March 6, 2021

Comments on the Proposed Interim Decision for Chlorpyrifos
Docket-HQ-OPP-2008-0850-0964
U.S. Environmental Protection Agency

I appreciate the opportunity to submit these comments on the proposed reregistration decision on chlorpyrifos. Over the last 40 years I have conducted research on chlorpyrifos use, testing, regulatory compliance, and residues in food and dietary risk levels and trends. I served as the ED of the Board on Agriculture in the National Academy of Sciences when two EPA-funded projects on pesticides were carried out-- *Regulating Pesticides in Food: The Delaney Paradox* and *Pesticides in the Diets of Infants and Children*. The later report contained substantial focus on chlorpyrifos. I carried out a detailed, quantitative analysis of the impact of the Food Quality Protection Act (FQPA) on pesticide residues and risk levels for the EPA's Office of Inspector General. My analytical work was part of the OIG's review of OPP's implementation of the FQPA.

I gained insights into the events leading up to, and in the wake of the year 2000 chlorpyrifos deal between EPA and Dow through my role as an expert witness in a mid-2000s chlorpyrifos case. The litigation arose from the communications between Dow AgroSciences and a formulator producing home products containing chlorpyrifos (*United Industries v. Dow AgroSciences*). I conducted extensive chlorpyrifos analytical work and had multiple interactions with EPA from 1996 through 2005 regarding the EPA's implementation of the FQPA. In the 1997-2004 period, I wrote multiple comments submitted to EPA and its Scientific Advisory Panel on various aspects of FQPA implementation, including the impact of the FQPA on chlorpyrifos.

I have explored the levels, distribution and trends in chlorpyrifos dietary risk levels for many years via the Dietary Risk Index (DRI) system (see Benbrook and Davis [2020] "The dietary risk index system: a tool to track pesticide dietary risks;" *Environmental Health*, 2020, 19(1); DOI: 10.1186/s12940-020-00657-z; submitted in support of these comments). Several of the tables and figures in these comments were generated by the DRI.

I am currently serving as the ED of the Heartland Health Research Alliance (HHRA, www.hh-ra.org), and am a member of the Management Team of the Heartland Study (HS), the HHRA's flagship project. The HS is a long-term clinical study in the Midwest focused on the impacts of prenatal and early life herbicide exposures on birth outcomes and children's development. I also am currently serving as an expert witness in litigation against Corteva stemming from the adverse developmental impacts of chlorpyrifos on children's neurodevelopment. My work over the last approximate two years on this litigation has provided me an opportunity to revisit in depth developments in the regulatory history of chlorpyrifos that I was previously involved in. It has also provided me an opportunity to study the implications of recently published peer-reviewed science on chlorpyrifos risks and the quality of the data submitted by Dow to EPA in

support of chlorpyrifos tolerances and registrations. I have been paid for my work on chlorpyrifos litigation. I have worked on Roundup-non-Hodgkin lymphoma litigation for four years. Since 2020, I also have served as an expert witness in paraquat-Parkinson's Disease litigation. My comments on the proposed chlorpyrifos registration decision are submitted on my own behalf.

Since the introduction of chlorpyrifos insecticides to the US market in 1965, chlorpyrifos-brand insecticides have been registered and sold by different corporations, but the Dow Chemical Company in various corporate configurations has always been the major manufacture and registrant of chlorpyrifos end-use products. In this report, the following companies are generally referred to as "Dow":

- Dow Chemical Company,
- Dow AgroSciences,
- DowElanco, and
- Corteva, the ag products company spun off after the merger of Dow and DuPont.

Each of the above companies were responsible for fulfilling chlorpyrifos-related EPA data requirements and communications with the Agency for blocks of time over the last 55 years. While there are now some generic chlorpyrifos brands on the market, the companies holding these registrations have played a trivial role in the testing and regulatory history of chlorpyrifos compared to Dow.

Chlorpyrifos has been the most prominent insecticide within the organophosphate, or OP, family of chemistry for four decades. OPs are acidic phosphate esters and come in a wide range of forms with diverse functional properties. They are relatively inexpensive to produce, which accounts for the breadth of their commercial uses, e.g. flame retardants, nerve agents, plasticizers, and insecticides.

A. Uses of Chlorpyrifos

Chlorpyrifos was for decades one of the most important and heavily used insecticides in the US and worldwide. Its use has fallen markedly in the last 20 years and is now insignificant in most crops and applications.

The U.S. Department of Agriculture (USDA) surveys pesticide use in major crops at the national level. Major row crops (e.g. corn, soybeans, cotton) have been covered by USDA pesticide use surveys in most years from 1991 through the mid-2000s, and every few years since. Fruits are surveyed in odd years, vegetables in even years.

Trends in chlorpyrifos use by crop at the national level and in California are covered in a series of tables focused on 1995, 2005, and 2015. I focus on these three years, 10-years apart, for the following reasons:

- 1995 is one year before passage of the 1996 Food Quality Protection Act (FQPA) and represents a pre-FQPA baseline of chlorpyrifos and OP use,
- 2005 represents the first year when the primary impacts of the FQPA implementation had occurred across registered OPs, including chlorpyrifos, and
- 2015 is the year EPA determined it appropriate to regulate chlorpyrifos on the basis of developmental neurotoxicity.

Seven metrics are required to track chlorpyrifos use on a given crop and over time:

1. Percent of crop acres treated.
2. Acres treated.
3. One-time rate of application (average rate across all applications).
4. Average number of applications.
5. Rate per crop year (average one-time rate multiplied by average number of applications).
6. Number of acre-treatments (acres treated multiplied by average number of applications).
7. Pounds of active ingredient applied.

Each of these parameters are reported, or can be calculated from the data in annual pesticide use surveys conducted by the USDA.

Over many years I have developed the Pesticide Use Data System (PUDS), drawing on the annual use data released by USDA. In short, the raw data from each, annual USDA survey is moved into a relational database that supports a range of analyses. Pesticide use data can be arrayed in tables covering an area (a state or national), use on a crop (grapes) or many crops (all vegetables). The PUDS supports analyses of differences across space (California versus Iowa), and changes over time. The methodology and data in PUDS are explained on my website Hygeia Analytics at https://hygeia-analytics.com/pesticides/usage/puds-the-pesticide-use-data-system/

The interactive, online tables generated by PUDS are accessible here:
https://hygeia-analytics.com/tools/puds/by-crop/
To access the table showing insecticide use on any crop, e.g. grapes in California in 2015, choose the following choices in the five dropdown boxes:

- Parent Pesticides,
- Grapes, all,
- Insecticides,
- California, and
- 2015.

Once the above choices are selected, a screenshot of the table that appears on Hygeia Analytics

is pasted in below.

Table 1: Insecticides Applied to California Acres Planted with 'Grapes, all' In 2015

Parent Pesticide	Percent Acres Treated	One Time Application Rate	Number of Applications	Rate per Crop Year	Surveyed Acre Treatments	Pesticide Pounds Applied	
						Surveyed Acres (856,000)	Total Acres (856,000)
Abamectin	26.0%	0.018	1.3	0.024	289,328	5,200	5,200
Acetamiprid	1.0%	0.085	1.2	0.100	10,272	600	600
Beta-cyfluthrin	1.0%	0.025	1.6	0.040	13,696	200	200
Bifenazate	3.0%	0.496	1.3	0.638	33,384	14,800	14,800
Buprofezin	4.0%	0.553	1.2	0.665	41,088	21,100	21,100
Chlorantraniliprole	3.0%	0.062	1.1	0.070	28,248	1,900	1,900
Chlorpyrifos	3.0%	1.786	1.1	1.967	28,248	43,100	43,100
Clothianidin	2.0%	0.126	1.1	0.133	18,832	2,100	2,100
Cryolite	3.0%	5.218	1.3	6.862	33,384	152,300	152,300
Cyflumetofen	3.0%	0.169	1.0	0.178	25,680	5,100	5,100
Cyfluthrin	0.3%	0.049	1.4	0.068	4,118	200	200
Etoxazole	5.0%	0.129	1.4	0.177	59,920	7,200	7,200
Fenpropathrin	3.0%	0.289	1.0	0.293	25,680	8,400	8,400
Fenpyroximate	1.0%	0.099	1.1	0.108	9,416	1,200	1,200
Flubendiamide	1.0%	0.106	1.1	0.112	9,416	1,200	1,200
Hexythiazox	1.0%	0.129	1.5	0.188	12,840	2,300	2,300
Imidacloprid	37.0%	0.213	1.3	0.282	411,736	88,400	88,400
Kaolin	0.4%	18.812	1.0	18.981	3,846	73,000	73,000
Methoxyfenozide	21.0%	0.187	1.4	0.261	251,664	46,600	46,600
Pyrethrins	1.0%	0.033	1.2	0.038	10,272	200	200
Spinetoram	13.0%	0.038	1.1	0.042	122,408	4,700	4,700
Spinosad	1.0%	0.101	1.0	0.105	8,560	1,300	1,300
Spirotetramat	20.0%	0.109	1.3	0.138	222,560	23,200	23,200
Thiamethoxam	4.0%	0.225	1.1	0.247	37,664	8,500	8,500
Other Insecticides	0.0%	0.000	0.0	0.000	0	25,800	25,800
Totals:	157.8%	--	--	--	1,712,260	538,600	538,600
Average per Acre:	1.58	--	--	--	2.000	0.629	0.629

The table reports that in 2015 grape production in California, 3% of crop acres were treated with chlorpyrifos at an average one-time rate of 1.786 pounds per acre, an average of 1.1 times. This resulted in a total of 43,100 pounds applied on grapes that year.

Agricultural Uses of Chlorpyrifos - All Crops in the U.S.

Table 1 below reports chlorpyrifos use in 1995 on six field crops, 11 vegetables, and 18 fruit and nut crops. Apples were the crop most frequently treated with chlorpyrifos in 1995 -- 74% of US apple acreage was sprayed with the insecticide. This level of reliance marked peak use of chlorpyrifos on apples, measured by percent of total apple acres treated. Although chlorpyrifos was used significantly on alfalfa, it is not included in this analysis, due to the lack of consistent and accurate data across years.

Other crops where a significant percentage of acres were treated with chlorpyrifos include walnuts (59%), broccoli (49%), and cauliflower (40%). Just 2% of the national grape crop was sprayed with the insecticide that year.

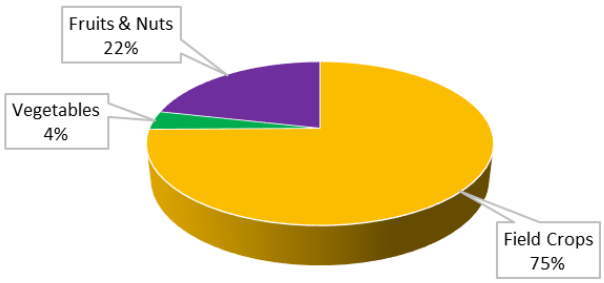


Figure 1. Pounds of Chlorpyrifos Applied in the U.S. as Percent Share of Total Pounds by Type of Crop: 1995

All told, 11,410,255 pounds of chlorpyrifos were sprayed on 9,834,223 acres of US crops in 1995. Field crops had 8,531,630 pounds applied, vegetables were sprayed with 422,341 pounds, and fruit and nuts with 2,453,704 pounds. The average rate of application across all crops was 1.1 pound per acre.

Table 1: Chlorpyrifos Use on Major Crops in the United States, 1995

	Percent Acres Treated	Acres Treated	Acre Treatments	Number of Applications	One-Time Rate of Application	Rate per Crop Year	Pounds Applied to Total Acres	Total Acres Planted
Field Crops								
Corn	7%	5,003,530	5,003,530	1	1.04	1.06	5,303,742	71,479,000
Cotton	9%	1,523,826	3,047,652	2	0.7	1.37	2,087,642	16,931,400
Wheat, winter	2%	971,820	971,820	1	0.4	0.4	388,728	48,591,000
Sugarbeets	24%	314,140				1.13	353,607	1,321,000
Soybeans	2.4%	298,300				0.71	210,800	12,190,000
Sorghum	4%	390,630	390,630	1	0.48	0.48	187,112	9,429,000
Total		**8,502,246**	**9,413,632**				**8,531,630**	**159,941,400**
Field Crops as % of Total Use		**86%**	**85%**				**75%**	**96%**
Vegetables								
Broccoli	49%	61,741	80,263	1.3	1.19	1.51	92,919	127,300
Corn, sweet, fresh	22%	54,976	118,197	2.15	0.76	1.64	89,885	255,700
Onions, dry	27%	45,446	56,808	1.25	1.23	1.51	68,533	171,495
Corn, sweet, proc	9%	41,344	43,411	1.05	1.21	1.27	52,507	486,400
Tomatoes, fresh	11%	13,870	62,415	4.5	0.75	3.36	46,603	132,095
Cauliflower	40%	20,530	33,875	1.65	0.95	1.59	32,540	51,325
Cabbage, fresh	17%	12,865	22,514	1.75	0.94	1.65	21,227	77,970
Asparagus	12%	9,705	10,190	1.05	0.96	1.01	9,754	80,875
Peppers, bell	5%	3,032	10,915	3.6	0.72	2.60	7,868	67,375
Cabbage, proc	7%	486	486	1	1	1	486	6,940
Eggplant	0.5%	17	20	1.2	1.01	1.2	20	3,300
Total		**264,010**	**439,093**				**422,341**	**1,460,775**
Vegetable Crops as % of Total Use		**2.7%**	**4%**				**3.7%**	**0.9%**
Fruit and Nuts								
Apples	74%	340,748	613,346	1.8	1.27	2.32	790,535	460,470
Oranges	19%	146,522	205,131	1.4	2.86	4.01	587,554	771,170
Peanuts	13%	199,875	209,869	1.05	1.75	1.91	381,761	1,537,500
Almonds	31%	120,900				1.80	217,862	390,000
Walnuts	59%	106,790				1.81	193,183	181,000
Lemons	33%	20,130	22,143	1.1	3.04	3.31	66,630	61,000
Grapefruit	17%	28,230	33,876	1.2	1.57	1.95	55,049	166,060
Peaches	17%	28,851	37,506	1.3	1.34	1.69	48,758	169,710
Cherries, sweet	30%	14,214	14,214	1	1.89	1.89	26,864	47,380
Pears	16%	11,288	12,417	1.1	1.81	1.91	21,560	70,550
Grapes, all	2%	15,084	19,610	1.3	0.93	1.21	18,237	754,220
Hazelnuts	30%	9,704	12,129	1.25	1.10	1.41	13,633	32,893
Strawberries	15%	7,455	8,946	1.20	0.94	1.14	8,499	49,700
Cherries, tart	19%	8,669	11,269	1.3	0.85	1.07	9,276	45,625
Nectarines	8%	2,592	2,592	1	1.89	1.9	4,925	32,400
Plums	4%	1,680	1,680	1	2	2	3,360	42,000
Prunes	3%	2,364	2,364	1	1.35	1.35	3,191	78,800
Tangerines	4%	1,372	1,784	1.3	1.54	2.06	2,826	34,300
Total		**1,066,468**	**1,208,876**				**2,453,704**	**4,924,778**
Fruit and Nuts as % of Total Use		**11%**	**11%**				**21.5%**	**3.0%**
All Uses Totaled		**9,832,724**	**11,061,601**				**11,407,675**	**166,326,953**

Notes: Hazelnuts and peanuts were not surveyed by NASS in 1995 and was interpolated from 1991-1999. Sorghum were not surveyed by NASS in 1995 and was interpolated from 1991-1998. Almonds, soybeans, sugarbeets and walnut use data (1992), is from the Pesticide Use in U.S. Crop Production Report. Although chlorpyrifos was used significantly on alfalfa, it is not included in this analysis, due to the lack of consistent and accurate data across years.

Sources: USDA-National Agriculture Statistics Service (NASS), Annual Chemical Use Survey Reports. For crops that are not surveyed by NASS in 1995, data was interpolated/extrapolated from known years. National Center for Food and Agricultural Policy, Pesticide Use in U.S. Crop Production, Leonard Gianessi et al. (February 1995), Table 1.

A smaller percentage of field crops was treated with chlorpyrifos, about 5% across the total 160 million acres. By crop, the percent of acres treated ranged from 2% in the case of winter wheat, 7% of corn, and to 24% in the case of sugarbeets. But because these crops account for such a high share of total, national cropland acreage, the chlorpyrifos applied to them accounts for most national use. In 1995, 8,531,630 pounds of chlorpyrifos were applied to field crops in the US, or 75% of the total pounds applied in the U.S. Vegetables accounted for only 3.7% of pounds applied, and 22% on fruit and nuts.

By 2005 as a result of the FQPA, chlorpyrifos use at the national level had dropped significantly across most major crop uses, as shown in Table 2. That year, it was used on 42 different crops in the US: eight field crops, 14 vegetable crops, and 20 fruit and nut crops. Apples continued to be sprayed with chlorpyrifos, at 50% crop acres treated. Other heavily sprayed crops include Brussel sprouts (71%), limes (46%), broccoli (35%), walnuts (30%), dry onions (29%), sweet cherries (26%), fresh sweet corn (24%), asparagus (23%), cauliflower (23%) and tangerines (23%). Average rates of application remained relatively consistent with 1995 levels.

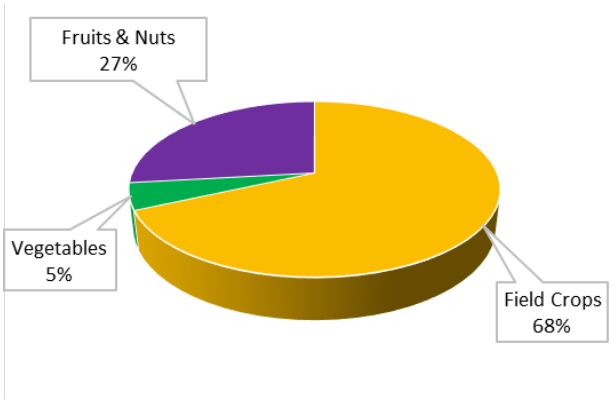


Figure 2. Pounds of Chlorpyrifos Applied in the U.S. as Percent Share of Total Pounds by Type of Crop: 2005

Total pounds applied in 2005 fell to 6,362,473, down 49% from 1995. Field crops still dominated use, but to a lesser extent with 4,344,419 pounds applied, accounting for 68% of total pounds. The share of total use accounted for by vegetables rose to 5%, with 314,237 pounds applied, and the fruit and nuts share rose to 27% with 1,703,817 pounds applied.

