. 25, 2013 Ltr. from S. Bradbury to PAN/NRDC at 4, EPA-HQ-OPP-2007-1005-0097.

- April 2013: Meeting between representatives from OPP and Columbia researchers, during which the Columbia researchers did not agree to provide the raw data. Response to Comments at 19. EPA did not provide public notice of the meeting, and there are apparently no minutes or transcripts of the meeting. *See* DAS Response to RHHRA at 28. According to EPA's Response to Comments, the Agency learned during that meeting "that the kinds of exposure information (*e.g.*, timing of applications) requested were not collected by the investigators and therefore unavailable." *Id.* The Agency thus

"concluded that access to the raw data would not provide answers to the EPA's questions." *Id.* The Agency provided no explanation for this conclusion. Moreover, as further discussed in DAS's Response to the 2014 RHHRA, EPA's closed-door meeting with Columbia researchers did not result in the production of the raw data that EPA repeatedly said it needed to be able to use the Columbia study in the Agency's risk assessment. DAS Response to RHHRA at 28.

- Summer of 2015: Another Agency request for raw data, in response to which Dr. Dana Barr of Emory University gave the Agency "limited raw urine and blood data in her possession from the three cohorts." Response to Comments at 19. The Agency described these files as "not useful for the agency's current purpose of assessing risk from chlorpyrifos." *Id.*

- March 29, 2016: EPA released an Issue Paper prior to the April 2016 SAP, in which it provided "additional summary information on the blood biomonitoring data." *Id.* at 20. This summary information did not include raw data.

- April 19, 2016: Letter from Jack Housenger at EPA to Dr. Linda Fried at Columbia University, in which EPA again requested raw data from Columbia researchers, observing that the study was supported by federal grant funds and noting concerns with EPA's ability to "address our transparency goals as well as public feedback regarding access to the original ('raw') data." Apr. 19, 2016 Ltr. from J. Housenger to Columbia University at 2, EPA-HQ-OPP-2008-0850-0871.

- August 1, 2016: Meeting between the Agency and Columbia researchers, during which Columbia "discussed the possibility of the EPA team visiting the data center to work with dataset in a secured enclave, however, EPA stressed that the transparency issue is not resolved by merely allowing access to EPA to the data and not making a dataset available for others to perform their own analysis." Chlorpyrifos Dataset Discussion: Columbia Center for Children's Environmental Health Mothers and Newborns Study at 2 (Aug. 1, 2016), EPA-HQ-OPP-2008-0850-0930.

- January 2, 2018: Letter from Richard Keigwin of EPA to Dr. Linda Fried at Columbia University, in which EPA once again requested dataset in order to address the "well-documented concerns on the reliance of this study in OPP's human health risk assessment for chlorpyrifos," and noting EPA's particular interest in "additional analyses of the available epidemiological studies using the actual data, including examining the log transformation for chlorpyrifos with WISC-IV scores."

- January 8, 2018: Email from Dr. Linda Fried to EPA stating that EPA needs to "clarify the information requests in [EPA's January 2, 2018] letter."

- No apparent progress in obtaining the raw data since EPA's January 2018 request.

This chronology illustrates that there are three categories of raw data at issue regarding the Columbia study: data that do not exist, data that are meaningless, and data that the Columbia researchers have refused to disclose.

As to the first category, EPA learned during a meeting with Columbia that data regarding pesticide product use among cohort participants were of "such poor quality"—essentially, non-existent—that they were of no use in assisting EPA "to better understand the pattern and frequency of organophosphate pesticide use among cohort participants." *See* 2014 RHHRA App. 6, at 387. In addition, the Columbia researchers informed EPA during that meeting that they had no data regarding the impact of postnatal exposures to polycyclic aromatic hydrocarbon ("PAH") on neurodevelopmental outcomes, which the 2012 SAP had identified as a concern because PAH is a "a ubiquitous air pollutant in inner-city areas such as NYC," and could have influenced the reported neurodevelopmental outcomes. *Id.* at 389. EPA's inability to have critical raw data underlying the Columbia study precluded EPA from testing the validity and reliability of the very controversial study results.

As to the second category, the information that Dr. Dana Barr disclosed to EPA was meaningless, and the "summary information" provided by the Columbia researchers to EPA and released prior to the 2016 SAP is insufficient to address concerns about the lack of raw data. This summary information appears to be the information referenced in the 2016 Chlorpyrifos Issue Paper, released prior to the April 2016 SAP. The "summary information" did not allay the 2016 SAP's concerns regarding unavailability of the raw data. Despite having this information at their disposal, the 2016 SAP nevertheless found numerous problems with the Columbia study's findings, and repeatedly criticized the lack of raw data. For example, the SAP stated that:

> [I]t's been said several times, having data would help people draw their own conclusions, including the agency, on how to proceed. . . . *[N]ot having data was just amazing, flabbergasting. What's going on?* . . . In order for a registrant to put a new pesticide on the market or to re-register a pesticide the data has to be very vigorous. Now we're looking at something the opposite. . . . So if we're basing this on one study where it's not been reproduced, you can't get the actual hard data, there's lots and lots of points below levels of detection, one has to give that really serious thought.

2016 SAP Tr. at 494, 766 (emphasis added). EPA may not satisfy its obligation to make regulatory decisions for chlorpyrifos based on reliable data by relying on summary information deemed insufficient by the SAP.

As to the third category of raw data—data in Columbia's possession that EPA has been unable to obtain—as more fully discussed in DAS's January 2017 comments, any EPA reliance on the Columbia study without obtaining and reviewing the underlying raw data would be arbitrary and capricious, in violation of the Administrative Procedure Act ("APA"). *See* DAS Comments on 2016 RHHRA at 59–61. Without all of the raw data from the Columbia study, EPA cannot meet its statutory obligations under the FFDCA to properly consider "the validity, completeness, and reliability of the available data from studies of the pesticide" under FFDCA § 408(b)(2)(D)(i), 21 U.S.C. § 346a(b)(2)(D)(i). *Id.* at 59. *See also* Seed Decl. ¶ 18 ("EPA is unable to assess the 'validity, completeness, and reliability of the data,' as it is statutorily required to do, without the raw data underlying the Columbia study and other epidemiology studies."). In addition, since registrants are required to provide EPA with access to data, Columbia's position creates a double standard. *See also* 2012 Bradbury Letter at 20 ("Registrant generated data, in response to FIFRA and FFDCA requirements, are conducted and evaluated in accordance with a series of internationally harmonized and scientifically peer-reviewed study protocols designed to maintain a high standard of scientific quality and reproducibility.").

DAS submitted a Freedom of Information Act ("FOIA") request to EPA for the raw data underlying the Columbia, Mt. Sinai and CHAMACOS epidemiology studies in December 2015, in response to which EPA released very limited files on March 1 and 2, 2016. However, "[n]one of the data files EPA provided for the Columbia, Mt. Sinai and CHAMACOS Studies in response to DAS's FOIA Request identify whether each study subject was the mother or the child. Such information is critically important to draw any conclusions from the data provided." Burns Decl. ¶ 34. What's more, only a few of the data files EPA provided appeared to be relevant to the Columbia study:

> [O]nly five of the 39 files provided by EPA in response to DAS's FOIA Request appear to have any relevance to the Columbia study. Of those five files, only two files appear to relate to chlorpyrifos levels in blood. Of those two files, one file has 141 unique study subjects and the other has 279 subjects. However, only 29 subjects in each of these two files have values for chlorpyrifos, representing 21% and 10% detection for each file, respectively. This number is vastly inconsistent with the number of blood samples purportedly having detectable levels of

> chlorpyrifos reported in published articles for the Columbia Study. . . . In sum, the data files provided by EPA do not come close to matching the sample sizes or percentages of chlorpyrifos detection reported in published articles for the Columbia study.

Id. ¶ 33.

In addition to these issues, the data files EPA released in response to the FOIA request "fail to provide any information regarding infant or maternal characteristics, or as to the results of any IQ or other neurodevelopment testing. Thus, it is impossible from the information provided by EPA to link any blood or urine samples or any alleged exposures to chlorpyrifos with neurodevelopment impacts." *Id.* ¶ 34. Moreover, "many of the data files are unlabeled and, thus, it is not known to what extent, if any, they are relevant to any of the epidemiology studies." *Id.* ¶ 35. "The deficiencies in the data EPA provided . . . make it impossible for an epidemiologist to draw any meaningful conclusions from the data or to replicate or otherwise support the published epidemiology studies which are purportedly based on the data." *Id.* ¶ 36. Thus, the data EPA provided in response to DAS's FOIA request were "meaningless and cannot be used to assess the accuracy and reliability of the epidemiology studies." *Id.* ¶ 30. The deficiencies in these data are such that "EPA does not have access to meaningful data underlying the Columbia, Mt. Sinai or CHAMACOS epidemiology studies." *Id.* ¶ 36.

In sum, none of the data EPA provided in response to DAS's FOIA request fall into the critical third category of data discussed above—data the Columbia researchers have refused to disclose that are necessary to fairly evaluate the study's conclusions. The data EPA did provide were incomplete and insufficient to assess the accuracy, reliability, and replicability of the Columbia, Mt. Sinai and CHAMACOS studies. Any reliance on the Columbia, Mt. Sinai and CHAMACOS studies in the face of these deficiencies in the raw data would not be consistent with sound and rational science. *See* Seed Decl. ¶ 18 ("Lack of access to raw data limits EPA's ability to assess the strength, accuracy, and generalizability of the Columbia study and other epidemiology studies. It also precludes replication of the research. These are cornerstones of robust scientific inquiry, which are absent from any effort to apply the epidemiology studies to chlorpyrifos."). The 2016 SAP was also deeply concerned that EPA did not have the raw data underlying the Columbia study. *See, e.g.,* 2016 SAP Tr. at 494. By any measure, the lack of access to the raw data for the epidemiology studies is inconsistent with science-based, transparent, and rigorous regulatory risk assessment and decision-making. This is especially true

given that these studies have been so heavily criticized and where the product at issue is of such importance to U.S. agriculture.

C. Even if the Cord Blood Results were Reliable and Valid, Several Factors Other than Exposure to Chlorpyrifos Can Explain the Effects Purportedly Observed in the Columbia Study.

Many factors can influence childhood development—both for better or worse—and could explain the effects purportedly observed in the Columbia study. The Columbia study does not address numerous confounding factors, calling into question the reliability of the study's findings. For example, "[t]he published articles [for the Columbia study] fail to account for iron deficiency and the paternal IQ, and the medical records assessment (*e.g.*, Apgar scores, maternal medication) and analysis are not explained." Dr. Banner Comments to April 2016 SAP at 5, EPA-HQ-OPP-2016-0119 (Apr. 18, 2016) ("Dr. Banner Comments") (citing Lozoff, B. et al., *Long-term Developmental Outcome of Infants with Iron Deficiency*, New England Journal of Medicine, 325: 687-694, Sept. 1991; Hulthén, L. *Iron deficiency and cognition, Scandinavian Journal of Nutrition*, 47(3): 152-156, Feb. 2013).

Other important factors can profoundly influence childhood development, but were similarly unmeasured in the Columbia study. These include nutritional deficiencies (lack of iodine, vitamin D, vitamin B, as well as unhealthy diets, including excessive intake of sugar and fat); exposure to other materials in the environment (such as heavy metals and solvents); and other external stressors. For example, the published articles for the Columbia study "fail to account for socioeconomic stressors, including alcohol and drug use and violence, which have been proven to have a direct impact on neurodevelopmental outcomes." Dr. Banner Comments at 5 (citing Mills, R. et al., *Child Abuse and Neglect and Cognitive Function at 14 Years of Age: Findings From a Birth Cohort*, Pediatrics, 4-10, Dec. 6, 2010; Shonkoff, J.P. *et al.*, *The Lifelong Effects of Early Childhood Adversity and Toxic Stress*, Pediatrics, 129: e232—e246, Dec. 2011; LaGasse, L. *et al.*, *Prenatal Methamphetamine Exposure and Childhood Behavior Problems at 3 and 5 Years of Age*, Pediatrics, 681-88, Mar. 2012; Johnson, S. *et al.*, *The Science of Early Life Toxic Stress for Pediatric Practice and Advocacy*, Pediatrics, 319-327, Feb. 2013). In addition, studies have shown that maternal stress, bereavement, and depression—also unaccounted for by the Columbia study

investigators—can result in decrements in childhood neurodevelopment. (Mink, Kimmel, and Li 2012; Eaton et al. 2008).

"Perhaps most concerning, however, is the published articles' failure to accurately account for gestational age ('GA') as a confounding variable." *Id.* Indeed, "[n]ew lines of research have demonstrated that gestational age has a significant effect on neurodevelopmental outcomes. The difference of even one week in a baby's age at birth can lead to adverse neurodevelopmental effects, including lower scores on the Bayley scales of mental and motor development." *Id.* at 5–6 (citing Espel, E.V. *et al.*, *Longer Gestation among Children Born Full Term Influences Cognitive and Motor Development*, PLOS ONE, Nov. 25, 2014). This research on gestational age "has led to changes in obstetrical practices during the time of the Columbia study." *Id.* at 6.

The Columbia study's authors do not explain how they calculated gestational age, yet:

> [t]he American College of Obstetrics and Gynecology ("ACOG") has guidelines for how to accurately measure gestational age for scientific research purposes, and cautions that, without a first-trimester ultrasound, a measure of gestational age is inaccurate by more than 5 days more than 40% of the time.[6] There is no indication that the Columbia Study investigators measured gestational age in accordance with ACOG guidelines, raising questions as to whether the Columbia Study data on this key covariate are scientifically sound. This is particularly concerning given that gestational age was a consistently significant covariate in the Perera (2003), Wyatt (2004), and Whyatt (2005) articles (indeed *the* strongest covariate in the 2003 Perera and 2004 Wyatt articles), and in light of new research suggesting that gestational age significantly influences neurodevelopmental outcomes.

Id. This failure to account for gestational age is especially concerning given that

> one of the Columbia Study's principal investigators, Dr. Virginia Rauh, co-authored an article in 2012 which found that gestational age was a key factor in predicting neurodevelopmental outcomes in children at eight years of age. This recognition clearly shows that gestational age is an important covariate, and yet the 2006 Rauh, *et al.* article, *Impact of Prenatal Chlorpyrifos Exposure on Neurodevelopment in the First 3 Years of Life Among Inner-City Children,* wholly fails to explain how the researchers measured gestational age. Moreover, in the model reported in the article, which claims to demonstrate an impact at 36 months, well-known covariates such as maternal IQ are not used. Without the underlying raw data and a more detailed explanation, it is impossible to assess whether these important confounding variables were accurately measured or used. The failure to explain how gestational age was measured also taints the sensitivity

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[6] Committee on Obstetric Practice, American Institute of Ultrasound in Medicine, Society for Maternal-Fetal Medicine, *Method for Estimating Due Date*, Comm. Op. No. 611, Oct. 2014.

> analysis for the Columbia Study since the inaccuracy may be 40% or more. Even if the investigators accurately measured gestational age, the inclusion of study subjects with a gestational age as low as 30 weeks and weights as low as 1295 grams in Rauh, *et al.* 2011 casts doubt on the article's conclusions, in light of the demonstrated link between severe prematurity, gestational age and neurodevelopmental outcomes. Indeed, in this article gestational age does not appear to have been used in the model as a covariate. Since birthweight is generally a function of [gestational age], it is also critical to consider whether these babies fell within normative data for weight based on their [gestational age]. Growth that is both small for [gestational age] and large for gestational age poses neurodevelopment risks to the baby at the time of birth.

Id. at 6–7.

In sum, the above alternate explanations for the effects purportedly observed in the Columbia study need to be fully considered and accounted for when assessing the Columbia study.

D. Other Epidemiology Studies Do Not Support the Columbia Study's Findings.

Petitioners' Objections suggest that the CHAMACOS and Mt. Sinai studies lend credibility to the Columbia study, and that they "produced strongly convergent results." Petitioners' Objections at 8. The CHAMACOS and Mt. Sinai studies, however, assessed non-specific organophosphate metabolites in maternal urine and did not examine chlorpyrifos specifically. PHHRA at 31. *See also* 2008 SAP Minutes at 31 ("[M]etabolites not specific to chlorpyrifos exposure were measured and reported [in the CHAMACOS and Mt. Sinai studies], including those of other OPs and carbamates.").

As a preliminary matter, "there are significant problems with the design and execution of the CHAMACOS and Mt. Sinai studies that preclude a determination that the associations observed represent causal ones, and that the contributions of chance, bias and confounding cannot be ruled out." Declaration of Dr. Gregory Bond ("Bond Decl."), Attach. E. ¶ 27. *See also* 2008 SAP Minutes at 36 ("The Panel acknowledged that there are potential confounders and issues that reduce the utility of both the Mt. Sinai and [CHAMACOS] cohorts for risk assessment. For example, both studies measure organophosphate metabolites in urine but chlorpyrifos is not specifically measured."). Further, "[w]ith respect to infant health, the CHAMACOS and Mount Sinai studies estimated chlorpyrifos reported exposure using the metabolite urinary 3,5,6-trichloro-2-pyridinol (TCPy) in maternal urine prior to delivery. The

data failed to show a statistically significant association of chlorpyrifos exposure and head circumference, birth weight or birth length." Burns Decl. ¶ 16. "Uniquely, the CHAMACOS study collected two urine samples during pregnancy and annually from the developing child. None of the urinary TCPy measures were reported to be associated with any adverse outcomes, including any neurodevelopmental outcomes measured." *Id.* ¶ 21. The CHAMACOS and Mt. Sinai studies have also not replicated hypotheses generated by the Columbia study:

> Working Memory (a domain of the Wechsler scale of intelligence (IQ) test) is another example for which other study results have not replicated the hypotheses generated by the Columbia study. While inversely associated with chlorpyrifos in plasma in the Columbia study children, Working Memory was not statistically associated with the urinary metabolite DEP in the CHAMACOS or Mt. Sinai studies. Two other similarly designed studies, (the Health Outcomes and Measures of the Environment Study conducted in Cincinnati, Ohio and the PELAGIE study in France), also did not replicate the Columbia study IQ findings.

Id. ¶ 19.

Moreover, the CHAMACOS and Mt. Sinai studies did not confirm the Columbia study's purported findings regarding attention-deficit hyperactivity disorder ("ADHD"):

> Among school age children, the Columbia study investigators reported that chlorpyrifos levels were associated with ADHD problems as measured with the Child Behavior Checklist ("CBCL") (OR = 6.50, 95% CI 1.09–38.69) (Rauh *et al.* 2006), but this association was not replicated in the CHAMACOS study using the mean of 2 prenatal urinary metabolite diethylphosphate (DEP) concentrations (OR = 0.59, 95% CI 0.21–1.68) (Eskenazi *et al.* 2007). The urinary metabolite, TCPy, that is more specific to chlorpyrifos than DEP, was not associated with any outcome in the CHAMACOS study. Further, the two publications of attention problems from the CHAMACOS study have mixed results across age groups of the children and different urinary organophosphate metabolites (Eskenazi *et al.* 2007, Marks *et al.* 2010). ADHD was not evaluated by the Mt. Sinai study. The CHAMACOS and Mt. Sinai studies therefore do not confirm the Columbia study's observations regarding ADHD.

Id. ¶ 17.

In sum, "[t]he neurodevelopmental outcomes have been overgeneralized across studies. The specific results are not reproduced from the other studies, which severely undermines any claim of a link between neurodevelopment effects and chlorpyrifos exposures." *Id.* ¶ 22. Thus, "[w]hen considering statistical testing in total across all studies, the other studies do not support or replicate the Columbia outcomes." *Id.* ¶ 20. Additionally, "[r]eliance on unreplicated epidemiology studies lacks scientific vigor, is contrary to Agency policies of data access and

transparency in scientific decision-making, [and] disregards EPA's statutory obligations to make decisions based on valid, complete, and reliable scientific data[.]" *Id.* ¶ 10. Reliance on unreplicated studies also "ignores a critical, scientifically robust database of toxicological and other studies submitted to EPA showing that current uses of chlorpyrifos meet relevant safety standards." *Id.*

Prior FIFRA SAPs have identified limitations with the Columbia, CHAMACOS, and Mt. Sinai studies, For example, the 2012 SAP, convened to review the Agency's preliminary conclusions regarding a "weight-of-evidence" approach to integrating epidemiologic research in its assessment of neurodevelopmental outcomes, observed that the studies were insufficient to derive a PoD. The panel recognized "the limitations of estimating chlorpyrifos exposures based on the exposure measures collected in [the Columbia study, the Mt. Sinai study, and the CHAMACOS study]" and thus "concur[red] with EPA that the data generated from these studies alone [were] not adequate enough to obtain a point of departure (POD) for the purposes of quantitative risk assessment." 2012 SAP Minutes at 19; *see also id.* at 50 ("[T]he use by the three studies of different exposure matrices . . . and different targeted analytes . . . [made] the effort of deriving a definitive POD based on those data alone impossible."). Importantly, the Panel found that the three epidemiology studies under consideration, including the Columbia study, "were primarily focused on assessing health outcomes associated with a variety of environmental factors, and were not designed to conduct a quantitative exposure assessment for chlorpyrifos." *Id.* (emphasis added).

The 2008 SAP also identified deficiencies in the Columbia, CHAMACOS and Mt. Sinai epidemiological studies: "[o]ne of the key limitations of the epidemiological studies is that the exposure data were collected at single time point and lack information on the long-term exposure level and duration." 2008 SAP Minutes at 45. A second key limitation the Panel identified was that "the subjects in two of the cohort studies [Mt. Sinai and CHAMACOS] had multiple chemical exposures including multiple AChE-inhibiting insecticides[.]" *Id.*

In addition, multiple published reviews of epidemiologic findings of Columbia, Mt. Sinai, and CHAMACOS describe the evidence as inadequate, inconsistent, and implausible (Eaton *et al.* 2008; Li *et al.* 2012; Mink *et al.* 2012; Needham 2005; Weselak *et al.* 2007; Zhao *et al.* 2005). Similarly, the authors of a hypothesis-based weight of evidence analysis of chlorpyrifos concluded that the epidemiologic data were inconsistent. Prueitt *et al.* (2011). In

short, the results of these birth cohort studies are conflicting and contradictory and do not implicate chlorpyrifos as a developmental toxicant. *See* Burns Decl. ¶ 20 ("When considering statistical testing in total across all studies, the [CHAMACOS and Mt. Sinai] studies do not support or replicate the Columbia outcomes.").

Indeed, as time has passed, more epidemiology studies have been conducted examining purported links between chlorpyrifos exposure and neurodevelopmental outcomes. Far from supporting the findings of the Columbia, CHAMACOS, and Mt. Sinai studies, this growing body of literature is confirming the opposite conclusion—that there is no consistent, clear evidence of associations between prenatal or childhood exposure to chlorpyrifos at levels below the current regulatory standard and adverse neurodevelopmental effects, including autism spectrum disorders ("ASD") and intelligence. *See, e.g.,* Schmidt *et al.* 2017 (no or non-significant association between chlorpyrifos exposure and ASD); Coker *et al.* 2017 and Gunier, Bradman, Harley, Kogut, *et al.* 2017 (no significant relationship between chlorpyrifos use and Full Scale IQ). Even a more recent publication by the CHAMACOS study investigators that examined residential proximity to chlorpyrifos use found no statistically significant associations between chlorpyrifos use and ASD-related traits. Sagiv *et al.* 2017.

VII. LEGAL FRAMEWORK

A. The FQPA and FFDCA, Including the Safety Factor Provision, Are Not Statutes Based on the Precautionary Principle.

Regulatory decisions under the FQPA and FFDCA, including the application of a safety factor, should be guided by two fundamental threshold principles. First, the food safety standard under the FFDCA and the FQPA is based on reasonable certainty of no harm, *not* absolute certainty of no harm. *See* Seed Decl. ¶ 16. While "a reasonable certainty of no harm" is not expressly defined in these two statutes, the term is described in the history of the 1958 Food Additives Amendments to the FFDCA with respect to the safety standard that the Food and Drug Administration is to apply in approving food additives under FFDCA § 409. In those amendments, Congress made it clear that the safety determination under the reasonable certainty of no harm standard does not require absolute proof of safety: "Safety requires proof of a reasonable certainty that no harm will result from the proposed use of an additive. It does not—and cannot—require proof beyond any possible doubt that no harm will result under any

conceivable circumstance." S. Rep. No. 2422, 85th Cong., 2d Sess. 6, *reprinted in* 1958 U.S.C.C.A.N. 5300, 5305; *see also* H.R. Rep. No. 2284, 85th Cong., 2d Sess. 4-5 (1958). FQPA established a single regulatory framework under FFDCA § 408 for pesticide residues in both raw and processed foods. *See* H.R. Rep. No.104-669, pt. 2, 104th Cong. 2d Sess. 43, *reprinted in* 1996 U.S.C.C.A.N. 1268, 1282; Food Quality Protection Act of 1996, Pub. L. No. 104-170, § 402, 110 Stat. 1489, 1513 (1996). Prior to that time, EPA was responsible for establishing any food additive regulations needed under FFDCA § 409 for pesticide residues in processed foods that exceeded the levels set in tolerances for raw agricultural commodities by EPA under FFDCA § 408.

Clear from the foregoing is that FQPA and FFDCA are not statutes based on the precautionary principle, under which all doubt must be exhausted before tolerances may be established for a crop protection product. Attempting to capture any doubt whatsoever to create "uncertainties" for purposes of applying an FQPA safety factor of 10X may be consistent with the precautionary principle, adopted by certain other countries, but it is not consistent with the statutory standard of reasonable certainty of no harm here in the United States.

B. The Agency Must Have Valid, Reliable Data to Make Regulatory Decisions, Including to Set a Safety Factor.

The second fundamental threshold principle that must guide the Agency is that its decisions must be based on valid, reliable data. This is especially true in deciding whether to apply a safety factor. Specifically:

- Tolerance revocations must be based on valid and reliable science – i.e., based on "the validity, completeness, and reliability of the available data from studies of the pesticide chemical and pesticide chemical residue[s]." FFDCA § 408(b)(2)(D)(i), 21 U.S.C. § 346a(b)(2)(D)(i). The application of a safety factor in order to revoke a tolerance is subject to no less a standard of validity, completeness, and reliability.

- "EPA uses available, *reliable* data when considering the need to raise, retain, modify, or remove the 10-fold additional safety factor." EPA, Progress Report: Implementing the Food Quality Protection Act (1999) ("EPA Progress Report") at 18 (emphasis added).

- Data that are not replicable, and in some cases not available, are not reliable. "In the context of epidemiology, reliability general[ly] refers to the ability to reproduce results . . . ." EPA, Draft Framework for Incorporating Human

Epidemiologic & Incident Data in Health Risk Assessment at 18 (Jan. 7, 2010) at 18 ("Draft Framework").

- Data that do not accurately reflect exposure are not valid. "In the context of epidemiology . . . validity generally refers to the extent that exposure estimates reflect true exposure levels." *Id.*[7]

Further, while "EPA considers all relevant data in its risk assessment analysis, [it] should act on only *reliable and valid* data. The same is true for FQPA safety factor determinations." Seed Decl. ¶ 14 (citing EPA, Determination of the Appropriate FQPA Safety Factor(s) in Tolerance Assessment ("Safety Factor Policy") at 29, 31 (2002) ("As part of the toxicological considerations, OPP evaluates potential pre- and postnatal toxicity on a case-by-case basis taking into account all pertinent information. . . . As in any weight-of-evidence approach, it is important to consider the *quality and adequacy of the data*, and the consistency of responses induced by the chemical across different studies.") (emphasis added)); EPA Progress Report, at 18.