Table 2: Chlorpyrifos Use on Major Crops in the United States, 2005

	Percent Acres Treated	Acres Treated	Acre Treatments	Number of Applications	One-Time Rate of Application	Rate per Crop Year	Pounds Applied to Total Acres	Total Acres Planted
Field Crops								
Corn	2%	1,635,580	1,635,580	1	1.11	1.11	1,818,765	81,779,000
Soybeans	5%	3,601,600	3,601,600	1	0.48	0.48	1,735,971	72,032,000
Wheat, winter	2.5%	1,010,450	1,010,450	1	0.37	0.37	372,856	40,418,000
Cotton	2%	284,908	341,890	1.2	0.61	0.71	201,715	14,245,400
Sugarbeets	12%	155,976	187,171	1.2	0.92	1.11	173,133	1,299,800
Sorghum	0.75%	48,405	48,405	1	0.72	0.72	34,852	6,454,000
Wheat, spring (excl. durum)	0.11%	15,298	15,298	1	0.3	0.3	4,589	14,036,000
Barley	0.25%	9,688	9,688	1	0.26	0.26	2,538	3,875,000
Total		**6,761,904**	**6,850,081**				**4,344,419**	**234,139,200**
Field Crops as % of Total Use		**87%**	**84%**				**68%**	**97%**
Vegetables								
Corn, sweet, fresh	24%	57,928	153,508	2.65	0.79	2.08	120,547	246,500
Onions, dry	29%	51,487	54,061	1.05	1.35	1.42	73,162	177,540
Broccoli	35%	45,150	49,665	1.1	1.32	1.42	64,203	129,000
Corn, sweet, proc	3.5%	14,753	15,490	1.05	1.04	1.13	16,685	421,510
Asparagus	23%	11,633	13,377	1.15	0.93	1.05	12,261	51,700
Cauliflower	23%	9,596	9,596	1	1.05	1.08	10,392	41,720
Brussel sprout	71%	2,531	9,617	3.80	1.00	3.87	9,794	3,564
Cabbage, fresh	3.5%	2,639	2,639	1	1.01	1.06	2,784	75,400
Kale	22%	958	2,205	2.30	0.97	2.29	2,195	4,357
Radish	6%	935	1,589	1.70	0.60	1.05	982	15,582
Beans, snap, fresh	2%	2,076	2,076	1	0.38	0.38	789	103,800
Collard	3%	403	726	1.80	0.48	0.86	347	13,447
Squash	0.1%	49	49	1	1	1.02	50	52,000
Lettuce, other	0.03%	40	40	1	1.12	1.13	45	129,250
Total		**200,177**	**314,638**				**314,237**	**1,465,370**
Vegetable Crops as % of Total Use		**3%**	**4%**				**5%**	**0.6%**
Fruit and Nuts								
Oranges	17%	126,786	215,536	1.7	1.61	2.75	348,788	745,800
Apples	50%	188,330	225,996	1.2	1.48	1.73	325,434	376,660
Peanuts	8%	139,924	160,074	1.14	1.56	1.83	255,782	1,657,000
Almonds	17%	108,837	119,721	1.1	1.67	1.86	202,437	640,218
Walnuts	30%	69,908	90,880	1.3	1.72	2.31	161,487	233,026
Grapes, all	5%	46,743	56,091	1.2	1.91	2.30	107,302	934,850
Lemons	22%	13,530	21,648	1.6	2.92	4.78	64,633	61,500
Grapefruit	14%	14,210	26,999	1.9	2.34	4.47	63,448	101,500
Cherries, sweet	26%	20,485	22,534	1.1	1.84	2.04	41,872	78,790
Peaches	18%	25,097	30,117	1.2	1.24	1.43	35,864	139,430
Tangerines	23%	8,303	10,794	1.3	2.63	3.41	28,322	36,100
Pears	16%	9,677	9,677	1	2.02	2.11	20,457	60,480
Nectarines	17%	6,273	6,900	1.1	1.88	2.04	12,778	36,900
Hazelnuts	20%	6,369	7,642	1.2	1.24	1.55	9,871	31,843
Plums	11%	3,960	4,356	1.1	1.92	2.12	8,375	36,000
Prunes	4%	2,680	3,216	1.2	1.87	2.18	5,842	67,000
Strawberries	8%	4,294	5,152	1.2	0.90	1.06	4,534	53,670
Cherries, tart	16%	5,816	6,979	1.2	0.56	0.69	4,036	36,350
Limes	46%	545	1,089	2	1.88	3.75	2,043	1,184
Melons, watermelon	0.5%	713	713	1	0.72	0.72	511	142,600
Total		**802,479**	**1,026,115**				**1,703,817**	**5,470,902**
Fruit & Nut Crops as % of Total Use		**10%**	**13%**				**27%**	**2%**
All Uses Totaled		**7,764,560**	**8,190,834**				**6,362,473**	**241,075,471**

Notes: Sugarbeets were only surveyed in 2000.Vegetables and strawberries were surveyed in 2004 and 2006 and interpolated in 2005. Barley, Sorghum and Peanuts were not surveyed by NASS in 2005 and therefore, interpolated from 2003-2011. Almonds & Walnuts were only surveyed in 1999, and extrapolated forward. Pounds applied are calculated based on 2005 acres planted. Hazelnuts were only surveyed in 1991 & 1999 and extrapolated forward. Pounds applied are calculated based on 2005 acres planted. Spring Wheat and Winter Wheat were not surveyed in 2005 and therefore, interpolated from 2004-2006.

Sources: USDA-National Agriculture Statistics Service (NASS), Annual Chemical Use Survey Reports. For crops that are not surveyed by NASS in 2005, data was interpolated/extrapolated from known years.

A decade later in 2015, USDA reported chlorpyrifos use on seven field crops, 11 vegetables, and 17 fruit and nut crops. Table 3 shows that grapefruit had a significant 3.4-fold increase in percent acres treated, rising from 14% to 61%. Pounds applied more than doubled since 2005. Apples remained roughly the same with 47% acres treated. Other heavily sprayed crops were asparagus (47%), tart cherries (36%) and walnuts (30%).

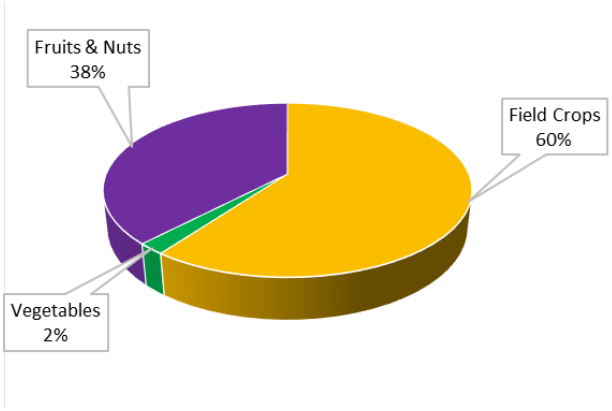


Figure 3. Pounds of Chlorpyrifos Applied in the U.S. as Percent Share of Total Pounds by Type of Crop: 2015

A total of 4,155,102 pounds of chlorpyrifos were applied on 6,705,814 acres treated of all 35 crops. Field crops accounted for 60% of the total pounds applied (2,498,507 pounds). Vegetables accounted for 2% (85,791 pounds), and another 1,570,804 pounds were applied on fruit and nuts, accounting for 38% of total use.

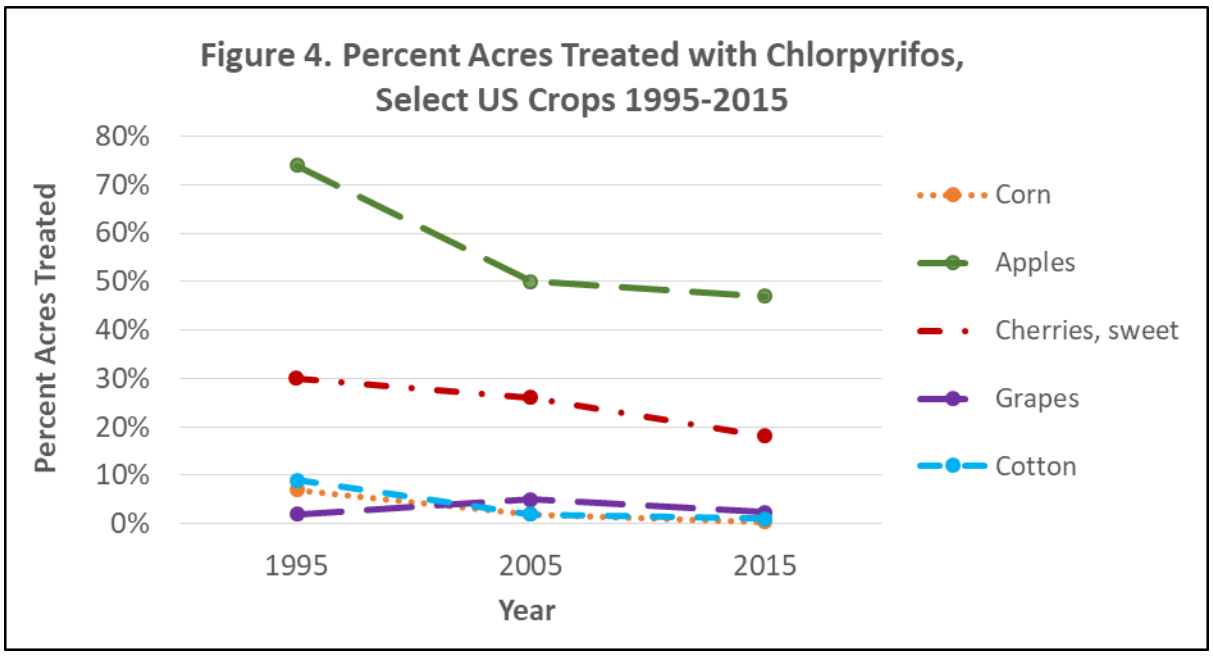
Table 3: Chlorpyrifos Use on Major Crops in the United States, 2015

	Percent Acres Treated	Acres Treated	Acre Treatments	Number of Applications	One-Time Rate of Application	Rate per Crop Year	Pounds Applied to Total Acres	Total Acres Planted
Field Crops								
Soybeans	5%	4,133,000	4,133,000	1	0.37	0.39	1,595,338	82,660,000
Wheat, winter	2%	793,620	793,620	1	0.39	0.39	312,686	39,681,000
Wheat, spring (excl. durum)	3%	401,010	401,010	1	0.47	0.50	198,901	13,367,000
Corn	0.4%	351,616	386,777	1.1	0.52	0.56	197,256	88,019,000
Sugarbeets	12%	139,176	167,011	1.2	0.92	1.11	154,485	1,159,800
Cotton	1%	85,805	94,386	1.1	0.38	0.41	35,094	8,580,500
Barley	0.5%	18,115	18,115	1	0.26	0.26	4,746	3,623,000
Total		**5,922,342**	**5,993,919**				**2,498,507**	**237,090,300**
Field Crops as % of Total Use		**88%**	**85%**				**60%**	**97%**
Vegetables								
Onions, dry	24%	34,704	45,115	1.3	0.83	1.04	36,196	144,600
Asparagus	44%	10,340	13,959	1.35	0.96	1.27	13,163	23,500
Corn, sweet, fresh	6%	14,525	20,336	1.4	0.62	0.90	13,015	242,090
Brussel sprout	71%	2,751	10,452	3.80	1.00	3.87	10,645	3,874
Broccoli	3%	3,792	4,550	1.2	1.18	1.40	5,297	126,400
Cabbage, fresh	4%	2,381	2,381	1	0.99	1.03	2,462	59,530
Kale	22%	879	2,021	2.30	0.97	2.29	2,012	3,994
Beans, snap, proc	1%	1,649	1,649	1	0.95	0.97	1,601	164,870
Radish	6%	876	1,489	1.70	0.60	1.05	920	14,599
Collard	3%	337	606	1.80	0.48	0.86	290	11,223
Squash	0.2%	75	75	1	2.54	2.54	190	41,250
Total		**72,308**	**102,633**				**85,791**	**835,930**
Vegetables Crops as % of Total Use		**1%**	**1.5%**				**2%**	**0.3%**
Fruit and Nuts								
Oranges	19%	109,421	142,247	1.3	2.17	2.92	319,838	575,900
Apples	47%	156,125	187,350	1.2	1.66	1.94	295,527	332,180
Almonds	17%	156,400	172,040	1.1	1.67	1.86	290,904	920,000
Walnuts	30%	90,000	117,000	1.3	1.72	2.31	207,900	300,000
Grapefruit	61%	41,053	86,211	2.1	1.59	3.33	136,501	67,300
Peanuts	2.8%	45,500	59,150	1.3	1.15	1.48	67,158	1,625,000
Cherries, sweet	18%	16,529	24,794	1.5	1.83	2.79	46,150	91,830
Tangerines	17%	10,778	25,867	2.4	1.74	4.12	44,416	63,400
Grapes, all	2.3%	23,610	24,714	1.05	1.78	1.86	43,926	1,025,700
Peaches	20%	19,958	25,945	1.3	1.42	1.79	35,665	99,790
Lemons	14%	7,742	9,290	1.2	3.30	4.11	31,820	55,300
Cherries, tart	36%	13,698	20,547	1.5	0.93	1.41	19,342	38,050
Hazelnuts	20%	6,800	8,160	1.2	1.24	1.55	10,540	34,000
Pears	8%	3,915	4,698	1.2	1.98	2.47	9,663	48,940
Strawberries	15%	8,726	9,598	1.1	0.90	1.01	8,839	58,170
Limes	46%	522	1,044	2.00	1.88	3.75	1,958	1,135
Plums and prunes	16%	387	426	1.1	1.61	1.70	658	2,420
Total		**711,164**	**919,083**				**1,570,804**	**5,339,115**
Fruit & Nut Crops as % of Total Use		**11%**	**13%**				**38%**	**2%**
All Uses Totaled		**6,705,814**	**7,015,635**				**4,155,102**	**243,265,345**

Notes: Vegetables were surveyed in 2014 and 2016 and interpolated in 2015. Sugarbeets were only surveyed in 2000. The last year that chlorpyrifos was reported in strawberries by NASS was in 2010. Almonds & Walnuts were only surveyed in 1999, and extrapolated forward. Hazelnuts were only surveyed in 1991 & 1999 and extrapolated forward. Raisins, table grapes and wine grapes are added together to account for all grape crops in 2015.

Sources: USDA-National Agriculture Statistics Service (NASS), Annual Chemical Use Survey Reports. For crops that are not surveyed by NASS in 2015, data was interpolated/extrapolated from known years.

Use of chlorpyrifos on all crops fell from 11,407,675 pounds in 1995 to 4,155,102 in 2015, a 64% reduction. Rates of application and acres planted have remained relatively consistent through this time period, but the percent of acres treated, especially of apples and other fruit crops that are important foods for children and pregnant women, have decreased markedly in many crops (e.g. see apples and sweet cherries Figure 4).

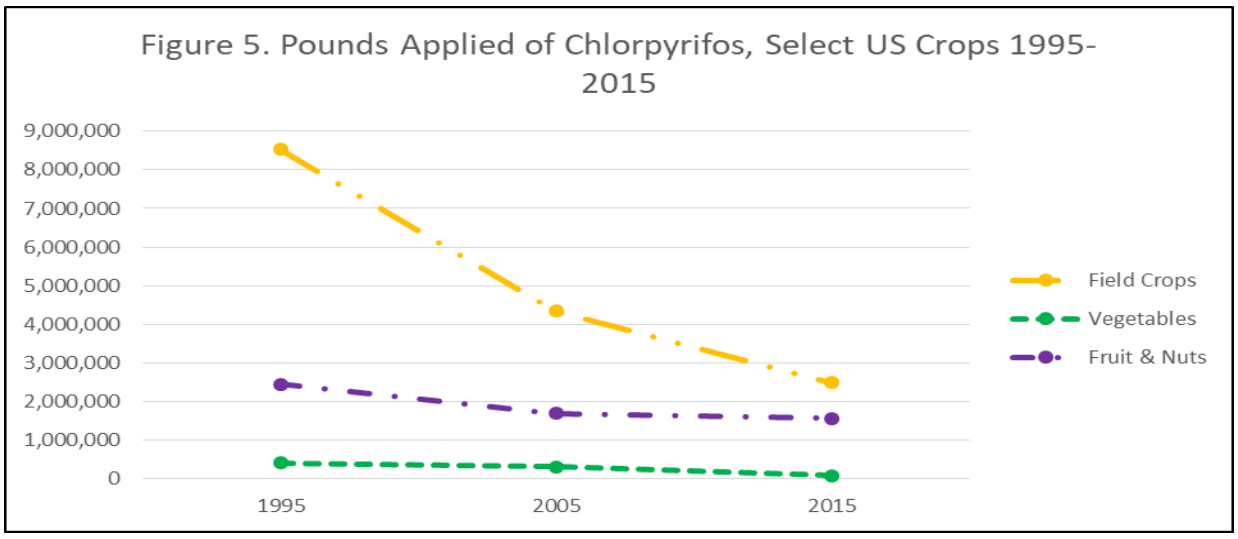


Overall chlorpyrifos pounds applied declined by 44% from ~11.4 million in 1995 to ~6.3 million in 2005, and another 35% to ~4.14 million in 2015. From 1995 to 2005, chlorpyrifos pounds applied to fruit and nuts declined 31% from 2.45 million to 1.7 million pounds, and then nearly leveled out to 1.56 million pounds in 2015. Although starting from a much smaller baseline pounds applied, vegetable uses declined 80% over the 20 years, from 422,341 to 85,791 pounds applied.

OP and Chlorpyrifos Acre Treatments

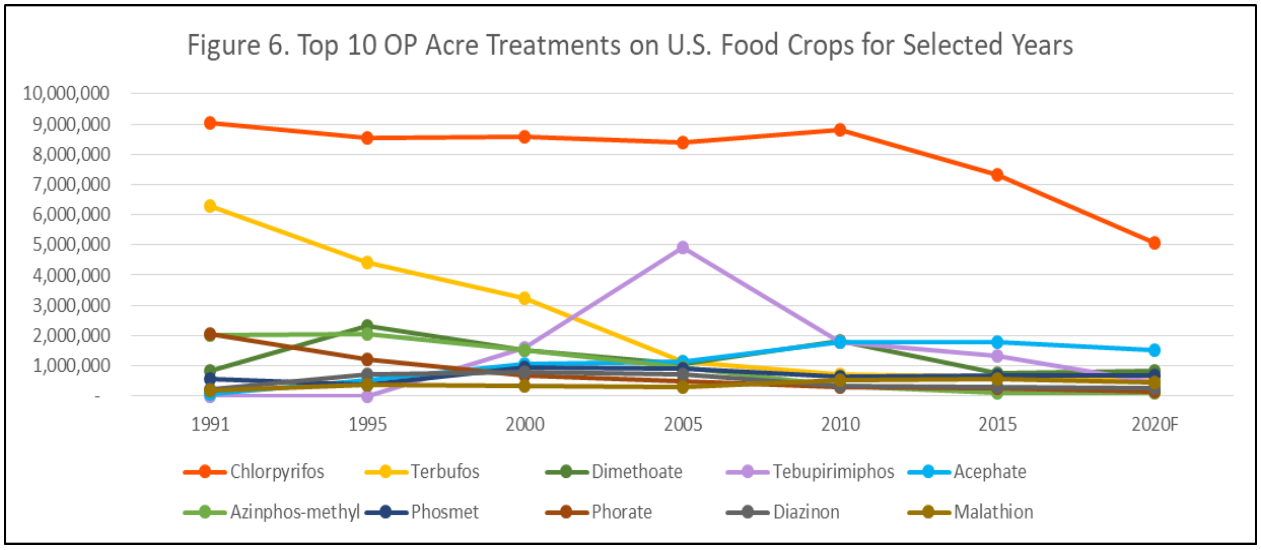
One of the best metrics to track changes in farmer reliance on different pesticides is "acre treatments." This metric for a given crop-pesticide combination is the percent of total acres planted of a crop in a given year that was treated with a pesticide, multiplied by the average number of applications made with that pesticide.

For several important children's foods on which chlorpyrifos and other OPs have been sprayed, more than one application has been required to control insects, and hence the importance of focusing on "acre treatments" instead of "acres treated" once or more times.



The following figures track changes in OP and chlorpyrifos acre treatments at the national level, and are derived from the PUDS. The figure displays trends in total acre treatments applied across 10 of the most-widely used OPs from 1991 through 2020 (forecasted). Note that throughout this 30 year time period, chlorpyrifos is by far the most widely used OP.

Also note that the trend in chlorpyrifos food crop acre treatments was hardly impacted by the FQPA and remained essentially stable from 1995 through about 2012. It is also surprising, given all the regulatory focus on chlorpyrifos, that this OP dominates overall acre-treatments made with these 10 leading OPs to a greater degree today than in the pre-FQPA era.



Changes in reliance on chlorpyrifos compared to other leading OPs is graphically displayed in the following three pie charts representing the shares of eight individual OPs in terms of acre treatments relative to the sum of acre treatments across these ten major OPs in 1995, 2005 and 2015.

Figure 7. 1995 Top 10 OPs

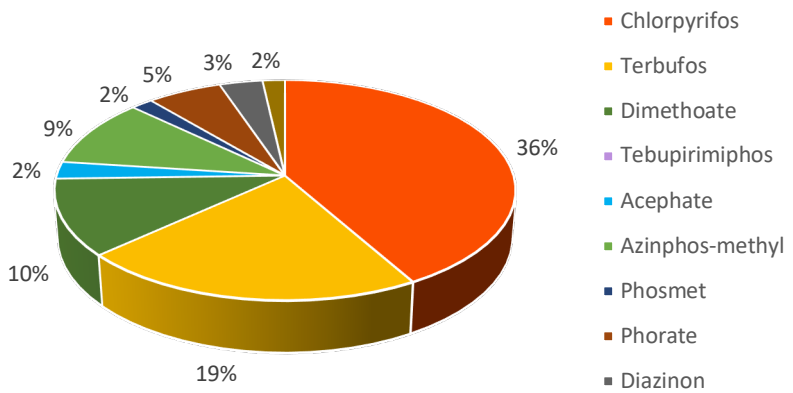
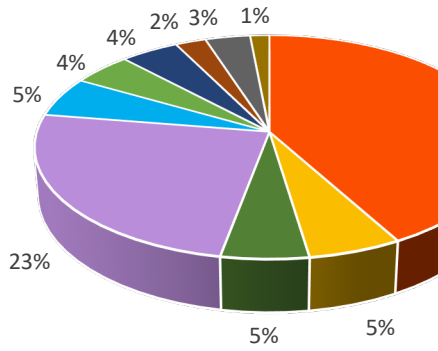
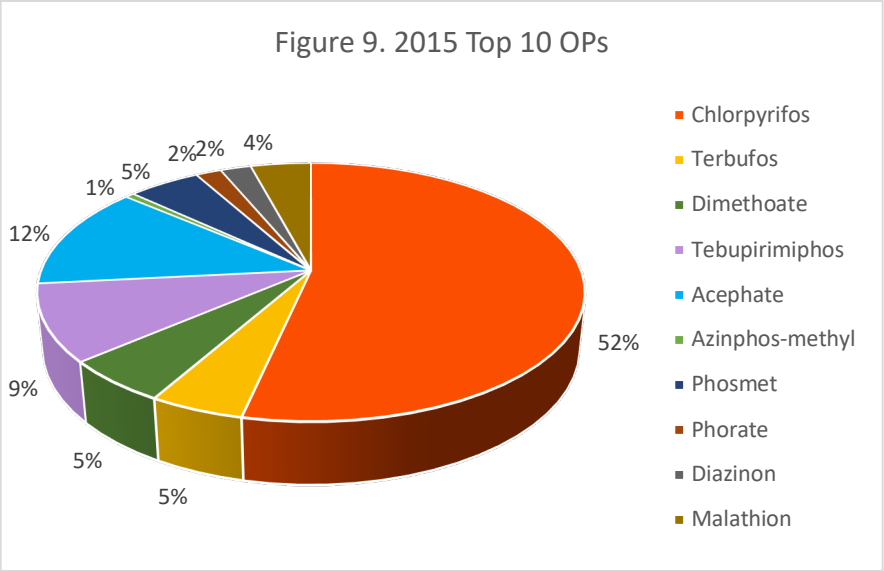


Figure 8. 2005 To





These figures drive home the point that overall farmer reliance on chlorpyrifos, compared to other leading OPs, has actually risen in the post-FQPA era. Chlorpyrifos accounted for 36% of the acre treatments across 10 major OPs in 1996. Its share rose to 40% in 2005 and then to 52% in 2015.

This steady increase was brought about by two primary factors.

First, the manufacturers of most other major OPs came to accept that the risks posed by this family of chemistry were too broad and significant to realistically mitigate via ever-more complex labels and all-encompassing requirements for personal protective equipment. They also knew that they, and other OP manufacturers, had discovered and registered safer and more effective alternative products, which also happened to earn greater profit per acre treated than their older OP products. Many of these new products had gained accelerated registration as a result of the reduced risk and OP-alternatives program called for by the FQPA and implemented by EPA in the 2000s, with considerable success as documented in the next section on alternatives to chlorpyrifos.

Second, unlike the rest of the industry, Dow was deeply committed to defense of chlorpyrifos for several reasons. One was simple pride in a legacy molecule that had served the company well for decades. Another was Dow's recognition that the company might one day face substantial legal risks and liability payments stemming from cases of developmental neurotoxicity (DNT) linked to prenatal chlorpyrifos exposures, as is now beginning to happen.

This Dow commitment to defend chlorpyrifos was hardwired into the genes of the company. It led to the determined defense of chlorpyrifos from the early 2002 until 2019, the year Corteva announced its plan to exit the chlorpyrifos business.

B. The Highly Contested Benefits Side of the Chlorpyrifos Equation

A risk-benefit balancing standard is embedded in the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). After passage of the Food Quality Protection Act (FQPA) in 1996, a different standard has applied to the setting of tolerances -- "reasonable certainty of no harm." The FQPA's health-based standard does not allow EPA to take into account a pesticide's benefits to farmers or pest managers when making decisions on tolerances.

But the lack of a tolerance covering a given pesticide-food crop use means that there can be no corresponding EPA registration for that use. For this reason, the purported economic impacts on farmers and society of ending chlorpyrifos uses on food crops has always been a major point of contention, since labels are issued and changed under FIFRA in accord with its cost-benefit balancing standard.

Dow, the pesticide industry and many growers have consistently emphasized the vital importance of chlorpyrifos in sustaining fruit and vegetable production. They have predicted significant increases in the cost of meeting consumer demand for fresh and processed produce if chlorpyrifos were removed from the insect pest management toolbox.

The economic impacts of chlorpyrifos on farmers and society, via changes in the supply or cost of fruits and vegetables, are a function of how widely chlorpyrifos is used by growers and whether there are effective and affordable alternatives. The tables and figures above drive home the point that chlorpyrifos has been used sparingly in the production of nearly all fruit, nut, and vegetable crops for nearly two decades.

A cost-benefit, or risk-benefit analysis of any pesticide should also take account any human health and environmental externalities, in addition to farm sector impacts. Studies quantifying the economic costs to society of OP-induced loss of IQ, mental acuity, learning and behavioral problems have been published and are assessed below to place into perspective the magnitude of these costs relative to those purportedly arising from within the agricultural sector.

Alternatives to Chlorpyrifos

In 1998, two university scientists published a paper entitled "GOLDEN AGE OF INSECTICIDE RESEARCH: Past, Present, or Future?" (Casida and Quistad, *Ann Rev Entomol* 43: 1-16; https://pubmed.ncbi.nlm.nih.gov/9444749/). The authors conclude the abstract with this observation:

> "Insecticide research, having passed through several Golden Ages, is now in a renaissance of integrating chemicals and biologicals for sustainable pest control with human safety."

Table 1 in the Casida-Quistad paper lists major classes of insecticides by economic importance globally in 1995. Five major classes of insecticides are listed, along with "Other Chemicals."

Organophosphates (OPs) account for the largest share of global expenditures (34%), with the synthetic pyrethroids ranking second with a 23% share.

Passage of the FQPA in 1996 generated considerable anxiety in the pesticide industry and farm community over the possible loss of many, or even all OPs. This anxiety was channeled into pressure on the EPA, Congress and the White House to assure that farmers were not left hanging as a result of rapid and broad-based restrictions on OP use.

The response among policy-makers and the EPA was swift and substantive.

Expediting Review of Reduced Risk Alternatives

On September 4, 1997, just a little more than a year after passage of the FQPA, and two years before the first regulatory actions reducing OP risks, the EPA issued Pesticide Registration Notice (PRN) 97-3, "Guidelines for Expedited Review of Conventional Pesticides under the Reduced-Risk Initiative and for Biological Pesticides." (https://www.epa.gov/pesticide-registration/prn-97-3-guidelines-expedited-review-conventional-pesticides-under-reduced)

This 23-page notice described a number of changes in the process adhered to in reviewing and approving registration applications for new active ingredients. The changes were structured to accelerate registration of safer, reduced risk, and biopesticide alternatives to the OPs. The FQPA called for the creation of such incentives for discovery and registration of OP alternatives.

The goal of the program is straight forward --encourage development and registration of pesticides that will lower risk compared to currently registered products, and especially the OPs. And according to the EPA Notice: "The major incentive which EPA offers for these pesticides is expedited registration review."

The reduced-risk initiative was first codified in a July 1992 Federal Register notice, which was superseded by the September 1997 notice. Between July 1992 and September 1997, registrants had applied for reduced-risk status for 39 new insecticides. Of these, 22 were granted reduced-risk status and 14 were registered on an accelerated basis. Of the 14, two were important OP alternatives -- Dow AgroSciences's spinosad and the insect growth regulator tebufenozide.

The benefit stemming from reduced-risk classification was significant. According to EPA:

> "For FY95 and FY96 (prior to passage of the FQPA in August 1996) the average total time required to register a new conventional pesticide was thirty-eight months. For reduced-risk pesticides the average total time for registration was only fourteen months."

The most important criterion considered by EPA in granting reduced-risk status is reduced human health risk, i.e. "toxicity generally lower than alternatives (10-100X)…[the alternative] displaces chemicals that pose potential human health concerns [e.g. OPs, probable

carcinogens]."

On August 24, 1998, EPA issued a second Pesticide Registration Notice (98-7) entitled "Changes to the Registration Priority System Involving OP Alternatives and Reduced Risk Candidates." (https://www.epa.gov/pesticide-registration/prn-98-7-changes-registration-priority-system-involving-op-alternatives-and). This notice left unchanged the #1 priority -- methyl bromide alternatives -- but elevated "OP alternatives that pass the reduced-risk screen" to priority #2. This Notice also placed at priority #4:

> "OP alternatives that are submitted to the reduced-risk committee, judged to be significant OP alternatives, denied reduced-risk status, but recommended by the Reduced Risk Committee for expedited review."

I accessed the section of the EPA website entitled "Reduced Risk and OP Alternative Decisions for Conventional Pesticides" on January 28, 2021. (https://www.epa.gov/pesticide-registration/reduced-risk-and-organophosphate-alternative-decisions-conventional) The list of reduced-risk actions taken was last updated June 2018.

From 1994 through 2018, Table 4 reports the number of major new uses of insecticides and new active ingredients included in the June 2018 accounting by EPA of all insecticides registered on an expedited basis because of classification as an OP Alternative, a Reduced-Risk (RR) insecticide, or an RR/OP Alternative.

A total of 153 new insecticide ***uses*** were registered in this 24 year period, or about 6.4 per year. Of these, about one-half (77) were classified by EPA as either OP alternatives, or Reduced Risk/ OP Alternative uses. A total of 28 OP Alternatives and RR/OP Alternative ***active ingredients*** were registered. These active ingredients now account for the majority of insecticide acre-treatments in most crops in the U.S. and globally. There are dozen or more uses registered for each these 28 new active ingredients.

Table 4. Number of Insecticidal OP Alternatives, Reduced Risk (RR), and RR/OP Alternatives Registered by EPA from 1994 to 2018		
	New Uses	**New Active Ingredients**
EPA Classification		
OP Alternatives	27	13
Reduced Risk	76	31
RR/OP Alternative	50	15
Totals	153	59

Since passage of the FQPA, EPA actions and voluntary registrant decisions have removed about 10 OPs from the insecticide toolbox. EPA has granted accelerated registration to 59 new insecticides, resulting in a substantial net gain in the number and diversity of chemical and biopesticide "tools" in the insect-pest-management toolbox.

As farmers moved away from OPs, including chlorpyrifos, beginning in the early 2000s, the insect pest control burden shifted to other conventional insecticides, relatively new reduced-risk products and low-risk bioinsecticides. Alternative insecticides were typically used in conjunction with varying degrees of prevention-based Integrated Pest Management (bioIPM). BioIPM systems use information and human skills to prevent pests from becoming a problem, but when they do, dozens of alternatives to chlorpyrifos can be applied that fall into four categories.

Other "Conventional" Pesticides – 20 to 30 active ingredients for any given crop use (common trade names in parentheses):

- An average of 3 to 4 lower-risk OPs including malathion, acephate (Orthene), formetanate hydrochloride (Carzol), and phosmet (Imidan),
- Typically 2 to 3 lower-risk carbamate insecticides including methomyl (Lannate) and carbaryl (Sevin), including granulars for control of soil borne insects,
- 4 to 6 synthetic pyrethroids, including permethrin, esfenvalerate, bifenthrin, cyfluthrin, lambda cyhalotrin, and cypermethrin,
- 6-8 miticides including emamectin benzoate (Proclaim), abamectin (AgriMek), etoxazole (Acramite, targets mites in nymph and larval stages), bifenazate (M-Pede, Intrepid), fenpryoximate (Akari, Forbid), and pyridaben (Endeavor),
- On average, 3 to 4 neonicotinoids, including Bayer's imidacloprid (Admire), clothianidin, acetamiprid, and Syngenta's thiamethoxam (Cruiser, Actara),

- Chlorantranilprole (Coragen), cyzapyr (Exeril, Verimark), and other Group 28 insecticides

Non-Conventional or "Reduced Risk" Pesticide Active Ingredients – 10 to 30 alternatives for any given crop:

- Spinosad (SpinTor, Success), a Dow AgroScience product that controls a wide range of insects (e.g. worms, thrips), and its next-generation, improved product spinetoram (Delegate, Radiant)
- 4-6 Insect Growth Regulators (IGRs) products targeting worms, white flies, nymphs, other insects that work by disrupting insect development, e.g. tebufenozide (Confirm), methoxyfenozide (Intrepid), buprofezin (Applaud) and clofentezine (Apollo), hexythiazox (Savey), pyripoxyfen (Knack) among others,
- Indoxacarb (Avaunt) for worm control,
- Pymetrozine (FulFill) targeting aphids,
- Spiromesifen (Oberon) for white fly nymphs, mites,
- Spirotetramat (Movento), a translaminar (i.e. moves into plants) for control of sucking/chewing insects,
- Fipronil (Regent),
- Flonicamid (Beleaf) aphicide,
- Sulfoxaflor (Closer, Transform) for aphids, white flies, and
- Pyrifluquinazon (PQZ, Rycar).

Biological Pesticides, or Biopesticides – 10 to 15 alternatives for most crops:

- Neem oil and products containing azadirachtin,
- Pyrethrins and other botanicals,
- Petroleum and dormant oils, and soaps,
- Biopesticides like Bacillus thuringiensis (*Bt*) [Zentari, Dipel] and *Beauveria bassiana*,
- Transformed kaolin clay (Surround) to coat fruit and limit insect damage,
- Multiple viruses for worm control, and
- Multiple pheromones for insect mating disruption.

Integrated Pest Management Systems and Other Biologically Based Practices – 6 to 10 proven tactics and practices for most crops:

- Support biodiversity of soil life by reducing tillage and planting cover crops,
- Mating disruption through use of pheromones – advances in chemistry, formulations, and delivery methods are lowering costs and enhancing efficacy,
- Targeted use of Insect Growth Regulators in combination with mating disruption,
- Area-wide reduction in pest populations through careful crop rotation and measures to reduce the areas accessible to insects to over-winter, among other area-wide tactics
- Release of beneficial organisms and classical biological control,
- Establishment of habitat supportive of beneficial insects in and around fields, and

- Trapping methods or trap crops, often in conjunction with pheromones or other attractants.

In the 1970s and 1980s, most widely used insecticides worked via lethal modes of action, many of which also posed risks to mammals (e.g. the OPs via AChE suppression in both insects and people).

There has been a marked expansion since 2000 in the number of insecticide-based pest management products and modes of action available. A majority of the newer active ingredients target a specific biochemical, physiological, reproductive or morphological processes that are unique to insects. Most work at low or very low rates of application, and some rarely leave detectable residues in food. Most pose modest or very low risks to farmworkers and bystanders, and most are far, far safer than chlorpyrifos.

These indisputable facts raise an important policy issue the EPA and Congress needs to address, beyond the endgame for chlorpyrifos. The "lack of essentiality" clause in FIFRA has made it much harder for the EPA to take needed actions to end high-risk pesticide uses, even when there are a plethora of proven, effective, affordable and much-safer alternatives. This has, in effect, turned the risk-benefit or cost-benefit standard embedded in FIRFA into a one-way street.

The industry has mastered use of the purported, and consistently exaggerated, "costs" that will arise in the wake of cancelling a given pesticide. In most cases, the industry is able to manufacture sufficient grower outrage to delay, lessen or avoid all together new restrictions on known, high-risk pesticides.

Such "costs" are always quantified by EPA relative to the next-best registered alternative. In fact, the EPA should also take into account non-chemical alternatives, but rarely does, and never does adequately in accord with current science.

The result is that despite EPA granting accelerated registrations to dozens of highly effective OP and chlorpyrifos alternatives, the Agency has not materially altered its assessment of the "costs" or banning chlorpyrifos nor the "benefits" to farmers and society from moving forward with chlorpyrifos cancellations, because there are so many more effective and demonstrably safer products available to farmers.