In addition, tolerances cannot be revoked without valid and reliable data because registrants have a protectable property interest in their registration. *Indus. Safety Equip. Ass'n v. EPA*, 656 F. Supp. 852, 856 (D.D.C. 1987), *aff'd*, 837 F.2d 1115 (D.C. Cir. 1988) ("It is well settled that an agency license can create a protectible [sic] property interest, such that it cannot be revoked without due process of law."); *Reckitt Benckiser, Inc. v. Jackson*, 762 F. Supp. 2d 34, 45 (D.D.C. 2011) ("A FIFRA registration is essentially a license to sell and distribute pesticide products in accordance with the terms of the registration and the statute."); Mem. & Order, *Pesticide Action Network of N. Am. v. EPA*, No. C 08-01814 MHP, at 4 (N.D. Cal. July 8, 2008), ECF No. 43 ("The registrations involved here are essentially government licenses to produce,

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[7] EPA has also recognized the need for *valid, reliable* data in other contexts. For example, FIFRA's interim administrative review provision states that "the Administrator may not initiate a public interim administrative review process to develop a risk-benefit evaluation of the ingredients of a pesticide or any of its uses prior to initiating a formal action to cancel, suspend, or deny registration of such pesticide, required under this subchapter, *unless such interim administrative process is based on a validated test or other significant evidence* raising prudent concerns of unreasonable adverse risk to man or to the environment." 7 U.S.C. § 136a(c)(8) (emphasis added). The term "validated test" is defined as "a test conducted and evaluated in a manner consistent with accepted scientific procedures," and the term "other significant evidence" is defined as "evidence that relates to the uses of a pesticide and their adverse risk to man or to the environment." Pesticides/Interim Administrative Reviews, Proposed Definitions of "Validated Test" and "Other Significant Evidence," 44 Fed. Reg. 9626, 9627 (Feb. 14, 1979).

distribute and sell pesticides . . . [and] therefore constitute property[.]"). It is therefore essential that the Agency have valid and reliable data and conduct a thorough, science-based assessment for its regulatory decision-making.

C. EPA Addressed the FQPA's 10X Safety Factor Provision by Relying on a Robust Set of Animal Toxicological Data that Accounted for Children's Susceptibility.

Starting in 2014 with the RHHRA, EPA has suggested that it should raise the FQPA safety factor to 10X due to "uncertainty" derived by the Agency on the basis of the Columbia study and other epidemiology studies. But that approach is not consistent with Agency guidance on setting safety factors. EPA's Safety Factor Policy states that "[i]f toxicity data indicate no concern for pre- and postnatal toxicity, then the risk assessor should treat the presumption for use of the default 10X safety factor as having been obviated with respect to the potential for pre- and postnatal toxicity." Safety Factor Policy at 29. Additionally, EPA "does not establish FQPA safety factors for chemicals based on speculation or the elimination of all possible doubt." Seed Decl. ¶ 16. Here, the Agency has "toxicity data in the form of robust and reliable animal studies which address children's susceptibility and showed no concern for pre- and postnatal toxicity." *Id* ¶ 23. The Agency therefore set a safety factor of 1X for chlorpyrifos in its 2006 Cumulative Risk Assessment. EPA thus addressed the FQPA 10X safety factor provision with a robust and reliable set of animal data. Due to their significant limitations and deficiencies, the epidemiology studies do not change this outcome.

It is clear from the FQPA that EPA cannot raise the safety factor to 10X based on data that do not meet standards of reliability and validity when the Agency has already made a safety factor determination based on a robust and reliable set of animal data that account for children's susceptibility. Seed Decl. ¶ 23 ("Studies like the Columbia study that are not reliable for regulatory decision-making cannot be used to increase that 1X safety factor determination.").

When Congress passed the FQPA, it did not contemplate that unreliable epidemiology studies could be used to upset the Agency's safety factor determination that was based on a complete, reliable set of animal toxicology data that accounts for children's susceptibility. "[T]he focus of EPA's 10X safety factor determination has been on the robustness and completeness of the animal toxicology data set." *Id.* ¶ 21. Indeed, DAS is not aware of any other chemical for which EPA had a complete, reliable animal toxicology data set supporting an FQPA safety factor below 10X, as is the case for chlorpyrifos, but relied on epidemiology

studies having numerous issues regarding validity and reliability and for which the underlying raw data were unavailable to drive up the FQPA safety factor to 10X. *See id.* ¶ 23. Here, "the epidemiology studies that are currently available with respect to chlorpyrifos exposure and possible neurodevelopmental effects are not valid and reliable for purposes of showing that there is an exposure hazard for chlorpyrifos that is not already accounted for in the current regulatory standard, and cannot be used to increase the Agency's 1X safety factor determination." *Id.* ¶ 4. The toxicological studies advanced as supporting epidemiology research linking chlorpyrifos exposure and neurodevelopmental effects are similarly not reliable as a basis for increasing the Agency's safety factor determination. *See, e.g.,* Section V.A., *supra*; Appendix A.

D. EPA Cannot Rely on the Epidemiology Studies for Regulatory Decision-Making without the Underlying Raw Data.

As detailed in DAS's prior comments, EPA's reliance on the Columbia study (or any of the additional epidemiology studies) without access to the raw data would violate principles of sound science, Agency policies regarding data access and transparency, and SAP guidance, and would be arbitrary and capricious. *See, e.g.,* DAS Comments on 2016 RHHRA at 59–61. In particular, OMB Circular A-110 mandates the public disclosure of data underlying federally funded studies used to develop agency action that has the force and effect of law. Moreover, without all of the raw data from the Columbia study and other epidemiology studies upon which the Agency may rely, EPA could not meet its statutory obligations under the FFDCA to properly consider "the validity, completeness, and reliability of the available data from studies of the pesticide." FFDCA § 408(b)(2)(D)(i), 21 U.S.C. § 346a(b)(2)(D)(i). In addition, without the underlying data from the Columbia study and other epidemiology studies, results cannot be replicated and are therefore not reliable under the FFDCA. *See* DAS Comments on 2016 RHHRA, § VII.

Several courts have held that an agency must have and make available all of the raw data underlying a study in order to rely on that study for rulemaking, and that such data must be "reliable." *See, e.g., United States v. Nova Scotia Food Prods. Corp.*, 568 F.2d 240, 251 (2d Cir. 1977) (failure to disclose scientific data relied upon by agency in fashioning a proposed rule prevented the agency from considering all "the relevant factors," made the rule procedurally erroneous and therefore invalid); *NRDC v. EPA*, 658 F.3d 200, 218 (2d Cir. 2011) (EPA had acted in an arbitrary and capricious manner by relying on a study that was not "reliable data" to

lower the FQPA safety factor); *Endangered Species Comm. of Bldg. Indus. Ass'n v. Babbitt*, 852 F. Supp. 32, 36–38 (D.D.C. 1994), *as amended on reconsideration* (June 16, 1994) (observing that "where an agency relies upon data to come to a rulemaking decision, it generally has an obligation under the APA to provide such data for public inspection[,]" and holding that agency's failure to make data available to interested parties violated the APA). *See also Zero Zone, Inc. v. U.S. Dep't of Energy*, 832 F.3d 654, 670 (7th Cir. 2016) (observing that "[s]everal of our sister circuits have held that among the information that must be revealed for public evaluation are the technical studies and data upon which the agency relied") (internal quotation marks and citation omitted).

It has been suggested in the past that *Coalition of Battery Recyclers Ass'n v. EPA*, 604 F.3d 613 (D.C. Cir. 2010), and *American Trucking Ass'ns v. EPA*, 283 F.3d 355 (D.C. Cir. 2002) stand for the proposition that EPA need not obtain the raw data. Both cases are readily distinguishable. In *Coalition for Battery Recyclers*, the petitioners failed to raise the need for the raw data until rebuttal at oral argument, and failed to identify errors that would make reliance on the study at issue arbitrary and capricious. In *American Trucking*, the agency was not relying on a taxpayer-funded study to take unprecedented regulatory action in the absence of underlying raw data, nor was there any indication that EPA failed to request and disclose the data in response to a FOIA request pursuant to OMB Circular A-110. In contrast, here, EPA is required to request and disclose the raw data underlying the Columbia study, which was supported by federal funds, in response to numerous FOIA requests submitted by DAS and others (most recently on August 19, 2016), pursuant to OMB Circular A-110, and EPA itself has repeatedly requested the raw data from the Columbia researchers, who have refused to provide them.[8]

[8] Indeed, if EPA were to shift course again and proceed with revoking all tolerances and canceling chlorpyrifos registrations, its failure to disclose the raw data on which its proposed rule was based would be procedurally deficient. *See Shands Jacksonville Med. Ctr. v. Burwell*, 139 F. Supp. 3d 240 (D.D.C. 2015) (observing that "it is especially important for the agency to identify and make available technical studies and data that it has employed") (quoting *Conn. Light & Power Co. v. Nuclear Reg. Comm'n*, 673 F.2d 525, 530 (D.C. Cir. 1982)); *Wash. Trollers Ass'n v. Kreps*, 645 F.2d 684, 686 (9th Cir. 1981) (agency must disclose data underlying proposed regulation so that public can provide meaningful comment).

VIII. DAS'S SPECIFIC RESPONSES TO THE OBJECTIONS

As set forth above, the Agency has a robust set of reliable animal toxicological data that support the current regulatory standard for chlorpyrifos. Petitioners and the States raise additional specific objections, set forth below, none of which are supported by the applicable law, the scientific evidence, or the regulatory history for chlorpyrifos.

A. The Objections Misrepresent the Scientific and Regulatory History for Chlorpyrifos.

The Objections contain numerous misstatements and inaccuracies regarding the scientific and regulatory history for chlorpyrifos. As is evident from Sections V–VI, *supra*, (and DAS's prior comments), the Objections are simply flat-out wrong to suggest that the lack of safety for chlorpyrifos at exposure levels below the current regulatory standard is uncontroverted. To the contrary, FQPA's standard of reasonable certainty of no harm continues to be met by a robust, reliable, and valid dataset.

Petitioners' misrepresent the scientific record, cherry-picking statements that they assert support their claims and insisting incorrectly that the science is beyond dispute and that only "purely legal issues" are presented in their Objections. Petitioners also present the Columbia and other epidemiology studies as if they were new evidence, misleadingly referring to the "growing body of published scientific research" allegedly linking chlorpyrifos exposure with adverse neurodevelopmental outcomes. Petitioners' Objections at 8. But Columbia researchers started publishing in 2002 on exposure, with the infant outcome studies first appearing in 2004. EPA was thus aware of the Columbia study results when it reaffirmed its confidence in the current regulatory standard, and the complete database of animal toxicology studies underpinning that standard, several times, including as recently as March 2015. *See* PHHRA at 7 ("[C]holinesterase inhibition (ChEI) provides the most sensitive dose-response information for deriving points of departure for chlorpyrifos."); *id.* at 22, 36 ("The toxicological database for chlorpyrifos is extensive and is adequate to support the registration review."); 2014 RHHRA at 24 ("[Acetylcholinesterase] inhibition remains the most robust quantitative dose response data and thus continues to be the critical effect for the quantitative risk assessment."); EPA's March 26, 2015 Ltr. to PAN/NRDC, *PANNA II*, ECF No. 14, Attach 1 at 3. SAPs convened during that time period also supported the continued use of cholinesterase inhibition as the PoD.

In another misstatement, the Objections assert that the 2011 PHHRA found that "chlorpyrifos likely played a role in long term neurological effects from early exposures that were evaluated in the epidemiology studies." Petitioners' Objections at 15. That is incorrect. Neither the PHHRA nor the PHHRA Reader's Guide made such a statement.

The Objections also repeatedly and wrongly assert that EPA has made negative "findings" and "determinations" about the safety of chlorpyrifos. In fact, however, EPA has made no final, reviewable determinations regarding the safety of chlorpyrifos that have changed its 2006 final determination that the use of chlorpyrifos consistent with the current regulatory standard presents a reasonable certainty of no harm. *See* EPA, Finalization of Interim Reregistration Eligibility Decision (IREDs) and Interim Tolerance Reassessment and Risk Management Decisions (TREDs) for the Organophosphate Pesticides, and Completion of the Tolerance Reassessment and Reregistration Eligibility Process for the Organophosphate Pesticides, July 31, 2006 ("EPA has concluded, after completing its assessment of the cumulative risk associated with exposures to all of the OPs, that . . . the pesticide tolerances [for chlorpyrifos] . . . meet the safety standard under Section 408(b)(2) of the FFDCA"). This is the only final determination regarding the safety of chlorpyrifos tolerances that is currently in effect, as EPA's Registration Review of chlorpyrifos is ongoing. *See New York v. EPA*, 350 F. Supp. 2d 429, 435–36 (S.D.N.Y. 2004) ("[T]he issuance of a RED, whether it be one revoking, modifying, or leaving in place a tolerance, constitutes the agency's final determination, at the conclusion of a statutorily mandated review process, on the safety of the tolerance in question."), *aff'd sub nom. Nat. Res. Def. Council v. Johnson*, 461 F.3d 164 (2d Cir. 2006).

Though EPA complied with the Ninth Circuit's mandamus order when it denied the Petition, EPA has not yet taken any final agency action subject to judicial review that departs from its 2006 final determination. To the contrary, the statements EPA made prior to its Petition denial were part of the Agency's non-binding, deliberative process. In particular, EPA's March 2015 letter to Petitioners indicating the Agency's intention to deny the Petition, its October 2015 Proposed Rule, and its 2014 and 2016 risk assessment proposals with respect to neurodevelopmental impacts purportedly linked to chlorpyrifos exposure represent the Agency's deliberations on potential agency action but are not final decisions that are binding on the Agency. *See Nat'l Ass'n of Home Builders v. Defs. of Wildlife*, 551 U.S. 644, 658–59 (2007) ("[F]ederal courts ordinarily are empowered to review only an agency's final action, and the fact

that [an agency's] preliminary determination . . . is later overruled at a higher level within the agency does not render the decisionmaking process arbitrary and capricious.").

EPA has itself acknowledged the tentative, non-binding nature of its recent risk assessments with respect to chlorpyrifos. EPA Order at 16,590 ("EPA has three times presented *approaches* and *proposals* to the FIFRA SAP for evaluating [the] recent epidemiologic data.") (emphasis added). And EPA has in the past characterized pesticide risk assessments as preliminary, interim steps in the agency decision-making process. For example, in a 2001 lawsuit against the Agency, EPA sought dismissal of a challenge to EPA's cancer reassessment for pyrethins and EPA's not yet completed risk assessment for dioxin on the grounds that "[b]oth the challenged actions are just interim steps in ongoing agency processes" and "not 'final agency action' so as to be reviewable under the [APA]." *See, e.g.,* Mot. Filed by Fed. Def. to Dismiss Compl. for Lack of Jurisdiction, *Tozzi v. EPA*, No. 1:00-CV-02604 (D.D.C. Feb. 5, 2001), ECF No. 14. EPA observed that a number of regulatory and scientific issues related to pyrethins remained "in flux" and that its evaluation of human health risks of dioxin and consideration of public comments on its latest assessment were ongoing.

It is well-established that agencies may depart from prior proposals and assessments in the course of the regulatory decision-making process. *See Nw. Coal. for Alts. to Pesticides (NCAP) v. EPA*, 544 F.3d 1043, 1051 (9th Cir. 2008) (according deference to EPA's decision to await results of certain studies before establishing pesticide tolerances, even though this departed from the Agency's prior position); *Ctr. for Biological Diversity v. U.S. Forest Serv.*, No. CV-09-8116-PHX-FJM, 2009 WL 3740732, at *3 (D. Ariz. Nov. 5, 2009), *aff'd*, 408 F. App'x 64 (9th Cir. 2011) (upholding agency decision to depart from preliminary biological assessments regarding a forest fire project, reasoning that "[r]efinement and modifications of positions are a natural part of the deliberative process" and an "agency is entitled to change its mind"). Moreover, EPA's Order is hardly the abrupt 180 degree turnabout Petitioners seek to portray, given that as recently as March 2015 EPA notified the Ninth Circuit and the Petitioners of its intention to *deny* the Petition. In fact, it was EPA's June 2015 status report in the mandamus action announcing its intention to grant the petition and subsequent Proposed Rule—which proposed to replace decades of established science with a single, unreplicated epidemiology study as the basis for major regulatory action—that marked an unprecedented sea change in the Agency's decision-making process. *See* Status Rep., No. 14-72794, ECF No. 20. Simply stated,

the EPA statements recounted by the Objectors were tentative, non-binding statements that were not "sufficiently final [for the Agency] to demand compliance with [an] announced position," *Ciba-Geigy Corp. v. EPA*, 801 F.2d 430, 436 (D.C. Cir. 1986).

EPA's Order recognizes that its assessments and proposals during 2015–2016 were based on inconclusive science that was not sufficient to support final regulatory action. Petitioners' assertions that EPA has already made conclusive "findings" ignore the non-binding, tentative nature of EPA's deliberative process. Objectors, through the administrative process provided under FFDCA and FIFRA for resolution of their objections, "still enjoy[] an opportunity to convince the agency to change its mind." *Id.*

The Objections ignore that EPA's Order is also consistent with recent findings in the European Union and Australia. *See, e.g.,* APVMA, Reconsideration of Chlorpyrifos, *supra* at 5. Notably, the EFSA as recently as 2014 conducted a reevaluation of chlorpyrifos-related toxicology and selection of regulatory endpoints for human health on behalf of the European Commission (EFSA, 2014). Chlorpyrifos had been included in Annex I (list of approved active substances) to Directive 91/414/EEC during 2006 as part of the EU Review process. In 2012, a data call-in for submission of new studies completed since the time of the EU Review was issued, and these new studies were first evaluated by Spain, the rapporteur member state, and subsequently subjected to peer review under the auspices of EFSA. The result of the EFSA peer review was that "[t]he experts agreed on the use of the Red Blood Cell cholinesterase inhibition to derive the reference values." EFSA J. 2014; 12(4):3640 at 2. This represented a change in approach in that, previously, endpoints for chlorpyrifos and other organophosphorus insecticides had been established based on brain cholinesterase inhibition and/or observation of cholinergic symptoms, which was less conservative than use of Red Blood Cell cholinesterase inhibition. Accordingly, EFSA took its recommendations for further peer review by its Panel on Plant Protection Products and their Residues ("PPR Panel") during 2014. The PPR Panel endorsed the proposed acetylcholinesterase-based Acceptable Daily Intake, Acute Reference Dose, and Acceptable Operator Exposure Level proposed by EFSA. PPR Panel Minutes at 9. This action thus aligned the endpoint with the RBC ChE inhibition endpoint currently used by EPA.

As part of the European Commission reevaluation of chlorpyrifos toxicology and human health (EFSA, 2014), EFSA paid particular attention to several epidemiology studies, including the Columbia study (Lovasi *et al.* 2011; Rauh *et al.* 2012; Rauh *et al.* 2011; Rauh *et al.* 2006;

Whyatt *et al.* 2009; Whyatt *et al.* 2007; Whyatt *et al.* 2004), the Mt. Sinai study (Berkowitz *et al.* 2004; Engel *et al.* 2007; Engel *et al.* 2011), and the CHAMACOS study (Bouchard *et al.* 2011; Eskenazi *et al.* 2004; Eskenazi *et al.* 2010; Eskenazi *et al.* 2007; Harley *et al.* 2011; Marks *et al.* 2010; Young *et al.* 2005). The EFSA peer review made the following conclusion regarding these studies:

> The epidemiology data are not sufficiently robust to support the hypothesis that CPF is a causal factor for neurodevelopmental effects. Exposures in the epidemiology studies are at least 1000-fold lower than those used in the animal studies, but the animal toxicity data do not provide clear evidence that CPF is associated with neurodevelopmental effects at doses that are below the threshold for inhibition of AChE in the brain.... Although multiple mechanisms have been proposed to explain the neurodevelopmental effects of chlorpyrifos, a coherent mode of action with supportable key events, particularly with regard to dose response and temporal concordance, has not been elucidated yet.

EFSA. (2014). Final addendum to the Art. 21 Review on chlorpyrifos – public version – Initial risk assessment provided by the Rapporteur Member State Spain for the existing substance CHLORPYRIFOS as referred to in Article 21 of regulation (EC) No. 1107/2009. February, 2014. Chapter: Add. III to Vol. 3, Ch. 6 to DAR. Pg. 53–54. Moreover, university researchers (Ntzani *et al.* 2013), under contract with EFSA reviewed the epidemiology studies published since 2006. Ntzani *et al., Literature review on epidemiological studies linking exposure to pesticides and health effects*, EFSA supporting publication 2013:EN-497. They concluded there is no evidence to suggest an association between pesticide exposure, including chlorpyrifos, and neurodevelopmental effects.

B. Chlorpyrifos Does Not Present a Volatilization Risk at the Current Regulatory Standard.

Petitioners claim that there is "extensive evidence that drift is reaching people and causing poisonings" and "EPA . . . found that chlorpyrifos can drift in harmful amounts." Petitioners' Objections at 12. Petitioners further assert that the DAS volatilization studies do not support EPA's finding of no risk from volatilization. *Id.* at 13–14.

However, EPA's 2014 Revised Human Health Risk Assessment ("RHHRA"), at 10, stated that "there are no anticipated risks of concern from exposure to the volatilization of either chlorpyrifos or chlorpyrifos oxon:"

> EPA lacked chlorpyrifos vapor toxicity data at the time it conducted the preliminary volatilization assessment in 2013. Following the release of the preliminary volatilization assessment, Dow AgroSciences LLC conducted . . . high quality nose-only vapor phase inhalation toxicity studies for both chlorpyrifos and chlorpyrifos-oxon to address this uncertainty. . . . Because these new studies demonstrated that no toxicity occurred even at the saturation concentration, which is the highest physically achievable concentration, then there is no anticipated risks of concern from exposure to the volatilization of either chlorpyrifos or chlorpyrifos oxon. In June 2014, the January 2013 volatilization assessment was revised to reflect these findings.

RHHRA at 83–84.

Petitioners have presented no evidence that chlorpyrifos poses risks from volatilization at the current regulatory standard,[9] or that DAS's volatilization studies do not support the Agency's prior findings. Indeed, in its 2013 Preliminary Evaluation of the Potential Risks from Volatilization for chlorpyrifos, the Agency stated that "the available data are insufficient to directly link respiratory effects to chlorpyrifos volatilization exposure." EPA, Chlorpyrifos; Preliminary Evaluation of the Potential Risks from Volatilization, Docket EPA-HQ-OPP-2008-0850-0114 at 20 (Jan. 31, 2013).

Petitioners also wrongly assert that there was a "lack of controls in the [DAS] study that demonstrated that the experiment was capable of successfully producing or detecting cholinesterase inhibition. Without such controls, the study results cannot be interpreted or used to claim that chlorpyrifos volatilization does not produce cholinesterase inhibition." Petitioners' Objections at 14. Petitioners' assertion is incorrect—the studies show tissue-specific cholinesterase activity, which is consistent across both the chlorpyrifos and oxon vapor studies. There were controls in both studies, and the studies measured the blood levels of the parent and the metabolite TCP, which proves that the animals were exposed and that the inhaled parent molecule was bioavailable. Further, the data from the chlorpyrifos aerosol study clearly shows that the same validated cholinesterase activity assay can detect inhibition if the systemic dose is

[9] Petitioners cite to an incident in which farmworkers in Kern County, California, were allegedly "poisoned" by chlorpyrifos exposure as a result of a company's spraying of a product containing chlorpyrifos on a nearby farm. However, investigators found that the company had improperly sprayed the chemical because it used a nozzle that violated the pesticide's label requirements. *See* https://ww2.kqed.org/news/2017/08/08/produce-company-behind-popular-cuties-fined-over-pesticide-drift/.

sufficient to inhibit ChEI. Finally, the volatilization studies were conducted according to Good Laboratory Practices.

Petitioners claim that volatilization rates could differ based on differing environmental conditions, but the toxicity study was done using the maximum amount of chlorpyrifos. Thus, the air could hold at saturation regardless of the rate of any release into the air, and rate of flux from the soil is therefore irrelevant.

Finally, any volatilization loss off site from treated fields would be expected to be low and very temporary and would not represent a chronic exposure or even significant acute exposure. Air monitoring data collected in California by the state supports this conclusion.

C. Petitioners Misrepresent the 2008 SAP's Findings.

Petitioners misleadingly suggest that the 2008 "SAP confirmed EPA's conclusion that early life exposures to chlorpyrifos pose a risk of long-lasting, adverse cognitive, behavioral, and motor impairments." Petitioners' Objections at 2; *see also id.* at 14–16. But the 2008 SAP did not make a conclusive determination about chlorpyrifos' potential for causing neurodevelopmental effects. Petitioners also fail to mention that the 2008 SAP found that "cholinesterase inhibition should continue to be used for PoD until, at such time[,] an alternative mode of action is identified and validated." 2008 SAP Minutes at 12. The Panel further stated that the Columbia, Mt. Sinai, and CHAMACOS epidemiology studies "should not be considered as the principal basis for characterization of the PoD." *Id.*

In addition, while Petitioners state that "[t]he Panel found that 'chlorpyrifos likely played a role in the birth and neurodevelopmental outcomes noted in the three cohort studies,'" Petitioners' Objections at 14, they fail to acknowledge that the Panel went on to state that "*it cannot be stated that chlorpyrifos is the sole contributor to the observed outcomes*," 2008 SAP Minutes at 37 (emphasis added). The Panel also stated that "[c]onfounding factors in the Mt. Sinai and [CHAMACOS] studies, particularly the fact that exposures were based on OP and carbamate metabolites and that chlorpyrifos was not specifically measured, reduce their utility in a quantitative context for risk assessment." *Id.* at 12–13. Finally, due to the limitations in the CHAMACOS, Columbia, and Mt. Sinai studies, the Panel discouraged EPA from using the studies quantitatively in risk assessment. Specifically, the Panel "agreed with the Agency that there were limitations in the three epidemiological studies that precluded them from being used to directly derive the PoD or the uncertainty factor." *Id.* at 46.

D. Petitioners Rely on a Declaration by Dr. Philip Landrigan that is Replete With Errors and Incorrect Assumptions.

Petitioners cite to a declaration by Dr. Philip Landrigan to support their argument that chlorpyrifos purportedly causes neurodevelopmental effects in children at levels of exposure below the current regulatory standard. Petitioners' Objections at 4 n.3. Dr. Landrigan, in turn, cites to an article by Dr. David Bellinger for the proposition that exposure to organophosphate pesticides has led to "a total loss of 16.9 million IQ points." Landrigan Decl. ¶ 36.

There are numerous flaws in Dr. Landrigan's declaration: first, Dr. Landrigan wrongly asserts that the human studies were conducted outside of the United States and were "criticized for not meeting the informed consent standards that would be required in the US and also for scientific deficiencies." Landrigan Decl. ¶ 27. But Dr. Landrigan's declaration does not identify the human studies he is criticizing, and two of the human studies relevant to the PBPK model that Dr. Landrigan references were in fact conducted in the United States: the Nolan (1982) study was conducted at Dow Chemical in Midland, Michigan, and the Kisicki (1999) study was conducted by MDS Harris Laboratories (now Celerion Lab) in Lincoln, Nebraska. Moreover, both human volunteer studies were approved by the US EPA Human Subjects Review Board ("HSRB"). The EPA HSRB 2009 review of the Nolan *et al.* (1982) study states that "[t]he Board concurred with the Agency's assessment that there was neither clear and convincing evidence that the study was fundamentally unethical, nor clear and convincing evidence that the study was significantly deficient relative to the ethical standards prevailing at the time the Nolan et al. (1982) study was conducted." *Id.* at 2. In addition, the Supplemental EPA ethics review of the Kisicki (1999) study from December 2014 states that

> the study was not deficient relative to the prevailing ethical standards in a way that placed participants at increased risk of harm or impaired their informed consent. Therefore, reliance on this study is not prohibited by 40 CFR §26.1704(2). This conclusion agrees with the recommendations of the HSRB in its October 2009 report.

EPA, Supplemental Ethics Review of Chlorpyrifos Human Toxicity Study by Kisicki *et al.* (Dec. 12, 2014) at 6.

Dr. Landrigan also incorrectly claims that "[a] key policy breakthrough occurred over the past three decades with the discovery that children are far more sensitive than adults to toxic chemicals in the environment." Landrigan Decl. ¶ 9. "To the contrary, most scientists agree that

the evidence actually shows that sometimes children are more, the same or even less sensitive to the effects of exposure to chemicals—it depends on the chemical, the effect and other factors." Bond Decl. ¶ 20 (citing National Academy of Sciences Report: Pesticides in the Diets of Infants and Children (1993), https://www.nap.edu/read/2126/chapter/2 (last visited Sept. 24, 2017) ("Children may be more sensitive or less sensitive than adults, depending on the pesticide to which they are exposed.")). In addition, Dr. Landrigan does not cite any empirical data or science to back up his assertion that exposure to pesticides can lead to permanent brain injury during the sensitive life stages.

Dr. Landrigan additionally contends that "[i]n the Columbia study, the degree of reduction in head circumference was proportional to the degree of maternal exposure to chlorpyrifos during pregnancy," and that "[t]he impact of chlorpyrifos on head circumference was no longer observed after the ban on residential application of chlorpyrifos was imposed." *Id.* ¶ 22. He does not present any proof for this. In fact, "the Columbia study authors found no association between head circumference and chlorpyrifos exposure (Whyatt *et al.* 2004)." Bond Decl. ¶ 29. Dr. Landrigan also erroneously asserts that the three epidemiology studies "found damage to children's brains from exposures to chlorpyrifos that produced no or less than 1% red-blood cell cholinesterase inhibition." Landrigan Decl. ¶ 24. However, "[t]here is no basis in these studies to support that conclusion, and authoritative bodies around the world have concluded the 10% cholinesterase inhibition is the appropriate regulatory standard for chlorpyrifos safety." Bond Decl. ¶ 29.

Further, Dr. Landrigan wrongly characterizes the discontinuation of residential uses of chlorpyrifos as a "ban." Landrigan Decl. ¶ 22. In fact, the Federal Register Notice announcing the discontinuation stated that registrants and EPA had agreed to "several voluntary measures" to reduce chlorpyrifos exposure. Chlorpyrifos; Cancellation Order, 65 Fed. Reg. 76,233, 76,234 (Dec. 6, 2000). Nowhere in that announcement did EPA characterize the discontinuation as a "ban." And, the agreement to discontinue residential uses was not reached because EPA deemed the uses unsafe, but because EPA changed key science policies under the FQPA, and applied standards far more restrictive than those historically established. *See* Chlorpyrifos Revised Risk Assessment and Agreement with Registrants (June 2000) at 1 ("The Food Quality Protection Act, enacted in 1996, sets a more stringent safety standard for most pesticides and offers special protection for children."). EPA did not find that these chlorpyrifos uses posed an imminent

hazard, and the phase-out of sales for affected residential use products was allowed to occur over a five-year period.

Dr. Landrigan also claims that the Columbia, CHAMACOS, and Mt. Sinai studies "produced strongly convergent results," Landrigan Decl. ¶ 22, and that all three studies showed reductions in motor function, decreases in working and visual memory, processing speed, verbal comprehension, perceptual reasoning and diminished IQ, *id.* ¶ 23. This is untrue:

> Contrary to Dr. Landrigan's view, a 2011 weight of evidence evaluation integrating the results of available epidemiology studies (including the Columbia study) and laboratory animal studies concluded that "[t]he weight of the available evidence more strongly indicates that a causal association between chlorpyrifos exposure and neurodevelopmental effects in the absence of AChE inhibition in the brain is not plausible for humans, and the few positive associations observed in epidemiology studies would be attributed to alternative explanations." Prueitt *et al.*, Hypothesis-based weight-of-evidence evaluation of the neurodevelopmental effects of chlorpyrifos. Crit Rev Toxicol 41(10): 822-903 (2011). *See also* Reiss *et al.*, *A review of epidemiologic studies of low-level exposures to organophosphorus insecticides in non-occupational populations*, Critical Reviews in Tox., 145:7, 531, 638 (2015); Burns *et al.*, *Pesticide Exposure and Neurodevelopmental Outcomes: Review of the Epidemiologic and Animal Studies,* Journal of Tox. and Environ Health, Part B, 16:127-283 (2013). . . . In addition, recent evidence from two similarly designed and executed studies, one in Ohio and the other in France, found no associations between urinary DAP levels and lower childhood intelligence scores (Cartier *et al.* 2016, Donauer *et al.* 2016). The weight of all the epidemiology evidence (human and animal) therefore does not prove a cause and effect connection between levels of chlorpyrifos exposure below the current regulatory standard and adverse human effects.

Bond Decl. ¶¶ 27–28.

Dr. Landrigan does not define "low-dose" when he states that neurobehavioral effects were purportedly observed in animal studies after "low-dose perinatal chlorpyrifos exposure." Landrigan Decl. ¶ 19. Nor does he put "low-dose" into the context of actual human exposure. He also makes incorrect statements about inter- and intra-species safety factors. *See id.* ¶ 27.

With respect to Dr. Landrigan's reliance on Dr. Bellinger's article for the proposition that exposure to organophosphate pesticides has led to "a total loss of 16.9 million IQ points," Landrigan Decl. ¶ 36, there is no indication that Dr. Bellinger reviewed the Columbia study or any other studies pertaining to chlorpyrifos. *See* Bond Decl. ¶ 43 ("[Dr. Bellinger] did not conduct a state of the art systematic review of the evidence, but instead took at face value the selected findings from published studies of two small groups of children—the CHAMACOS and

Mount Sinai birth cohort —which . . . have inconsistent results and have been significantly criticized for having design and executions errors."). The publication itself recognizes the limitations in its own conclusions due to assumptions made and the lack of available data. *See* Bellinger (2012), *A Strategy for Comparing the Contributions of Environmental Chemicals and Other Risk Factors to Neurodevelopment of Children*, 120 Environ Health Persp 501–07 at 506 ("Any effort to compare the neurodevelopmental burden associated with different risk factors is limited by the data available and the assumptions required."). The Columbia, CHAMACOS, and Mt. Sinai studies simply do not establish a causal effect between exposure to organophosphates and loss of IQ points. *See* Bond Decl. ¶ 43 (Dr. Bellinger "also proceeded to confuse mere correlation with causation by not systematically evaluating the studies for bias or checking to see if the criteria for causation were satisfied."). In addition, Dr. Bellinger's entire analysis is based on an alleged correlation between DAP levels and loss of IQ points, even though "it is not scientifically valid to rely on DAP levels detected in urine to conclude that exposure to chlorpyrifos has occurred." Burns Decl. ¶ 23. Importantly, "DAP is not specific to chlorpyrifos. Thus, the specific OP pesticides contributing to urinary DAP levels may be different for the California farm worker participants (CHAMACOS) and the urban New York City participants (Mt. Sinai Study)." *Id.* Further, "the sample results may reflect contacts with one or more of the parent pesticide OPs that metabolize to DAP, or may reflect its environmental residue metabolite that then metabolized to DAP." *Id.* Thus, "DAP levels should not be used for interpreting outcomes for an individual pesticide." *Id.*

Despite the inconsistencies in the epidemiology studies, "Dr. Bellinger did not engage in any critical review of either [the Mt. Sinai or CHAMACOS] study, but simply assumed that the associations that were reported were indeed causal. Such an assumption was not justified." Bond Decl. ¶ 38. In sum, Petitioners' claim that chlorpyrifos exposure has led to a loss of IQ points is unsubstantiated because "Dr. Bellinger's article is not specific to chlorpyrifos, failed to adequately analyze the CHAMACOS and Mt. Sinai epidemiology studies and drew unfounded conclusions about the studies' findings, and ignored robust animal toxicology data that support the current regulatory standard for chlorpyrifos." *Id.* ¶ 44.

E. Petitioners Wrongly Assert that EPA has Found Unsafe Drinking Water Contamination from Chlorpyrifos.

Petitioners and the States cite to EPA's drinking water assessment as further evidence that chlorpyrifos is purportedly unsafe. Petitioners' Objections at 31; States' Objections at 8. But, as described in DAS's prior comments, EPA's drinking water assessment remains only a screening-level evaluation and is therefore incomplete. *See* DAS Comments on 2016 RHHRA at 72-85. The Agency's drinking water assessment is inadequate for purposes of conducting a human health risk assessment, as it is merely a slightly modified screening-level assessment. The input parameterization of the modeling carried out in the April 2016 Refined Drinking Water Assessment ("RDWA") (EPA-HQ-OPP-2015-0653-0437) employs a series of compounding conservative factors, especially related to the intensity of product use.

The Agency's statement that "if the chlorpyrifos use profile changes, [the data] are provided to quickly facilitate estimating the potential exposure" without having to update this assessment, RDWA at 124, is indeed applicable as the use profile assumptions used in the assessment do not reflect realistic product use. Such refinements would employ readily available data and well-understood methodologies for defensible and straight-forward refinements that would much more realistically reflect the potential for human exposure. *See* DAS Comments on 2016 RHHRA at 73–77. Indeed, DAS presented a Preliminary Refined Drinking Water Assessment (MRID 50016001), a next-tier highly refined assessment, to the Agency in February 2016, which the Agency has not yet finished reviewing.

In sum, DAS is hopeful that the Agency will work on these critical drinking water issues during registration review and will consider refinements that DAS has previously provided to the Agency in preparing its final decision.

F. The Petition Does Not Shift the Burden to EPA to Again Prove that Chlorpyrifos is Safe.

The Objections repeatedly and wrongly assert that EPA has the burden to make a new safety determination in response to a petition to revoke tolerances. Petitioners' Objections at 32; States' Objections at 9.

Under Section 408 of the FFDCA, as amended by the FQPA, "[t]he Administrator may establish or leave in effect a tolerance for a pesticide chemical residue in or on a food only if the Administrator determines that the tolerance is safe. The Administrator shall modify or revoke a

tolerance if the Administrator determines it is not safe." FFDCA § 408(b)(2)(A)(i), 21 U.S.C. § 346a(b)(2)(A)(i). "Safe" is defined by the FFDCA as meaning that "there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information." FFDCA § 408(b)(2)(A)(ii), 21 U.S.C. § 346a(b)(2)(A)(ii). In determining whether to revoke a tolerance, EPA must consider "the validity, completeness, and reliability of the available data from studies of the pesticide." FFDCA § 408(b)(2)(D)(i), 21 U.S.C. § 346a(b)(2)(D)(i). Contrary to Petitioners' assertion, there is nothing in either FFDCA or FQPA suggesting that the burden is on the Agency or the registrant to make a new safety determination in response to a petition to revoke tolerances.

Under the FFDCA, "[a]ny person may file with the Administrator a petition proposing the issuance of a regulation . . . establishing, modifying, or revoking a tolerance for a pesticide chemical residue in or on a food." FFDCA § 408(d)(1), 21 U.S.C. § 346a(d)(1). After giving "due consideration" to the petition, the Administrator must either issue a final regulation establishing, modifying, or revoking a tolerance, issue a proposed regulation, or issue an order denying the petition. *Id.* § 346a(d)(4). Nowhere does the statute indicate that the petition cannot be denied unless and until EPA affirmatively makes a new "safety" determination under the FFDCA.

Indeed, the FFDCA's implementing regulations place the burden squarely on the *petitioner* to prove that the pesticide is not safe:

> The petition shall furnish reasonable grounds for the action sought. Reasonable grounds shall include an explanation showing wherein the person has a substantial interest in such tolerance or exemption from tolerance and an assertion of facts (supported by data if available) showing that . . . new data are available as to toxicity of the chemical, or that experience with the application of the tolerance or exemption from tolerance may justify its modification or revocation.

40 C.F.R. § 180.32(b). EPA's Order is consistent with these standards and with the Agency's prior responses to PAN/NRDC regarding the petition. *See, e.g.,* 2012 Bradbury Letter at 18 ("To show a lack of safety, petitioners would have to present a factual analysis demonstrating that . . . the [cumulative risk assessment] for chlorpyrifos poses unsafe cumulative exposures to the OP

pesticides. Petitioners have not made such a showing. For this reason . . . EPA intends to deny the petitioners' request . . . .").

When the petition is denied, petitioners must submit objections to EPA, to which EPA must respond, *before* petitioners may obtain judicial review of the merits of EPA's Petition denial. *See* 21 U.S.C. § 346a(g)(2)(C) (Administrator must issue an order stating the action taken on each objection) *Id.* § 346a(h)(1) (order denying objections issued under § 346a(g)(2)(C) is reviewable in the court of appeals); *see also* 40 C.F.R. § 180.30(b) (review of an order denying a petition "shall not be the subject of judicial review under any other provision of law," and "judicial review is not available *unless an adversely affected party exhausts the[ ] objection procedure*s, and any petition procedures preliminary thereto") (emphasis added). Thus, there is nothing in the FFDCA or its implementing regulations that places the burden on the Agency or the registrant to prove safety in response to a petition.

The only case cited by Petitioners in support of their burden-shifting argument, *Environmental Defense Fund, Inc. v. U.S. Department of Health, Education & Welfare*, 428 F.2d 1083 (D.C. Cir. 1970), a case not involving EPA, is readily distinguishable. There, petitioners challenged the Secretary of Health, Education and Welfare's refusal to publish their petition to establish a "zero tolerance" for DDT residues (an alleged carcinogen) in or on raw agricultural commodities. *Id.* at 1086. The court held that the agency had the burden of proving the safety of the existing tolerances for DDT, the pesticide at issue, *in light of findings by a government commission that "the evidence for the carcinogenicity of DDT in experimental animals is impressive." Id.* at 1085 (emphasis added). The court stated, in a footnote, that "[o]nce new evidence bearing on the safety of pesticide residues has been adduced or cited sufficient to justify reopening the issue of the validity of existing tolerances, as in the present case, the burden of establishing the safety of any tolerance remains on those who seek to permit a residue." *Id.* at 1092 n.27. The court relied on a provision of the FFDCA that is not in the current version of the statute, namely "that the procedures for amending or repealing tolerances should be the same as those for establishing tolerances." *Id.* (citing 21 U.S.C. § 346a(m)). The cited provision states that "[t]he Administrator shall prescribe by regulations the procedure by which regulations [establishing tolerances] under this section may be amended or repealed, and such procedure shall conform to the procedure provided in this section for the promulgation of regulations

establishing tolerances." 21 U.S.C. § 346a(m). That provision was repealed in 1996 and replaced with 21 U.S.C. §§ 346a(d) and (e). H.R. Rep., pt. 1, 104th Cong. 2d Sess. 669 (1996). There is nothing in the current version of the FFDCA suggesting that the procedures for revoking tolerances should be the same as for establishing tolerances.

Petitioners' interpretation of the Agency's obligations in the face of a petition would lead to the unprecedented result that EPA is required to renew its safety finding each and every time a petition is filed, irrespective of the strength and quality of the evidence cited in support of the petition, and regardless of whether EPA is engaged in an ongoing scientific review of issues addressed in the petition through Registration Review. This is neither a logical nor workable interpretation of FFDCA's requirements, and there is nothing to indicate that Congress intended such a result.

In addition, unlike in *Environmental Defense Fund,* the unreliable and invalid epidemiology studies at issue here are far from "sufficient to justify reopening the issue of the validity of existing tolerances." Indeed, as discussed in detail above, neither EPA nor any of the SAP meetings convened to review the epidemiology studies found the studies to be conclusive or causal. In further contrast to *Environmental Defense Fund,* where petitioners were challenging the Secretary of Health, Education and Welfare's *refusal* to publish a petition, the Petition here underwent extensive public comment, and the Agency subsequently found that petitioners had failed to provide sufficient evidence that chlorpyrifos was not safe at existing tolerance levels. And, as EPA indicated in its denial of the Petition, its science-based review of chlorpyrifos will continue during registration review. This fact also clearly distinguishes the current matter from *Environmental Defense Fund.*

In sum, EPA made a safety determination in 2006, and that determination still remains in effect. The burden is on the petitioners seeking revocation of chlorpyrifos tolerances to demonstrate that the current regulatory standard for chlorpyrifos is not safe.

IX. CONCLUSION

For the foregoing reasons, EPA's March 29th, 2017 Order correctly denied the Petition because there is an extensive and complete set of animal toxicology data that support the current regulatory standard for chlorpyrifos, and the epidemiological and other studies advocated by

Petitioners are not reliable enough for regulatory decision-making. The Agency should therefore deny all of the Objections submitted in response to EPA's Order.

Appendix A: Analysis of Additional Animal Toxicology Studies

Appendix A to Dow AgroSciences LLC's Response to Objections to EPA's Denial of Petition to Revoke All Tolerances and Cancel All Registrations for Chlorpyrifos: Analysis of Additional Animal Toxicology Studies

In recent years, Petitioners and others have claimed that there is a growing body of human epidemiology and experimental animal evidence showing associations between exposure to chlorpyrifos at levels below EPA's current regulatory standard and neurodevelopmental outcomes. However, as repeatedly demonstrated in Dow AgroSciences LLC's ("DAS's") prior and current comments, the epidemiology studies cited in support of these claims suffer from significant scientific limitations, precluding their use in regulatory decision-making. The same result applies to the experimental animal studies. Indeed, in 2012, EPA convened a Scientific Advisory Panel ("SAP") to address experimental animal studies involving chlorpyrifos, and the Panel found that the studies had significant limitations. EPA itself examined the animal literature with respect to chlorpyrifos in 2014, and again in 2016 with respect to organophosphates ("OPs") generally, and similarly identified weaknesses in the scientific research, further undermining claims of adverse effects at levels below the current regulatory standard.

This Appendix summarizes the SAP and EPA's critiques of animal toxicology studies examining (1) possible modes of action/adverse outcome pathways other than the well-established mode of action of cholinesterase inhibition, and (2) potential associations between chlorpyrifos exposure and neurodevelopmental outcomes. This Appendix then addresses additional animal toxicology studies not addressed in DAS's prior comments submitted to the Agency, including studies recently reviewed by the California Department of Pesticide Regulation, that alleged adverse neurodevelopmental outcomes. As demonstrated herein, these additional studies suffer from many of the same deficiencies and weaknesses noted by EPA and the SAP in their review of the animal literature, and do not support a claim that there is evidence supporting a departure from the current regulatory endpoint for chlorpyrifos.

A. EPA and SAP Criticisms of the Experimental Toxicology Research Regarding Chlorpyrifos

In 2012, EPA convened an SAP to evaluate the scientific research associating chlorpyrifos with neurodevelopmental and neurobehavioral outcomes. In its Issue Paper

provided to the 2012 SAP, EPA identified a number of limitations in the animal toxicology studies examining non-cholinergic modes of action:

- [T]here are several lines of evidence for actions of chlorpyrifos distinct from the classical mode of action of cholinesterase inhibition . . . however, . . .most of these studies have not been designed with the specific goal of construction or testing an adverse outcome pathway. *Thus, there are not sufficient data available to test rigorously the causal relationship between effects of chlorpyrifos at the different levels of biological organization in the nervous system.* EPA, Meeting of the FIFRA Scientific Advisory Panel, Draft Issue Paper: Scientific Issues Concerning Health Effects of Chlorpyrifos (2012) ("EPA 2012 Issue Paper") at 35 (emphasis added).

- Because many of these papers report a number of positive as well as negative findings, *the Agency had previously taken the approach of comparing responses that were observed following various exposures to a common dose,* 1 mg/kg/d (FIFRA Scientific Advisory Panel (SAP), 2008a; [USEPA], 2011). A more robust approach is taken here, to include important factors such as dose-response and differences in exposure scenarios. . . . *unfortunately, many of the chlorpyrifos studies have evaluated only one dose*. *Id.* at 39 (emphasis added).

- All testing reported herein was conducted after weaning, and there is a presumption that the effects are permanent; however, no study has directly addressed this issue, and there is a range in test ages. *Dose-response is not always evident, since many studies only use one dose*, and of those using two or more doses, there is not always a monotonic response. Furthermore, the summary presented herein combines studies of different dosing regimens. *Id.* at 52 (emphasis added).

- Overall, these data do not clearly show specific critical periods of exposure, or definitive sensitive behavioral outcomes. *Unfortunately, no laboratory has provided systematic comparisons across exposure period, dosing regimen, and age of testing*; such studies would improve understanding of the impact of these critical factors. *Id.* (emphasis added).

- These studies have almost exclusively focused on doses that could produce some degree, however minimal, of AChE inhibition. Thus *it is not possible to know whether effects would be present at lower doses, since they have not been adequately studied; thus far, only one study (Braquenier, et al., 2010) has tested a dose lower than the point of departure.* The broad profile of neurological effects that have been reported do not aid in the development of a specific AOP, and as described in section 3.2.1., existing experimental studies have not been designed to examine and track possible mechanisms from early initiating events to the final neurological outcome. Such studies represent longer term research efforts by the different laboratories." *Id.* at 52–53 (emphasis added).

EPA sought the SAP's guidance on these and other issues. Following its review of the animal toxicology research, the SAP similarly found the evidence insufficient to establish a plausible mode of action/adverse outcome pathway linking chlorpyrifos exposure with adverse outcomes:

> Question 2.1
> As discussed in Section 3.2.1, although there are numerous mechanistic studies in the scientific literature, the research on different hypotheses does not provide sufficient data to establish causal linkages among different levels of biological organization to show how effects lead to adversity. As such, a mode of action or adverse outcome pathway leading to effects on the developing brain cannot be established at this time. Moreover, although multiple biologically plausible hypotheses are being pursued by researchers, based on the current state of the science, no one pathway has sufficient data to be considered more credible than the others. *Please comment on the Agency's preliminary conclusion that although there are multiple biologically plausible hypotheses being evaluated by research scientists, the mechanistic experimental toxicology data do not yet support a coherent set of key events in a mode of action/adverse outcome pathway.*
>
> The Panel agrees with the Agency's conclusion that based on the current state of the science, no one pathway has sufficient data to be considered more credible than the others with respect to a causal link between chlorpyrifos exposure and neurodevelopmental outcome.

EPA, Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting held April 10-12, 2012 on "Chlorpyrifos Health Effects" at 13 (July 11, 2012) ("2012 SAP Minutes").

The 2012 SAP noted limitations in the designs of many of the experimental studies and expressed concern with the use of the dimethyl sulfoxide (DMSO) as a vehicle:

> [S]tudies evaluating neurodevelopmental effects entailed experimental designs that do not permit an efficient means of determining a point of departure for chlorpyrifos. . . . ***Also in keeping with the 2008 SAP, this Panel expresses concern about the use of Dimethyl Sulfoxide (DMSO) as a vehicle because of its intrinsic toxicity, its potential influence on absorption and interaction with chlorpyrifos, and the impact of this interaction on the developing organism.***

Id. at 12 (emphasis added). The 2012 SAP also found that there were "no studies . . . identified that showed effects on behavior at low levels of AChE inhibition, including at 1.0 mg/kg of chlorpyrifos" and that "*[d]oses below 1.0 mg/kg/day chlorpyrifos did not show convincing evidence of neurobehavioral effect; hence, no extrapolation to lower doses in terms of AChE inhibition is possible* from the data reviewed herein." *Id.* at 39 (emphasis added).

Ultimately, the 2012 SAP expressed confidence in the current regulatory standard for chlorpyrifos, stating that, "just as . . . in the 2008 SAP, this Panel advises that the Agency continue to use AChE data at the most sensitive lifestages for dose-response analysis and deriving points of departure." *Id.* at 12.

B. EPA Has Been Critical of Experimental Toxicology Research Purporting to Link OP/Chlorpyrifos Exposure with Adverse Neurodevelopmental Effects

EPA's more recent reviews of the experimental toxicology research have echoed the 2012 SAP's conclusions. As demonstrated below, EPA's 2014 and 2016 literature reviews demonstrate that EPA places low confidence in animal toxicology studies reported since 2008 regarding neurodevelopmental effects associated with chlorpyrifos exposure, certainly at exposure below the threshold for 10% red blood cell cholinesterase inhibition ("RBC ChEI").[1]

For example, in the December 29, 2014 Revised Human Health Risk Assessment for Chlorpyrifos ("2014 RHHRA"), EPA expressed confidence in AChE as a health-protective endpoint:

> Since the MOA(s)/AOP(s) is/are not established for neurodevelopmental outcomes . . . it is not possible to describe the concordance in key events or biological steps leading to neurodevelopmental outcomes. As such, the quantitative linkages between MIEs, intermediate steps, and ultimately the adverse outcome (i.e., neurodevelopmental effects) cannot be determined. Experimental toxicology studies in rodents suggest that long-term effects from chlorpyrifos exposure may occur. Due to the dose selections in most of these *in vivo* studies evaluating effects such as behavior and cognition, *it is not known whether such adverse effects would be shown at doses lower than those which elicit 10% RBC AChE inhibition.* It is notable, however, that comparing the lowest NOAEL observed in the *in vivo* animal studies (0.2 mg/kg/day; Billauer-Haimovitch et al., 2009) for the neurodevelopmental outcomes to the repeated dosing reliable $BMDL_{10}$ ranging from 0.05-0.17 mg/kg/day for RBC AChE inhibition suggests that AChE inhibition is a sensitive endpoint.

2014 RHHRA at 44–45 (emphasis added).

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[1] As set forth in Dow AgroSciences LLC's Response to Objections, acetylcholinesterase ("AChE") inhibition ("ChEI") is the mode/mechanism of action for effects to the mammalian system with respect to chlorpyrifos. EPA regulates on a particular type of AChE which is Red Blood Cell Acetylcholinesterase ("RBC AChE") inhibition, or simply Red Blood Cell cholinesterase inhibition ("RBC ChEI"). RBC ChEI is not an adverse effect in itself, but a marker of exposure and a conservative and protective endpoint that occurs well below levels required to inhibit other types of AChE that could be considered an adverse health effect.

In its 2014 RHHRA, EPA reviewed six animal toxicology studies published since the 2012 SAP. EPA concluded that the study findings were inconsistent with prior research showing no effects, and studies that reported adverse effects employed doses that exceeded those known to cause cholinesterase inhibition:

> For half of the studies, the lowest dose was 1 mg/kg/d, and two studies used the oxon, making it difficult to compare dose levels. Only one study used a lower dose, 0.36 mg/kg/d, in feed, and even this level was sufficient to produce a great degree of RBC ChE inhibition. . . .
>
> *Conclusions: There continue to be inconsistencies in effects in relation to functional domains, dosing paradigms, and gender-specificity. The only studies reporting effects used doses that inhibited fetal/pup brain ChE activity to some degree, even though there were many negative effects at these same doses.*

Id. at 196–97 (emphasis added).

EPA also found that newer lines of research were not sufficient to establish a biologically plausible mode of action/adverse outcome pathway:

> With respect to modes of action/adverse outcome pathways leading to neurodevelopmental effects, *at the present time, there is no established series of causal key events at a biological level of organization relevant to the risk assessment (i.e., adverse neurodevelopmental effects from gestational and/or postnatal exposure*). . . . Some of the new studies since 2012 have been integrated in this section. *Despite the newest studies, the agency does not believe that any of the current lines of research support a coherent set of key events and that much work remains to elucidate the modes of action and adverse outcome pathways of chlorpyrifos toxicity.*

Id. App. 1, p. 144 (emphasis added).

In its December 29, 2016 Updated Literature Review on Neurodevelopment Effects & FQPA Safety Factor Determination for the Organophosphate Pesticides (the "2016 Literature Review"), EPA conducted a review of the scientific literature examining links between exposure to organophosphate pesticides ("OPs") with neurodevelopmental outcomes. EPA summarized several of the key 2012 SAP and 2014 RHHRA findings as follows:

> A review of the scientific literature on potential MOA/AOP leading to effects on the developing brain was conducted for the 2012 FIFRA SAP meeting . . . and updated for the [2014 RHHRA]. In short, multiple biologically plausible hypotheses and pathways are being pursued by researchers including: AChE as a morphogen; cholinergic system; endocannabinoid system; reactive oxygen species; serotonergic system; tubulin, microtubule associated proteins and axonal transport.

> However, no one pathway has sufficient data to be considered more plausible than the others. . . . The SAP concurred with the agency in 2008 and 2012 about the lack of definable key events in a MOA/AOP leading to developmental neurobehavioral effects.

Id. at 7. EPA noted that "[s]ince the 2014 [RHHRA], *there have been no substantive changes in the ability to define and quantify steps in an MOA/AOP leading from exposure to effects on the developing brain.*" *Id.* (emphasis added).