In the 1996 FQPA, Congress had good reasons to require EPA to provide incentives to bring safer OP alternatives onto the market more quickly. Today, equally good reasons exist to amend FIFRA to dampen the impact of the "lack of essentially" clause, so that the cost-benefit balancing standard at the heart of FIFRA works to spare farmers from major adverse economic consequences and society from lingering and unnecessary human health and environmental

risks and costs.

The magnitude of such costs in the case of the OPs and chlorpyrifos are summarized below. These worrisome estimates drive home the need for FIFRA reforms to make it easier for EPA to end uses of high-risk products when there are many effective alternatives ready for wider use.

Economic Impacts of Chlorpyrifos Impacts on the Brain, IQ, and Behavior

In 2012, Dr. David Bellinger, then a professor at Harvard University, published a seminal paper on the economic costs of lost IQ as children grow up. "A Strategy for Comparing the Contributions of Environmental Chemicals and Other Risk Factors to Neurodevelopment of Children" was published in *Environmental Health Perspectives (Vol.* 120:4). He used a measure of life-long loss of IQ, called Full-Scale IQ (FSIQ), and coupled it with the economic costs to society from a loss of one FSIQ over a person's lifetime. He derived his estimate of the reduction in lifelong earning potential in dollars per FSIQ from a variety of econometric analyses.

Bellinger collected data on multiple factors known to impact a child's IQ, with special focus on health conditions and environmental exposures. Pre-term birth was the factor accounting for the largest number of lost FSIQ points in a given year, 34 million. Lead was number two at 23 million, and organophosphate insecticides (OP) were third at 17 million FSIQs.

The fact that Bellinger's analysis projected that the impact of OPs on FSIQ loss was roughly three-quarters of the impact stemming from lead exposure was an unexpected finding, especially in light of the enormous costs associated with societal efforts to reduce children's lead exposures.

Another academic analysis estimated the economic cost of the EPA's failure to ban chlorpyrifos in the early 2000s. (Trasande [2017] When enough data are not enough to enact policy: the failure to ban chlorpyrifos, *PLOS Biology*, December 21, 2017; https://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.2003671)

After reviewing the multiple lines of evidence linking prenatal and early life exposures to chlorpyrifos to neural developmental deficits, Trasande projects the impacts of the EPA's 2017 decision to reverse the ban called for by the Agency in 2015-2016:

> "…Administrator Pruitt's decision [to reverse the ban] fails to consider the reality that the cohort of US children born in 2010 lost 1.8 million IQ points and 7,500 children had their IQs shifted into the intellectual disability range as a result of prenatal organophosphate exposures."

Trasande then cites studies projecting that each IQ point lost leads to a 2% reduction in lifetime economic productivity, or about $20,000 per IQ point. Added education and health care costs must also be taken into account for a full accounting of the economic impacts of early-life OP exposures. Taking into account all sources of economic impact, Trasande projects that combined OP exposures over the lifetimes of the children born each year would cost society $44.7 billion annually.

A team led by Trasande published a 2020 paper entitled "Trends in Neurodevelopmental Disability Burden Due to Early Life Chemical Exposure in the USA from 2001 to 2016: A Population-Based Disease Burden and Cost Analysis." (Gaylord et al., [2020] *Mol Cell Endocrino*l; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7073246/) In this analysis, the team focused on polybrominated diphenyl ethers (PBDEs), OPs, methylmercury, and lead. Biomonitoring data from the CDC's National Health and Nutrition Evaluation Study (NHANES) was used, in conjunction with the results of epidemiology studies establishing statistically significant associations between prenatal and early life exposures and adverse neurodevelopmental outcomes.

These updated estimates of lost IQ points adhered to a methodology outlined by the Institute of Medicine and applied in Bellinger's seminal 2012 study. For the OPs, Trasande's 2020 team estimated that 4.25 IQ points would be lost per 10-fold increase in prenatal OP exposure. Each lost IQ point was valued at $22,268. Each case of intellectual disability was projected to impose lifetime costs of $1,272,470.

Based on these estimates, the four chemicals in this 2020 study imposed on society an estimated $6 trillion in lifetime costs over the 15-year study period (i.e. life-long impacts across all children born in the 15-year period.) PBDEs accounted for the largest impact at $3.6 billion, lead was second at $1.7 billion, and ***OPs were third, accounting for an estimated $594 billion in societal costs over 15 years, or nearly $40 billion on average per year.***

Even if Trasande et al.'s analysis overstates the costs of OPs by 10-fold, their economic toll on society would still be staggering.

Annual net farm income over expenses has been about $100 billion in the US over the last few decades. Annual costs stemming from OP exposures on the order of $4 to $40 billion annually are surely large enough to dramatically alter the cost-benefit trade-offs entailed in continued reliance on OPs.

But what share of total OP costs imposed on society via lost IQ and disability is likely caused by chlorpyrifos? Table 5 provides a basis for an approximate empirical estimate.

Table 5. Chlorpyrifos Share of FS-DRI and Number of Residues Found of All OPs in Domestic Conventional Food Samples Tested by PDP in 1995, 2005, and 2015			
	1995	**2005**	**2015**
PDP Sampling			
Number of Foods Tested	11	26	20
Total Number of Samples	6,294	12,381	7,510
Chlorpyrifos --			
Number of Residues Found	400	237	18
Percent Share All OP residues Found	16%	9%	3%
Aggregate FS-DRI	0.162	0.036	0.077
Percent Share All OP Aggregate FS-DRI	8%	2%	9%
All OPs --			
Number of Residues Found	2,530	2,541	586
Aggregate FS-DRI	2.113	2.069	0.827

As explained earlier, the FS-DRI metric stands for "Food Supply Dietary Risk Index" score and is a metric of relative pesticide risks stemming from a single serving of different foods in light of the pesticide residues found in the food. The residue data come from the USDA's Pesticide Data Program (PDP). The DRI takes into account the level of residue in a food, the chronic toxicity of the pesticide as quantified by EPA's chronic Reference Dose, the grams in a serving, and the weight of a person consuming a food.

Aggregate chlorpyrifos FS-DRI in Table 5, is the sum of FS-DRI scores across all the foods tested by PDP in 1995, 2005, and 2015 that were found to contain a residue of chlorpyrifos. All-OP aggregate FS-DRI is the sum of FS-DRIs across all OPs. So, the share of chlorpyrifos FS-DRI of total OP FS-DRI is one way to approximate the contribution of chlorpyrifos to total OPs risks.

All EPA-set chronic Reference Doses for OPs are set on the basis of cholinesterase inhibition, not developmental neurotoxicity (DNT), so the estimates in Table 5 are not grounded in DNT data. However, based on the assumption that chlorpyrifos is roughly as potent a developmental neurotoxin as all other OPs, the percentage shares in this table are a crude indicator of chlorpyrifos's likely share of the approximate $40 billion in annual OP costs.

The average annual costs of chlorpyrifos use imposed on society over the last 15 years stemming from IQ lost and additional cases of disability likely falls in the range of a few to $5

billion. Costs of this magnitude are enormous by any measure relative to the modest farm-sector economic benefits of continued use of this insecticide.

C. Impact of the FQPA on Chlorpyrifos Risk Assessment and Regulation

The seminal NAS report *Pesticides in the Diets of Infants and Children* was released in 1993. It explained why prenatal and early life exposures to certain pesticides, such as and including chlorpyrifos, posed neurodevelopmental risks that existing EPA toxicological test requirements and risk assessment methods would rarely detect.

The Committee recommended a number of changes in EPA test protocols, science policies and risk assessment procedures, as well as changes in the FIFRA and the FDCA. The most consequential recommendations, if passed into law, would direct EPA to:

1) Add an additional 10-fold safety factor in setting pesticide chronic Reference Doses to account for the heightened vulnerability of pregnant women, infants and children.
2) Aggregate all exposures to a given pesticide across all possible routes of exposure (diet, drinking water and other beverages, dermal exposure, and via inhalation), and ***assure that there is a "reasonable certainty of no harm" in the wake of estimated aggregate exposure.***
3) For different pesticides that pose risk to humans through a common mechanism of action, like inhibition of cholinesterase, the EPA must assure that ***cumulative exposures*** across all such pesticides meet the FQPA safety standard.

The NAS report's Executive Summary describes the many changes needed in the way the EPA tests pesticides and quantifies exposures. The collective purpose of the changes would be to help EPA more accurately determine levels of exposure above which vulnerable populations, and especially pregnant women, infants, and children, might manifest the same developmental problems and diseases evident in laboratory animals exposed to pesticides. The Committee outlined new risk assessment methods that I helped develop, and applied them to quantify total OP dietary exposure and risk:

> "Through this new analytical procedure, the committee estimated that for some children, total organophosphate exposures may exceed the reference dose [presumptively safe level]."

In the section addressing "Toxicity Testing" in the report's summary, the Committee calls for a new set of tests:

> "Of particular importance are tests for neurotoxicity and toxicity to the developing immune and reproductive systems."

In the chapter addressing methods for testing pesticides, the Committee highlights the need for better methods to investigate developmental neurotoxicity:

> "Because neurotoxicity is such an important consideration for the newborn, EPA should

> continue to revise its published guidelines on developmental and functional neurotoxicity testing as new information emerges from the actual conduct of preregistration studies and from ongoing research in rodent neurotoxicity." (Page 155)

The FQPA was historic because it replaced the risk-benefit balancing standard in FIFRA that had governed EPA tolerance setting and regulatory decisions for 24 years with a strictly health-based standard -- "reasonable certainty of no harm."

Congress did set forth conditions under which the Administrator of EPA could reduce or remove the mandated, added 10-fold FQPA safety factor. In short, if the Administrator determines that: (a) the toxicological and other studies available to the EPA rule out any heightened risk to vulnerable populations, and (b) the Agency has current and high-quality exposure data, the FQPA safety factor could be reduced below 10-X or eliminated (i.e. set at 1).

The FQPA's aggregate and cumulative exposure requirements were particularly important in how the EPA would bring the organophosphate (OP) and carbamate insecticides into compliance with the FQPA.

At passage, some 37 OPs held valid food use registrations and tolerances. There were 1,691 tolerances on the books covering OP residues in food, of which 109 covered chlorpyrifos residues. Across all pesticides, foods, and food forms there were 9,721 tolerances in need of reassessment, so OPs accounted for 17% of all tolerances subject to the FQPA, but a much higher share of total dietary risks.

Concerns and Backlash Came Quickly

A September 19, 1996 editorial in the *Wall Street Journal* began with this observation:

> "Like a tornado, the FQPA whirled through Congress in just a week, in the aftermath, American farmers are beginning to realize that when it comes to pesticide regulation they are not in Kansas anymore." (Jonathan Tolman)

After a brief recount of Congressional action on the FQPA, Tolman's *WSJ* piece states:

> "Yet despite the National Academy of Sciences findings [in the *Pesticides in the Diets of Infants and Children* report] that pesticides pose virtually no health threat, the new law will make it more difficult to register and use pesticides. Welcome to the land of Oz."

The 1993 NAS report does not say "pesticides pose virtually no health risk*."* It highlighted a number of pesticide-related chronic disease risks, but focused particular attention on developmental neurotoxicity, which is why the report led to so much focus on chlorpyrifos.

The first published paper reporting changes in the development of the brain in rat pups following prenatal exposure to the dam appeared in 1975. By the time the NAS Committee

began its work in 1988, about 100 studies reporting similar neurodevelopmental impacts following pre-natal exposures to chlorpyrifos had been published in peer-reviewed journals.

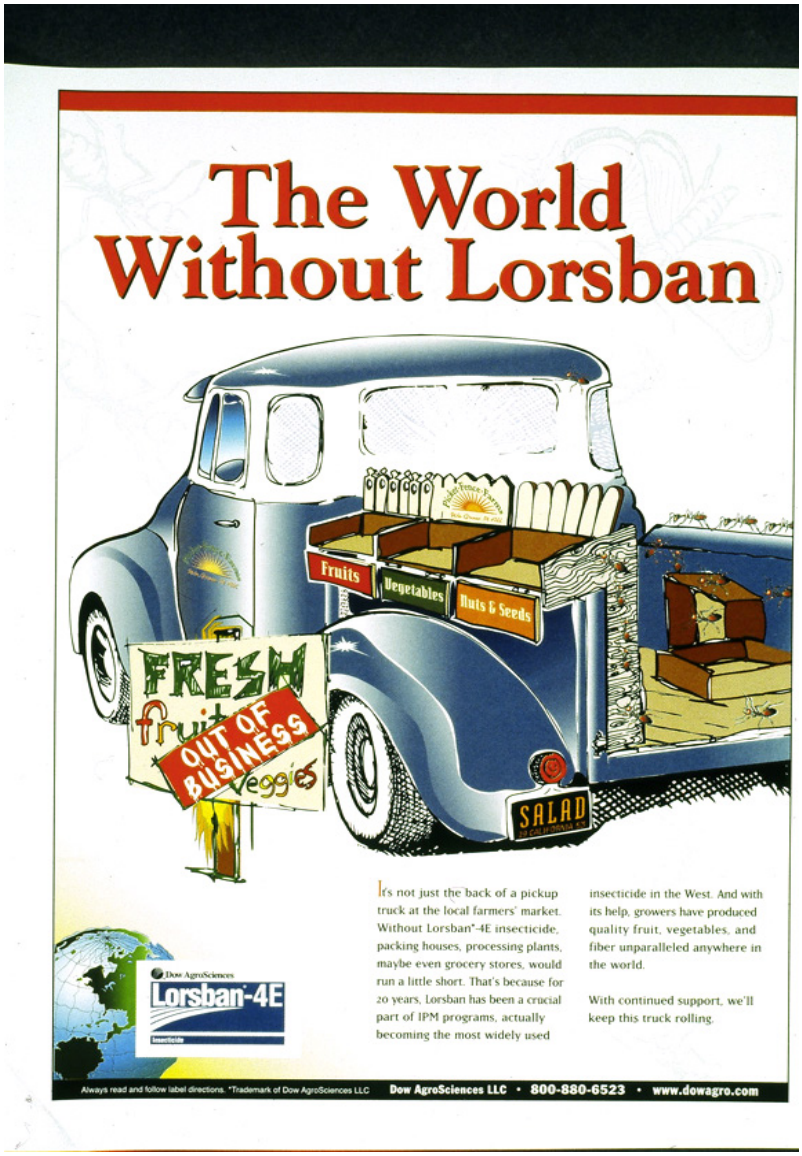
A hearing on FQPA implementation was held before the Subcommittee on Department Operations, Nutrition, and Foreign Agriculture on June 25, 1998 (the Subcommittee I served as Staff Director in 1981-1983). Ken Evans, then President of the American Farm Bureau shared concerns widely shared in the ag community:

> "Passage of the FQPA was viewed as the successful conclusion of a 15-year effort...to modernize our food safety and pesticide laws…Our support for these provisions [in the FQPA] was tempered with concern that…[the FQPA] could result in unjustified restriction of essential crop production products.
>
> "Our experience has been that 'reasonable certainty of no harm' is being interpreted by EPA as essentially the same as zero risk, threatening cancellation of safe crop protection products.
>
> "'Reasonable certainty has become de facto Delaney Clause and is being used to carry out the same anti-pesticide agenda.
>
> "Last, the agricultural community and members of Congress were repeatedly reassured by EPA that FQPA was merely the codification or formalization of existing EPA authority. This is the source of our greatest sense of betrayal. It is now clear that EPA's planned implementation of FQPA will force unjustified cancellation of dozens -- perhaps most of entire classes of essential crop protection products." (Evans statement, pages 1-2)

The reference by Evans to "entire classes" of pesticides was to the OPs and carbamates, a notion that Dow AgroSciences was actively promoting in the farm community at the time via advertisements like the one in the figure below. Evans closes his Subcommittee statement with this:

> "There is an old saying in government that, 'Silence means everything is O.K.' The silence has been broken when it comes to FQPA. Farmers and agricultural interests are raising their voices. The volume is growing louder every day." (Evans, p. 9)

And indeed predictions of dire, FQPA-driven consequences for farmers and the food supply were voiced everywhere the FQPA was addressed in the farm community or within the pesticide industry.



The text of the "World Without Lorsban" ad warns:

> "It's not just the back of a pickup truck at the farmers' market. Without Lorsban 4-E [chlorpyrifos] insecticide, packing houses, processing plants, and maybe even grocery stores will run a little short."

The suggestion that banning chlorpyrifos might lead to shortages of fruit and vegetables achieved its goal, triggering substantial commentary and anxiety in the farm community over the loss of chlorpyrifos. Thousands of letters were sent to the EPA. This catchy ad was a frequent topic of discussion among people working on FQPA implementation

A piece entitled "Growing Debate" in the *Los Angeles Times* (Martha Groves, July 12, 1998)

begins with a fruit grower attesting to his need for OPs to control the Oriental fruit moth, but according to the piece:

> "Come next year, under a sweeping new food safety law [the FQPA], the federal government might very well plow them [the OPs] under."

The *LA Times* piece goes on to say "It is likely to mean unprecedented prohibitions against widely used pesticides…The environmental community says it will settle for nothing less, citing concerns that OPs can disrupt the brain development of fetuses and infants."

After highlighting the dependence of many California farmers on OPs and noting the 6,600 poisoning episodes in the State between 1982 and 1992, "Growing Debate" then conveys that "When it comes to pesticides, farmers are often likened to Chicken Little," and quotes a number of farmers and commodity organization representatives who view impending EPA action on the OPs as an existential threat to their livelihood and ability to meet demand for fruits and vegetables. My voice is then added to the mix:

> "But such dire scenarios are unlikely, said Chuck Benbrook, a longtime consultant on OPs and other pesticides…Offering one of the most reasoned viewpoints in the vitriolic debate, Benbrook predicts that only one-third of the organophosphate and carbamates now in use will be banned over the next five years because of EPA-imposed restrictions. Several others will be modified."

My 1998 prediction has proven inaccurate. Upon passage of the FQPA, there were 37 OPs on the market (import tolerances were in a place for a few others). As of July 2006, 31 had been reregistered and had their tolerances assessed. Only six OPs were driven off the market a decade after passage of the FQPA, or about 16% (one-half of what I had predicted). The FQPA has had a similarly light touch on the carbamate insecticides (one of about a half-dozen driven off the market by the FQPA).

The *LA Times* piece also addresses the issue of alternatives to chlorpyrifos and other OPs and carbamate insecticides then used by fruit and vegetable growers. Growers are quoted expressing concern over the higher cost of newer, safer alternatives. On the issue of alternatives and costs:

> "One solution, he [Benbrook] said, would be for chemical producers to drive down the cost of safer pesticides. Dow AgroSciences, an Indianapolis-based unit of Dow Chemical Co., recently registered one such alternative, called Success. It treats a broad range of pests in minor crops [e.g. fruits and vegetables] without harming people or beneficial insects, but Benbrook said it is too expensive to win wide acceptance.
>
> "Success [Dow's new spinosad insecticide] is so important that 'we're betting the farm on it,' said Elin D. Miller, director of government affairs for Dow AgroSciences. In the meantime, though, the company continues to sell huge quantities of two highly toxic OP

products Lorsban and Dursban [both containing chlorpyrifos]."