While the 2016 Literature Review specifically focused on OPs other than chlorpyrifos, some of the agency's conclusions are consistent with conclusions reached for chlorpyrifos, relative to studies investigating potential neurodevelopmental effects. For example, EPA concluded:

> Overall, in the studies for which there are direct or comparable data, it is clear that the dosing paradigms produced AChE inhibition and in some cases maternal toxicity. Indeed, there are no studies reporting or even suggesting a lack of AChE inhibition in the dam and/or fetus/pup at any time during dosing. Thus, it is not known whether exposure paradigms that do not inhibit AChE would produce any neurobehavioral effects.

Id. at 23. As discussed below, this conclusion is important because it confirms that animal toxicology studies using doses at or above those known to cause cholinesterase inhibition do not justify a departure from the current point of departure.

In addition, in Section 2.1.5 of the 2016 Literature Review, Conclusions on In Vivo Laboratory Animal Studies, EPA stated:

> For chlorpyrifos, there are >30 papers on developmental neurotoxicity; for the remaining OPs, the literature is sparse with very few studies for each OP.... The studies span over decades, and many of the lower quality studies were the earlier ones; however, some very recent papers also have significant deficits. Methodological detail is lacking, inappropriate statistical analyses are applied, results are cursorily described and /or inaccurately presented, and interpretation of some behavioral changes is faulty. Overall, most studies have significant shortcomings and/or are of low quality.
>
> The most commonly tested behaviors considered aspects of cognition. In the majority of studies, some sort of cognitive deficit was detected, especially with working memory performance (radial arm maze) and conditioned response retention (passive avoidance). However, in many cases there was no dose-response, there was some gender specificity which did not replicate in multiple studies, and cognitive improvement instead of deficit was noted in a few papers. Changes in motor activity in offspring were generally not reported, and the direction of change differed in the papers reporting such effects. There is generally not enough

> information to make definitive statements about OP effects on other types of neurological disorders.

Id. at 24–25. While these statements refer to studies involving OPs other than chlorpyrifos, the same observations and criticisms apply to the literature on chlorpyrifos and putative neurodevelopmental toxicity. These statements also show that the Agency recognizes the importance of scientific study design and conduct and of sound interpretation and reporting of observed effects.

EPA also recognized in the 2016 Literature Review the importance of considering cholinesterase inhibition in studies assessing potential neurodevelopmental toxicity, observing that:

> Few published papers included AChE measurements of the dams and/or offspring, but where measured, all doses used inhibited AChE to some degree. . . . Since there are no studies with low doses that definitively do not inhibit AChE, there is no information in the animal literature that shows whether or not there would be developmentally neurotoxic outcomes at those lower exposures.

Id. at 25.

In its overall conclusion of the 2016 Literature Review, EPA stated:

> Overall, a definitive mode of action or adverse outcome pathway leading to effects on the developing brain cannot yet be established because of insufficient data establishing the causal linkages among different levels of biological organization to adversity. For example, while there is *in vitro* evidence relating binding of chlorpyrifos or the chlorpyrifos oxon to AChE and the subsequent decrease in neurite outgrowth at the cellular level, the relationship between neurite outgrowth and neurodevelopmental consequences has not been established. As described in the NRC report "Toxicity Testing in the 21st Century". . . , to develop an adverse outcome pathway not only is it necessary to establish plausible relationships among the key events, but quantitative relationships also need to be established.

Id. at 175.

The above summary of EPA's most recent analysis on OPs and potential neurodevelopmental toxicity as reported in the open scientific literature is relevant to a review of the literature specific to chlorpyrifos. Many of EPA's criticisms of the scientific literature claiming links between OP exposure and adverse neurodevelopmental outcomes apply with equal force to the scientific literature for chlorpyrifos, further demonstrating that there is no scientific basis for proposing a point of departure for chlorpyrifos other than cholinesterase inhibition. There is simply not sufficient and replicated scientific evidence, nor a plausible and

proven MOA/AOP, connecting exposure to chlorpyrifos at levels below the current regulatory standard with adverse neurodevelopmental outcomes.

C. Recent Experimental Toxicology Studies Reviewed by EPA Do Not Support Adverse Effects for Chlorpyrifos at Levels Below the Current Regulatory Standard

In recent years, DAS has reviewed and commented publicly on many of the same experimental toxicology studies and literature examined by EPA in its 2014 and 2016 reviews and advanced by Petitioners and others as showing adverse neurodevelopmental effects at levels below the current regulatory standard.[2] As detailed in DAS's prior comments, there is no compelling or consistent animal toxicology evidence to support the contention that neurodevelopmental outcomes occur at exposures below 10% RBC ChEI. In virtually all of these studies, the lowest dose employed was at or above levels known to result in 10% RBC ChEI, cholinesterase inhibition was not measured at all, findings were inconsistent, and/or there were design flaws and methodological confounders undermining the validity of the study's findings.

Several additional studies referenced in EPA's 2016 Literature Review but for which DAS has not previously submitted specific comments are summarized in Table 1, below. These studies are very similar to literature evaluating potential effects and numerous endpoints relative to chlorpyrifos exposure in *in vitro* and *in vivo* test systems. A collective analysis of the eleven studies in Table 1 reveals that they suffer from many of the same deficiencies and limitations EPA identified in its 2014 and 2016 reviews and in DAS's prior comments of studies of similar nature and design.

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[2] *See, e.g.,* Dow AgroSciences LLC's Response to EPA's [RHHRA] for Chlorpyrifos Registration Review, EPA Dkt. EPA-HQ-OPP-2008-0850-0845, at 57–64 (Apr. 2015); Dow AgroSciences LLC's Comments on 2016 [NODA/RHHRA] and Refined Drinking Water Assessment for Chlorpyrifos, EPA Dkt. EPA-HQ-OPP-2015-0653-0651, at 33 and Appendix D (Jan. 2017); Dow AgroSciences LLC's Amicus Brief in Support of EPA, *League of United Latin Am. Citizens, et al. v. Wheeler*, No. 17-71636, ECF No. 72-2, at 20–23 (9th Cir. Mar. 15, 2018).

Table 1. Summary of Investigative Studies Associating Chlorpyrifos Exposure with Neurodevelopmental Outcomes

Citation	Test System	General Focus	Dose(s)	Exposure Route	Exposure Duration	Vehicle	Dose-Response	ChEI Measured	NOEL Defined
Ridano et al. 2017	In vitro	Placenta as target of toxicity	10, 50, 100 uM	N/A	N/A	DMSO	Yes/No	No	Yes/No
Icenogle et al. 2004	Rat	Behavioral effects	1, 5 mkd	SC inj.	GD 9-12	DMSO	Yes/No	No	Yes/No
Billauer-Haimovitch et al. 2009	Mouse	Visuospatial effects	1, 3, 5, 10, 20 mkd	SC inj.	GD 9-18	DMSO	Yes/No	No	Yes/No
Turgeman et al. 2011	Mouse	Neurobehavioral effects	3 mkd	SC inj.	GD 9-18	DMSO	No	No	No
Braquenier et al. 2010	Mouse	Anxiety effects	0.2, 1, 5 mkd	Oral gavage	GD15-PND14	Corn oil	No	Yes – brain only at 5 mkd	Yes – 0.2 mkd
Venerosi et al. 2010	Mouse	Anxiety effects, aggressive behavior	6 mkd	Oral gavage	GD 14-17	Peanut oil	No	No	No
Levin et al. 2001	Rat	Learning and memory effects	1 mkd 5 mkd	SC inj.	PND1-4 PND 11-14	DMSO	No	No	No
Vatanparas et al. 2013	Rat	Passive avoidance performance	1 mkd	SC inj.	GD15-18 PND1-4	DMSO	No	No	No
Mamczarz et al. 2016	Guinea Pig	Spatial learning	25 mkd	SC inj.	GD 53-63	Peanut oil	No	Yes – RBC ChEI at 25 mkd	No
Slotkin et al. 2015	Rat	Expression of serotonin receptors	1 mkd	SC inj.	PND 1-4	DMSO	No	No	No
Venerosi et al. 2008	Mouse	Social behavior effects	3 mkd	SC inj.	PND 11-14	Peanut oil	No	No	No

Specifically, there are various test systems employed in these studies (*in vitro*, *in vivo* studies using different animal species), different endpoints or outcomes of interest, and often inconsistent results within and across studies. Taken together, these issues preclude drawing reliable conclusions on the ability of chlorpyrifos to elicit neurodevelopmental effects, certainly

not below the current regulatory point of departure (10% RBC ChEI). Among these eleven studies, only one used a dose level below 1 mg/kg/day (Braquenier et al. 2010; 0.2 mg/kg/day) and this was a NOEL in this study with 1 mg/kg/day representing a LOEL. Moreover, many studies employed only a single dose (exposure scenario) and only two used three or more doses, which is the standard for discerning whether a true dose-response relationship exists.

In addition, many of the studies used subcutaneous injection as the route of exposure, which is not relevant to human exposure scenarios. A number of the studies also used the known neurotoxicant DMSO as the vehicle. Because DMSO has neurotoxic properties of its own, its use in experimental studies that specifically are addressing neurodevelopmental outcomes is a significant confounder and challenge relative to study result interpretation. As noted above, the use of DMSO as a vehicle has been the subject of criticism by multiple scientific and regulatory entities, including the FIFRA SAP.

Finally, and perhaps most importantly, cholinesterase inhibition, specifically RBC inhibition, was measured in only one study, Mamczarz et al. 2016, which employed a very high dose (compared to other experimental studies and to human exposure scenarios). The failure of investigators in the other studies to concomitantly measure and quantify the degree of RBC cholinesterase inhibition precludes a conclusion that there are neurodevelopmental effects below the lowest dose employed, and certainly below the threshold of 10% RBC ChEI (a dose level which is far below those used in any of these eleven studies above).[3]

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[3] All of these studies stand in stark contrast with the results of the EPA-required Marty et al. 2012 study. There, during the repeated dosing part of the study, pups and dams were administered chlorpyrifos at levels of 0, 0.05, 0.1, 0.5, 1.0, and 3.5 mg/kg/day. The lower end of the dose range in this study is substantially lower than those testing regimes in the vast majority of other studies cited by EPA. Results of this study show that there were no effects on neurobehavior as evaluated through a functional observation battery and motor activity evaluation in the repeat portion of the study in either dams or pups at dose levels that were associated with less than 10% RBC ChEI in both female pups (0.1 mg/kg/day) and dams (0.05 mg/kg/day). Male pups also had no effects associated with functional observation battery or motor activity, but had approximately 14% RBC ChEI at the lowest dose (0.05 mg/kg/day) tested. This study thus provides an example of where neurodevelopmental effects were not observed in *in vivo* testing at exposures associated with approximately 10% RBC ChEI or lower. In addition, while there is a misperception that 1 mg/kg/day is the threshold for cholinesterase inhibition, the Marty et al. study (2012) clearly demonstrates following repeated dosing in young and adult rats that 1 mg/kg/day is associated with in excess of 70% RBC ChEI in adults, and in excess of 60% and 40% RBC ChEI in male and female pups, respectively. This study confirms

D. Recent Experimental Toxicology Studies Cited by the California Department of Pesticide Regulation Do Not Support Adverse Effects for Chlorpyrifos at Levels Below the Current Regulatory Standard

The California Department of Pesticide Regulation ("DPR") has reviewed additional studies, during its deliberations over the listing of chlorpyrifos as a Toxic Air Contaminant ("TAC"). Specifically, DPR has reviewed five studies, summarized in Table 2, below, allegedly supporting its contention that neurodevelopmental outcomes in experimental animals following exposure to chlorpyrifos occur below the threshold for cholinesterase inhibition.

Table 2. Summary of Recent Studies Cited by CA DPR as Indicative of Neurodevelopmental Effects Associated with Chlorpyrifos Exposure Below the Threshold for Cholinesterase Inhibition

Citation	Test System	General Focus	Dose(s)	Exposure Route	Exposure Duration	Vehicle	Brain ChEI	RBC ChEI	Notes
Carr et al., 2017	Rat	Anxiety behavior	0.5, 0.75, 1.0 mkd	Oral gavage	PND10-17	Corn oil	19% decrease at 1 mkd	Not measured	No effects on brain ChEI at lower doses; reported decreased anxiety – opposite of Silva et al.
Lee et al., 2015	Mouse	Adult behavior and cognitive impairment	0.1, 1.0, 5.0 mkd	Oral gavage	PND10	Egg lecithin/ peanut oil emulsion	No significant brain ChEI	Not measured	Results questionable as 5 mkd should cause brain ChEI
Gomez-Gimenez et al. 2017a	Rat	Motor activity and coordination	0.1, 0.3, 1.0 mkd	Oral gavage	GD7-PND21	Corn oil – given in sweet jelly	Not measured	Not measured	
Gomez-Gimenez et al. 2017b	Rat	Spatial learning	0.1, 0.3, 1.0 mkd	Oral gavage	GD7-PND21	Corn oil – given in sweet jelly	Not measured	Not measured	
Silva et al., 2017	Rat	Anxiety behavior	0.01, 0.1, 1.0, 10.0 mkd	Oral gavage	GD14-20	9% saline with Tween 20	Not measured	Not measured	Reported increased anxiety – opposite of Carr et al

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the protective and conservative nature of using 10% RBC ChEI as a point of departure for risk assessment purposes.

These studies, suffer from the same flaws and limitations as the eleven studies summarized in Table 1. Only two studies measured brain cholinesterase activity, with only one of them (Carr et al., 2017) reporting modest ChEI at the highest dose (1 mkd). Notably, *none* of the studies measured RBC cholinesterase inhibition, the current point of departure used by EPA and other global authorities as the conservative endpoint upon which to base permissible exposure levels to humans.

Because Silva et al. (2017) used the lowest dose (0.01 mg/kg/day) of any of the studies, this study in particular warrants comment as DPR has claimed that "the most important implication of this study is that the threshold for CPF-induced neurobehavioral effects in young rats following gestational exposure may be as much as 10-fold lower than the reported threshold of 1 mg/kg/day established for RBC AChE inhibition in adult rats." DPR, Draft Evaluation of Chlorpyrifos as a Toxic Air Contaminant: Risk Characterization of Spray Drift, Dietary, and Aggregate Exposures to Residential Bystanders, at 57 (Dec. 2017). But, this statement is factually incorrect, as there is clear evidence that the threshold for RBC AChE is well below 1 mg/kg/day (Marty et al., 2012 and footnote included above).

A closer review of Silva et al. (2017) reveals that this study reported on anxiety-like behavior in rat offspring following exposure to chlorpyrifos during pregnancy (i.e., GD14-20). They employed doses ranging from 0.01 to 10 mg/kg/day, but failed to report on purity of the test material and did not measure cholinesterase inhibition of any type. The group size ranged from eleven to fourteen pregnant females per group. The actual number of offspring tested for behavioral effects on PND 21 and PND 70 is not stated. It is not clear whether testing included littermates and, if so, how the study controlled for the presence of littermates. Silva et al. (2017) reported effects at 0.1-1.0, citing axiogenic-like, but not depressive-like behavior at PND21 (without causing fetal toxicity), but the effect was reversed by PND 70. This begs the question whether increased or decreased anxiety-like behavior is biologically significant and whether both are adverse, or whether one is adverse while the other is not, particularly as other investigators have reported decreased anxiety related to chlorpyrifos exposure (Carr et al., 2017). There was no dose-response for this reported effect among the top three dose levels; while locomotor activity was reported as statistically significant, the increased (relative to control) motor activity at 0.1 mg/kg/day was virtually the same as that reported following exposure to 10 mg/kg/day.

While the inferred NOEL for this study would be 0.01 mg/kg/day, the absence of a defined dose-response at the top three dose levels calls into question whether this reported effect is treatment-related at all.

In short, a review of these additional five studies reveals that, as with the eleven studies summarized in Table 1, it cannot be claimed that neurodevelopmental outcomes in animals occurr below the threshold for ChEI, as virtually no study to date has included measurements of RBC ChEI. Moreover, as discussed above, Marty et al. (2012) demonstrates that this threshold is well below 1 mg/kg/day.

E. Conclusion

Chlorpyrifos continues to be investigated in experimental settings relative to claims that it is associated with neurodevelopmental outcomes and that *in vitro* and *in vivo* animal studies are supportive of epidemiology studies alleging links between chlorpyrifos exposure below the current regulatory standard and reduced IQ, loss of working memory, attention deficit disorders, and delayed motor development in young children. This expansive body of animal literature has been evaluated for over ten years by the EPA and its FIFRA SAP, as well as international regulatory bodies. To date, a plausible and biologically meaningful/replicated mode of action explaining how chlorpyrifos could be exerting effects on neurodevelopment at dose levels below the current regulatory endpoint, in either animals or humans, has not been identified. This has been confirmed by EPA and the SAP. In fact, very few studies, despite claims to the contrary, have employed sufficiently low dose levels (below 1 mg/kg/day), particularly those below the threshold for RBC cholinesterase inhibition, to even probe this hypothesis. Moreover, the vast majority of studies, including the sixteen (eleven in Table 1; five in Table 2) reviewed above, have multiple confounding variables and experimental challenges which preclude their use for regulatory decision-making. There is simply no credible support for the statement that there are multiple studies indicative of neurodevelopmental effects caused by exposure to chlorpyrifos below the threshold for cholinesterase inhibition. Global regulatory authorities have utilized inhibition of cholinesterase inhibition, specifically RBC cholinesterase inhibition, as the conservative and protective point of departure which protects against all other putative toxicities. There is no scientific basis to change this conclusion.

References:

Billauer-Haimovitch, H., et al. 2009. Reversal of chlorpyrifos neurobehavioral teratogenicity in mice by nicotine administration and neural stem cell transplantation. Behav. Brain Res. 205:499-504.

Braquenier, J.B., et al. 2010. Anxiety in adult female mice following perinatal exposure to chlorpyrifos. Neurotox Teratol. 32:234-239.

Carr, R.L. et al. 2017. Decreased anxiety in juvenile rats following exposure to low levels of chlorpyrifos during development. Neurotoxicology. 59:183-190.

DPR, Draft Evaluation of Chlorpyrifos as a Toxic Air Contaminant: Risk Characterization of Spray Drift, Dietary, and Aggregate Exposures to Residential Bystanders, at 57 (Dec. 2017).

EPA, Meeting of the FIFRA Scientific Advisory Panel. Draft Issue Paper : Scientific Issues Concerning Health Effects of Chlorpyrifos. April 10-13, 2012.

EPA, Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting held April 10-12, 2012 on Chlorpyrifos Health Effects. July 11, 2012.

EPA. Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review. December 29, 2014.

EPA. Updated Literature Review on Neurodevelopment Effects & FQPA Safety Factor Determination for the Organophosphate Pesticides. December 29, 2016.

Gomez-Gimenez, B. et al. 2017a. Sex-dependent effects of developmental exposure to different pesticides on spatial learning. The role of induced neuroinflammation in the hippocampus. Food and Chemical Toxicology. 99:135-148.

Gomez-Gimenez, B. et al. 2017b. Developmental exposure to pesticides alters motor activity and coordination in rats: sex differences and underlying mechanisms. Neurotox Res. DOI 10.1007/s12640-017-9823-9.

Icenogle, L.M., et al. 2004. Behavioral alterations in adolescent and adult rats caused by a brief subtoxic exposure to chlorpyrifos during neurulation. Neurotoxicol. Teratol. 26:95-101.

Lee, I. et al. 2015. Developmental neurotoxic effects of two pesticides: Behavior and biomolecular studies on chlorpyrifos and carbaryl. Toxicol. Appl. Pharmacol. 288:429-438.

Levin, E.D., et al. 2001. Persistent behavioral consequences of neonatal chlorpyrifos exposure in rats. Dev. Brain Res. 130:83-89.

Mamczarz, J., et al. 2016. Spatial learning impairment in prepubertal guiea pigs prenatally exposure to the organophosphorous pesticide chlorpyrifos: Toxicological implications. Neurotoxicology. 56:17-28.

Marty, M.S., et al. 2012. Cholinesterase inhibition and toxicokinetics in immature and adult rats after acute or repeated exposures to chlorpyrifos or chlorpyrifos-oxon. Reg. Toxicol. Pharmacology. 63:209-224.

Ridano, M.E., et al. 2017. Impact of chlorpyrifos on human villous trophoblasts and chorionic villi. Toxicol. Appl. Pharmacol. 329. 26-39.

Silva, J.G. et al. 2017. Chlorpyrifos induces anxiety-like behavior in offspring rats exposed during pregnancy. Neuroscience Letters. 641-94-100.

Slotkin, T.A., et al. 2015. Prenatal nicotine changes the response to postnatal chlorpyrifos: Interactions targeting serotonergic synaptic function and cognition. Brain Res. Bull. 111:84-96.

Turgeman, G., et al. 2011. Reversal of chlorpyrifos neurobehavioral teratogenicity in mice by allographic transplantation of adult subventricular zone-derived neural stem cells. J. Neuroscience Res. 89:1185-1193.

Vatanparast, J., et al. 2013. Developmental exposure to chlorpyrifos and diazinon differentially affect passive avoidance performance and nitric oxide synthase-containing neurons in the basolateral complex of the amygdala. Brain Res. 1494:17-27.

Venerosi, A., et al. 2010. Gestational exposure to the organophosphate chlorpyrifos alters social-emotional behavior and impairs responsiveness to the serotonin transporter inhibitor fluvoxamine in mice. 208:99-107.

Venerosi, A., et al. 2008. Neonatal exposure to chlorpyrifos affects maternal responses and maternal aggression of female mice in adulthood. Neurotoxicol. Teratol. 30:468-474.

Appendix B: A Commentary on Some Epidemiology Data for Chlorpyrifos by Toxicology Excellence for Risk Assessment

Title

New Analysis of Data from Columbia Study Publication (Rauh et al. 2011) Demonstrates Need for Raw Data to be Made Available and Raises Additional Questions about the Scientific Validity of Alleged Link Between Exposures to Chlorpyrifos and Neurodevelopmental Effects

Data Requirements

N/A

Authors

GR Oliver[1] and DR Juberg[2]

Study Completed Date

July 9, 2018

Performing Laboratory

Dow AgroSciences, LLC
9330 Zionsville Rd
Indianapolis, IN 46268

Study ID: GRO-072018

STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS

Compound: Chlorpyrifos

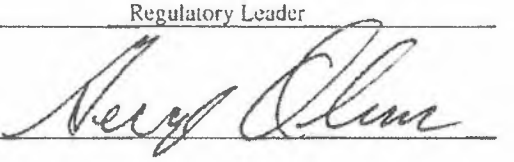
Study Title: New Analysis of Data from Columbia Study Publication (Rauh et al. 2011) Demonstrates Need for Raw Data to be Made Available and Raises Additional Questions about the Scientific Validity of Alleged Link Between Exposures to Chlorpyrifos and Neurodevelopmental Effects

No claim of confidentiality, on any basis whatsoever, is made for any information contained in this document. I acknowledge that information not designated as within the scope of FIFRA sec. 10(d)(1)(A), (B), or (C) and which pertains to a registered or previously registered pesticide is not entitled to confidential treatment and may be released to the public, subject to the provisions regarding disclosure to multinational entities under FIFRA sec. 10(g).

Company: Dow AgroSciences LLC

Company Agent: George Oliver

Title: Regulatory Leader

Signature: 

Date: July 9, 2015

THIS DATA MAY BE CONSIDERED CONFIDENTIAL IN COUNTRIES OUTSIDE THE UNITED STATES

STATEMENT OF COMPLIANCE WITH GOOD LABORATORY PRACTICE STANDARDS

Compound: Chlorpyrifos

Title: New Analysis of Data from Columbia Study Publication (Rauh et al. 2011) Demonstrates Need for Raw Data to be Made Available and Raises Additional Questions about the Scientific Validity of Alleged Link Between Exposures to Chlorpyrifos and Neurodevelopmental Effects

The study described in this report was conducted in accordance with the following Good Laboratory Practice Standard:

United States Environmental Protection Agency
Title 40 Code of Federal Regulations Part 160
Federal Register, 17 August 1989

Organization for Economic Co-Operation and Development
ENV/MC/CHEM(98)17, Paris – January 26, 1998

All phases of this study were conducted according to the final rule of the FIFRA Good Laboratory Standards, 40 CFR 160.

George Oliver
Sponsor
Dow AgroSciences LLC

July 9, 2018
Date

George Oliver
Submitter
Dow AgroSciences LLC

July 9, 2018
Date

George Oliver
Study Director
Dow AgroSciences LLC

July 9, 2018
Date

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Summary

As part of its statutorily required Registration Review of the pesticide chlorpyrifos, EPA has been evaluating an epidemiology study conducted by researchers with the Columbia Center for Children's Environmental Health (CCCEH) (the "Columbia study"). The Columbia study, and the articles published under that study, claim an association between de minimis amounts of chlorpyrifos allegedly found almost twenty years ago in the umbilical cord blood of a cohort of mothers enrolled in the study and neurodevelopmental effects in their children later in life

EPA has previously proposed using the Columbia study as a primary basis for setting new regulatory endpoints for chlorpyrifos. The proposed use of the Columbia study for regulatory decision making has been challenged in public comments, independent reviews and even by EPA's FIFRA Scientific Advisory Panel (SAP). In light of the continuing concerns regarding the validity of the Columbia study, Dow AgroSciences (DAS) asked Toxicology Excellence for Risk Assessment ("TERA"), an independent nonprofit with a mission to protect public health, to examine certain aspects of the Columbia study. TERA looked at the alleged link between chlorpyrifos exposure and neurodevelopmental outcomes reported in one of the most cited publications from the Columbia study (Rauh et al. 2011), by analyzing the data that could be derived from the figures and text of the published article. TERA's methodology and findings are summarized in detail in the attached report

The TERA report's findings raise a number of serious scientific concerns about the reliability of the Columbia study's data and validity of the Columbia study's conclusions. Concerns similar to these have been expressed by prior SAPs and other experts. The TERA findings revealed that not all data were included in the Rauh et al. (2011) analyses. Any exclusion or missing data could impact the conclusions. The TERA report's findings underscore the critical importance of obtaining and analyzing the underlying raw data in order to assess the replicability of the Columbia study's claims. In addition, the TERA report notes that use of different, but generally accepted, graphical representations or plots of the data impacted the trends observed and therefore the conclusions drawn. The impact of simple replotting of the data raises further

questions about the scientific validity and strength of conclusions drawn in the Rauh et al. (2011) publication and the Columbia study.

The TERA findings reported here regarding Rauh et al. (2011), along with challenges raised by other experts, show the findings cannot be considered reliable for purposes of any regulatory decision-making, including but not limited to establishing a new health-based regulatory endpoint or assigning additional or increasing Uncertainty or Safety Factors. EPA should continue to insist upon access to the full set of raw data. The TERA analysis relies on the limited data shared with the scientific community by Rauh et al. (2011). EPA access to and independent analysis of all the raw data would help to address and work towards resolution of the questions and concerns raised in this report. EPA is encouraged to share any progress on obtaining the full set of raw data and resolving these concerns.

US EPA's History of Proposed Uses of the Columbia Study

During 2015-2016, the Columbia study served as the foundation for EPA to propose a link between exposure to chlorpyrifos below the current regulatory standard and neurodevelopmental effects. In November 2015, EPA issued a proposed rule to revoke all tolerances previously established for food uses of chlorpyrifos (*Chlorpyrifos; Tolerance Revocations; Proposed Rule and EPA Analysis of the Small Business Impacts of Revoking Chlorpyrifos Food Tolerances*). Then, in 2016, EPA advanced another regulatory standard for chlorpyrifos (*Chlorpyrifos: Tolerance Revocations; Notice of Data Availability and Request for Comment*). Each time, the Columbia study was the centerpiece for EPA's new proposal. The EPA has given weight to this particular study since it measured chlorpyrifos, not the metabolite, in maternal and cord blood. But, DAS along with other external experts and including USDA have raised serious challenges to EPA's reliance on the Columbia study. Even EPA's own FIFRA Scientific Advisory Panel (SAP) in 2016 strongly criticized EPA's proposed use of this study to set a new regulatory endpoint. Concerns have been raised over the methodology of the study and scientific validity of the conclusions. A major criticism raised repeatedly has been that, despite repeated requests, and the fact that the Columbia study was federally funded, the researchers have refused to make the full raw dataset from the study available for review and validation.

Claims also have been made that the findings reported by the Columbia study are supported by some toxicological studies and other epidemiology studies. However, the scientific validity of these cited toxicological studies has been repeatedly challenged (Oliver, et al. 2016). And, when looking across the epidemiology studies, the neurodevelopmental outcomes have been over-generalized. The specific results are not reproduced in the other studies, challenging any claim of a link between neurodevelopment effects and chlorpyrifos exposures. In fact, consideration of the findings *in total across* these studies does not support and even counters the claim that the epidemiology studies support the Columbia study (Burns and Oliver, 2018; Refer to Section IV of this report). With the validity of the results and conclusions claimed by the Columbia study already in question, TERA's analysis of data from the Rauh et al. (2011) publication casts further doubt on the scientific validity of the findings of the Columbia study.

The Columbia Study – Background on the study

The Columbia University researchers have been studying a group of New York City children born between 1998 and 2002. The investigators have followed certain aspects of the development of these inner-city children of African American and Dominican descent for approximately 15 years. The study started by looking at the many problems and environmental challenges existing in public housing such as holes in the ceiling, leaking pipes and unrepaired water damage, each reported by more than a third of the mothers, which in turn were associated with cockroach and rodent sightings. Measures of, "unmet needs" that included inadequate food, housing or clothing during pregnancy were counted. The investigators also evaluated the education, intelligence, and income of the mothers, which are predictors of childhood development. Unavailable was information about the father including paternal IQ. From the many publications from the Columbia study it is evident that this was a very disadvantaged group of children.

The Columbia study was designed to look at many environmental factors that may affect childhood health. To this end, the investigators tested the household air and infant cord blood for numerous different chemicals, elements (such as lead), and pesticides. The Columbia study researchers have multiple publications in the peer-reviewed literature on correlations between a few of these exposure estimates from birth and subsequent development during childhood, but have not yet reported on all.

The Columbia study only reported statistical correlations, did not prove cause and effect, and failed to consider other plausible causes for their reported developmental outcomes

While the Columbia researchers attribute some correlations of lower test scores with higher chlorpyrifos levels, correlation alone does not prove a causal relationship. The long-standing and well-documented effect for chlorpyrifos used as the regulatory endpoint by regulatory agencies globally is cholinesterase inhibition. EPA is not able to find a biological explanation (i.e., mode of action), despite numerous attempts to identify one, demonstrating how chlorpyrifos in the body might affect neurodevelopment at levels below the current regulatory endpoint of cholinesterase. Extensive research outside the EPA in both humans and animals also shows there is no biological plausibility for the claim of a cause and effect relationship between the alleged low levels of exposure to chlorpyrifos and findings reported in the Columbia study. As discussed in the attached brief (Burns and Oliver, 2017; Refer to Section III of this report) there are multiple other plausible causes for the effects reported in the Columbia study. Most of these were either not considered or unmeasured in the Columbia study, but are important in understanding the underlying factors of childhood development. These alternate explanations need to be fully considered and accounted for when attempting to establish any cause-and-effect relationships.

Analysis of the Columbia study's publication by Rauh et al. (2011) raises serious challenges to the study's conclusion

One of the most cited publications from the Columbia study is Rauh et al. (2011), which claimed statistically significant associations for some reported neurological effects in infants with low levels of chlorpyrifos (CPF) allegedly detected in cord blood at the time of birth. Specifically, the publication reported findings of deficits in Working Memory Index and Full-Scale IQ of the children at 7 years old and alleged an association with prenatal exposure to chlorpyrifos. Although the underlying data have not been made available for validation, despite repeated requests from EPA, as discussed in the report by TERA, an analysis of the Figures in the publication enabled partial data extraction and analysis. The analysis of these extracted data raise significant questions about the conclusions put forward by Rauh et al. (2011).

Missing data likely impacted findings and conclusions

The analysis by TERA revealed that data from 35% of 265 children described in the text of the publication by Rauh et al. (2011) were missing from one of the figures and 15% of the data were missing from another figure. Both figures were the basis in the publication for the claim of an alleged association with developmental effects. While some of the data which appear to be missing are possibly a result of overlay of data points not observable in these published figures, such overlay cannot reasonably be expected to account for the extent of missing data. Furthermore, as noted in the TERA report, in correspondence to the USEPA, Rauh et al. admit to selectivity of the data included in their analysis and publication (see Footnote 10 and Appendix A of TERA report). Specifically, data from the four children having the alleged highest levels of chlorpyrifos detected were removed from these figures because, according to Rauh et al. (2011) at least one data point "drastically impacts inference", which strongly suggests that the statistical significance of the findings might have changed if those data points had been included.

Plotting the data by different methods shows differing results, thereby challenging the strength and validity of claimed associations

TERA also demonstrates that a simple reanalysis/replotting of data from Rauh et al. (2011) significantly impacts the scale or direction of the effects trend reported. When the data for Full-Scale IQ are replotted in a different manner, consistent with a standard risk assessment approach, the evidence for an effect does not exist. And when the Working Memory Composite Scores are plotted differently, a reduced effect is found. As TERA points out, whether one method of plotting these data is superior to another can be debated, but if the reported association between claimed exposure levels and effects were scientifically strong, the resulting interpretations should not be affected by the method of plotting used

Conclusion

The new analysis of the data presented in Rauh et al. (2011) shows the reported associations between alleged chlorpyrifos levels in the mother's cord blood and Working Memory and Full

Scale IQ in their children have serious shortcomings and cannot be independently replicated. Potential impact of missing data, which appear not to have been included in the Rauh et al. (2011) figures, along with the demonstrated impact of replotting of the data using different approaches, raise serious questions about the conclusions of the paper by Rauh et al (2011). These issues, along with the other issues raised by various commenters and independent experts, need to be resolved before the Columbia study can be used, if at all, as the basis for regulatory decisions. The Columbia study researchers providing a complete set of all the raw data suitably marked or coded, and not just summaries or selective data, is a necessary step for further analysis and validation.

The analysis included in the TERA report focuses on the impact that missing data and different approaches to plotting data can have on the Columbia study's conclusions and strength of any trends reported. The statistical considerations and approaches to how cognitive testing results are analyzed and interpreted related to epidemiology studies which make reference to chlorpyrifos have also been previously reviewed and challenged (Edwards et al. 2013). The underpinning common denominator here is that whether it be replotting of data points, statistical comparisons, or other experimental variables which influence interpretation, the raw data availability and transparency of those data, while honoring confidentiality, are needed to reach objective, consistent, reliable, scientifically valid, and biologically plausible interpretations regarding exposure and effect. This is especially true of studies which cannot otherwise be repeated, or which are not consistent with the body of experimental and human data available on chlorpyrifos are needed to reach objective, consistent, and biologically plausible interpretations regarding exposure and effect.

References

Burn, CL., Oliver, GR. 2018. Reproducibility is critical for determining scientific validity. *Lack of consistency with other epidemiology studies challenges rather than supports Columbia study findings.* Brief by Dow AgroSciences LLC, Indianapolis, IN.

Burns, CL., Oliver, GR. 2017. Alternate Explanations for Alleged Effects in the Columbia Study. Brief by Dow AgroSciences LLC, Indianapolis, IN.

Edwards, D., Juberg, D. Burns, C., Goodman, J., Li, A., Bartels, M., Lickfeldt, D. (2013). Epidemiology Studies Pertaining to Chlorpyrifos Exposures: Consideration of Reliability and Utility. Submitted to EPA public docket: EPA-HQ-OPP-0850-0224 and submitted by Dow AgroSciences, Indianapolis, IN to EPA (MRID 49371401)

Oliver, G., Burns, C., Juberg, D., Hastings, K., Racke, K., Havens, P. Dow AgroSciences LLC's Comments on 2016 Notice of Data Availability, Revised Human Health Risk Assessment and Refined Drinking Water Assessment for Chlorpyrifos (EPA Docket: EPA-HQ-OPP-2015-0653). January 17, 2018. Dow AgroSciences LLC, Indianapolis, IN.

Rauh et al. (2011). Seven-Year Neurodevelopmental Scores and Prenatal Exposure to Chlorpyrifos, a Common Agricultural Pesticide, Environmental Health Perspectives, Volume 119 (number 8): 1196-1201.

US Environmental Protection Agency (EPA) FIFRA Scientific Advisory Panel (SAP). 2016. MEETING ON CHLORPYRIFOS: ANALYSIS OF BIOMONITORING DATA. DOCKET NUMBER: EPA-HQ-OPP-2016-0062. Transcript of April 19 – 21, 2016 meeting.

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II. Report: A Commentary on Some Epidemiology Data for Chlorpyrifos

A Commentary on Some Epidemiology Data for Chlorpyrifos

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June 13, 2018

Toxicology Excellence for Risk Assessment (*TERA*) is a 501c3 nonprofit organization with a mission to protect public health.

Summary

Rauh et al. (2011), one of the published studies from the Columbia Center for Children's Environmental Health (CCCEH), claimed statistically significant associations for some reported neurological effects in children with detection of low levels of chlorpyrifos (CPF) in cord blood at the time of birth. It is stated that the mothers may have been exposed to residential uses of chlorpyrifos sometime during pregnancy. These reported effects are surprising in light of the extensive animal and human studies on chlorpyrifos that point to changes in a blood enzyme as its first biological effect, occurring at much higher levels. The chlorpyrifos-specific neurodevelopmental findings reported in the CCCEH have not been replicated in other epidemiology publications, nor have the data on which these publications depend been made available to government scientists for independent confirmation, despite the fact that the CCCEH was supported in part by public funds and the data have been requested by the U.S. Environmental Protection Agency (EPA).

Specifically, Rauh et al. (2011) reported evidence of deficits in Working Memory Index[1] and Full-Scale IQ in children at 7 years old as a function of prenatal CPF exposure. Although these data have not been made available, we were able to extract them in part through an analysis of Figures 1A and 1E of Rauh et al. (2011). This analysis uncovered a surprising fact. Data from approximately 35% of the 265 children described in the text of Rauh et al. (2011) were missing from Figure 1A; approximately 15% of these data were missing from Figure 1E. Although some of the missing data are possibly due to overlay of data points not observable in these published figures, such overlay cannot reasonably account for the extent of these missing data. Further, CCCEH correspondence to EPA admits that data of the four highest exposed children from Rauh et al. (2011) were removed from these figures because at least one data point "drastically impacts inference," suggesting that the statistical significance of these findings may have changed had these data been included.

The data extracted from the figures were analyzed in a number of ways, including a plot of data as response versus log dose, a typical toxicological and risk assessment approach. In contrast to Rauh et al. (2011), our analysis does not suggest any evidence of an effect on Full-Scale IQ (Figure 1E). We also find less of a negative association (reduction) in Working Memory Index (Figure 1A). Obviously, having all of the available data for analysis are preferred, since the lack of raw data from these studies makes statistical analysis and confirmation, a hallmark of scientific inquiry, impossible. The receipt of the raw data would also allow us to consider adjusting responses for other confounding variables, as was done by Rauh et al. (2011). Disclosure of the four truncated data points with the highest chlorpyrifos levels would also permit evaluation of their impact on the interpretation of the claimed association.

In conclusion, the reported associations of chlorpyrifos levels with Working Memory and Full Scale IQ have significant shortcomings and were not replicated in our analysis. The inconsistency with cholinergic responses in other research raises doubts about the validity of the

[1] Working Memory Index assesses children's ability to memorize new information, hold it in short-term memory, concentrate, and manipulate information.

CCCEH findings.

Introduction

EPA Administrator Pruitt's recent announcement that EPA will be strengthening the transparency in regulatory science or otherwise not using science for which the underlying data cannot be procured, has provoked significant discussion.[2] Much has been made about this new proposed EPA policy, including op-eds against it (e.g., McCarthy and McCabe),[3] and arguments for it based on a risk assessment perspective (e.g., Dourson).[4] All of this discussion serves to focus attention on an important issue. Specifically, how is science considered acceptable and useful in EPA's rulemaking?

In the case of the pesticide chlorpyrifos (CPF), scores of studies[5] suggest that its sentinel[6] effect, that is, the first biological effect (or marker of exposure) or its known precursor, is cholinesterase inhibition, and that this inhibition occurs at roughly the same dose and time course in experimental animals and humans.[7] This finding is so well accepted that health agencies across the world have focused on cholinesterase inhibition as the basis for determining chlorpyrifos' safe dose. Therefore, it came as a surprise to many scientists that Rauh et al. (2011), one of the published studies from the Columbia Center for Children's Environmental Health (CCCEH), claimed neurological effects in children associated with prenatal levels of CPF that were much lower that than those that showed cholinesterase inhibition.[8] The claims reported by Rauh et al, (2011) were in contrast to the weigh-of-evidence of decades of accepted studies on chlorpyrifos, and were used by some to suggest an alternative hypothesis, specifically, that the sentinel effect for chlorpyrifos should be based on human neurological effects rather than cholinesterase inhibition.

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[2] See: https://www.federalregister.gov/documents/2018/04/30/2018-09078/strengthening-transparency-in-regulatory-science).

[3] See: https://www.nytimes.com/2018/03/26/opinion/pruitt-attack-science-epa.html.

[4] See: https://www.washingtonexaminer.com/opinion/op-eds/the-epas-new-secret-science-rule-makes-sense-from-a-risk-assessment-perspective.

[5] U.S. Environmental Protection Agency. 2014. Revised Human Health Risk Assessment for Registration Review. Office of Pesticide Programs, Washington, DC. December 29.

[6] This is also referred to as the chemical's critical effect.

[7] See Zhao et al. 2006. A Review of the Reference Dose (RfD) for Chlorpyrifos. Reg. Toxicol. Pharmacol. 44:111-124.

[8] Rauh et al. (2011). Seven-Year Neurodevelopmental Scores and Prenatal Exposure to Chlorpyrifos, a Common Agricultural Pesticide, Environmental Health Perspectives, Volume 119 (number 8): 1196-1201.

Specifically, Rauh et al. (2011), show statistically significant, negative associations of Working Memory and Full Scale IQ scores[9] after adjustment by the natural logarithm with dose shown in normal units. This adjustment of the IQ scores compresses the top of the y-axis in relationship to the bottom. This compression of top IQ scores and stretching out of the lower IQ scores gives the subtle appearance of a downward shift, which lessens when IQ scores on the y-axis are not mathematically so adjusted.

From a risk assessment perspective, a more typical data display would be to show unadjusted IQ scores, which are already expected to be normally distributed, as a function of dose that is in either normal units or itself adjusted by logarithm (based 10). Note that the dose x-axis when adjusted into log units will also stretch out the lower part of the axis in relationship to the higher part of the axis. In this case the logarithm adjustment is appropriate, however, because most of the exposure data lie in the lower part of the dose x-axis.

The purpose of this white paper is to summarize points to consider when contemplating whether or not this alternative hypothesis is supportable by analysis of the available data from these epidemiology findings, and in light of the more extensive CPF human/animal database.

Methods

Figures 1A (Working Memory) and 1E (Fill Scale IQ) of Rauh et al. (2011) were viewed by TERA scientists and the results for chlorpyrifos levels and test scores entered into an excel spreadsheet for further analysis. For Figure 1A of Rauh et al. (2011), 33 data points were shown by Rauh et al. as zero or non-detectable. For Figure 1E, 60 points were shown as zero or non-detectable. Consistent with the approach of Raul et al. (2011, page 1198), ~80% of these values were assigned a chlorpyrifos level of 0.5 pg/g and ~20% of them were assigned a level of 1.0 pg/g.

The results were then plotted as natural logarithm-adjusted response versus reported dose (as per Rauh et al., 2011), and as un-adjusted response versus $\log_{10}$ dose. Linear regressions were developed using excel spreadsheet software. During this reanalysis, we discovered that approximately 35% of the data, as stated to be available in the publication in Rauh et al. (2011, page 1197), were missing in Figure 1A and approximately15% of the data were missing from Figure 1E, Moreover, four high dose data points were missing in both graphs. The CCCEH response to US EPA staff suggests to us that the inclusion of these four truncated data points would have attenuated or perhaps even eliminated the statistical significance of their findings.[10]

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[9] Each of the measurements in the Rauh et al. (2011) study are a "standardized scale has [with] a mean of 100 and SD of 15." (See Rauh et al. page 1197, column 3, line 16-17.). This means that the y-axis is expected to be a normal bell-shaped distribution.

[10] Memo to: Carrol Christensen, Ph.D; From: Robin M. Whyatt, DrPH; Date: April 9, 2015
Re: July 2011 letter to Deborah Smegal, M.P.H.: [Full memo available as Appendix A]

Furthermore, our examination of Figure 1A in Rauh et al. (2011) revealed a tremendous amount of scatter at CPF blood concentrations of 5 pg/g or less, but little scatter at higher blood levels. Consequently, it would seem reasonable to include these 4 data points in the higher blood concentration range in any calculation.

Results

Figure 1 is taken from the Rauh et al. (2011) publication, specifically their Figure 1A (Working Memory). Figure 2 attempts to replicate the Rauh et al. Figure 1. This replication seems reasonable from a comparison of where the regression lines lie in relationship to the high dose points in either figure, despite the fact that we are missing approximately 35% of the data stated to be available in Rauh et al. (2011) (see Appendix B for our raw data and Appendix C for a comparison between data sets). However, and importantly, Rauh et al. also do not include high dose data on their charts (e.g., see reference to 63 pg/g on Rauh et al. page 1198, column 2, which is not found on Figure 1A). Apparently also missing is one child with a value of 32 pg/g (see stated CPF range in Rauh et al., Table 1).

EPA comment: In Figure 1 page 29, the upper bound of the x axis (chlorpyrifos) is shown to be 25 pg/gm. However, in the second paragraph of page 11 it was reported that the maximum CPF exposure is 63 pg/g. It was not clear to us why in Figure 1 the range of CPF was truncated.

CCCEH response: The maximum CPF exposure in the sample was indeed 63 pg/g. The number of children with CPF levels above 25 pg/g were 4. The x-axis was truncated at 25 pg/gm for the following reasons:

1) One of the subjects did not have the outcomes measured.

2) The subject with 63 pg/g was a highly influential observation (outlier) and drastically impacts inference. This was confirmed based on residual analysis in most analyses. Where appropriate, this observation was removed from the analysis. This influence was observed in the spline plots as well and this lone outlier at the extreme end of the exposure made the plot unstable and uninformative.

3) With just two observation left in this range, the data were too sparse and the splines too unstable in this region.

Moreover, being exploratory in nature, the spline plots were constructed to assess the adequacy of a linear relationship between log-transformed CPF and WISC scores. We therefore restricted the splines to the range of CPF values were the data were not sparse and the curves were stable.

Figure 1. Ln Working Memory Index Versus Dose of Rauh et al. (2011, Figure 1A).

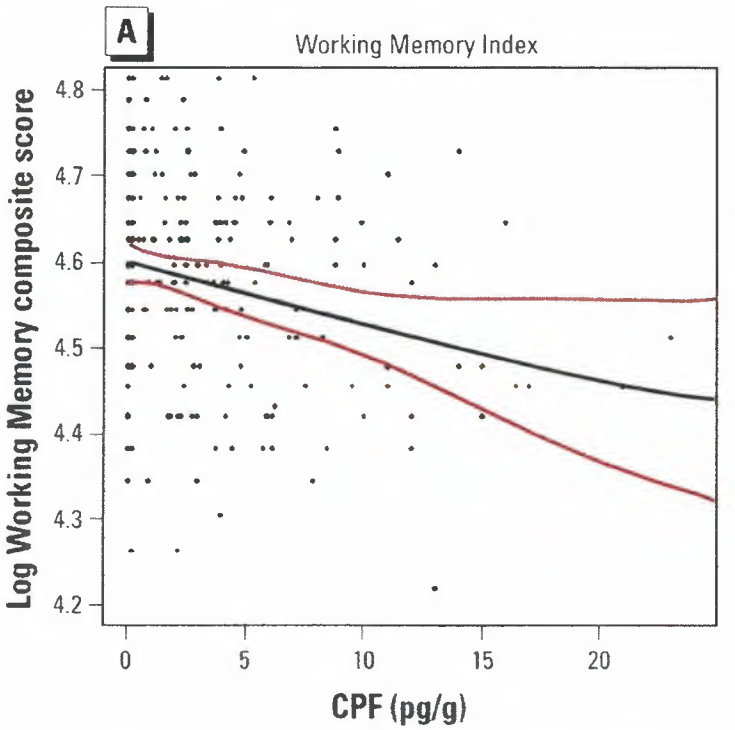


Figure 2. Ln Working Memory Index Versus Dose

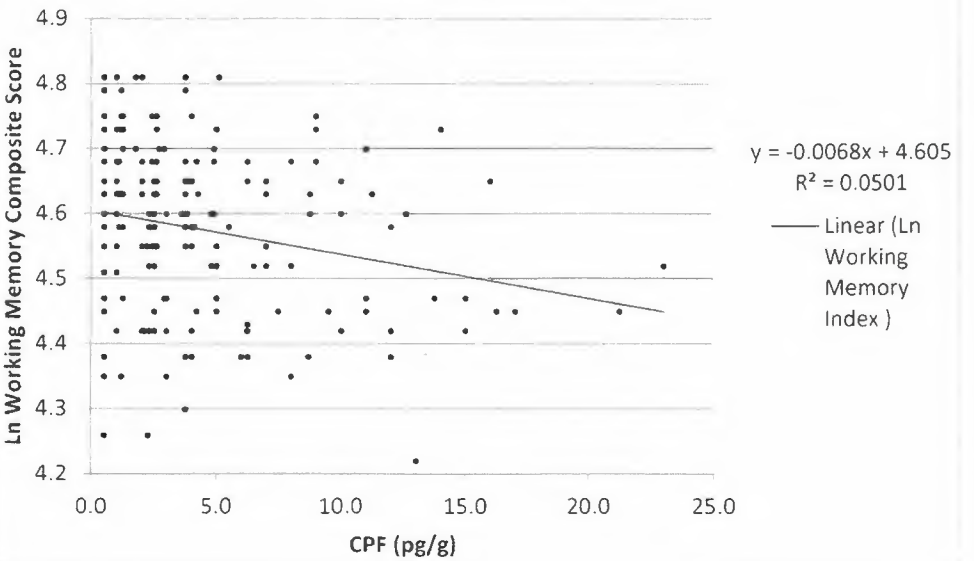


Figure 3. Working Memory Index Versus Log10 Dose

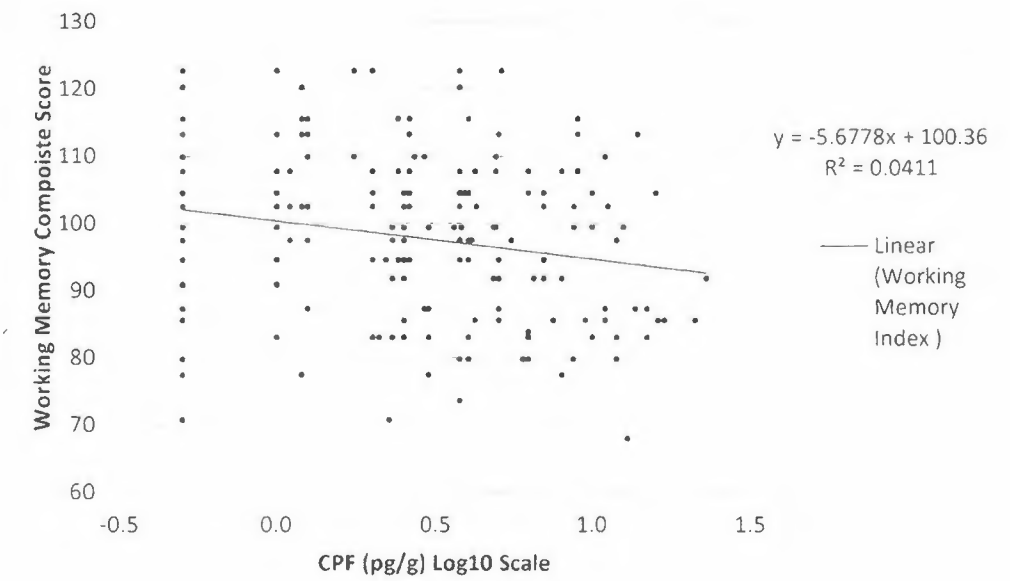


Figure 3 reflects the data from Figure 2 plotted with the response unadjusted and the dose in logarithmic units (log_{10}). Figure 3 shows a reduced effect on Working Memory Index when compared with Figure 2, found by comparing where the regression lines lie in relationship to high dose data points. This indicates that the way Rauh et al. (2011) presented the data had an effect on interpretation. Moreover, the response y-axis is not compressed in our Figure 3, eliminating the subtle visual effect of downward trend due to this compression of the y-axis found in Figure 2. The R^2 for both regression lines are very small, which indicates that chlorpyrifos does not well explain the data variability (i.e. the scatter).

Figure 4 is from Rauh et al. (2011), specifically their Figure 1E (Full Scale IQ). Figure 5 here attempts to replicate these findings. This replication is not as close as Figures 1 and 2. (Again, compare where the regression lines lie in relationship to high dose points in either Figure 4 or 5.) As in the previous comparison of Figures 1-3, some of the data stated to be available in Rauh et al. (2011) are missing (in this case approximately 15%; see Appendix B for our raw data).

Figure 6 reflects the data from Figure 5 plotted with the response unadjusted and the dose in logarithmic units (log_{10}). Figure 6 shows no effect on Full Scale Composite score when compared with Figure 5. As before, the y-axis is not compressed in our Figure 6, eliminating the subtle visual effect of downward trend due to this compression in the y-axis of Figure 5. The R^2 is for Full Scale IQ is even smaller than for Working Memory, suggesting that chlorpyrifos is a poor predictor of the outcome.

Figure 4. Ln Working Full-Scale IQ Versus Dose of Rauh et al. (2011, Figure 1E).