EPA's First Concrete Actions under the FQPA

The first concrete action impacting the OPs was announced by EPA Administrator Carol Browner in an August 2, 1999 statement. It began by stating:

> "In 1993, this Administration went to Congress with a plan -- based on recommendations from the National Academy of Sciences -- to better protect our children from the risks of pesticide residues in the fruits and vegetables they eat. Three years later that plan -- the Food Quality Protection Act -- passed Congress unanimously and was signed into law by President Clinton.
>
> "Today -- after an extensive scientific review -- we are announcing the first major steps under this act that will safeguard our kids from two of the older and more widely used pesticides on the market. And that means greater protection for all of us." (Browner written statement)

Administrator Browner then announced a voluntary cancellation agreement with registrants of methyl parathion, the most toxic of the 37 OPs then holding current registrations. According to EPA's analysis:

> "The acute dietary risk to children one to six exceeded the acute population adjusted dose (or amount that can be consumed safely in one day or less) by 880%." (EPA, Methyl Parathion Risk Management Decision, August 2, 1999)

Significant restrictions were also announced on azinphos methyl, another OP used widely in tree fruit production. The Administrator then adds:

> "Even as we begin to take specific actions on these chemicals, I am here today challenging the manufacturers of these older pesticide products to voluntarily come forward with the kind of risk reduction strategies similar to those we are announcing today.
>
> "What's important here is that in developing these new risk standards, for the first time we used children -- not the average adult -- as the benchmark for setting safety.
>
> "We often talk about the legacy each generation leaves for the generations to come. By ensuring the safety of the foods our children eat, we are helping create a healthier America now and for all the years to come."

Among the many responses to this first set of FQPA-driven actions, Consumers Union (CU) issued a statement on the same day as Administrator Browner's. It criticized the Agency for failing to act more comprehensively on the new mandates in the FQPA, for falling behind in the implementation schedule in the stature and not addressing other major OP risk drivers like

chlorpyrifos. Then the CU statement asserts:

> "This afternoon, the EPA will claim that it has accomplished what the [FQPA] stature required it to do…Our analysis, released today, shows in sharp relief what the Agency hasn't done, what it could have done, and what it should have done." (Emphasis in original; CU Statement August 2, 1996, page 1)

The analysis released that day by CU identified the 125 pesticide-food combinations accounting for the largest shares of total pesticide dietary risks. These 125 pesticide-food combinations were listed in the CU report called *Worst First*. I conducted the dietary risk analysis and was the principal author of this CU report. Nineteen of the top 30 pesticide-food combinations among the 125 worst-first involved OPs and accounted for 89% of total risk. According to the August 2, 1999 CU statement:

> "Actually, a very small fraction of pesticide uses accounts for the lion's share of dietary residues and risk. Consumers Union's analysis shows that a mere 125 uses account for 99 percent of the dietary risk.
>
> "Today, we expect EPA to announce decisions on tolerances for important food uses of two high-risk insecticides, methyl parathion and azinphos methyl. Twelve uses of these two very toxic insecticides are among the 125 highest-risk uses…[and] account for 23 percent of the overall dietary risk in our analysis."

The top 13 pesticide-food combinations in *Worst First* accounted for 72% of total risk across all food uses of pesticides. ***So, the top 13 -- or 0.002% of 9,700 pesticide-food combinations-- accounted for almost three-quarters of total risk***. Two uses of chlorpyrifos (wheat and apples) were among the top 13, as was use of chlorpyrifos-methyl on wheat (form of chlorpyrifos sold for use in grain storage).

The *New York Times* editorial page reacted to Administrator Browner's August 2nd announcement in an editorial titled "Pesticides and Politics" (*NY Times*, August 9, 1999):

> "In 1996, in a rare display of bipartisanship and without a single dissenting vote, Congress passed the FQPA…Last week, Carol Browner, the EPA Administrator, fired her first shot…But it was merely the opening round in what is sure to be a long, politically charged regulatory struggle."

Chlorpyrifos -- The FQPA's Acid Test

From the day the NAS started the *Pesticides in the Diets of Infants and Children* project, through the analytical work done by the Committee, the deliberations of Congress as it crafted the provisions of the FQPA in 1995-1996, and throughout the FQPA implementation process, everyone involved (including EPA staff) recognized that the single most important risk-driver and test case was the most heavily and widely applied OP, chlorpyrifos -- the active ingredient in some 825 registered insecticide products around year 2000.

I have tracked the impact of the FQPA on overall pesticide dietary risks continuously since the statute's passage in 1996. The need for a quantitative accounting of the impact of the FQPA over time was one of the reasons I developed the Dietary Risk Index (DRI) system. The methodology and data sources in the DRI are described in Benbrook and Davis (2020), "The dietary risk index system: a tool to track pesticide dietary risks" (*Environmental Health*, 19(1); DOI: 10.1186/s12940-020-00657-z).

The relevant metric in the DRI to track the impact of the FQPA on chronic exposures and risks arising from the OPs and chlorpyrifos is the Food Supply-DRI, or FS-DRI. The FS-DRI values for each OP in a given year take into account all residues found in the foods tested by the USDA's Pesticide Data Program (PDP) in a given year. This is the same primary source of residue data relied ion by EPA in its cumulative risk assessment of the OPs, in the OIG's mid-2000s analysis of the impact of the FQPA and the DRI system. Hence, the alignment of basic results is not surprising.

The FS-DRI is a ratio. Values in tables and figures that follow are based on the average weight of a 4-year old child and the:

- Mean of the residue levels in all positive samples measured in milligrams of pesticide per kilogram of food (mg/kg/day)…
- Divided by the maximum residue level of the pesticide that can be present in the food without pushing the child's exposure above their acceptable, daily limit (i.e. without filling the child's "risk cup."), also measured in mg/kg/day…
- Multiplied by the percent of all samples tested with a reported, positive residue.

The larger the FS-DRI, the higher the relative chronic dietary risk. Any FS-DRI values over 0.1 in are "of concern" and values over 1.0 are highly worrisome. Values over 0.1 should trigger EPA's "level of concern" because the FS-DRI is based on the mean of the positives. For nearly all pesticide-food combinations, the upper end of the residue distribution curve contains values five to 10-fold higher than the mean residue.

A serving of an apple with a chlorpyrifos DRI value greater than 1 means that the child consuming the apple will get his/her total, maximum one-day chlorpyrifos dose from just a single serving of one apple, and one food.

Given that in the mid-1990s, chlorpyrifos residues were present in dozens of foods, and people were consuming several other OP residues daily, no one serving of a single food can take up the entire daily allowable intake of a single OP, let alone all OPs together. But this was happening with regularity in the late-1990s as the EPA started the FQPA implementation process.

Table 6. OP Residues and Relative Risks in Domestic Conventional Foods Tested by the USDA's PDP in 1996					
	Samples Tested	**Number of Positives**	**Percent Positive**	**FS-DRI**	**Share of Total FS-DRI**
Parathion-methyl	1,672	134	8%	0.783	33%
Methamidophos	2,159	241	11%	0.571	24%
Chlorpyrifos	3,365	344	10%	0.215	9%
Acephate	2,291	199	9%	0.215	9%
Azinphos-methyl	2,542	304	12%	0.154	6%
Chlorpyrifos methyl	340	249	73%	0.135	6%
Phosmet	1,411	111	8%	0.091	4%
Parathion-ethyl	761	4	0.5%	0.090	4%
Dimethoate	2,742	132	5%	0.037	2%
Other OPs	12,321	482	4%	0.104	4%
Total Positives and Aggregate DRI	**29,604**	**2,200**		**2.396**	**100%**

The PDP tested 14 foods in 1996. Across these foods, there were 2,200 samples with OP residues. Chlorpyrifos accounted for 344 of these residues, or 15.6% of the total. Aggregate chlorpyrifos FS-DRI in 1996 was 0.215, well above the level which should trigger EPA's -- and the food industry's -- level of concern. As noted before, this is because the FS-DRI value for a given pesticide-crop combination (e.g. chlorpyrifos-apples) is based on the ***mean residue level*** across all reported, positive chlorpyrifos residue levels. Hence, about one-half of the actual residue levels in a single sample of apples containing chlorpyrifos will have higher residue levels and hence, higher DRI values. Plus, **a few samples will have *much higher residue levels and DRI values*.**

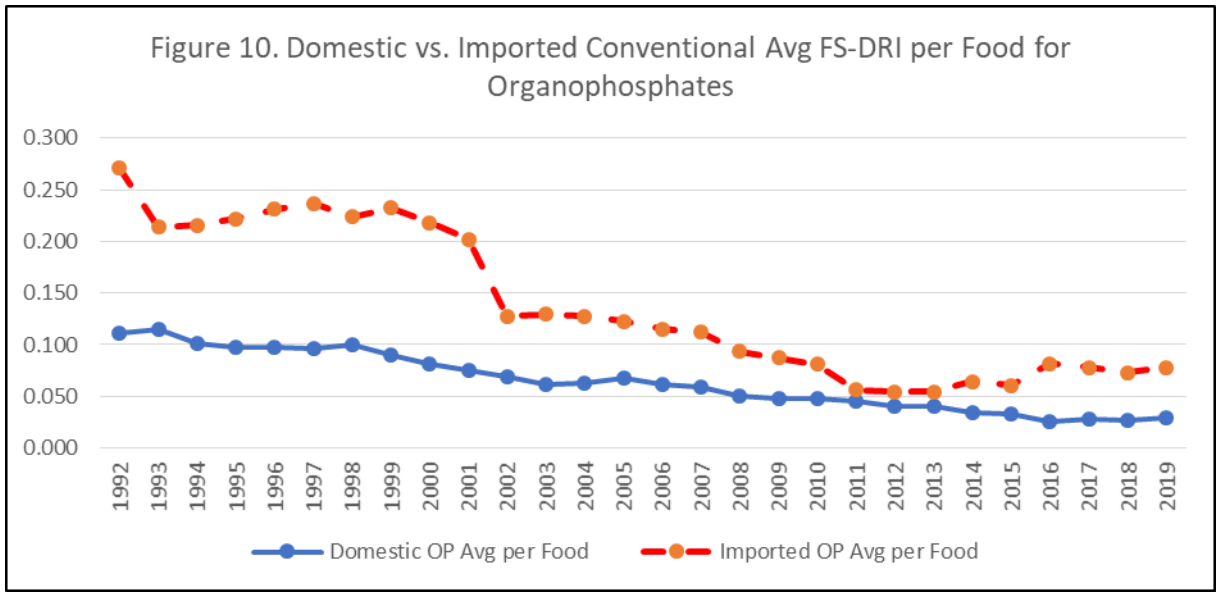
The FQPA has contributed to an overall reduction in OP residues and risk, but to a lesser extent than it should have. The early 2000s backlash from the agricultural community and pesticide industry over EPA's actions targeting the OPs and chlorpyrifos was significant and politically sophisticated. The incremental spread of insects resistant to the OPs, concern of OP neurodevelopmental impacts in the food industry and pressure to reduce farmworker exposures and poisonings, especially in California, also played important roles.

Two figures appear below. Each depicts the average, aggregate FS-DRI value per crop tested by PDP in a given year. This metric is more reliable than overall aggregate changes in FS-DRI. This is because the number of foods tested by PDP each year can vary substantially. The selection of foods year-to-year also impacts overall FS-DRI values. In some years, relatively few high-residue and risk foods are selected for monitoring, and the converse is true. But all things considered,

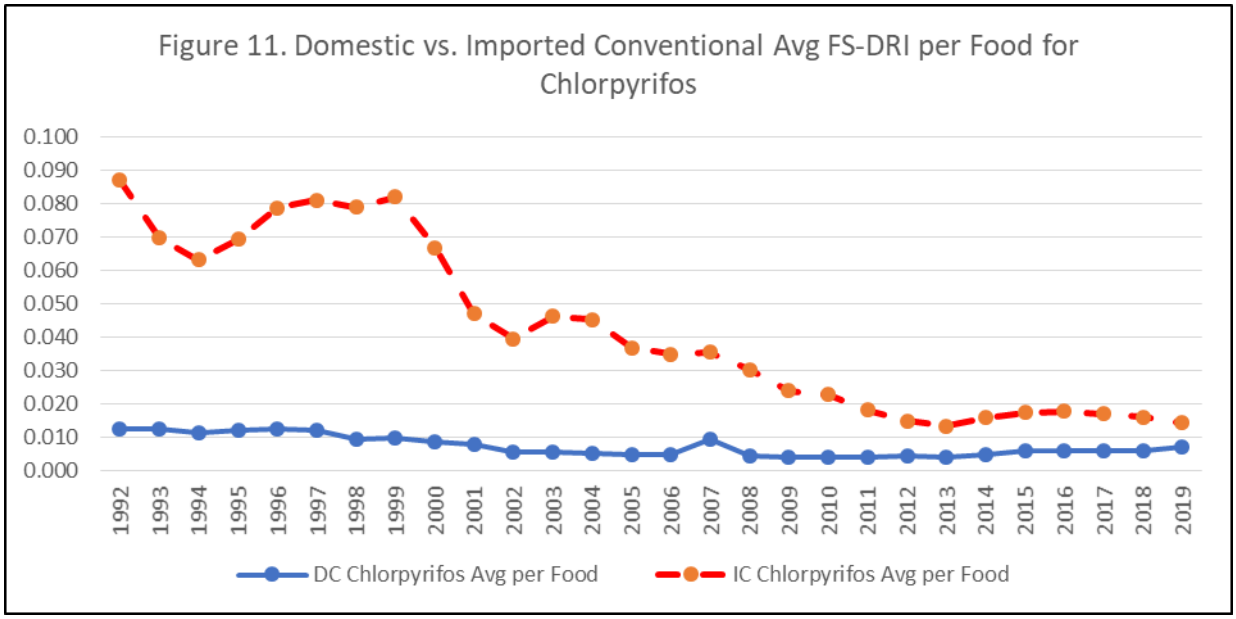
the average FS-DRI per food tested by PDP is the best metric to track trends over time.

The first figure compares changes in average aggregate FS-DRI per food tested by PDP from 1992 to 2019 in domestically grown, conventional food to imported, conventionally grown food. As predicted by me, Consumers Union and many others in the late 1990s, the EPA had to be aware -- and address -- the fact that the way the EPA was implementing the FQPA would bring about decreases in OP residues and risk in US-grown food, but not imported food, in the absence of international tolerance reductions or revocations.

The figures below bear out the validity of those concerns. Prior to passage of the FQPA, imported food contained residues accounting for about twice the overall DRI risk level compared to domestically grown food. While the trend lines have gone down in both domestic and imported foods, imports still pose about twice the risk per serving. For a variety of reasons, the discrepancy between OP risks in US-grown food and imported food will undoubtedly increase absent EPA actions to revoke more OP tolerances and an international effort to do the same with international OP Maximum Residue Levels (MRLs, the functional equivalent of EPA tolerances).



What about trends in chlorpyrifos risk levels in domestically grown versus imported food? In this case, some striking changes have occurred, and not occurred, as evident in the figure below.



First, note than in the pre-FQPA era, chlorpyrifos residues in imported foods posed 5-8 fold higher FS-DRI risk levels. The focus on chlorpyrifos risks among produce industry buyers and retailers in the late 1990s triggered the steep reduction in chlorpyrifos residues and risks in imported foods beginning in 1999.

While the FQPA did hasten the end of commercial sales for several high-risk OPs, it has had remarkably little impact on chlorpyrifos risk levels in the average food tested by PDP from four years before passage of the FQPA to 23 years after passage. The average chlorpyrifos FS-DRI risk level in foods tested by PDP over this span of time has declined less than 50%. If this figure were based on just fresh fruit and vegetable crops tested by PDP, the average FS-DRI level per food tested would be much higher, and in some years of concern, for both domestically grown and imported foods.

One point warrants emphasis. It is likely that EPA will soon revert back to its 2016 chlorpyrifos Human Health Risk Assessment, and again determine that the Agency cannot make the required FQPA "reasonable certainty of no harm" safety finding relative to chlorpyrifos tolerances. This will lead EPA to restart the tolerance revocation process. The 9th Circuit Court of Appeals is likely to impose a tight, and this time irrevocable deadline for completing this action. But this does not mark the endgame.

Without action by Codex to revoke all chlorpyrifos food use MRLs, foods shipped to the US from abroad will continue to contain chlorpyrifos residues. America's ability to detect foods contaminated with chlorpyrifos residues, and keep them out of the food supply, is limited. Enhancing this capability enough to catch even one-tenth of food shipments containing soon-

to-be-illegal chlorpyrifos residues would require changes in law, policy and federal and state funding that is simply unimaginable in light of other priorities.

Plus, absent international action, this high-risk OP will continue to poison farmworkers and rural residents the world over. It will continue to shave off a few IQ points from millions of children born every year, and increase the number of children that grow up with learning and mental disabilities and behavior problems. Their earning capacity will be much lower than it would otherwise be, and their care will pose a lifelong tax on both families and society as a whole.

Last, aquatic ecosystems and bird populations will continue to suffer as a result of chlorpyrifos use, and continued use of this broad-spectrum insecticide will erode farmers' ability to adopt and perfect prevention-based Integrated Pesticide Management systems.

For all these reasons, EPA bears an obligation to take all needed actions to end the use of chlorpyrifos not just in the US, but worldwide. The surest path to that goal is advocating revocation of all chlorpyrifos MRLs in Codex, an effort that dozens of countries, including all of Europe, will undoubtedly support.

D. Genesis of the Dow-EPA Deal

In the spring of 2000, those following the FQPA implementation process knew that EPA's decision on chlorpyrifos would soon be announced. It was widely regarded as the real acid test for how the EPA will utilize the mandates and its new authorities in the FQPA in dealing with high-risk OPs known to disrupt neurological development.

Two Dow AgroSciences products were in play. Lorsban is the trade name of the major chlorpyrifos formulations used by farmers; Dursban was the trade name used for all the home and urban formulations, many registered for use inside people's homes. While EPA was concerned about both exposures to people through the diet from residues in food, it was more acutely concerned about chlorpyrifos uses inside people's homes, and ***especially homes in which pregnant women and small children resided***.

Seven weeks before the deal was announced by EPA, Dr. Phil Landrigan, then Director of the Center for Children's Health at the Mount Sinai School of Medicine and Dr. Lynn Goldman, the EPA Assistant Administrator for Office of Prevention, Pesticides and Toxic Substances until just a few months before, were the lead authors in a letter signed by twelve "prominent scientists," according to a April 13, 2000 story by *ENN News*.

The letter urged tighter restrictions on "the pesticide chlorpyrifos, sold as Dursban," an early sign that the non-ag uses of chlorpyrifos might be the prime target of EPA risk-reduction efforts.

The letter urges EPA, in the last year of the Clinton-Gore Administration, to:

> "… tightly restrict the agricultural use of chlorpyrifos and to ban outright all applications of chlorpyrifos in residential settings….Recent studies indicate that exposure may cause severe and lasting nerve damage in infants and children."