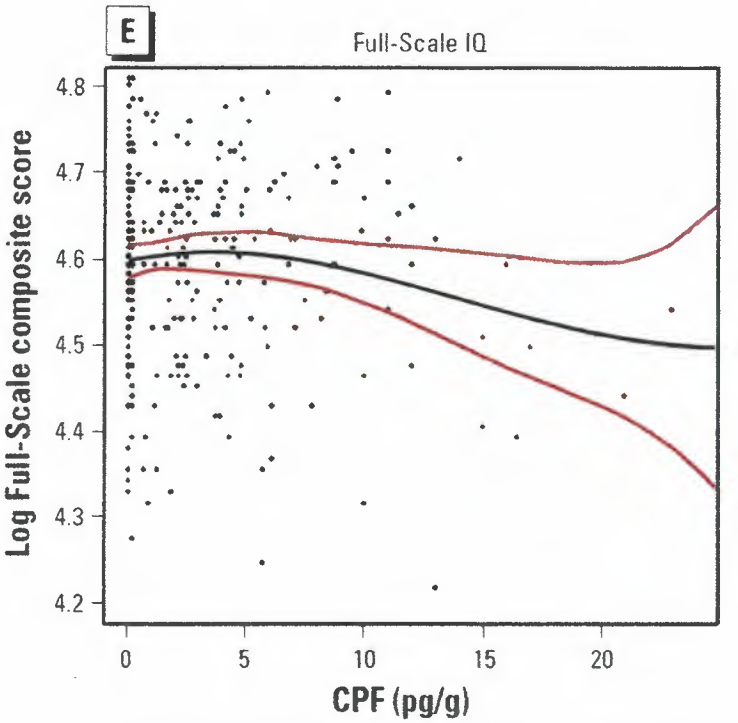


Figure 5. Ln Full Scale IQ Versus Dose

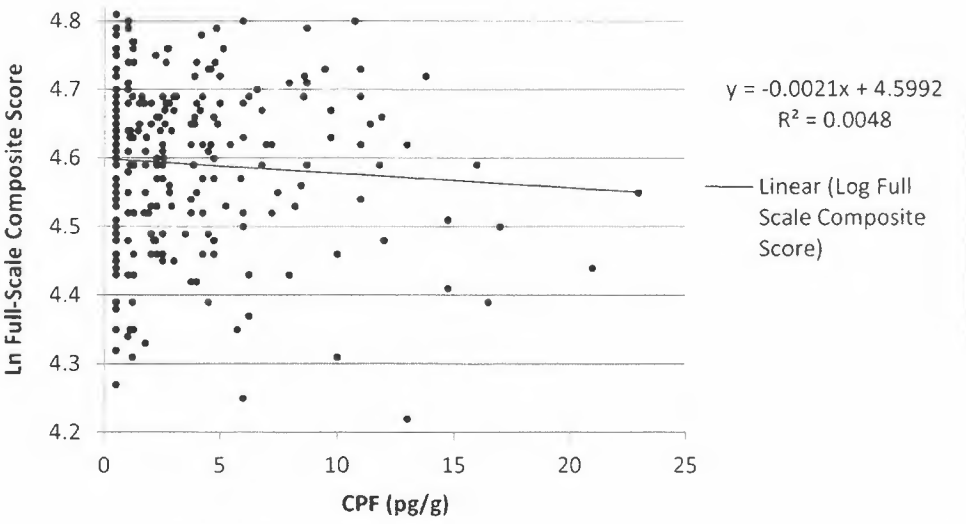
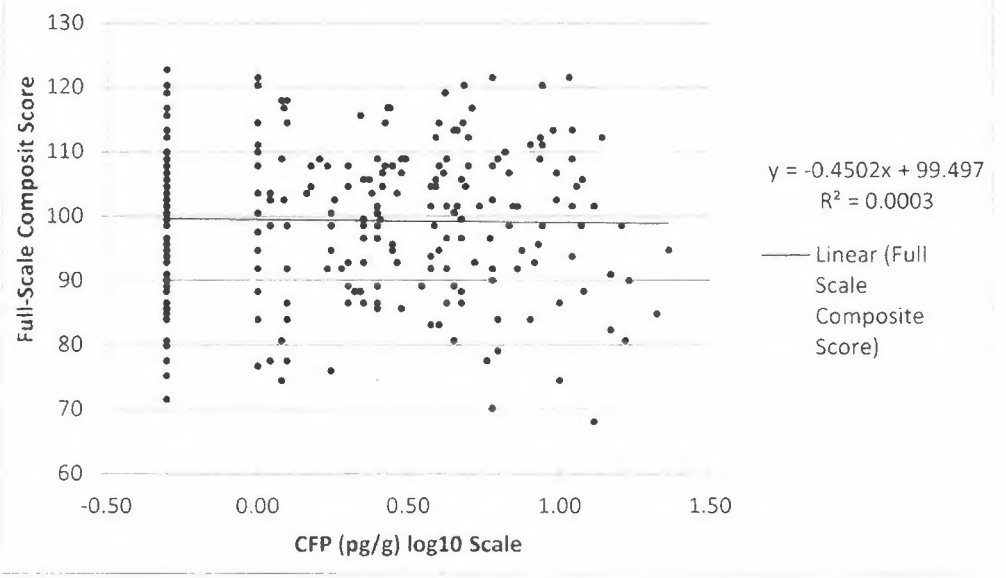


Figure 6. Full Scale IQ Versus Log10 Dose



The bottom line of this simple reanalysis is that evidence of effect for Full-Scale IQ does not exist when the study data are presented in another manner (Figure 6). Working Memory shows evidence of a negative statistical association with dose (Figure 3), but this evidence is problematic due to missing data, including data for the highest exposed individual that Rauh et al. (2011) state "was a highly influential observation (outlier) and drastically impacts inference."

Overall, the lack of raw data from this study makes statistical analysis and confirmation of the authors' data and results, a hallmark of scientific inquiry, impossible.

Discussion

The most significant challenge, by far, in any reanalysis of the Rauh et al. (2011) study is the absence of data to conduct a credible replication to confirm the data analysis. For example, Rauh et al. (2011) state that:

> "Of 725 consenting women, 535 were active participants in the ongoing cohort study at the time of this report, and 265 of their children had reached the age of 7 years with complete data on the following: *a*) prenatal maternal interview data, *b*) biomarkers of prenatal CPF exposure level from maternal and/or cord blood samples at delivery, *c*) postnatal covariates, and *d*) neurodevelopmental outcomes."

However, the Results section of Rauh et al. (2011) show a series of 5 graphs, each of which

would be expected to offer a complete picture of effects based on 265 children (as suggested from the quotation above). Yet, our analysis of two of these graphs (Figures 1A and 1E) show ~35% or ~15% missing data points, respectively, and neither of these graphs include the data points from the highest cord blood CPF exposures of 63 pg/g, or another higher dose data point of 32 pg/g, as stated by Rauh et al. (2011, Table 1) (see Appendix B for our raw data).

Despite these missing data, what do our analyses show? Although negative neurological associations are reported in the Rauh et al. (2011) with CPF exposure when a plot of Working Memory Composite Scores are normalized by their natural logarithm, and plotted against dose, this manner of data display is not the only one possible. A standard risk assessment approach would be to plot the unadjusted scores, which are already expected to be normally distributed in the human population (as per Rauh et al., 2011 Experimental Design), against the logarithm of dose.

When the results of Rauh et al. (2011) are plotted using logarithmic scales in this way, a reduced association is found. For example, Figure 2 is a representation of Rauh et al.'s Figure 1A (shown here as Figure 1) plotted as the natural logarithm of response versus dose. Figure 3 shows these same data, but where the response, Working Memory, is plotted as unadjusted response versus $\log_{10}$ dose. A comparison of Figures 2 and 3 will show that the negative trend of Figure 2 for the Working Memory is less in Figure 3. When a similar analysis is performed for Full Scale IQ (or Composite Score) the slight negative trend of Figure 5, which is a representation of Rauh et al. (2011) Figure 1E and shown here as Figure 4, disappears; compare Figures 5 and 6.[11]

Whether one method of plotting these data is superior to another may be important, but a strong true association should not be affected by the method of data plotting. A more appropriate, scientific approach to confirm our findings would be to have access to the underlying raw data. For example, access to the raw data would enable us to discuss our results in more statistical terms, by comparing the differences in the slopes of the regressions and the low r^2 values. This would allow a stronger statement on whether a statistical significant association is found (or not). Further, access to the raw data would allow us and others to adjust for confounding factors as was performed by Rauh et al. (2011) in their regression. Moreover, we might be able to refine our analysis from a simple linear approach to an alternate approach in a manner similar to that shown by Rauh et al. (2011) who presented a smooth cubic spine curve.

[11] What about including the missing high dose data? Adding the two high dose data points described in Rauh et al. (2011) to figures 3 and 6 and supposing only average responses further decrease the negative slopes, but only slightly (data not shown). This indicates even less of an effect, if any, from chlorpyrifos exposure.

We acknowledge that our analysis from published graphs is a rudimentary way to obtain the raw data of Rauh et al. (2011), because data points may often overlay one another in published figures.[12] Still, such an analysis of the Rauh et al. (2011) data shows that no CPF exposures greater than 25 pg/g are plotted. So, where are these high dose data described by Rauh et al. (2011)?

Not surprisingly, as co-sponsors of the study, scientists with the EPA have asked for the raw data from Rauh et al. (2011) and earlier publications.[13] Such a request would seem reasonable, because as described by Rauh and coworkers:

> "This study was supported by the National Institute of Environmental Health Sciences (grants 5P01ES09600, P50ES015905, and 5R01ES08977), the U.S. Environmental Protection Agency (grants R827027, 8260901, and RR00645), the Educational Foundation of America, the John and Wendy Neu Family Foundation, the New York Community Trust, and the Trustees of the Blanchette Hooker Rockefeller Fund."

As EPA has noted in its request for the raw data, its scientists are familiar with rules for handling confidential data. Moreover, personal information of the subjects can be redacted while maintaining the ability to replicate findings.

Unfortunately, the raw data have not been forthcoming.

A number of additional questions or comments can be raised with regard to this epidemiology study. For example:

- How is it that the full scale composite score graph of Rauh et al. (2011; Figure 1 E) has more data points than Rauh et al. (2011) graph of working memory composite score (Figure 1A), if the former depends on the latter?

- According to Rauh et al. (2011), umbilical cord blood samples were not collected at birth in 12% of the study population. Nor were prenatal blood lead levels, a known neurological risk for children, collected for 66% of the maternal study population. In addition, blood lead samples were only collected in 89 out of 265 children, or 34%.

- Epidemiologists often study associations among a plethora of effects versus exposures to multiple chemicals. This is a good strategy since associations can lead to further, more definitive, investigations, based on a more clearly defined hypothesis. The hypothesis

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[12] It is essentially impossible that all of the missing data points in the Rauh et al. (2011) Figures 1A and 1E are underneath the other points. One point is ~0.01% of the graph area and all data points combined covers less than ~2% of the graph area. There are 265 children in the study, but only approximately 170 data points observable in Figure 1A. Thus, the chance that all of the missing data points are hidden below other data points is miniscule. Rather it appears that many of these data points were not added to these figures.

[13] US EPA. 2014. Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review. Appendix 6, page 384 and Addendum, page 394. December 29.

developed from the Rauh et al. (2011) study, in particular, would be that neurological effects occur at doses lower than cholinesterase inhibition. This hypothesis can be tested...

- ...And it has been tested with CPF in a number of experimental animals, and found not to be supported. Specifically, neurological effects do occur in experimental animals, but only at doses that exceed those which cause cholinesterase inhibition in the experimental animals (EPA, 2014). Although it may be that these experimental animal studies are not able to monitor for the types of neurological effects associated with increasing CPF dose in Rauh et al. (2011) and related studies, the observed neurological effects in experimental animals are more than 100-fold greater on the dose scale than the purported epidemiology associations. This disparity in dose makes it difficult to accept the epidemiological associations as credible, especially when human and experimental animal studies are similar in dose with respect to cholinesterase inhibition, the current sentinel or critical effect for CPF as demonstrated by Zhao et al., (2006). Should one expect that neurological effects would differ in the dose scale between experimental animals and humans, when the critical effect, cholinesterase inhibition, does not?

- The metabolite responsible for the toxicity of cholinesterase inhibition, CPF-oxon, is formed in the liver and 99% of this oxon derivative irreversibly binds to cholinesterase in the blood at levels (EPA, 2014). Since it is so bound, it would not be expected to reach the brain to affect neurological development of the fetus at levels much lower than levels which do not otherwise show any effect on the sentinel blood enzyme In fact, an analysis by Marty et al. (2012)[14] showed no systemic bioavailability, nor any brain cholinesterase inhibition with the CPF-oxon at doses comparable to the established safe doses.

- A number of other factors are known to affect neurodevelopmental effects in infants and children. These other documented, potential causes of the effects reported need to be fully evaluated.

- The specific results described by Rauh et al. (2011) are not reproduced in other epidemiology studies, which challenge the claim of a link between neurodevelopment effects and chlorpyrifos exposures. In fact, Burns (2018) shows that consideration of the findings *in total across* these studies does not support and even counters such a claim.[15]

Conclusion

One of the papers from the CCCEH, specifically Rauh et al. (2011), has been cited as showing a statistical association between CPF exposure and intelligence. This study has significant scientific shortcomings. An analysis of the published figures shows that up to 35% of the data

[14] M.S.Marty, A.K.Andrus, M.P.Bell, J.K.Passage, A.W.Perala, K.A.Brzak, M.J.Bartels, M.J.Beck, D.R.Juberg, Cholinesterase inhibition and toxicokinetics in immature and adult rats after acute or repeated exposures to chlorpyrifos or chlorpyrifos–oxon. Reg. Toxicol. Pharmacol. 63 (2): 209-224. July 2012.

[15] Burns, C.J. 2018. Reproducibility is critical for determining scientific validity. Sanford, MI. June 6.

appear to be missing, and that the data adjustment used was not typical from a risk assessment perspective. The associations are lessened or no longer apparent when different logarithmic assumptions were used in the reanalysis. Moreover, the data, generated in part by public funds, have not been made available for independent review. These shortcomings make it difficult to confirm this study's findings and raise serious scientific doubt about the validity of the published results.

Appendix A

COLUMBIA CENTER FOR CHILDREN'S ENVIRONMENTAL HEALTH

MAILMAN SCHOOL OF PUBLIC HEALTH
Columbia University

Memo to: Carrol Christensen, Ph.D
From: Robin M. Whyatt, DrPH
Date: April 9, 2015

Re: July 2011 letter to Deborah Smegal, M.P.H.

In reading through the 2014 chlorpyrifos risk assessment document, we were pleased to see that it contained almost all of our correspondence answering questions from both the SAP and EPA on our various chlopyrifos articles. However, the letter we prepared answering a series of questions from Deborah Smegal, MPH, on our 2011 manuscript[1] was not included in document and, we believe, should also be part of the docket. As you will see, the letter first lists each question from Ms. Smegal followed by our answers to that question. Please let us know if you have any questions.

[1]Rauh V, Arunajadai S, Horton M, Perera F, Hoepner L, Barr DB, Whyatt R. Seven-year neurodevelpmental scores and prenatal exposure to chlorpyrifos, a common agricultural pesticide, Environ Health Perspect. 119(8): 1196-201, 2011. PMCID: PMC3237355

722 West 168th Street, 12th Floor, Room 1200, New York, NY 10032
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Dear Debbie,

The questions are quite straight-forward , so hopefully this will clarify your reading of the results. The important point is that we have modest yet meaningful findings that are consistent across several different analytic approaches. We note that you have suggested other statistical approaches, such as generalized Linear Model, which is typically employed in situations where departures from normality are more extreme than the present case. It is always a judgment call to select the single 'best' approach . Thank you for pointing out the one digit error in the on line version of the paper (Table 2), and this has been corrected in the final version . Otherwise, please let us know if you have additional questions

1 The paper reports the decline of IQ and Working memory in terms of 1 standard deviation increase of CPF However it is recognized that usually chloropyriphos exposure follows log- normal distribution. Infect the authors made the same distributional assumption of CPF while imputing the non-detects. It would be more helpful for interpretation purposes to express the decline of IQ and Working memory in terms of geometric standard deviation of CPF instead of arithmetic standard deviation In table 9 2 of page 262 of Environmental Statistics and Data Analysis by Wayne R Ott relationship between arithmetic parameters (mean and standard deviation) and geometric parameters (mean and standard deviation) were provided Using these transformation CEB found that 1 geometric standard deviation increase of CPF prenatal exposure will decrease the full scale IQ by 0 87 % and working memory by 1 73%

We are not sure how exactly the calculations above were done. We computed the Geometric Mean (GM) and Geometric Standard Deviation (GSD) of the Chlorpyrifos exposure from the data and were found to be 0.65 and 6.22 respectively. Thus for one GSD increase in CPF, the Fu ll Scale IQ on average decreases by 1.85% and Working Memory by 3.66%.

2 In Figure 1 page 29, the upper bound of the x axis(Chlorpyrifos) is shown to be 25 pg/gm However in the second paragraph of page 11 it was reported that the maximum CPF exposure is 63 pg/g. It was not clear to us why in figure 1 the range of CPF was truncated

The maximum CPF exposure in the sample was indeed 63 pg/g . The number of children with CPF levels above 25 pg/g were 4. The x-axis was truncated at 25 pg/gm for the following reasons
1) One of the subjects did not have the outcomes measured
2) The subject with 63 pg/g was a highly influential observation (outlier) and drastically impacts inference. This was confirmed based on residual analysis in most analyses Where appropriate this observation was removed from the analysis. This influence was observed in the spline plots as well and this lone outlier at the extreme end of the exposure made the plot unstable and uninformative
3) With just two observation left in this range, the data were too sparse and the splines too unstable in this region .

Moreover, being exploratory in nature, the spline plots were constructed to assess the adequacy of a linear relationship between log-transformed CPF and WISC scores. We therefore restricted the splines to the range of CPF values were the data were not sparse and the curves were stable.

3 In table-2 for the fully adjusted model of Full scale IQ the 95% confidence interval for the coefficient of CPF includes 0 Therefore the CPF is not statistically associated with Full scale IQ based on C I. However the p value for the same coefficient is shown to be less than 0 05 It is statistically impossible to have p value less than 0 05 and 95% confidence interval includes 0 at the same time The author should explain this inconsistency between the p value and the C I -- perhaps this inconsistency is simply due to round ing?

The Fully adjusted coefficients in Table 2 should have values consistent with the values in the supplementary material Table 1. Thus for Full scale IQ , rounded to three significant digits, the 95% CIs were -0 006 to 0.000, and the p-value rounded to 2 decimal places is equal to 0.05 (0.048). The values in table 2 in the main paper should have read -0 006, 0 000 as opposed to -0.006, 0.001 . Thanks so much for picking up this incorrect digit.

4. Using Lasso model it was shown in Table 2 that prenatal exposure and Full scale IQ is not statistically associated at alpha=0.05 level. However in the result section of the abstract it was stated that for each standard deviation increase in exposure of CPF full scale IQ declined by 1.4. The paper should include a discussion about non significance of prenatal exposure of CPF for the Full scale IQ when interpreting the association between IQ and CPF exposure

We direct the reader to the comparability of the LASSO and the fully adjusted models in terms of effect size (coefficient). The fully adjusted model is the more famil iar approach to regression analysis, and includes all of the covariates. We were interested in using LASSO to demonstrate that the effect sizes do not vary in a meaningful way, using a procedure that may be less vulnerable to over-fitting . In interpreting the results , the effect size may be more important than statistical significance alone, as the significance can be affected by sample size and power. Specifically, when sample size and power are modest, the results of significance tests can be misleading because of being subject to Type II errors (incorrectly failing to reject the null hypothesis) In these situations, it can be more informative to use the effect sizes (how much of an effect), especially with the confidence intervals.

5 The authors stated in the data analysis section of page 9 that WISC-IV composite index scores have been log transformed to stabi lize the variance and to improve the linear model fit. Another alternate approach may be to use the generalized linear model which may be better able to deal with the issues of concern

The intention here is to investigate the shape and the strength of the possible doseeffect relationship. While a Generalized Linear Model might also be used , log transformation usually provides consistent results when we have normal residuals (as we do here). Generalized Linear Models are a kind of extension of the linear modeling process that allows models to be fit to data that follow probability distributions other than

the Normal distribution, such as the Poisson, Binomial, Multinomial, and etc. Generalized Linear Models also relax the requirement of equality or constancy of variances that is required for hypothesis tests in traditional linear models. While it is certainly possible to use Generalized Linear Models (and there are many different ways to test our hypotheses), there is no indication that this procedure would result in a better fit or a more precise estimate.

Appendix B: TERA Reading of Rauh et al. (2011) Figure 1A

The first 33 points are zero or non-detectable and have been assigned chlorpyrifos levels with Rauh et al. 2011 page 1198. Specifically 80% at 0.5pg/g and 20% 1.0pg/g. This set of data points was manually read from Figure 1A Rauh et al. (2011).

CPN (pg/g)	log Chlorpyrifos (pg/g)	ln Chlorpyrifos (pg/g)	ln Working Memory Index	Working Memory Index	Probits
0.5	-0.3	-0.7	4.26	71	-1.95
0.5	-0.3	-0.7	4.35	77	-1.50
0.5	-0.3	-0.7	4.38	80	-1.34
0.5	-0.3	-0.7	4.38	80	-1.34
0.5	-0.3	-0.7	4.45	86	-0.96
0.5	-0.3	-0.7	4.47	87	-0.84
0.5	-0.3	-0.7	4.47	87	-0.84
0.5	-0.3	-0.7	4.51	91	-0.61
0.5	-0.3	-0.7	4.55	95	-0.36
0.5	-0.3	-0.7	4.55	95	-0.36
0.5	-0.3	-0.7	4.58	98	-0.17
0.5	-0.3	-0.7	4.58	98	-0.17
0.5	-0.3	-0.7	4.6	99	-0.03
0.5	-0.3	-0.7	4.63	103	0.17
0.5	-0.3	-0.7	4.63	103	0.17
0.5	-0.3	-0.7	4.65	105	0.31
0.5	-0.3	-0.7	4.68	108	0.52
0.5	-0.3	-0.7	4.68	108	0.52
0.5	-0.3	-0.7	4.7	110	0.66
0.5	-0.3	-0.7	4.7	110	0.66
0.5	-0.3	-0.7	4.73	113	0.89
0.5	-0.3	-0.7	4.75	116	1.04
0.5	-0.3	-0.7	4.75	116	1.04
0.5	-0.3	-0.7	4.79	120	1.35
0.5	-0.3	-0.7	4.81	123	1.52
1.0	0.0	0.0	4.42	83	-1.13
1.0	0.0	0.0	4.51	91	-0.61
1.0	0.0	0.0	4.55	95	-0.36
1.0	0.0	0.0	4.6	99	-0.03

CPN (pg/g)	log Chlorpyrifos (pg/g)	ln Chlorpyrifos (pg/g)	ln Working Memory Index	Working Memory Index	Probits
1.0	0.0	0.0	4.65	105	0.31
1.0	0.0	0.0	4.68	108	0.52
1.0	0.0	0.0	4.73	113	0.89
1.0	0.0	0.0	4.81	123	1.52
2.25	0.1	0.2	4.26	71	-1.95
13	1.1	2.6	4.22	68	-2.13
3.75	0.6	1.3	4.3	74	-1.75
8	0.9	2.1	4.35	77	-1.50
3	0.5	1.1	4.35	77	-1.50
1.2	0.1	0.2	4.35	77	-1.50
12	1.1	2.5	4.38	80	-1.34
8.7	0.9	2.2	4.38	80	-1.34
6.25	0.8	1.8	4.38	80	-1.34
6	0.8	1.8	4.38	80	-1.34
4	0.6	1.4	4.38	80	-1.34
3.75	0.6	1.3	4.38	80	-1.34
15	1.2	2.7	4.42	83	-1.13
12	1.1	2.5	4.42	83	-1.13
10	1.0	2.3	4.42	83	-1.13
6.25	0.8	1.8	4.42	83	-1.13
6.24	0.8	1.8	4.42	83	-1.13
6.23	0.8	1.8	4.42	83	-1.13
4	0.6	1.4	4.42	83	-1.13
3	0.5	1.1	4.42	83	-1.13
3	0.5	1.1	4.42	83	-1.13
2.5	0.4	0.9	4.42	83	-1.13
2.3	0.4	0.8	4.42	83	-1.13
2	0.3	0.7	4.42	83	-1.13
2.1	0.3	0.7	4.42	83	-1.13
6.25	0.8	1.8	4.43	84	-1.07
21.3	1.3	3.1	4.45	86	-0.96
16.3	1.2	2.8	4.45	86	-0.96
17	1.2	2.8	4.45	86	-0.96
11	1.0	2.4	4.45	86	-0.96
9.5	1.0	2.3	4.45	86	-0.96
7.5	0.9	2.0	4.45	86	-0.96
5	0.7	1.6	4.45	86	-0.96
4.2	0.6	1.4	4.45	86	-0.96

CPN (pg/g)	log Chlorpyrifos (pg/g)	ln Chlorpyrifos (pg/g)	ln Working Memory Index	Working Memory Index	Probits
2.5	0.4	0.9	4.45	86	-0.96
15	1.2	2.7	4.47	87	-0.84
13.8	1.1	2.6	4.47	87	-0.84
11	1.0	2.4	4.47	87	-0.84
5	0.7	1.6	4.47	87	-0.84
3	0.5	1.1	4.47	87	-0.84
2.9	0.5	1.1	4.47	87	-0.84
1.25	0.1	0.2	4.47	87	-0.84
23	1.4	3.1	4.52	92	-0.54
8	0.9	2.1	4.52	92	-0.54
7	0.8	1.9	4.52	92	-0.54
6.5	0.8	1.9	4.52	92	-0.54
5	0.7	1.6	4.52	92	-0.54
4.8	0.7	1.6	4.52	92	-0.54
2.5	0.4	0.9	4.52	92	-0.54
2.3	0.4	0.8	4.52	92	-0.54
7	0.8	1.9	4.55	95	-0.36
5	0.7	1.6	4.55	95	-0.36
4	0.6	1.4	4.55	95	-0.36
3.75	0.6	1.3	4.55	95	-0.36
2.6	0.4	1.0	4.55	95	-0.36
2.5	0.4	0.9	4.55	95	-0.36
2.4	0.4	0.9	4.55	95	-0.36
2.2	0.3	0.8	4.55	95	-0.36
2	0.3	0.7	4.55	95	-0.36
1	0.0	0.0	4.55	95	-0.36
1	0.0	0.0	4.55	95	-0.36
12	1.1	2.5	4.58	98	-0.17
5.5	0.7	1.7	4.58	98	-0.17
3.75	0.6	1.3	4.58	98	-0.17
4	0.6	1.4	4.58	98	-0.17
4.1	0.6	1.4	4.58	98	-0.17
2.5	0.4	0.9	4.58	98	-0.17
2.3	0.4	0.8	4.58	98	-0.17
1.25	0.1	0.2	4.58	98	-0.17
1.1	0.0	0.1	4.58	98	-0.17
12.6	1.1	2.5	4.6	99	-0.03
10	1.0	2.3	4.6	99	-0.03

CPN (pg/g)	log Chlorpyrifos (pg/g)	ln Chlorpyrifos (pg/g)	ln Working Memory Index	Working Memory Index	Probits
8.75	0.9	2.2	4.6	99	-0.03
4.9	0.7	1.6	4.6	99	-0.03
4.8	0.7	1.6	4.6	99	-0.03
3.8	0.6	1.3	4.6	99	-0.03
2.5	0.4	0.9	4.6	99	-0.03
3	0.5	1.1	4.6	99	-0.03
3.6	0.6	1.3	4.6	99	-0.03
2.3	0.4	0.8	4.6	99	-0.03
11.3	1.1	2.4	4.63	103	0.17
8.75	0.9	2.2	4.63	103	0.17
7	0.8	1.9	4.63	103	0.17
3.75	0.6	1.3	4.63	103	0.17
4.25	0.6	1.4	4.63	103	0.17
2.5	0.4	0.9	4.63	103	0.17
2.6	0.4	1.0	4.63	103	0.17
1.25	0.1	0.2	4.63	103	0.17
1.2	0.1	0.2	4.63	103	0.17
2	0.3	0.7	4.63	103	0.17
1	0.0	0.0	4.63	103	0.17
1.1	0.0	0.1	4.63	103	0.17
16	1.2	2.8	4.65	105	0.31
10	1.0	2.3	4.65	105	0.31
6.25	0.8	1.8	4.65	105	0.31
7	0.8	1.9	4.65	105	0.31
3.75	0.6	1.3	4.65	105	0.31
3.8	0.6	1.3	4.65	105	0.31
3.9	0.6	1.4	4.65	105	0.31
4	0.6	1.4	4.65	105	0.31
2.5	0.4	0.9	4.65	105	0.31
2.6	0.4	1.0	4.65	105	0.31
2	0.3	0.7	4.65	105	0.31
9	1.0	2.2	4.68	108	0.52
8	0.9	2.1	4.68	108	0.52
6.25	0.8	1.8	4.68	108	0.52
4.9	0.7	1.6	4.68	108	0.52
4.2	0.6	1.4	4.68	108	0.52
3.75	0.6	1.3	4.68	108	0.52
2.6	0.4	1.0	4.68	108	0.52

CPN (pg/g)	log Chlorpyrifos (pg/g)	ln Chlorpyrifos (pg/g)	ln Working Memory Index	Working Memory Index	Probits
2.4	0.4	0.9	4.68	108	0.52
2	0.3	0.7	4.68	108	0.52
1.1	0.0	0.1	4.68	108	0.52
11	1.0	2.4	4.7	110	0.66
4.9	0.7	1.6	4.7	110	0.66
2.7	0.4	1.0	4.7	110	0.66
2.9	0.5	1.1	4.7	110	0.66
1.75	0.2	0.6	4.7	110	0.66
1.25	0.1	0.2	4.7	110	0.66
14	1.1	2.6	4.73	113	0.89
9	1.0	2.2	4.73	113	0.89
5	0.7	1.6	4.73	113	0.89
2.6	0.4	1.0	4.73	113	0.89
1.25	0.1	0.2	4.73	113	0.89
1.2	0.1	0.2	4.73	113	0.89
9	1.0	2.2	4.75	116	1.04
4	0.6	1.4	4.75	116	1.04
2.6	0.4	1.0	4.75	116	1.04
2.4	0.4	0.9	4.75	116	1.04
1.25	0.1	0.2	4.75	116	1.04
1.2	0.1	0.2	4.75	116	1.04
3.75	0.6	1.3	4.79	120	1.35
1.2	0.1	0.2	4.79	120	1.35
5.1	0.7	1.6	4.81	123	1.52
3.75	0.6	1.3	4.81	123	1.52
1.75	0.2	0.6	4.81	123	1.52
2	0.3	0.7	4.81	123	1.52

TERA Reading of Rauh et al. (2011) Figure 1E

The first 60 Points are zero or non-detectable and have been assigned chlorpyrifos levels consistent with the Rauh et al. 2011 page 1198. Specifically 80% at .05pg/g and 20% 1.0 pg/g. This set of data points was manually read from Figure 1E of Rauh et al. (2011).

Chlorpyrifos (pg/g)	log Chlorpyrifos (pg/g)	ln Chlorpyrifos (pg/g)	ln Full Scale Composite Score	Full Scale Composite Score
0.5	-0.30	-0.7	4.27	72
0.5	-0.30	-0.7	4.32	75
1	0.00	0.0	4.34	77
0.5	-0.30	-0.7	4.35	77
0.5	-0.30	-0.7	4.38	80
0.5	-0.30	-0.7	4.39	81
0.5	-0.30	-0.7	4.43	84
1	0.00	0.0	4.43	84
0.5	-0.30	-0.7	4.44	85
0.5	-0.30	-0.7	4.45	86
0.5	-0.30	-0.7	4.46	86
0.5	-0.30	-0.7	4.46	86
1	0.00	0.0	4.48	88
0.5	-0.30	-0.7	4.48	88
0.5	-0.30	-0.7	4.49	89
0.5	-0.30	-0.7	4.5	90
0.5	-0.30	-0.7	4.51	91
1	0.00	0.0	4.52	92
0.5	-0.30	-0.7	4.53	93
0.5	-0.30	-0.7	4.53	93
0.5	-0.30	-0.7	4.54	94
0.5	-0.30	-0.7	4.55	95
1	0.00	0.0	4.55	95
0.5	-0.30	-0.7	4.56	96
0.5	-0.30	-0.7	4.56	96
0.5	-0.30	-0.7	4.57	97
0.5	-0.30	-0.7	4.57	97

Chlorpyrifos (pg/g)	log Chlorpyrifos (pg/g)	ln Chlorpyrifos (pg/g)	ln Full Scale Composite Score	Full Scale Composite Score
1	0.00	0.0	4.58	98
0.5	-0.30	-0.7	4.59	98
0.5	-0.30	-0.7	4.59	98
0.5	-0.30	-0.7	4.6	99
0.5	-0.30	-0.7	4.61	100
1	0.00	0.0	4.61	100
0.5	-0.30	-0.7	4.62	101
0.5	-0.30	-0.7	4.62	101
0.5	-0.30	-0.7	4.63	103
0.5	-0.30	-0.7	4.63	103
1	0.00	0.0	4.64	104
0.5	-0.30	-0.7	4.64	104
0.5	-0.30	-0.7	4.65	105
0.5	-0.30	-0.7	4.66	106
0.5	-0.30	-0.7	4.67	107
1	0.00	0.0	4.68	108
0.5	-0.30	-0.7	4.68	108
0.5	-0.30	-0.7	4.69	109
0.5	-0.30	-0.7	4.69	109
0.5	-0.30	-0.7	4.7	110
1	0.00	0.0	4.71	111
0.5	-0.30	-0.7	4.72	112
0.5	-0.30	-0.7	4.72	112
0.5	-0.30	-0.7	4.73	113
0.5	-0.30	-0.7	4.73	113
1	0.00	0.0	4.74	114
0.5	-0.30	-0.7	4.75	116
0.5	-0.30	-0.7	4.76	117
0.5	-0.30	-0.7	4.78	119
0.5	-0.30	-0.7	4.79	120
1	0.00	0.0	4.8	122
0.5	-0.30	-0.7	4.81	123
0.5	-0.30	-0.7	4.81	123
13	1.11	2.6	4.22	68
6	0.78	1.8	4.25	70
10	1.00	2.3	4.31	74
1.2	0.08	0.2	4.31	74
1.75	0.24	0.6	4.33	76

Chlorpyrifos (pg/g)	log Chlorpyrifos (pg/g)	ln Chlorpyrifos (pg/g)	ln Full Scale Composite Score	Full Scale Composite Score
5.75	0.76	1.7	4.35	77
1.25	0.10	0.2	4.35	77
1.1	0.04	0.1	4.35	77
6.25	0.80	1.8	4.37	79
16.5	1.22	2.8	4.39	81
4.5	0.65	1.5	4.39	81
1.2	0.08	0.2	4.39	81
14.75	1.17	2.7	4.41	82
4	0.60	1.4	4.42	83
3.75	0.57	1.3	4.42	83
8	0.90	2.1	4.43	84
6.25	0.80	1.8	4.43	84
1.25	0.10	0.2	4.43	84
21	1.32	3.0	4.44	85
3	0.48	1.1	4.45	86
2.5	0.40	0.9	4.45	86
10	1.00	2.3	4.46	86
4.75	0.68	1.6	4.46	86
4.25	0.63	1.4	4.46	86
2.5	0.40	0.9	4.46	86
2.25	0.35	0.8	4.46	86
2	0.30	0.7	4.46	86
1.25	0.10	0.2	4.46	86
12	1.08	2.5	4.48	88
4.75	0.68	1.6	4.48	88
2.2	0.34	0.8	4.48	88
2.1	0.32	0.7	4.48	88
4.5	0.65	1.5	4.49	89
3.5	0.54	1.3	4.49	89
2.5	0.40	0.9	4.49	89
2	0.30	0.7	4.49	89
17	1.23	2.8	4.5	90
6	0.78	1.8	4.5	90
14.75	1.17	2.7	4.51	91
7.25	0.86	2.0	4.52	92
6	0.78	1.8	4.52	92
4.25	0.63	1.4	4.52	92
3.75	0.57	1.3	4.52	92

Chlorpyrifos (pg/g)	log Chlorpyrifos (pg/g)	ln Chlorpyrifos (pg/g)	ln Full Scale Composite Score	Full Scale Composite Score
1.9	0.28	0.6	4.52	92
1.7	0.23	0.5	4.52	92
1.25	0.10	0.2	4.52	92
8.25	0.92	2.1	4.53	93
5.25	0.72	1.7	4.53	93
2.9	0.46	1.1	4.53	93
2.25	0.35	0.8	4.53	93
2	0.30	0.7	4.53	93
11	1.04	2.4	4.54	94
3.75	0.57	1.3	4.54	94
23	1.36	3.1	4.55	95
7.5	0.88	2.0	4.55	95
4	0.60	1.4	4.55	95
2.8	0.45	1.0	4.55	95
1.75	0.24	0.6	4.55	95
8.5	0.93	2.1	4.56	96
2.8	0.45	1.0	4.56	96
5.9	0.77	1.8	4.57	97
4.75	0.68	1.6	4.57	97
4.25	0.63	1.4	4.57	97
2.5	0.40	0.9	4.57	97
2.25	0.35	0.8	4.57	97
16	1.20	2.8	4.59	98
11.8	1.07	2.5	4.59	98
8.75	0.94	2.2	4.59	98
6.8	0.83	1.9	4.59	98
3.85	0.59	1.3	4.59	98
2.5	0.40	0.9	4.59	98
2.25	0.35	0.8	4.59	98
1.75	0.24	0.6	4.59	98
1.25	0.10	0.2	4.59	98
1.1	0.04	0.1	4.59	98
4.75	0.68	1.6	4.6	99
2.55	0.41	0.9	4.6	99
2.25	0.35	0.8	4.6	99
4.5	0.65	1.5	4.61	100
2.5	0.40	0.9	4.61	100
1.75	0.24	0.6	4.61	100

Chlorpyrifos (pg/g)	log Chlorpyrifos (pg/g)	ln Chlorpyrifos (pg/g)	ln Full Scale Composite Score	Full Scale Composite Score
13	1.11	2.6	4.62	101
11	1.04	2.4	4.62	101
7.25	0.86	2.0	4.62	101
7	0.85	1.9	4.62	101
5.45	0.74	1.7	4.62	101
4.6	0.66	1.5	4.62	101
4.25	0.63	1.4	4.62	101
3.75	0.57	1.3	4.62	101
2.5	0.40	0.9	4.62	101
9.75	0.99	2.3	4.63	103
6	0.78	1.8	4.63	103
1.8	0.26	0.6	4.63	103
1.22	0.09	0.2	4.63	103
1.1	0.04	0.1	4.63	103
2.9	0.46	1.1	4.64	104
2.4	0.38	0.9	4.64	104
1.45	0.16	0.4	4.64	104
1.1	0.04	0.1	4.64	104
11.4	1.06	2.4	4.65	105
4.9	0.69	1.6	4.65	105
3.9	0.59	1.4	4.65	105
3.75	0.57	1.3	4.65	105
2.6	0.41	1.0	4.65	105
2	0.30	0.7	4.65	105
1.5	0.18	0.4	4.65	105
11.9	1.08	2.5	4.66	106
4.75	0.68	1.6	4.66	106
3.9	0.59	1.4	4.66	106
2.35	0.37	0.9	4.66	106
2.25	0.35	0.8	4.66	106
9.75	0.99	2.3	4.67	107
6.8	0.83	1.9	4.67	107
4.15	0.62	1.4	4.67	107
3	0.48	1.1	4.67	107
2.6	0.41	1.0	4.67	107
6	0.78	1.8	4.68	108
5	0.70	1.6	4.68	108
4	0.60	1.4	4.68	108

Chlorpyrifos (pg/g)	log Chlorpyrifos (pg/g)	ln Chlorpyrifos (pg/g)	ln Full Scale Composite Score	Full Scale Composite Score
2.8	0.45	1.0	4.68	108
2.65	0.42	1.0	4.68	108
2	0.30	0.7	4.68	108
1.7	0.23	0.5	4.68	108
1.5	0.18	0.4	4.68	108
11	1.04	2.4	4.69	109
8.6	0.93	2.2	4.69	109
6.25	0.80	1.8	4.69	109
4.25	0.63	1.4	4.69	109
3.1	0.49	1.1	4.69	109
3	0.48	1.1	4.69	109
2.5	0.40	0.9	4.69	109
1.6	0.20	0.5	4.69	109
1.2	0.08	0.2	4.69	109
6.6	0.82	1.9	4.7	110
1	0.00	0.0	4.7	110
8.75	0.94	2.2	4.71	111
8	0.90	2.1	4.71	111
13.8	1.14	2.6	4.72	112
8.65	0.94	2.2	4.72	112
5	0.70	1.6	4.72	112
3.9	0.59	1.4	4.72	112
11	1.04	2.4	4.73	113
9.5	0.98	2.3	4.73	113
4.6	0.66	1.5	4.73	113
4.5	0.65	1.5	4.73	113
4.8	0.68	1.6	4.74	114
4	0.60	1.4	4.74	114
2.65	0.42	1.0	4.74	114
1.25	0.10	0.2	4.74	114
2.2	0.34	0.8	4.75	116
5.15	0.71	1.6	4.76	117
2.75	0.44	1.0	4.76	117
2.7	0.43	1.0	4.76	117
1.22	0.09	0.2	4.76	117
1.25	0.10	0.2	4.77	118
1.2	0.08	0.2	4.77	118
4.2	0.62	1.4	4.78	119

Chlorpyrifos (pg/g)	log Chlorpyrifos (pg/g)	ln Chlorpyrifos (pg/g)	ln Full Scale Composite Score	Full Scale Composite Score
8.75	0.94	2.2	4.79	120
4.85	0.69	1.6	4.79	120
1	0.00	0.0	4.79	120
10.75	1.03	2.4	4.8	122
6	0.78	1.8	4.8	122

Appendix C

Table of Comparisons of data points in IQ analysis							
	Rauh et al. (2011)			This Analysis		Difference	
	Published	truncated > 25 pg/g	<= LOD	Scanned	<= LOD	Difference	%
Working Memory	265	4	115	170	33	91	35%
Full Scale IQ	265	4	115	222	60	39	15%

III. Brief on Alternate Explanations for Alleged Effects in the Columbia Study

Alternate Explanations for Alleged Effects in the Columbia Study

Situation overview

Researchers for the Columbia Center for Children's Environmental Health (CCCEH) epidemiology study (the "Columbia study") have claimed in their publications a correlation between levels of chlorpyrifos allegedly found in the umbilical cord blood of a group of mothers almost 20 years ago with neurodevelopmental effects allegedly observed in their children later in life. EPA is proposing to use the findings from the Columbia study as proof of a causal relationship and to then set a new, dramatically lower, regulatory health endpoint or Point of Departure (PoD) for chlorpyrifos based on that study.

Background on Columbia study

The Columbia University researchers have been studying a group of New York City children born between 1998 and 2002. The investigators have followed the health of these inner-city children of African American and Dominican decent for 15 years. The study started by looking at the many problems existing in public housing such as holes in the ceiling, leaking pipes and unrepaired water damage , each reported by more than a third of the mothers, which in turn were associated with cockroach and rodent sightings. Measures of "unmet needs" that included inadequate food, housing or clothing during pregnancy were counted. The investigators also evaluated the education, intelligence, and income of the mothers, which are predictors of childhood development. Unavailable was information about the father, including paternal IQ. From the many publications from the Columbia study it is evident that this is a very disadvantaged group of children.

The Columbia study was designed to look at many environmental factors that may affect childhood health. To this end, the investigators tested the household air and infant cord blood for numerous different chemicals, elements (such as lead), and pesticides. They have multiple publications in the peer-reviewed literature on correlations between a few of these exposure estimates from birth and subsequent development during childhood, but have not yet reported on all.

Claims of health effects in the Columbia study

Publications by the Columbia study researchers noted that by age 2 nearly half of the study children were diagnosed with moderately delayed mental development and many were physically delayed. By age 7, while the mean IQ for the children was average, some were severely mentally challenged. It is worth noting, researchers found the children's IQs are greater on average than their mothers, since the mothers' mean IQ was 85.

Columbia study researchers also published correlations between various neurodevelopment or health effects in the study children with other factors such as phthalates, polycyclic aromatic hydrocarbons, and second-hand tobacco smoke.

Alternate explanations for claimed health effects

While the Columbia researchers attribute some correlations of lower test scores with higher chlorpyrifos levels, correlation alone does not prove cause and effect, and a causal relationship. Further, EPA even admits, there is no biological explanation, despite numerous attempts to identify one, of how the action of chlorpyrifos in the body would affect neurodevelopment at low levels. The well-documented effect for chlorpyrifos is cholinesterase inhibition not neurodevelopmental effects. Extensive research in both humans and animal clearly show there is no biological plausibility to the claim of a cause and effect between exposure to chlorpyrifos and findings reported in the Columbia study.

It is important to understand that many factors can influence childhood development – both for better or worse and could also be correlated with the effects reported.

- Characteristics at birth, with gestational age (being born too early) being most notable among the explanations for the effects on the test scores reported. Differences in as little as one week in gestational age have been shown to be linked to adverse outcomes in infant and child development, including lower scores on Bayley scales of mental and motor development. Gestational age proved to be a strong covariate in several of the Columbia articles. Yet, there is no indication the gestational age was accurately measured and experience shows that it can be off by more than 5 days 40% of the time.
- Nutritional deficiencies such as lack of iodine, vitamin D, vitamin B, and iron or unhealthy diets as well as excessive intake of sugar and fat.
- Exposure to other materials in the environment such as heavy metals and solvents.
- Other issues such as living in settings of violence, drug abuse and other stressors such as maternal stress, bereavement, and depression can also result in decrements in neurodevelopment.
- Conversely, activities as simple as reading aloud have been shown to improve test scores.

Most of these factors were unmeasured in the Columbia study, but are important in understanding the underlying factors of childhood development. These alternate explanations need to be fully considered and accounted for when attempting to establish any causation.

Authors: Carol J. Burns, MPH, PhD, Fellow ACE), George R Oliver, PhD (Dow AgroSciences)

Date: June 2017

IV. Brief: Reproducibility is critical for determining scientific validity. *Lack of consistency with other epidemiology studies challenges rather than supports Columbia study findings.*

Background

The US EPA has relied primarily on the Columbia Center for Children's Environmental Health epidemiology study ("Columbia study") to suggest that exposures to chlorpyrifos below the current regulatory endpoint may result in neurodevelopmental effects in infants and children. EPA references papers from two other epidemiology studies (Mt Sinai and CHAMACOS) as also claiming neurodevelopmental outcomes associated with chlorpyrifos and thereby strengthening the validity of the Columbia study claims. Two other studies (HOME and PELAGIE) are also now being cited.

Conclusions

The neurodevelopmental outcomes have been over-generalized across studies. The specific results are not reproduced from the other studies, which challenge the claim of a link between neurodevelopment effects and chlorpyrifos exposures. In fact, the following discussion shows that consideration of the findings *in total across* these studies does not support and even counters such a claim.

Epidemiology studies

The Columbia study relied on measurements of chlorpyrifos, along with other chemicals, in blood at birth from a group of inner city New York City mothers and their children born between 1998 and 2003. The study followed various characteristics in the children later in life, with multiple publications. The Mt Sinai study was also based in New York City, CHAMACOS in California, the HOME study in Ohio, and the PELAGIE study in France. These four studies used urinary metabolites of organophosphate insecticides, potentially including but not limited to chlorpyrifos, to estimate pesticide exposure.

Reproducibility of results is the hallmark of the scientific method

Reproducibility is crucial to giving credence to scientific observations. Even research of the highest quality may have irreproducible findings because of random or systemic error.[1] Since it is impossible to measure and control for all factors that may relate to health effects, epidemiology studies can have false conclusions. There are many examples of specific food items that have been touted as healthy in one study and harmful in another. Scientists, therefore, look for consistency of results in more than one study.

Consistency is built on the findings for the same exposure and same effect

The definition of consistency across studies has led to controversy. Some claim that any observed health effects from these epidemiology studies support those reported in the Columbia study since they are all *childhood neurodevelopmental effects*. Importantly outcomes like autism, hyperactive behavior and low intelligence, are all very different. Secondly, associations with a class of insecticides do not implicate a specific insecticide, such as chlorpyrifos. The credibility of a true association is in doubt because the epidemiology studies don't link the same exposure and same effect.

As a specific example, all five studies administered an IQ test to the children.[2] The test has several components, such as Working Memory, Verbal Comprehension and Processing Speed, that together make up the overall Full-Scale IQ score. A summary of these publications is shown in the Table.[3-7] Since the Columbia study reported Working Memory and Full-Scale IQ to be inversely associated with chlorpyrifos levels, it makes sense to see if other studies can reproduce this result. Looking crudely at only absolute relationships (direction of scores, i.e. does the score increase or decrease) from left to right across studies, the results do not show consistency. Some scores decrease with increasing exposure levels and other scores increase.

A more robust manner to compare studies is to look for statistical significance. This calculation incorporates the size of the study and strength of the association. Scientists use this calculation to determine the role of chance to say if an association is true or random. As shown below, the Columbia study observed a significant association with chlorpyrifos and Working Memory scores. Mt Sinai and CHAMACOS also reported a decrease in Working Memory scores, but neither found the finding was statistically significant. While CHAMACOS also reported borderline statistical significance for decrease in Full IQ scores, Mt Sinai and HOME studies did not. When considering statistical testing in total across all studies, the other studies *do not* support or replicate the Columbia outcomes.

Conclusion.

The publication by the Columbia University generated the hypothesis that levels of chlorpyrifos in blood at birth were associated with lower IQ and working memory scores in children. Four other studies *have not* consistently reported similar results for *in utero* chlorpyrifos exposure and childhood intelligence.

Comparison of results for 5 epidemiology studies

Scores	Columbia (age 7)	Mt Sinai (ages 6-9)	CHAMACOS (age 7)	HOME (age 5)	PELAGIE (age 6)
Working memory	Decreased	Decreased	Decreased	Not tested	Increased
Was the finding statistically significant?	Yes	No	No	Not tested	No

	Columbia	Mt Sinai	CHAMACOS	HOME	PELAGIE
Processing speed	Increased	Decreased	Decreased	Not reported	Not reported
Was the finding statistically significant?	No	No	Yes	Not reported	Not reported

	Columbia	Mt Sinai	CHAMACOS	HOME	PELAGIE
Full Scale IQ	Decreased	Decreased	Decreased	Increased	Not reported
Was the finding statistically significant?	Yes	No	Yes*	No	Not reported

*P = 0.08 (not significant) in one analysis and p = 0.05 (statistically significant) in another analysis.

Authors: Carol J. Burns, MPH, PhD, Fellow ACE (Burns Epidemiology Consulting, LLC), George R Oliver, PhD (Dow AgroSciences). June 2018

References

1. Open Science Collaboration. 2015. Estimating the reproducibility of psychological science. Science. Vol 349. Issue 6251. http://science.sciencemag.org.
2. Wechsler Preschool and Primary Scale of Intelligence 3rd (WPPSI-III) and/or 4th (WISC-IV) editions
3. Columbia: Rauh, V., et al., *Seven-year neurodevelopmental scores and prenatal exposure to* chlorpyrifos, a common agricultural pesticide. Environ Health Perspect, 2011. 119(8): p. 1196-201.
4. Mt. Sinai: Bouchard, M.F., et al., Prenatal exposure to organophosphate pesticides and IQ in 7-year-old children. Environ Health Perspect, 2011. 119(8): p. 1189-95.
5. CHAMACOS: Engel, S.M., et al., Prenatal exposure to organophosphates, paraoxonase 1, and cognitive development in childhood. Environ Health Perspect, 2011. 119(8): p. 1182-8.
6. HOME: Donauer, S., et al., An Observational Study to Evaluate Associations Between Low-Level Gestational Exposure to Organophosphate Pesticides and Cognition During Early Childhood. Am J Epidemiol, 2016. 184(5): p. 410-8.
7. PELAGIE: Cartier, C., et al., Organophosphate Insecticide Metabolites in Prenatal and Childhood Urine Samples and Intelligence Scores at 6 Years of Age: Results from the Mother-Child PELAGIE Cohort (France). Environ Health Perspect, 2016. 124(5): p. 674-80.

Appendix IV

A Review of Recent Studies - Red Blood Cell Cholinesterase Inhibition as a Point of Departure for Regulation of Chlorpyrifos is Protective Against Neurodevelopmental Toxicity

Daland R. Juberg, PhD, ATS and Jeffrey H. Driver, DrPH, DABT, MT, CLS

June 17, 2020

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Summary

In the July 2019 United States Environmental Protection Agency (USEPA) *Chlorpyrifos; Final Order Denying Objections to March 2017 Petition Denial Order* (EPA-HQ-OPP-2007-1005; USEPA, 2019) five laboratory animal studies were referenced as under review for consideration within an assessment of potential neurodevelopmental/behavioral effects. To facilitate USEPA's consideration of these studies, Corteva Agriscience submits this review of the five studies, particularly in relation to inhibition of red blood cell (RBC) acetylcholinesterase.

A review of these studies confirms RBC cholinesterase inhibition (ChEI) as a definitive point of departure (POD) that is protective of potential toxicity, including neurodevelopmental/behavioral

toxicity. Based on the outcomes, limitations and uncertainties associated with these five studies, indications of neurodevelopmental/behavioral effects below RBC ChEI, specifically 10% RBC cholinesterase inhibition, are not demonstrated.

Background

Red blood cell cholinesterase inhibition (RBC ChEI) has been used historically as the relevant and sensitive regulatory marker of exposure for chlorpyrifos and subsequently as the POD for use in human health risk assessment. The scientific database for chlorpyrifos continues to be consistent with this position and several of USEPA's FIFRA Scientific Advisory Panels have also confirmed the use of RBC ChEI as the appropriate POD in regulatory decision-making. Over the past several years, investigators have explored non-cholinergic modes of action for chlorpyrifos and some have contended that neurodevelopmental outcomes/effects are occurring below the threshold for cholinesterase inhibition (brain, RBC, or plasma cholinesterase). A review of these five studies (Table 1) reveals that two measured brain ChEI, but none measured RBC ChEI. Further, some studies measure cholinesterase inhibition well after the time of peak effect. Inhibition peaks sometime after maximal RBC concentrations are achieved and after the oxon of chlorpyrifos is cleared, the cholinesterase enzyme begins reactivating and new cholinesterase is produced. Studies that measure cholinesterase inhibition past the time of peak effect underestimate cholinesterase inhibition relative to the methods used by EPA to estimate points of departure for risk assessment using measurements at peak time of inhibition. USEPA regulates on both peak (acute) and steady state (21-day) cholinesterase inhibition, which requires a measurement at the time of peak effect and estimation of 21-day steady state inhibition. By underestimating cholinesterase inhibition, these studies may erroneously conclude that other endpoints are more sensitive than cholinesterase inhibition.

In its preliminary human health risk assessment for chlorpyrifos, USEPA (2011) derived an acute RBC 10% AChE inhibition benchmark dose (BMD10) value of 0.06 mg/kg/day (60 μg/kg/day) from laboratory animal data. In 2014, USEPA used the chlorpyrifos physiologically-based pharmacokinetic and pharmacodynamic model (PBPK-PD) model to determine doses (PoDs) corresponding to 10% RBC AChE inhibition (USEPA 2014). For example, the acute dietary (food) dose level for infants (<1 yr) associated with 10% RBC ChEI (the point of departure on

which it regulates acute exposure to chlorpyrifos in the US), was determined to be 600 µg/kg/day (USEPA 2014). The 21-day steady state dietary (food) PoD value for infants was determined to be 103 µg/kg/day. In comparison, the acute and steady-state dietary (food) PoD values for females, 13 – 49 yrs old, are 467 and 78 µg/kg/day, respectively (USEPA 2014). In 2016 (USEPA 2016), USEPA presented a revised, alternative PoD derivation based on use of the PBPK model to determine the Time-Weighted Average (TWA) blood levels expected from post-application exposures from a chlorpyrifos indoor crack and crevice use scenario. This scenario was selected as a scenario assumed to be relevant for women in the Columbia Center for Children's Environmental Health (CCCEH) epidemiology study cohort, i.e., it was presumed that crack and crevice treatment was the predominant application type during the time of the CCCEH study. The TWA blood levels were assumed to be a lowest-observed-adverse-effect-level (LOAEL). However, due to significant concerns regarding the validity and reliability of the results derived from the CCCEH blood samples, the USEPA's review by its FIFRA Scientific Advisory Panel did not endorse or recommend reliance on the CCCEH results for quantitative risk analysis (see USEPA July 20, 2016, Transmittal of Meeting Minutes of the April 19-21, 2016 FIFRA SAP Meeting Held to Consider and Review Scientific Issues Associated with "Chlorpyrifos: Analysis of Biomonitoring Data). Overall, the Panel found significant deficiencies associated with use of the CCCEH blood data in quantitative risk assessment.

Scientific Review

Cholinesterase Measurement and Threshold Analysis

To understand if reported neurodevelopmental effects associated with chlorpyrifos exposures could be observed below the threshold for RBC ChEI, Corteva Agriscience undertook a review of five studies published from 2015-2017. As part of the review of these studies, it is important to distinguish the biological significance of brain versus red blood cell cholinesterase inhibition. Brain cholinesterase inhibition is considered an adverse effect, while inhibition of RBC ChEI is not associated with any known physiological or biological/toxicological consequence. RBC ChEI occurs at lower dose levels and before inhibition of brain cholinesterase. Marty et al (2012) reported decrements in RBC ChEI following exposures as low as 0.05 mg/kg/day, consistent also with marked RBC ChEI decrements (45% lower than controls) in Maurissen et al (2000) following exposure to 0.3 mg/kg/day (lowest dose administered). These decrements are consistent with the

previously reported EPA-derived acute BMD10 associated with 10% RBC ChEI (USEPA, 2011). In this respect, RBC ChEI serves as a conservative, protective marker of exposure that has been used historically by many global regulatory bodies as a point of departure for risk assessment purposes.