Two weeks later, Dow AgroSciences asked EPA to cancel registrations of chlorpyrifos-methyl, the form of chlorpyrifos used to treat wheat and other grain crops in storage. In 1996, ***73% of the wheat samples tested by USDA contained residues of chlorpyrifos-methyl***, as shown in Table 3.2. The highest-risk chlorpyrifos use on the CU's list of the riskiest 125 pesticide-food combinations was also on wheat. Just this one of a few thousand uses of OPs (chlorpyrifos on wheat) accounted for over 6% of total, estimated risk from ***all pesticides in foods***, based on then-recent USDA residue testing.

Gary Hamlin, the chief media spokesperson for Dow AgroSciences at the time told *Chemical News and Intelligence* that:

> "We simply don't have sufficient sales of chlorpyrifos-methyl in the US to justify the cost of additional studies the EPA is requiring." ("Dow Agro asks EPA to cancel registration of insecticide," Glenn Hess, May 2, 2000)

Defending chlorpyrifos-methyl use in stored grain would have required new testing, but based on my extensive experience in tracking the regulation of chlorpyrifos, the cost of additional studies was not the primary reason Dow asked EPA to cancel all uses of chlorpyrifos-methyl. A more important reason was the company's need to open room in chlorpyrifos's "risk cup" in order to convince EPA to retain other, larger volume and more profitable agricultural uses. (The "risk cup" concept emerged in the FQPA implementation process. It refers to the maximum amount of a pesticide that consumers can be exposed to in a day, while still meeting the FQPA's "reasonable certainty of no harm" standard. This amount is measured in milligrams of chlorpyrifos per kilogram of a person's bodyweight, and determines the "volume" of the chlorpyrifos "risk cup.").

The Deal

I gained my familiarity with the events leading to, and in the wake of the Dow-EPA deal through a lawsuit I previously participated in as an expert witness. The case was filed by a formulator of chlorpyrifos home use products against Dow, and was triggered by the formulator's business losses in the wake of the EPA-Dow deal.

The formulator alleged Dow had not been forthcoming or honest regarding the status of negotiations over how overall risks to chlorpyrifos would be reduced, once EPA and Dow had reached their agreement. The formulator had bought several million dollars of pure chlorpyrifos, formulated it into consumer products, only to have the ready-to-sell products

returned soon after shipment, after the EPA announced its agreement with EPA to ban most chlorpyrifos home products.

The EPA media office issued a June 8, 2000 press release entitled “Clinton-Gore Administration Acts to Eliminate Major Uses of the Pesticide Dursban to Protect Children and Public Health.” After years of new testing and analysis, conflict and controversy, Dow AgroScience and EPA reached a simple and straightforward deal.

Dow AgroSciences agreed to voluntarily cancel chlorpyrifos-methyl and almost all uses of Dursban. The EPA agreed to only modest action to reduce agricultural sales and uses of Lorsban. Only one of nearly 70 ag uses was canceled (tomatoes), and tolerances were reduced in just two other crops (grapes and apples). In the release, Administrator Browner states that:

> “Now that we have completed the most extensive scientific evaluation ever conducted on the potential health hazards from a pesticide, it is clear the time has come to take action to protect our children from exposure to this chemical.”

It is important to highlight here that when the EPA made this deal with Dow in 2000, the Agency had still not been able to sort out questions over the results of the first-ever developmental neurotoxicity study that Dow had submitted to EPA in 1998. Given the long-standing concerns over prenatal chlorpyrifos exposures and neurodevelopment, the inability of EPA to factor developmental neurotoxicity into its chlorpyrifos safety evaluation cast a shadow over the whether the just-announced changes in chlorpyrifos went far enough to protect pregnant women, infants and children.

This concern and issue remains front and center as EPA considers how to alter current chlorpyrifos tolerances and registered uses.

In 2000 upon announcement of the deal, the EPA knew it would be criticized for its light touch on the dozens of high-risk agricultural uses of chlorpyrifos. The Agency also knew that Dow AgroSciences could -- and would -- delay any final actions on both the agricultural and non-ag uses of chlorpyrifos for years, in the absence of a mutually acceptable agreement.

Via the agreement reached, EPA was able to take credit for actions that essentially eliminating the highest-risk uses of chlorpyrifos as a result of the voluntary cancellation of most Dursban uses, and Dow AgroSciences succeeded in shielding its major crop markets from new restrictions that would have materially to cut sales and profit.

In addition to the above, big-ticket items in the EPA-Dow agreement, Dow also pledged to phase out all consumer market, outdoor use chlorpyrifos products sold for insect control in gardens and landscaping, and all remaining chlorpyrifos registrations were classified as “restricted use.

Reaction to the announced agreement was swift. Grower crops who pushed EPA to retain all chlorpyrifos tolerances and registered uses bemoaned the new restrictions on apples, grapes, and tomatoes, but some stated they could "live with" the changes. The V-P of US Apple Associates, Jim Cranney, said:

> "This is just another case where the EPA is cancelling pesticides because of overly conservative science policies that are impacting the industry and causing harm to apple growers." (Jeff Geiski, "Growers Seek Pest Control Options," *The Packer*, June 12, 2000)

Consumers Union issued a press release the day of the announcement. The title sums up its message: "Consumers Union Praises EPA Decision on Chlorpyrifos: New Measures will Make Foods/Homes/Schools Safer, Especially for Children, But More Needs to be Done." (CU press release, June 8, 2000) This closing comment was made by Adam Goldberg, a CU policy analyst:

> "The FQPA was perhaps the most important health initiative of the 1990s. Chlorpyrifos is a poster child for why we needed this new law and we are pleased that the EPA's decision will make everyone, particularly children, safer. We look forward to EPA action on other high risk pesticides."

Changes in Chlorpyrifos Toxicity Thresholds and Regulation Over Four Reregistration Cycles

Chlorpyrifos has been on the market for some 54 years. FIFRA requires a periodic reregistration review every 15 years to assure that all data requirements have been fulfilled, and that there are no "unreasonable adverse effects on man or the environment" from the ways a pesticide is being used in the real world.

Accordingly, chlorpyrifos should have gone through three rounds of reregistration reviews by 2020: the first in the 1980s, another by or around 2000-2004 and a third around 2015-2020. The latter two rounds occurred roughly on time. A number of assessments of chlorpyrifos uses and risks were carried out in the 1980s. So, in terms of timing, the EPA has roughly adhered to statutory mandates governing reregistration of chlorpyrifos.

The most recent reregistration cycle started in the late 2000s and is still ongoing. Since issuance of the July 2006 interim reregistration document, chlorpyrifos has been, for all intents and purposes, under perpetual reregistration review.

In the current, ongoing round of reregistration, the preliminary chlorpyrifos human health risk assessment (HHRA) was published for public comment in 2011. A first revision and response to

public comments was released as a draft 2014 HHRA. Further comments were sought and responded to in another revised chlorpyrifos HHRA issued in 2016. The proposed 2020 reregistration decision document reverted to the 2014 HHRA with very few meaningful changes.
Over the last 50 years, the science supporting chlorpyrifos risk assessment has continuously evolved. Each step forward in risk assessment methods or data has clarified some questions, but raised others. Dow in all its configurations has pursued and defended science that lowers the concern of regulators over chlorpyrifos exposures, and it has done so in three ways.

First, by conducting science and supporting independent science published in journals that supports no change, or an increase in the amount of exposure deemed acceptable relative to existing toxicological endpoints and EPA policies. These efforts have evolved on parallel tracks, one covering exposures to the general public via residues in food, and a second addressing exposures to applicators, bystanders and others who are occupationally exposed.

This body of mostly toxicological science leads to the identification of adverse impacts in animal testing. The EPA then identifies the adverse impact occurring at the lowest level across all tox studies. For this effect, the Agency identifies the "Lowest Observed Adverse Effect Level" (LOAEL) and the "No Observable Adverse Effect Level" (NOAEL; the next dose lower than the LOAEL).

These two key exposure thresholds are then used to calculate acute and chronic Reference Doses (aRfD and cRfD).

After the passage of the FQPA, the EPA began calculating acute and chronic Population Adjusted Doses (aPAD, cPAD). PADs are calculated by dividing RfDs by the applicable FQPA safety factor -- usually 10-X, but sometimes reduced to 1, and occasionally set at 3 or 5.

In the case of chlorpyrifos and other organophosphate (OP) insecticides in the 2000s, the EPA adopted a "Point of Departure" (POD) methodology for choosing the functional equivalent of a NOAEL, except the POD for the cholinesterase inhibition caused by OPs is set at 10% inhibition, instead of zero observed impact, as in the case of other NOAELs. The basis or justification for doing so, as explained by EPA, is that 10% AChE inhibition is not an ***adverse*** impact, because it is minor and reversible.

The second key component governing all pesticide risk assessments is setting the ***safety factors*** that are applied to convert a NOAEL or POD (and occasionally a LOAEL) to an acute or chronic RfD or PAD.

Over the regulatory history of chlorpyrifos, the combined safety factors applied to set the volume of the "risk cup" -- i.e. how much chlorpyrifos a person of known weight can be

exposed to in a day without triggering EPA's "level of concern" -- has ranged from 10 to 1,000. ***This 100-fold difference in combined safety factors*** explains why the back-and-forth between Dow and the EPA, the scientific community, and stakeholders has focused so much on the appropriate safety factors to apply in setting a given exposure threshold.

The above two critical parameters in the pesticide regulatory process -- the RfD or PAD, coupled with combined safety factors -- set the benchmarks dividing acceptable from unacceptable exposures. The third critical component in the risk assessment process is quantifying exposure.

Dow's efforts over the years have often been focused on convincing EPA of the need to "refine" its exposure estimates. This is done by Dow agreeing to collect and provide to the EPA more or better data on residues in food, water, other beverages, levels in the air, or dermal exposures to farmers, farm workers, applicators, or people living near treated fields.

In all rounds of chlorpyrifos reregistration since 2002, when EPA and Dow agreed to a process designed to "refine" exposure estimates, the end result has almost always been a reduction in estimated chlorpyrifos exposure levels. Such refined estimates, in turn, usually avoided imposition by EPA of stricter, mandatory provisions on labels designed to reduce occupational exposures to restore Margins of Exposure (MOEs) to 100 or greater.

The Basis of EPA Approval of Chlorpyrifos Tolerances

One way to track the basis of EPA regulation of any food-use pesticide is to track the contents of EPA memos and actions in response to tolerance petitions. Whenever EPA decides to approve a new tolerance or alter an existing one, it issues an analysis of how the change in tolerances impacts the percentage of a pesticide's "risk cup" taken up by EPA's estimate of total food and beverage exposures.

When total estimated dietary exposures after approval of requested tolerance changes is less than the level allowed by the applicable Reference Dose or Population Adjusted Dose, the EPA deems that the request for the tolerance is "supported," and hence approved.

Changes in Endpoints, Safety Factors and Risk Assessment Values over 50 Years

Table 7 tracks changes in how the EPA has regulated chlorpyrifos from the 1970s through 2020. In seven of the eight time periods in table columns, AChE inhibition was the basis for establishing exposure thresholds, and in one -- the 2016 HHRA -- the EPA made the switch to developmental neurotoxicity (DNT). The impact was tetonic.

Table 7. Changes in Chlorpyrifos Risk Assessment Parameters and Outcomes 1970s-2020								
	1970s	**Early 1980s**	**1996**	**2000**	**2011**	**2014**	**2016**	**2020**
Acute Dietary								
Basis	AChE	AChE	AChE*	AcheE	ACHE	AChE	DNT	AChE
NEL/NOAEl/BMD/ POD (mg/kg/day)	0.1	0.1	0.03	0.5	0.36	0.099	0.00017	0.099
Interspecies SF	10	10		10	10	0	0	0
Intraspecies SF			10	10	10	4	10	4
FQPA SF				10	1	10-X	10**	10-X
Total Safety Factor	**10**	**10**	**10**	**1,000**	**100**	**40**	**100**	**40**
ADI or aRfD	0.01	0.01	0.003	0.005	0.0036			
aPAD				0.0005	0.0036	0.015	0.0000017	0.015
Steady State aPAD						0.0025	0.0000017	0.0025
Dietary Exposure								
Most Sensitive Cohort	NS	NS	Infants < 1	Children 1-6	Children 1-2 year	Children 1-2 year	Children 1-2 year	Children 1-2 year
Food Intake (mg/kg/day)	0.04	0.010	0.00215	0.00041	0.000323	0.000242	0.000242	0.000242
% Risk Cup	40%	~100%	71.6%	82%	9%	9.7%	14000%	9.7%
Notes:								
* The AChE NOAEL in 1996 was based on a Dow study in human volunteers, (Coulston et al., 1972)								
** The second 10-X safety factor imposed was justified by the lack of a NOAEL for AChE in a DNT study, and so is not technically an FQPA safety factior.								
NS = Not Specified								

In the 1970s and through 1984, the chlorpyrifos NOAEL was based on AChE inhibition in lab animal studies. During this period, EPA policy called for only a single 10-X safety factor accounting for interspecies differences in the case of OP risk assessments.

Major changes unfolded in each of the chlorpyrifos HHRAs. Many nuances and details regarding how aPODs were selected are not covered herein, nor are all the details of how and why EPA adjusted safety factors across specific populations subgroups.

From 1985 through 1999, EPA regulated chlorpyrifos based on a Dow-commissioned 1972 human study focused on AChE (Coulston et al., 1972). The Agency concurred with a Dow assertion that the 0.03 mg/kg/day dose level was the NOAEL for AChE suppression. A 10-X safety factor was applied, since it was a human study, resulting in an aRFD of 0.003 mg/kg/day.

Late in 1999 and now post-passage of the FPQA, the EPA switched back to AChE inhibition in laboratory animal studies as the basis of the chlorpyrifos aPODs and aPADs in the 2000, 2011, and 2014 HHRAs. It switched to developmental neurotoxicity in 2016, and then back to AChE in 2017.

In 2011, the EPA switched to pharmacokinetic-pharmacodynamic (PBPK-PD) modeling as the basis for setting the chlorpyrifos AChE aPOD. The aPOD fell modestly from 0.05 mg/kg/day in 2000 to 0.036 mg/kg/day in 2011.

The Agency dropped the FQPA 10-X safety factor in 2011, but retained the traditional 100-X combined safety factor. The combination of these changes resulted in a 7.2-fold increase in the 2011 aPAD (volume of risk cup) to 0.0036 mg/kg/day from the 2000 value of 0.0005 mg/kg/day.

All three safety factors changed in the 2014 HHRA, compared to the 2011 HHRA. The EPA dropped the interspecies safety factor, reduced the intraspecies safety factor to 4-X (down from 10), and re-imposed the 10-X FQPA safety factor. The net result of these three changes in safety factors was a reduction in the combined safety factor in 2011 of 100, to 40 in 2014.

The EPA made another change in 2014 that resulted in shrinking the chlorpyrifos risk cup by about a factor of six. Instead of basing the aPOD on acute (1-7 day) dietary exposure, the EPA followed the advice of its Scientific Advisory Panel and switched to a 21-day, steady-state measure of AChE suppression. Research had shown that daily exposures to low-levels of chlorpyrifos incrementally increase AChE suppression up to a limit after about 21 days, after which no further suppression is observed even with rising doses.

After all these changes were made in the 2014 HHRA, the chlorpyrifos risk cup fell to 0.0025 mg/kg/day in 2014, modestly down from its 2011 level of 0.0036 mg/kg/day.

The size of the chlorpyrifos risk cup dropped by about 50% from the 1970s through 2000, and then fell a bit more to 0.0036 mg/kg/day in 2011 and a little more in 2014 to 0.0025 mg/kg/day.

Since 2000, however, the science base supporting a switch to developmental neurotoxicity (DNT) as the basis for regulating chlorpyrifos became progressively compelling. In the EPA's 2011 chlorpyrifos HHRA, the Agency acknowledged that both it, and its SAP, were convinced prenatal chlorpyrifos exposures raised the risk of DNT. In the 2014 HHRA, the EPA and its SAP had further concluded, and state clearly, that chlorpyrifos poses a risk of DNT in humans at dose levels below those necessary to trigger 10% or more AChE inhibition.

This finding would, under standard EPA policy, trigger a shift from regulating chlorpyrifos on the basis of AChE suppression to regulation based on DNT. But the EPA lacked a method to establish a chlorpyrifos aPOD based on DNT, and so continued to base the chlorpyrifos aPAD on AChE suppression in the 2014 HHRA.

The Scientific Advisory Panel had, however, suggested a way to establish a DNT-derived aPOD. The EPA continued work and established in 2015 what the Agency regarded as a sound basis for

identifying an acute Point of Departure based on DNT.

The AChE-based aPOD from the 2014 chlorpyrifos HHRA was 0.099 mg/kg/day. The new, DNT-based aPOD fell to 0.00017 mg/kg/day, ***a 582-fold reduction***.

The intraspecies, 10-X safety factor was retained, and the 10-X interspecies safety factor was dropped, since the DNT aPOD was derived from human epidemiological data. An additional 10-X safety factor was added, justified by a combination of the FQPA and the absence of a NOAEL in the chlorpyrifos DNT study.

So, the 0.00017 mg/kg/day aPOD and a combined 100-fold safety factor produced an aPAD of 0.0000017 mg/kg/day. ***The chlorpyrifos risk cup had nearly disappeared, falling by 1,470-fold from the 2014 level.*** With such a low aPAD the EPA had no choice but to initiate cancellation of all chlorpyrifos tolerances, a process that started in late 2015, but was stopped in early 2017 by the Trump EPA.

The EPA incorporates refinements in every new round of review for a major pesticide like chlorpyrifos, but the magnitude of the swing in the size of the chlorpyrifos risk cup from 2014 to 2016 to 2020 has no equal in the history of EPA pesticide regulation.

F. Quality of the Studies Supporting Chlorpyrifos Toxicology Benchmarks

Over about 15 years (1984 to 1999), the chlorpyrifos dietary Reference Dose was based on an AChE inhibition study in human volunteers conducted by Coulston et al. for Dow Chemical Company.

In the 1970s, pesticide registrants began exploring a way to reduce the standard, 100-fold safety factor applied in calculating acute and chronic Reference Doses. By conducting a toxicology study in humans, a registrant could -- and did -- argue that the 10-fold interspecies SF was no longer warranted. If successful, this argument would lead EPA to increase a pesticide's Reference Dose 10-fold, and expand the size of its risk cup by 10-fold, other things being equal.

This tactic was particularly attractive to registrants of organophosphate (OP) insecticides like chlorpyrifos. Several registrants in addition to Dow started conducting in-house AChE inhibition studies in healthy adult volunteers, under the supervision of doctors. This eventually led the EPA to convene a special Human Studies Review Board (HSRB) to address the ethical issues of using human studies to support pesticide risk assessments and regulatory reviews.

Dow's decision to conduct studies of chlorpyrifos AChE inhibition in human volunteers was not an isolated aberration, but part of an effort by the pesticide industry to find a new way to convince EPA to allow higher levels of exposure to certain pesticides.