None of the five studies listed in Table 1 measured RBC ChEI and thus, any inference from these studies that neurodevelopmental effects are occurring below the threshold for cholinesterase inhibition is not supported by data generated within these studies. In any study design that seeks to determine whether neurodevelopmental outcomes are occurring below the threshold for RBC inhibition, a range of dose levels along with concomitant measurement of RBC ChEI should be included. The threshold for RBC ChEI is significantly lower than 1 mg/kg/day as documented in two definitive, Good Laboratory Practice (GLP) regulatory toxicological studies (Maurissen et al, 2000; Marty et al, 2012 – see Table 2), along with the benchmark dose value determined by the USEPA (Table 2) in establishing the threshold for 10% RBC ChEI as 0.06 mg/kg/day. Empirical data from Maurissen et al (2000) demonstrates significant RBC ChEI at the lowest dose employed (0.3 mg/kg/day), well below 1 mg/kg/day. Marty et al (2012), in the Comparative Cholinesterase Assay for chlorpyrifos, used a low dose of 0.05 mg/kg/day and at this dose level there were measurable decrements in RBC ChEI in both male pups and adult females, again well below 1 mg/kg/day. Both the Maurissen and Marty studies included measures that evaluated potential neurodevelopmental toxicity and there were no effects at doses lower than those associated with RBC ChEI.

Table 1. Summary of 5 Chlorpyrifos Toxicity Studies

Study/MRID	Species/Age at Exposure	Administered Doses (mg/kg/day)	Brain ChEI	RBC ChEI	Notes
Silva et al 2017 51123801	Rat GD14-20	0.01, 0.1, 1.0, 10.0	Not measured	Not measured	Reported neurodevelopmental LOAEL of 0.1
Carr et al 2017 51123802	Rat PND10-17	0.5, 0.75, 1.0	Decrements of 0, 0, 19%	Not measured	No effects on brain ChEI at 2 lower doses
Gomez-Gimenez et al 2017a 51123803	Rat GD7-PND21	0.1, 0.3, 1.0	Not measured	Not measured	
Gomez-Gimenez et al 2017b 51123804	Rat GD7-PND21	0.1, 0.3, 1.0	Not measured	Not measured	
Lee et al 2015 51123805	Mouse PND10	0.1, 1.0, 5.0	No significant decrement	Not measured	Questionable brain ChEI as should be decrement at 5.0 mkd

Table 2. Summary of Studies/Reviews Evaluating Cholinesterase Inhibition

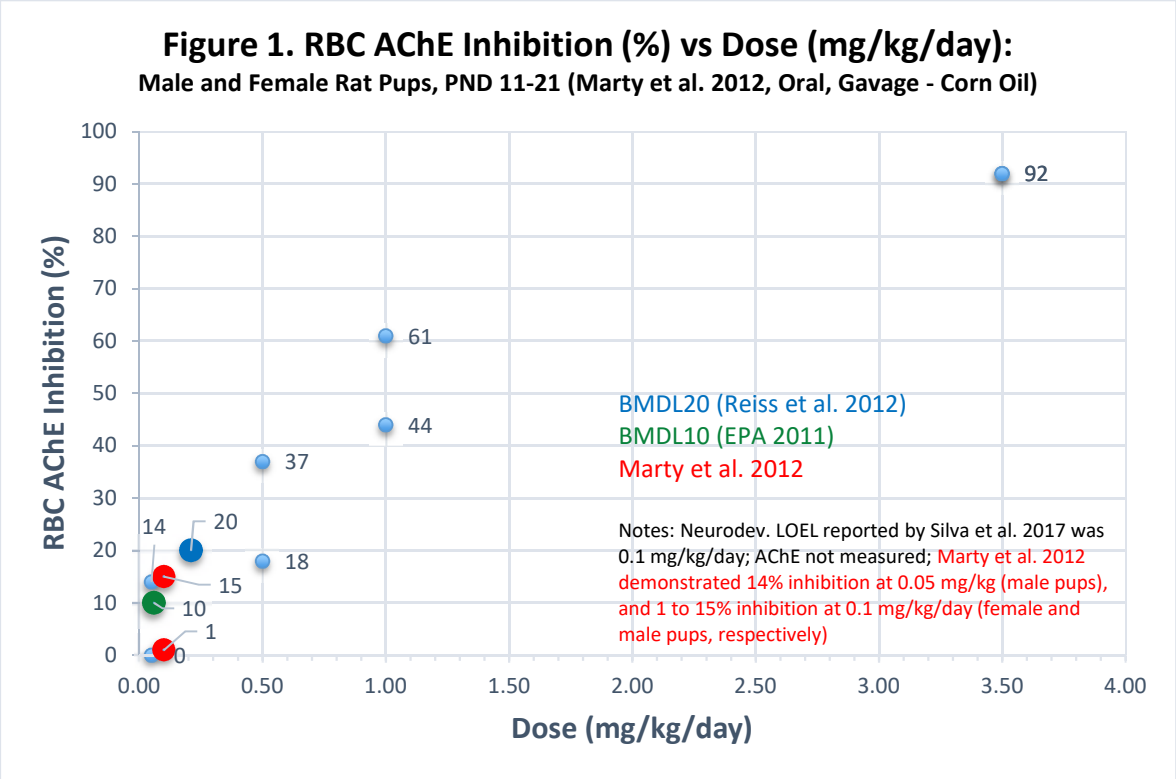
Study or Evaluation	Species/Age at Exposure	Doses (mg/kg/day)	Brain ChEI	RBC ChEI	Notes
Marty et al 2012 48139301	Rat PND11-21 PND80 (adult)	0.05, 0.1, 0.5, 1.0, 3.5	Decrements of 0, 1, 6, 28, and 68% in male pups Decrements of 0, 0, 0, 19, and 59% in female pups Decrements of 0, 0, 0, 9, and 69% in adult females	Decrements of 14, 15, 37, 61, and 92% in male pups Decrements of 0, 1, 18, 44, and 92 in female pups Decrements of 5, 16, 19, 73, and 93% in adult females	
Maurissen et al 2000 44556901	Rat GD6-LD10	0.3, 1.0, 5.0	Decrements of 0, 18, and 90% in dams	Decrements of 41, 84, and 100% in dams	
Reiss et al 2012	Adults and pups	NA	NA	0.21 for 10% RBC ChEI	BMD20; repeat doses; Meta analysis
USEPA, 2011 Preliminary HHRA	Female pregnant rats	NA	NA	0.06 for 10% RBC ChEI	BMD10

NA – not applicable

The only study in Table 1 using a lower dose level than Marty et al (2012) was Silva et al (2017) who employed a low dose level of 0.01 mg/kg/day although there were no reported effects at this level. Silva et al (2017) concluded that "gestational exposure to the CPF in the dose of 0.1 mg/kg/day was considered the low observed adverse effect level (LOAEL) for the anxiogenic-like behavior." However, there was no dose-response for this effect (i.e., anxiogenic-like behavior) at the 0.1, 1.0, and 10.0 dose levels which brings into question the biological significance of this effect and its relevance to human health risk analysis. Additionally, the study conducted by Silva et al. (2017) in rats did not measure either RBC or brain ChEI. Marty et al (2012) reported decrements of RBC ChEI at 0.05 mg/kg/day, a level below which no neurodevelopmental effects have been reported. Thus, RBC ChEI continues to represent the most sensitive POD and is protective against all other toxicities.

Graphical representation of these various data points is provided in Figures 1 - 3. Figures 1 and 2 present the dose-response data for RBC and brain cholinesterase inhibition, respectively, from Marty et al. (2012) and demonstrate a quantitative relationship between RBC ChEI and dosage (non-linear at low doses). Figure 3 presents the adult brain ChEI dose-response data from Maurissen et al. (2000), which is consistent with Marty et al. 2012.

As shown in Figure 1, the benchmark dose (BMD) metrics for RBC ChEI (Reiss et al., 2012; USEPA 2011) have been defined and provide a reliable Point of Departure (POD) that is protective of neurodevelopmental toxicity, consistent with dose-response measurements reported by Marty et al (2012).



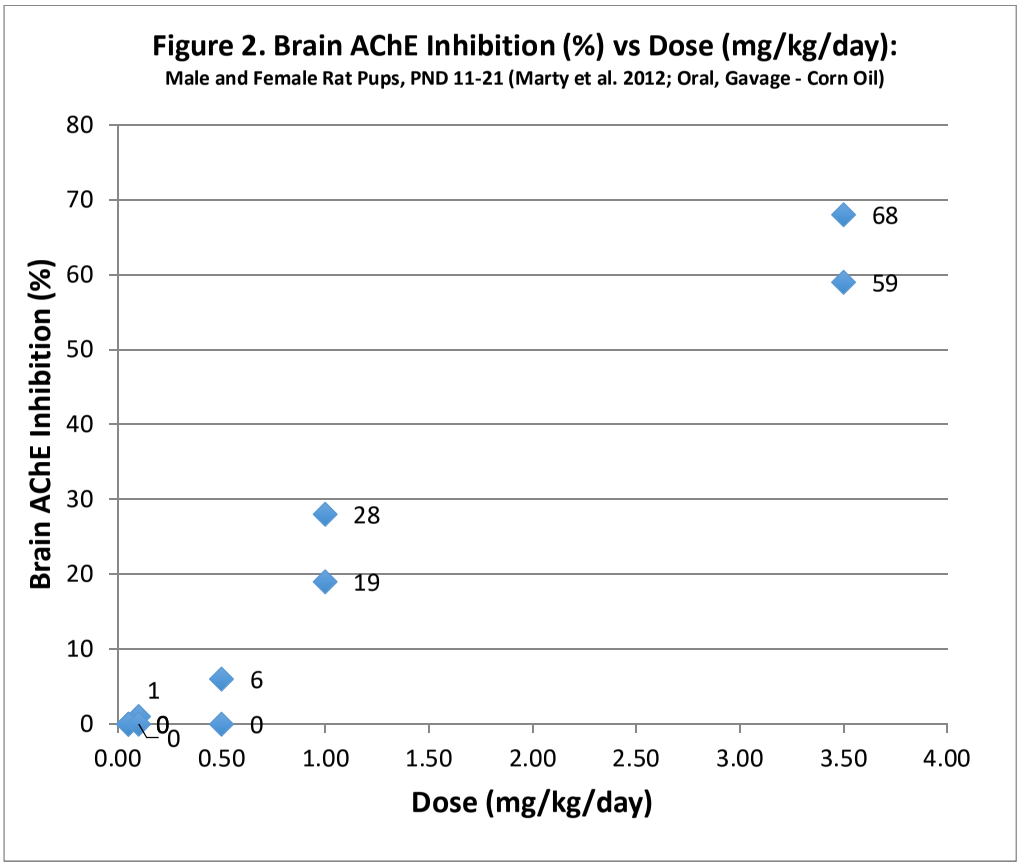


Figure 2. Brain AChE Inhibition (%) vs Dose (mg/kg/day):
Male and Female Rat Pups, PND 11-21 (Marty et al. 2012; Oral, Gavage - Corn Oil)
Brain AChE Inhibition (%)
80
70
60
50
40
30
20
10
0
68
59
28
19
6
1
0
0
0
0.00
0.50
1.00
1.50
2.00
2.50
3.00
3.50
4.00
Dose (mg/kg/day)

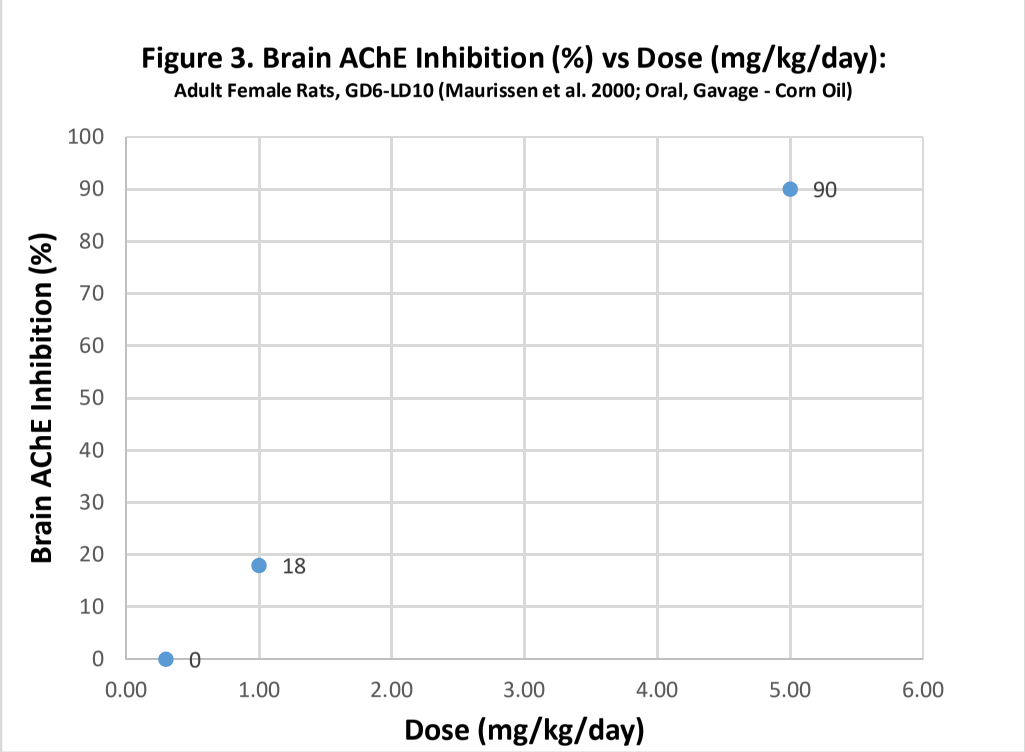


Figure 3. Brain AChE Inhibition (%) vs Dose (mg/kg/day):
Adult Female Rats, GD6-LD10 (Maurissen et al. 2000; Oral, Gavage - Corn Oil)
Brain AChE Inhibition (%)
100
90
80
70
60
50
40
30
20
10
0
90
18
0
0.00
1.00
2.00
3.00
4.00
5.00
6.00
Dose (mg/kg/day)

Individual Study Evaluation

1. Gomez-Gimenez et al (2017a) evaluated sex-dependent effects of developmental exposure to different pesticides on spatial learning. With respect to chlorpyrifos, the investigators tested chlorpyrifos at 0.1, 0.3 and 1.0 mg/kg/day from GD7 through PND 21. The pups were exposed postnatally through the mothers' milk (and perhaps from ingesting the test material directly (see below)). Gomez-Gimenez et al (2017a) reported on a number of parameters/measurements (performed when pups were 2-3 months of age) including spatial learning, reference errors, working memory, learning indices, and hippocampal content of pro- and anti-inflammatory cytokines and do not appear to have established an overall NOEL considering the number of parameters evaluated. Results were varied with some statistically significant effects reported, but in a scattered fashion where dose-responsiveness was rare and outcomes were gender specific (i.e., reported decreased learning in males, but not females).

   The study authors did not report the source or the purity of chlorpyrifos used in experimentation. The test material was administered by mixing chlorpyrifos in a "sweet jelly." According to the authors, "We confirmed that all rats ate all the sweet jelly and, therefore, the dose of pesticide." This is an unusual method of administering a test material orally. Also, it is not clear how the pups were prevented from ingesting the test material in the sweet jelly since the dams and pups were presumably housed together until weaning. No information was provided on the housing conditions of the animals. The group size was small, with the offspring from only 6 dams per dose group used. The publication states: "the litter effects were controlled by using pups from different litters per treatment group in each experiment." However, the authors do not explain how this was done. The actual number of pups used per dose group, which were provided in Figure 1, ranged from 6 to 13 per dose. This means that some of the pups must have been littermates since there were only 6 dams per group. It is not clear how littermates were selected for testing. The authors do not state whether the litter or the pup was considered to be the statistical unit.

Finally, Gomez-Gimenez et al. (2017a) did not measure cholinesterase inhibition of any type, nor did the authors comment on their findings relative to the threshold for cholinesterase inhibition.

2. Gomez-Gimenez et al. (2017b) also conducted a study evaluating the motor activity and coordination of rats exposed to multiple pesticides, including chlorpyrifos. Like the other study by these authors, pregnant rats and their offspring were exposed to chlorpyrifos from GD 7 to PND 21 at dose levels of 0.1, 0.3, and 1.0 mg/kg/day. Motor activity and coordination were evaluated when the offspring were adults. Among the reported findings were that chlorpyrifos impairs motor coordination in females but not males, inconsistent effects on GABA concentration in the cerebellum, and that a low (but not high) dose of chlorpyrifos increased motor activity in both males and females. Another reported finding was that chlorpyrifos at 0.1 mg/kg/day (but not at the higher doses) increased the content of NR2A and NR2B subunits of NMDA receptor in the hippocampus in male, but not female rats.

   Gomez-Gimenez (2017b) did not report on the source or purity of chlorpyrifos. The number/size of exposed groups was small with offspring from only 4, 7, 7 dams per dose group used. Dose-response was varied and inconsistent depending on the endpoint measured and as noted, statistical significance was achieved with the lowest dose of chlorpyrifos, but not with higher doses for certain measurements/endpoints. Overall NOELs were not noted given the varied outcomes and multiple measurements taken by the authors. It was not stated whether the litter or pup was considered as the statistical unit, nor was the assignment of parental animals to groups described. Relative to cholinesterase inhibition, neither brain or RBC ChEI was measured, although the authors comment that large, but not low (not defined) doses of CPF inhibit acetylcholinesterase.

3. Silva et al (2017) reported on anxiety-like behavior in rat offspring following exposure to chlorpyrifos during pregnancy (i.e., GD14-20). They employed doses that included 0.01, 0.1, 1.0, and 10.0 mg/kg/day. The source, but not purity, of the chlorpyrifos used was stated. The authors did not measure cholinesterase inhibition of any type. The group size ranged from 11 to 14 pregnant females per group which was adequate. The actual number

of offspring tested for behavioral effects on PND 21 and PND 70 is not stated. It is not clear whether testing included littermates and, if so, how the study controlled for the presence of littermates, nor was it stated as to whether the litter vs. pup was considered the statistical unit.

Silva et al (2017) reported statistically-significant decrements in time spent in the open arm of the maze apparatus in high cross with males on PND21 (top 3 doses, not lowest dose), but non-statistically significant increased (not for lowest dose) time spent in the open arm in males on PND70. Silva et al. (2017) also reported effects at 0.1-1.0, citing axiogenic-like, but not depressive-like behavior at PND21 (without causing fetal toxicity), however the effect was reversed by PND 70. This begs the question whether increased or decreased anxiety-like behavior is biologically significant and whether both are adverse, or is one adverse, while the other is not, particularly as other investigators have reported decreased anxiety related to chlorpyrifos exposure (Carr et al, 2017). There was no dose-response for this reported effect among the top 3 dose levels; while locomotor activity (i.e., related to anxiogenic-like behavior) was reported as statistically significant, the increased (relative to control) motor activity at 0.1 mg/kg/day was virtually the same as that reported following exposure to 10 mg/kg/day.

Silva et al (2017) reported that according to the USEPA, the NOAEL of CPF for an acute dietary exposure for inhibition of red blood cholinesterase is 0.5 mg/kg/day (References to USEPA from 2000 and 2013). They also comment on increasing evidence of neurotoxicity effects at low doses with different mechanisms from those at higher doses. However, the authors, in their conclusions, focus on their findings related to neurobehavior and do not discuss any relationship to altered mechanisms above or below the threshold for ChEI.

Silva et al (2017) reported a developmental LOAEL of 0.1 mg/kg/day in this study although the absence of a defined dose-response at the top three dose levels calls into question where the true LOAEL/NOAEL exist on the dose continuum. If certainty in a clearly defined point of departure from this study is important, then one needs to question whether the reported outcome (increased anxiety-like behavior) is beneficial or adverse, particularly

when others (Carr et al., 2017) have reported that CPF decreases anxiety-like behavior. Certainty in clarifying and determining what is adverse (versus perhaps adaptive or even beneficial) is the first step in establishing a POD and LOAEL and how these compare to the threshold for RBC ChEI. There is clear evidence that the threshold for RBC ChEI is below the LOAEL (0.1 mg/kg/day) reported by Silva et al (2017) as demonstrated by Marty et al (2012) in rat pups (14% inhibition at 0.05 mg/kg in male pups). Finally, USEPA (2011) has estimated the RBC ChEI BMDL10 as 0.06 mg/kg/day, again below the reported LOAEL from Silva et al (2017) of 0.1 mg/kg/day.

4. Carr et al. (2017) evaluated the effect of low level exposure to chlorpyrifos in juvenile rats given daily doses of 0, 0.5, 0.75, or 1.0 mg/kg/day by gavage on PND 10 through 16. The basis for the study was to evaluate CPF's effect on endocannabinoid metabolizing enzymes with the broader theme of how this system affects nervous system development. The authors were interested in studying whether low levels of CPF (that do not inhibit ChE) will cause persistent effects on anxiety-like behavior.

   Carr et al (2017) noted the source of the chlorpyrifos used and the purity (99%). Rats from 15 litters were used, while the number of animals tested ranged from 13-23 per dose group which is satisfactory. The method used to assign pups to the various treatment groups is not described. It is not clear whether the pups were assigned randomly, on the basis of body weight, or some other method. The method for administering the test material by gavage is described as delivering the solution "to the back for the throat." Normally, gavage administration is delivered into the esophagus or stomach.

   Anxiety was evaluated on PND 25 by placing juvenile rats in a dark container and measuring the length of time before the rats emerged into the light. Interestingly, all three chlorpyrifos treated groups (both males and females) spent less time in the dark container prior to emerging as compared to the control group, suggesting a decreased level of anxiety, according to the study authors. For decreased anxiety, a NOEL was not achieved as the lowest dose (0.5 mg/kg/day) was statistically different from the control. Carr et al (2017) did measure forebrain ChE inhibition and reported 19% inhibition (statistically significant)

at 1.0 mg/kg CPF, but there was essentially no difference in ChEI at 0.5 or 0.75 mg/kg CPF from controls. Carr et al (2017) include significant discussion on their findings relative to ChE activity and inhibition, but relate this only to brain, not RBC inhibition, whose threshold is lower than that of brain. Carr et al (2017) conclude that "our data indicate that the decreased anxiety-like behavior observed in preadolescent rats exposed developmentally to CPF occurs at dosages that either induce low levels of brain ChE inhibition or do not induce any inhibition." Carr et al (2017) measured brain ChEI activity at 12 hours following the last dose, reporting this as the time of peak inhibition (determined from a previous time-course study), but did not measure RBC or plasma ChEI and thus, no comparisons of their findings can be made relative to these more sensitive endpoints resulting from exposure. Finally, these results (decreased anxiety) should be contrasted with those of Silva et al (2017) who reported increased anxiety-like behavior.

5. Lee et al. (2015) studied the developmental neurotoxicity of chlorpyrifos in juvenile male mice, more specifically on spontaneous behavior and protein levels. These investigators administered 0, 0.1, 1, or 5 mg/kg/day of chlorpyrifos as a single oral (gavage) dose on PND 10. Both the source and purity (99%) of chlorpyrifos were noted. It was noted that litters contained from 4-7 animals and that 12 animals per treatment per timepoint were used. According to the authors, PND 10 was selected as the day of test material administration because it represents the peak of the "brain growth spurt." At 2 and 4 months of age, the mice were subjected to behavioral testing. It is not clear how the juvenile mice were assigned to the various treatment groups.

   Lee et al (2015) reported a few significant effects on protein levels in the brain from exposure to 5.0 mg/kg/day CPF, while the two lower doses were not evaluated. Moreover, there were no significant differences for many of the proteins evaluated in the cortex and hippocampus. Spontaneous behavior was evaluated at 2 and 4 months and there were a few statistically significant decrements in behavior, but typically juts at the high dose. Across all doses, a dose-response relationship was not consistently apparent. Lee et al (2015) did measure brain ChEI following administration of 5.0 mg/kg/day and reported

essentially no decrements in brain cholinesterase activity through 36 hours. While they did monitor ChEI for 36 hours post-exposure, there is no indication of where time to peak effect occurred as the response was monotonic in nature. The results from Lee et al (2015) are in contrast to effects in rats (Marty et al 2012) whereby administration of 5.0 mg/kg to PND11 pups resulted in more than 50% brain ChEI, which is perhaps species-specific, but notable nonetheless. Lee et al (2015) suggest that the classical cholinergic mechanism may not be involved in behavioral effects they reported as they saw minimal (10% decrement at 3 hours) change in brain cholinesterase activity following exposure to 5.0 mg/kg CPF. However, as noted, these results need to be compared to rats for evaluation of species sensitivity and additionally it is noted that no assessment of RBC ChEI was undertaken in this study.

Conclusions

Reports of neurodevelopmental effects occurring in laboratory animal studies (Table 1 above) at levels below the threshold for RBC cholinesterase inhibition are not supported. None of the recent laboratory studies reviewed measured RBC ChEI which also precludes the ability to determine where peak inhibition occurred, the importance of which was discussed earlier. The failure to measure the degree of RBC ChEI precludes any conclusion that observed effects can be attributed to doses lower than those that elicit the threshold of 10% RBC ChEI. In addition, the dose levels used in these studies are, with one exception, above the demonstrated threshold for RBC ChEI. The USEPA (2011) established, in its preliminary human health risk assessment for chlorpyrifos, an acute RBC 10% AChE inhibition benchmark dose (BMD10) value of 0.06 mg/kg/day (60 µg/kg/day) from laboratory animal data. Further, in 2014, USEPA used the chlorpyrifos physiologically-based pharmacokinetic and pharmacodynamic model (PBPK-PD) model to determine doses (PoDs) corresponding to 10% RBC AChE Inhibition (USEPA 2014). For example, the acute dietary (food) dose level for infants (<1 yr) associated with 10% RBC ChEI (the point of departure on which USEPA regulates acute exposure to chlorpyrifos in the US), was determined to be 600 µg/kg/day (USEPA 2014). The 21-day steady state dietary (food) PoD value for infants was determined to be 103 µg/kg/day. In conclusion, there are no known neurodevelopmental effects/outcomes in studies that are below the threshold associated with 10%

RBC ChEI and this POD continues to be protective of all toxicities, including neurodevelopmental toxicity.

References

Carr, R.L. et al. 2017. Decreased anxiety in juvenile rats following exposure to low levels of chlorpyrifos during development. Neurotoxicology. 59:183-190.

Gomez-Gimenez, B. et al. 2017a. Sex-dependent effects of developmental exposure to different pesticides on spatial learning. The role of induced neuroinflammation in the hippocampus. Food and Chemical Toxicology. 99:135-148.

Gomez-Gimenez, B. et al. 2017b. Developmental exposure to pesticides alters motor activity and coordination in rats: sex differences and underlying mechanisms. Neurotox Res. DOI 10.1007/s12640-017-9823-9.

Lee, I., Eriksson, P., Fredriksson, A., Buratovic, S., and Viberg, H. 2015. Developmental neurotoxic effects of two pesticides: behavior and biomolecular studies on chlorpyrifos and carbaryl. Tox Appl. Pharmacol. 288:429-438.

Marty, M.S., et al. 2012. Cholinesterase inhibition and toxicokinetics in immature and adult rats after acute or repeated exposures to chlorpyrifos or chlorpyrifos-oxon. Reg. Toxicol. Pharmacology. 63:209-224.

Maurissen, JP, Hoberman AH, Garman RH, Harvey TR. 2000. Lack of Selective Developmental Neurotoxicity in Rat Pups from Dams Treated by Gavage with Chlorpyrifos. Toxicological Sciences 57:250-263.

Reiss, R., Neal, B., Lamb, J.C., and Juberg, D.R. 2012. Acetylcholinesterase inhibition dose-response modeling for chlorpyrifos and chlorpyrifos-oxon. Reg. Toxicol. Pharmacol. 63:124-131.

Silva, J.G. et al. 2017. Chlorpyrifos induces anxiety-like behavior in offspring rats exposed during pregnancy. Neuroscience Letters. 641-94-100.

USEPA, 2011. Preliminary Human Health Risk Assessment for Chlorpyrifos. USEPA, Washington, DC.

USEPA, 2016. Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review. USEPA, Washington, DC.

USEPA, 2019. Chlorpyrifos; Final Order Denying Objections to March 2017. Petition Denial Order. FRL #: 9997-06. Docket ID #: EPA-HQ-OPP-2007-1005. July 18, 2019.