EPA Takes Stock of Three Chlorpyrifos Human Studies

In 2010 the EPA issued a memo entitled "Chlorpyrifos: review of the Coulston (1972), Nolan (1982), and Kisicki (1999) studies with human volunteers including comments from the Human Studies Review Board Meeting (June 2009)." (John Doherty to Veronique LaCapra, January 7, 2010).

The 1982 Nolan study used only one oral dose level -- 0.05 mg/kg -- that produced at peak 89% AChE inhibition in plasma, but no inhibition of RBC AChE, the primary toxicological endpoint used by EPA in regulating OP insecticides. In a second component of the Nolan study, a 5 mg/kg dermal dose with an estimated ~1% dermal penetration produced inconsistent results that were regarded by EPA as uninformative, except providing some insight into the pharmacokinetics of oral versus dermal chlorpyrifos dosing.

This study did not produce a LOAEL or NOAEL for any type of AChE inhibition, nor any sense of a dose response. While EPA classified the Nolan study as "*Acceptable/Non-Guideline*," it's utility was limited, and EPA concluded that:

> "The study, however, should not be used for endpoint selection or for informing the uncertainty factors for risk assessment." (page 4).

In an effort to rectify some of the obvious limitations in the 1982 Nolan study, a new Dow-commissioned study was done by Kisicki et al. and submitted to the EPA in 1999. Instead of a single oral dose, phase one in the Kisicki et al. study used two doses plus control (0, 0.5 mg/kg, 1.0 mg/kg). Because no signs of AChE suppression were evident at the higher dose level, a phase two was carried out, adding a third dose level of 2.0 mg/kg. One female subject displayed depressed RBC AChE at this higher dose level, which peaked at 28% inhibition at 12 hours post-exposure.

On the basis of this finding, the EPA set the LOAEL for Kisicki et al at 2.0 mg/kg/day and the NOAEL at 1.0 mg/kg/day. The EPA again classified Kisicki et al as "*Acceptable/Non-Guideline*," but not useful for endpoint selection nor setting safety factors. The Agency noted several design aspects of the study that limited its usefulness and various other "serious problems."

But the 1972 Coulston et al. study commissioned by Dow was considered as sufficiently credible to be used as the basis for regulating dietary exposures to chlorpyrifos. The EPA first relied on the data from the Coulston et al. study to set the chlorpyrifos Reference Dose in 1984, and continued to do so into 1999. It is clear that by completion of the preliminary chlorpyrifos human health risk assessment in late 1999, the EPA had decided to no longer rely on Coulston et al. data in setting the chlorpyrifos acute Point of Departure and aPAD.

Coulston was a professor at the Albany Medical College's Institute of Experimental Pathology

and Toxicology. The 16-healthy prison inmates involved in the study were recruited from the Clinton Correctional Facility in Dannemore, N.Y., and were divided into four groups (control, 3 oral dose levels).

The male prisoners in the three treatment groups were dosed on a daily basis with chlorpyrifos (0.014 mg/kg, 0.03 mg/kg, and 0.1 mg/kg). According to Dow, the only treatment-related effect observed was depressed ChE in plasma. The degree of suppression at the 0.1 mg/kg dose level was 46% on day 6 post treatment, and 66% on day 9. According to EPA, dosing at the 0.1 mg/kg/day level was stopped by the Coulston et al. team on day 9 because AChE was depressed by 20% or more in all volunteers in the study. One person treated at the 0.1 mg/kg/day level had greater than 80% inhibition of ChE activity in plasma, clearly approaching a physiologically dangerous level. Plasma AChE was actually depressed on average at least 66% from baseline on Day 9.[1]

EPA set the LOAEL in the Coulston et al. study at 0.1 mg/kg/day based on the decrease in plasma ChE, and the corresponding NOAEL was judged to be 0.03 mg/kg/day. These thresholds were used with a 10-fold safety factor to set a chlorpyrifos Reference Dose of 0.003 mg/kg/day for purposes of dietary risk assessments. This level defined the size of the chlorpyrifos risk cup from 1984 through most of 1999.

Problems with the Coulston et al. Study

In the 1980s and 1990s the EPA regarded the Coulston et al. study as of sufficient quality to use in setting the chlorpyrifos Reference Dose. The Agency changed its position in late-1999. By 2010 the Coulston et al. study was classified by EPA as "*Unacceptable-Non-Guideline*." According to EPA:

> "Although the study contains some useful data that describes the potential for chlorpyrifos to inhibit plasma ChE in human volunteers, there are several deficiencies (incomplete details of the methodology) that precludes using the data for endpoint election for risk assessment or for informing uncertainty factors." (page 4)

The full range of problems with the Coulston et al. study would remain buried in inaccessible raw data for another decade.

A June 2020 paper was published in the peer-reviewed journal *Environment International* entitled "Flawed analysis of an intentional human dosing study and its impact on chlorpyrifos risk assessment." (Sheppard et al. Vo. 143, 105905; access at https://www.sciencedirect.com/science/article/pii/S0160412020318602)

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[1] Based on reanalysis of raw data by Sheppard et al. *Environment International*, Vol. 143, 105905; access at https://www.sciencedirect.com/science/article/pii/S0160412020318602

The lead author, Dr. Lianne Sheppard, is a Professor in the Environmental and Occupational Health Sciences Department in the School of Public Health at the University of Washington in Seattle. The two other co-authors -- Seth McGrew and Richard Fenske -- were University of Washington colleagues in the same department. Dr. Fenske had been involved with farmworker exposure and health effect studies on chlorpyrifos and other OPs for decades via a research program focused on farmworker health in the fruit growing regions of central Washington State.

Dr. Fenske was well aware of the risks posed by chlorpyrifos to those handling and applying the insecticide, or working in or near recently treated fields or blocks of fruit trees. He was among the scientists asked to serve on the EPA-convened Human Studies Review Board that assessed several human AChE inhibition studies involving OP insecticides, although not the Coulston et al. study.[2]

One unusual detail about the Coulston et al. study is noteworthy. While the Coulston-led team at the Albany Medical College conducted the experiment, the detailed statistical analysis of the AChE inhibition data was conducted by a Dow statistician named Colin Park.[3] The results were reported in an unpublished 1972 Dow report by Park submitted to EPA, along with the Coulston et al. report. Accordingly, it was Dow that carried out and is responsible for the statistical analysis that led to the study's findings as reported to the EPA, not the Albany School of Medicine team that carried out the experiment.

In my career analyzing pesticide-registrant commissioned toxicology studies, I cannot recall another example where the registrant did the primary statistical analysis of raw data generated by an external laboratory commissioned to conduct a study.[4]

Because of the importance of the Coulston et al. study in the regulation of chlorpyrifos, Sheppard and her colleagues decided to carry out an independent review of the study's data. After an extended effort to gain access to the data, Sheppard was able to secure the Park-Dow analysis and the study's raw data. The team re-analyzed the study design, conduct and results. They successfully replicated Park's results using his statistical methods. In addition, the Sheppard et al. team applied modern and more powerful statistical techniques to more

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[2] The reason the HSRB did not review Coulston et al. is curious -- Dow officially requested EPA to not include Coulston et al. in the review carried out by the HSRB, and the Agency agreed to not include it.

[3] In some places, EPA refers to the Park analysis as a separate document with a unique MRID number; the Park/Dow analysis is also referred to as an Appendix to the Coulston et al. report.

[4] I cannot say there are no other examples, but this circumstance is unusual.

accurately explore possible associations between the chlorpyrifos treatment groups and depression of plasma ChE levels.[5]

At the end of the paper's introduction, Sheppard et al. write:

> "The central questions we ask are: Why did a study so critical to risk assessment and protection of the public health never receive a rigorous review? What were the consequences of this failure to review? Are there safeguards in place to assure that evidence used in risk assessments produced and reported in accordance with accepted scientific procedures?"

Based on the Sheppard et al. teams intensive review of the Coulston et al. study data, their major findings were that:

> " 1) the design of the study reduced its power to discern a treatment effect; and 2) the researchers' omission of valid data obscured an effect that their method would have otherwise identified. Examination of the data by both the original and modern methods finds a treatment effect at levels below the dose identified by Coulston and colleagues as the NOAEL."

The *Environment International* paper describes in detail how the Sheppard-led team reanalyzed the Coulston et al. study and data, and is submitted to the docket along with these comments. It explains where and why the Coulston et al. study and Park-Dow statistical analysis deviated from accepted scientific procedures in conducting toxicology studies. The most glaring deviation from accepted data analysis protocols occurred in the way the Dow statistician Park analyzed the impact of the 0.03 mg/kg/day dose level.

Park calculated the magnitude of AChE depression for each treatment day for each person given the 0.03 mg/kg/day dose from day 1 through the final treatment day (dosing was terminated at day 22 because of the degree of ChE depression noted). So, there were 20 measures for each of the volunteers in the 0.03 mg/kg/day treatment group. For each person, there was a similar upward trajectory in the degree of depression in AChE from treatment day 1 through treatment day 20.[6]

But instead of using the average, day-21 level of ChE depression in plasma across the four

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[5] The study protocol was altered midway through the treatment period, creating complicated challenges in statistical inference. But Sheppard et al. were aware of relatively new techniques to assess such datasets, and deployed them in their re-analysis.

[6] The steady increase in AChE suppression over 20 treatment days aligns with the 21-day steady state level of AChE inhibition the EPA is now using in conducting dietary risk assessments of chlorpyrifos.

individuals in this treatment group as the impact of concern, ***Park used the average of all 20 separate, daily measures of AChE depression for each of the four individuals in this treatment group***. Given the linear dose response over the 20 days of treatment, the average level of AChE over the 20 days would obviously be well below the day 22, peak level.

The Park/Dow 21-day average method produced a mean AChE decrease of only 13%, close to the level of ChE depression EPA regarded as representative of a meaningful degree of cholinesterase inhibition (10%). But on day 21 when the 0.03 mg/kg/day treatment was ended, the Park report notes 23% plasma ChE depression, a level clearly associated with a biologically meaningful impact of the treatment. According to Sheppard et al.:

> "The levels of [plasma ChE] depression observed in this study would have triggered workplace investigations under California regulations during the 1970s."

The Sheppard team also explains the importance of the Dow statistician's decision to ignore valid data that should have been included in the statistical analysis of AChE inhibition. The team writes:

> "The inconsistency in selection of [baseline] data for the analysis -- use of two baseline measurements for the 0.1 mg/kg and 0.14 mg/kg dose groups, but only one baseline measurement for the 0.03 mg/kg does group -- is unexplained and frankly inexplicable. All of the pre-treatment values for the 0.03 mg/kg [group] were valid measurements. Removal of 10% of the valid [baseline] data reduced the power of the analysis, leading to the incorrect conclusion that there was no statistically significant difference between this [0.03 mg/kg/day] treatment group and its concurrent controls."

Sheppard et al. show that if these data had been included and analyzed with proper statistical methods, the primary finding of the study would have been invalidated. ***Even worse, the NOAEL of 0.03 mg/kg/day reported by Park and Dow was not even the LOAEL.*** Sheppard et al. concluded that AChE activity was also depressed in the lowest dose tested of 0.014 mg/kg/day, and go on the state:

> "Such an omission of valid data without justification is a form of data falsification that violates all standard codes of ethical research practice and is classified as outright research misconduct."

Instead of the 0.03 mg/kg/day NOAEL reported by Park and Dow, the lowest dose tested, 0.014 mg/kg/day, was the LOAEL.

In setting a Reference Dose based on such results, EPA policy is clear. The Agency would likely have used a 100-fold combined safety factor composed of: (a) a 10-X safety factor to account for intraspecies variability, and (b) an additional 10-X for the lack of a NOAEL.

Accordingly, based on a proper statistical analysis of Coulston et al. and adherence to EPA

policy when a toxicology study fails to produce a NOAEL, the chlorpyrifos Reference Dose should have been set by EPA at 0.00014 mg/kg/day in the mid-1980s, instead of at 0.003 mg/kg/day. This difference is substantial, and would have led the EPA to set the chlorpyrifos Reference Dose for dietary risk assessment purposes at a level 21-times lower than what they did (0.003 mg/kg/day divided by 0.00014 mg/kg/day).

Setting chlorpyrifos's Reference Dose at 0.00014 mg/kg/day in the mid-1980s would almost certainly have resulted in cancellation of many chlorpyrifos food use tolerances. ***As of 1996, EPA had estimated chlorpyrifos dietary exposure at 0.00215 mg/kg/day, a level that would have exceeded the chlorpyrifos Reference Dose by over 15-fold (0.00215 mg/kg/day divided by 0.00014 mg/kg/day)***.

Even after progressive "refinements" by EPA in estimated dietary exposure levels to chlorpyrifos in 2000, 2011, 2014, 2016, and 2020, the Agency's estimates of dietary intake of chlorpyrifos would have remained well above this acceptable level.

Moreover, recall that the 1996 FQPA required EPA to assess all organophosphate insecticide dietary exposures together, since they pose risks through a common mechanism of action -- plasma and RBC AChE inhibition. For this reason, the combined-OP risk cup into which chlorpyrifos would have to fit would be mostly filled by residues of the approximate 25 other OPs that farmers were still routinely spraying on most human-food crops.

Last, had EPA decided to continue to base chlorpyrifos based on AChE suppression in the Coulston et al. study beyond FQPA passage in 1996, the Agency would have applied the FQPA 10-X to the aRfD of 0.00014 mg/kg/day, producing an aPAD of 0.000014 mg/kg/day for dietary exposure and risk assessment. ***An aPAD at this level would have almost certainly resulted in cancellation of all chlorpyrifos tolerances and food-use registrations.***

Dow Submits the First Chlorpyrifos DNT Study in 1998

Passage of the FQPA in 1996 was an historically significant development in pesticide law and regulation. Its primary goal was to focus the EPA's attention on pesticides that might be disrupting fetal development and/or impairing the ability of newborns to grow up and become healthy adults.

Without doubt, the adverse impact of pesticides on neurological development was the most pressing concern that motivated Congress to pass the FQPA. This is why chlorpyrifos was so prominently featured in the 1993 NAS report, in Congressional deliberations and debate leading to the passage of the FQPA, and in the EPA's efforts to implement the FQPA's important new provisions. ***It is also why so much was riding on the results of, and conclusions drawn from the first EPA-guideline developmental neurotoxicity done on chlorpyrifos, a study Dow submitted to the EPA in 1998.***

The long-awaited chlorpyrifos DNT study was carried out by Argus Research Laboratories under contract with Dow. Hoberman is listed as the author of the unpublished Dow study MRID #44556901 (1998), "Developmental Neurotoxicity Study of Chlorpyrifos Administered Orally via Gavage to Crl:CD BR VAF/Plus Presumed Pregnant Rats: Lab Project Number 304-001: K-044873-109."

Despite the importance of this study, it is barely mentioned in the 2002 chlorpyrifos IRED. In the 2011 updated chlorpyrifos HHRA in the section on toxicology data deficiencies, the EPA writes:

> "870.6300 [DNT study requirement]: Developmental Neurotoxicity (MRID 4456901). While the offspring NOAEL and LOAEL have not yet been identified for this developmental neurotoxicity study, it is recognized that the study was well-conducted according to Agency guideline [section symbol] 83-6, and under GLP regulations. Remaining questions can be resolved with additional information and statistical analysis, but there are no outstanding concerns regarding the quality of the animal data. The study is currently classified as 'guideline-unacceptable, but upgradeable'. The study may be upgraded to 'acceptable' pending submission and review of additional morphometric data for PND 66 low-dose females (parietal cortex and hippocampus measurements) (S. Makris, 3/3/00)." (2011 HHRA, page 17)

Giving the importance of this study in the regulation of chlorpyrifos, and the intensity of the search for clarity relative to the capacity of this insecticide to trigger DNT, it is striking that more than 10 years after the Hoberman study was submitted to the EPA, ***the Agency still had not been able to determine what it showed, and was still waiting for additional data it had requested from Dow to support its analysis.***

In the first lengthy discussion of chlorpyrifos DNT in the 2014 EPA human health risk assessment (HHRA) summary document, about 6.5 pages are devoted to multiple studies reporting evidence of DNT effects in animal studies. The EPA had identified at the time 31 papers from 14 laboratories that carried out relatively low-dose DNT studies (i.e. doses not over 1 mg/kg/day).

Based on the EPA's review of these papers, and consistent with judgements and insights offered at SAP meetings in 2008 and 2012, the Agency wrote in the 2014 HHRA:

> "In spite of considerable differences in study design, upon review of the published literature a pattern of neurodevelopmental adverse outcomes emerges…***the consistency of finding neurological effects is striking***…At both the 2008 and 2012 SAP meetings, the Panel agreed that exposure to doses of 1 mg/kg/day and greater, during the developmental period, produced significant and long-term effects on animal behavior." (page 26)

The 1998 Dow DNT study is not mentioned in this 6.5 page section of the 2014 chlorpyrifos HHRA. Perhaps even more surprising, the Hoberman (1998) DNT study is not mentioned once, nor referenced in the 95 page "Appendix I: Evaluation of Experimental Toxicology Data" compiled by EPA as part of the 2014 HHRA. ***The long awaited, highly anticipated Dow chlorpyrifos DNT study had seemingly become by 2014 out of sight, out of mind.***

Problems with the 1998 Dow Chlorpyrifos DNT Study

There are two explanations for the minimal impact of Hoberman (1998) on chlorpyrifos regulation, despite its direct focus on the endpoint of greatest concern at the center of over 20-years of intense scientific exploration and controversy.

There were clearly problems and gaps with the Hoberman study that the EPA was still hoping to rectify 15 years after the Agency received the study. Recall that 15 years had passed since EPA receipt of Hoberman (1998) and the Agency's 2014 acknowledgement that the study was possibly upgradeable, if missing data were provided.

Why had these data not been provided by Dow much earlier so that the EPA's questions could be resolved, and so that this critical study could be used in setting the DNT point of departure for chlorpyrifos?

Why Dow failed to provide EPA the data it had requested remains a mystery, but the impact of this failure is clear -- EPA moved on and did not look anydeeper into what the Hoberman study had actually shown regarding chlorpyrifos DNT.

The EPA moved on from Hoberman for three reasons. First, because the Agency had received several dozen newer, likely more sensitive DNT animal studies from numerous academic laboratories. Much time and effort was needed to review and incorporate the findings of these newer studies in the Agency's chlorpyrifos HHRA.

Second, just a few years after receipt of Hoberman, a series of high-quality human epidemiological studies were published reporting statistically significant -- and according to EPA and its SAP, generally consistent -- associations between prenatal chlorpyrifos exposures and DNT outcomes in children born to exposed women. The availability of such high-quality human epidemiological data reduced EPA's reliance on animal data.

Third, the EPA had lingering doubts about the completeness of the Hoberman study data, as shared with EPA. Something was clearly missing. Despite Agency efforts over many years, two SAP meetings, and multiple discussions with Dow representatives, the EPA still did not regard the Hoberman study as sufficiently reliable to use in setting the chlorpyrifos PNT Point of Departure and exposure thresholds.

The plausibility of the third point is heightened by an important fact. I am aware of no written evidence that Dow provided EPA with the Hoberman data it had requested, the data EPA needed to upgrade the study to "Guideline acceptable." Dow's failure to provide these data suggests that, for some reason, the company did not want EPA to have access to the information.

Independent Analysis of Hoberman Raw Data Reaches Surprising Conclusions

An open-access paper entitled "Safety of Safety Evaluation of Pesticides: developmental neurotoxicity of chlorpyrifos and chlorpyrifos-methyl" was published November 16, 2018 in the peer-reviewed journal *Environmental Health* and is submitted to the docket along with my comments. (Mie et al. 17:17, accessible at https://ehjournal.biomedcentral.com/articles/10.1186/s12940-018-0421-y)

The lead author was Dr. Axel Mie, a scientist affiliated with the Karolinska Institute in Stockhom, Sweden, and an expert for plaintiffs in this litigation. Mie's co-authors included Dr. Christina Ruden, a statistician at another Swedish academic institution, and Dr. Phillipe Grandjean, a professor in the Department of Public Health in the University of Southern Denmark and in the Chen School of Public Health at Harvard University.

The team had been tracking for years the difficulties and controversies arising from the ongoing reregistration review of chlorpyrifos in Europe. They recognized the importance of the 1998 Hoberman DNT study on chlorpyrifos, and the 2014 Dow-sponsored DNT study on chlorpyrifos-methyl.[7]

Dr. Mie embarked on a multi-year effort to obtain the raw data for these two DNT studies and was eventually able to secure it from a European regulatory authority via a public records request. The team explains why it took on the project in the paper's "Background" section:

> "Independent academic studies and industry-sponsored toxicity studies may lead to fundamentally different conclusions, as is the case for chlorpyrifos."

After listing the various types of data pointing to a linkage between prenatal chlorpyrifos exposures and DNT outcomes, Mie et al. write that:

> "…the evidence points to adverse health effects of chlorpyrifos exposure on the developing nervous system, associated with lowered IQ at school age, at current levels pf exposure. These outcomes have been observed at exposure levels far below those recognized to cause effects on brain development in an industry-funded developmental neurotoxicity (DNT) study commissioned for regulatory purposes." (Mie, in reference to

[7] Maurissen et al. chlorpyrifos-methyl study published in *Toxicology Science* 2000 Vol. 57(2): 250-263

the unpublished Hoberman (1998) chlorpyrifos study)

In the team's initial assessment of the Dow-commissioned chlorpyrifos DNT studies, possible effects were apparent on the height of the cerebellum. This adverse effect is an indicator of possible damage to the architecture of the developing brain, changes that both EPA and its SAP knew would likely to lead to life-long, negative consequences.

Hoberman (1998) treated rat pregnant rats from day 6 of gestation through post-natal day 11 with varying doses of chlorpyrifos (0, 0.3 mg/kg/day, 1 mg/kg/day, and 5 mg/kg/day). Hoberman concluded that there were no adverse effects at the two lower doses, but multiple signs of DNT at the high dose level (5 mg/kg/day). These included reduced brain weight, and lessened brain size at PND 6, but not on PND 65. Hoberman attributed these adverse impacts not to DNT, but to malnutrition in the pups, a secondary effect caused by the toxic effects of chlorpyrifos on the dams.

Hoberman further argued that the average impact on overall brain size was similar to the overall impact on brain weight. EPA regarded this analytical comparison to be an "inappropriate and inconclusive manipulation of the data." (EPA [2000], https://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/059101/059101-427-03-03-2000.pdf)

Mie et al. wondered whether these average and overall impacts might be masking significant impacts on certain regions of the brain, and in particular the cerebellum, the region that had initially caught their attention. Recall as well that in the 2014 HHRA, EPA included among the Hoberman DNT study inadequacies, the Agency's need for "…additional morphometric data for PND 66 low-dose females (parietal cortex and hippocampus measurements)."

These are among the data that would be essential to assess inconsistent growth patterns in specific brain regions. The EPA staff scientist that carried out the review of Hoberman recognized problems with the statistical analysis in Hoberman, and highlighted the need for supplemental data to further explore changes in brain architecture hinted at by the data in Hoberman. (March 2, 2000 Memo from Susan Markris, Tox Branch to Deborah Smegal, Reregistration Branch; accessed from EPA chlorpyrifos archive)

According to this March 2000 memo:

> "One of the outstanding critical issues concerned review of the morphometric data for Subset 1 (PND 12) and Subset 4 (PND 66) males and females in the developmental neurotoxicity study with chlorpyrifos. These issues originated with the manner in which the statistical analyses of the brain measurements were presented and interpreted." (Makris memo, page 2).

Critically, according to the Makris review, there were clearly signs of developmental perturbations early in life in adult offspring (PND 66). Makris concludes that:

> "…adverse findings in the adult (~PND 66) offspring, i.e. alterations in motor activity, auditory startle response, and brain structure (decreased measurements of parietal cortex and hippocampal gyrus, in the absence of brain weight deficits) can be interpreted to represent the long-term sequellae of developmental exposure to chlorpyrifos." (Page 4)
>
> "…the morphometric findings in the parietal cortex of female offspring indicate a treatment-related effect at the mid- and high-dose levels (1 and 5 mg/kg/day)…The differences between the mid- or high-dose group means are between 3 to 4 raw units [of measurement, 24_{um}), and thus at least 3 times the value of a minimal threshold for detection." (page 10)
>
> "***In conclusion, the morphological alternations in the parietal cortex of female offspring at PND 66 are both statistically and biologically significant at the mid- and high-dose levels and are a clear indication that the structure of the brain has been altered by treatment***." (Page 11)

After noting several irregularities in how Dow had conducted the statistical analysis of changes in brain growth patterns, the Makris analysis states that:

> "These [Dow] comparisons, however, are an inappropriate and inconclusive manipulation of the data, since a numerical value derived from averaging the relative values for all external and internal morphometric measurements is not meaningful. ***Such a derived number would not evaluate the differences between the alternations in growth patterns or disruption in discreet areas of the brain, which could be differentially altered as an adverse consequence of treatment***." (Page 11)

The highlighted sentence in the Makris review shows clearly that she suspected there might have been differential growth patterns in various parts of the brain. But to prove or discount such differences, EPA had identified the need for Dow to submit additional data, and the Agency had requested the data.

But because Dow never, as far as I can tell, provided the data to EPA, the Agency's deeper analysis of this critical study fell by the wayside. As a result, this critical, well-conducted study was not used to set the chlorpyrifos DNT Point of Departure, despite EPA determining treatment-related effects had occurred at the upper two of three dose levels.

The significance of this series of developments becomes clear in the wake of the results of the Mie et al. re-analysis of the rat pup brain data. Mie et al. properly compared the weight of each brain region relative to total brain weight, following EPA guidelines and widely accepted

statistical tests. They did this to determine whether there were shifts up or down in growth rates across brain regions, what Makris referred to in her review as a "***differentially altered***" pattern of growth. Mie et al. report:

> "Our re-analysis of the raw data shows that when expressed relative to brain weight, cerebellum height in PND 11 pups is decreased by 8-11% in low and mid-dose groups in both sexes, as compared to controls."

Moreover, Mie et al. report that the "…low and mid-dose effects are highly statistically significant, consistent in both sexes, and observed in the absence of general maternal toxicity, hence indicating the presence of DNT at all dose levels tested."

While the Makris review highlighted evidence of a treatment-related effect in the two highest dose groups, Mie et al. recognized significant effects even in the low-dose treatment group.

Accordingly, when analyzed in accord with accepted statistical procedures, the Hoberman study LOAEL is the lowest does tested -- 0.3 mg/kg/day.

In light of the absence of a NOAEL in this rat study, the EPA would typically apply a 1,000-fold safety factor in converting the LOAEL to an acute Reference Dose for use dietary risk assessment -- 100-fold for the interspecies and intraspecies uncertainty, and an additional 10-X for the absence of a NOAEL.

The result would be an aRfD of 0.0003 mg/kg/day. But given that EPA would have reached this judgement after the passage of the FQPA, the Agency almost certainly would retained the FQPA 10-X safety factor, based on clear adverse impacts on brain development in the pups. This would result in a 10,000-fold total safety factor, and an acute PAD of 0.00003 mg/kg/day.

Given the significant uncertainty in the early 2000s over the level at which chlorpyrifos induces DNT effects following prenatal exposures in both lab animals and humans, it is unlikely the EPA would have dropped the added FQPA 10-X safety factor in converting the DNT LOAEL to an acute PAD. It is also not likely the EPA would have considered the added 10-X for lack of a NOAEL to obviate the justification for retaining the FQPA 10-X; these two added safety factors are appropriate for separate reasons.

Last, recall that EPA regarded the 1998 Hoberman chlorpyrifos DNT study to be sound and conducted in accord with GLPs, or in EPA's words "it is recognized that the study was well-conducted according to Agency guideline".

Dow would have known in the late 1990s and early 2000s that if the EPA was able to identify a lower, DNT-based LOAEL in the data from the Hoberman study compared to the lowest AChE-inhibition based LOAEL, the Agency would have used the DNT results in regulating chlorpyrifos.

But for this to happen, the chlorpyrifos aPAD based on DNT effects would have to be lower than the aPAD based on AChE suppression. ***And indeed it would have been -- by 120-fold***.[8]

The DNT-based aPAD would have resulted excessive dietary exposures by a wide margin (8-fold too high). This finding would have led to significant reductions in chlorpyrifos use, and ***almost certainly the revocation of all tolerances on major children's foods, including grapes***.

Had Dow provided the extra data EPA had requested in the early 2000s, or if Dow had carried out a proper statistical analysis of the DNT data from the Hoberman study prior to submission in 1998, the EPA would have determined in the 2000s that its highly refined estimate of dietary exposure was far higher than what chlorpyrifos's risk cup could accommodate. Tolerance reductions and revocations would have occurred as a result.

Occupational and Bystander Exposure and Risks

EPA regulates occupational and bystander risk by quantifying dermal and inhalation exposures. The term "bystander" in the context of EPA human health risk assessments (HHRAs) refers to people spending time near or in treated fields or areas, but not working in the fields nor applying pesticides.

In general, the EPA has more limited tools to mitigate bystander exposures, since it cannot reach nor require bystanders to wear the personal protective equipment (PPE) that applicators and other people subject to occupational exposures are required to use on pesticide product labels.

EPA's primary exposure-reduction tool to mitigate bystander exposures is establishing buffer strips between the edge of a treated field and where bystanders might frequent. Pesticide applicators can be required via product labels to assure no one enters a buffer strip area until a specified time period after an application is made. Buffer strip requirements usually are accompanied by a requirement for whoever is responsible for an application to post signs marking the edge of a buffer strip. The signage must warn people passing by not to enter the area until a specified day and time, and in California, signs must do so in English and Spanish.

Over the years, the EPA has required or identified the need for buffer strips between the edge of a fruit and vegetable fields sprayed with chlorpyrifos that range from 10' wide to several hundred feet. The width of required buffer strips is a function of chlorpyrifos application rates and how the insecticide is applied (e.g. groundboom sprayer versus airblast sprayer).

[8] 2011 HHRA aPAD of 0.0036 mg/kg/day divided by the DNT-derived aPAD of 0.00003 mg/kg/day.

The EPA released an updated chlorpyrifos human health risk assessment in 2016 calling for a buffer strip of at least 300 feet around treated fruit and vegetable fields in order to protect against adverse neurodevelopmental outcomes. The impracticality of this requirement with real world chlorpyrifos application scenarios was one of the reasons the EPA decided to move forward in 2016 with the cancellation of all chlorpyrifos food uses.

The Lorsban labels on chlorpyrifos products in the last 10 year contains language addressing buffer zones when an application is made in or near a "sensitive site." Most labels define a sensitive site as:

> "…areas frequented by non-occupational bystanders (especially children.) These include residential lawns, pedestrian sidewalks, outdoor recreational areas such as school grounds, athletic fields, parks and all property associated with buildings occupied by humans for residential or commercial purposes. Sensitive sites include homes, farmworker housing, or other residential buildings, schools, daycare centers, nursing homes, and hospitals." (Specimen Lorsban Advanced label revised 06-10-14)

Setting Occupational and Bystander Exposure MOEs

The MOE for occupational and bystander exposures is derived by dividing the applicable Point of Departure (POD) based on toxicology studies by estimated exposures. The Point of Departure is the lowest level the EPA expects adverse impacts to occur based on animal studies.

When exposures are 100-fold or more lower than the POD (10-fold in the case of a human-study based POD), the EPA deems the exposures acceptable.

In the 2011, 2014, 2016 and 2020 HHRAs, EPA estimated excessive occupational and/or bystander exposures in many scenarios involving applications of chlorpyrifos using a groundboom or airblast sprayer. The Agency was able to reach MOEs of 100 or higher only with reduced application rates in conjunction with extensive PPE requirements and engineering controls (e.g. a steel-glass cab for the applicator to sit in, while wearing a respirator).

Mitigating Occupational and Bystander Risks

Starting with the 2011 chlorpyrifos HHRA, all chlorpyrifos risk assessments have pointed to potentially excessive risks to workers and bystanders in and around chlorpyrifos treated fields and orchards. In an effort to mitigate such risks, EPA had to come up with a quantitative estimate of the combined effects of the multiple exposure-reduction measures it was incrementally adding to Lorsban product labels.

This daunting task led EPA to produce and refine over several years a surrogate table of expected reductions in exposure as a function of combinations of exposure-mitigation

interventions.[9] This surrogate table of estimated reductions in exposure allowed EPA to estimate in the 2020 HHRA cycle the impact of dozens of combinations of PPE and engineering controls across 758 worker, applicator and bystander exposure scenarios for chlorpyrifos.

In the case of several hundred of these scenarios, EPA could not identify any combinations of PPE and engineering control sufficient to restore MOEs to the acceptable, >100 level.

Important questions linger, as well, over the differences in chlorpyrifos worker exposures and risk stemming from the spraying of formulated chlorpyrifos products, in contrast to pure technical chlorpyrifos. Virtually the entire toxicity database supporting chlorpyrifos uses and acceptable occupational exposures is derived from studies using pure technical chlorpyrifos.

Because of the adjuvants and surfactants incorporated in formulated chlorpyrifos products, the rate of dermal absorption associated with chlorpyrifos formulations as applied are almost certainty much higher than EPA's current estimates. This is a serious deficiency in the EPA's current chlorpyrifos HHRA and should be rectified and addressed in detail, if he EPA decides to allow continued use of chlorpyrifos products.

G. Conclusions

The toxicological basis of chlorpyrifos regulation has been depression of RBC or blood plasma cholinesterase activity. Throughout this period and across many changes in risk-assessment protocols, methodologies, and terminology, the EPA has regarded 10% AChE suppression as the threshold between no meaningful effect, and a biologically relevant, treatment-related effect.

In 2015 and through early 2017, the EPA decided the weight-of-evidence supported a switch to developmental neurotoxicity (DNT) as the basis for regulating all routes of chlorpyrifos exposure. As a result, the acceptable level of dietary exposure to chlorpyrifos fell by 1,470-fold and EPA concluded that chlorpyrifos food uses could no longer be supported.

To my knowledge, ***this was by far the largest decline in a pesticide's acceptable daily intake in the history of EPA pesticide regulation***.

It is also why EPA started the process in 2015 to revoke all chlorpyrifos tolerances as incompatible with the FQPA's "reasonable certainty of no harm" standard.

Soon after confirmation of the Trump-appointed Administrator of the EPA in 2017, the EPA disavowed the results of the 2016 chlorpyrifos Human Health Risk Assessment (HHRA). The

[9] Access the surrogate tables at https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/exposure-surrogate-reference-table-pesticide-risk .

Office of Pesticide Programs was directed to revert to the regulatory status quo of 2014, and did so.

This was by far the largest increase in a pesticide's acceptable daily intake in the history of EPA pesticide regulation.

Then-EPA Administrator Pruitt explained that more science was needed to better understand the impact of prenatal chlorpyrifos exposures on DNT. At the time of this reversal, EPA pointed to no new science or insights alleviating the Agency's stated concerns in 2015 and 2016. The decision was political and likely motivated, to some unknown extent, by sizable donations from Dow Chemical Company and/or its officers to the Trump inaugural committee and other Trump-affiliated political allies and organizations.

Since 1966, chlorpyrifos has been regulated on the basis of AChE inhibition, despite EPA's decision to switch to developmental neurotoxicity in 2015. Since there were no impacts on chlorpyrifos's tolerances or registrations brought about in 2015-2017 period based on the switch to DNT, AChE inhibition has remained the foundation of chlorpyrifos regulation.

Accordingly, all routes of chlorpyrifos exposure to all people have been regulated over the last 50-plus years on the basis of cholinesterase inhibition. A diversity of mouse, rat, dog, and human studies have served as the basis of chlorpyrifos acute and chronic Reference Doses (aRfD, cRfD) and Population Adjusted Doses (aPAD, cPAD).

While EPA made the scientific judgement in 2015 that chlorpyrifos should be regulated based on DNT, this decision has yet to be translated into changes in tolerances or chlorpyrifos product labels.

Solid Studies But Skewed Statistics Kept Chlorpyrifos on the Market

Regulators in both EPA and California's Department of Pesticide Regulation (DPR) have struggled to make sense of the enormous and continuously growing dataset on chlorpyrifos toxicology and human health risks. Their task has been made harder by the poor quality, gaps, and misleading statistics in key Dow studies submitted to EPA and DPR.

The Dow-commissioned, 1972 Coulston et al. study of AChE suppression in human volunteers supported chlorpyrifos regulation for about 15 years, 1984 through 1999. A Dow statistician, Dr. Park, conducted the detailed statistical analysis of the raw data generated by the Coulston et al. study.

Park concluded that the highest of three dose levels (1.0 mg/kg/day) was the study LOAEL, and the mid-dose of 0.3 mg/kg/day was the NOAEL. This was the value EPA used in setting the chlorpyrifos aRfD at 0.03 mg/kg/day, and the basis for EPA approving chlorpyrifos tolerances

and reregistering uses.

The Sheppard et al. re-analysis of the 1972 Coulston et al. study in human volunteers castes a dark shadow over 50 years of EPA and DPR regulatory risk-assessments focused on AChE inhibition. Their analysis showed that the human LOAEL was 0.014 mg/kg/day, the lowest dose level in the study, ***and 71-times lower than the Dow-reported LOAEL***.

The proper LOAEL in the Coulston et al. study, as identified by Sheppard et al., would have led to a much lower, EPA-set aRfD for chlorpyrifos in the 1970s. It may well have led EPA to revoke most or all chlorpyrifos tolerances and end many food uses over 40 years ago.

The fact that it took so long for the flaws in the Dow-reported results of the Coulston et al. study to be recognized is a testament to the effectiveness of Dow's efforts to obscure the actual degree of AChE suppression evident in the study's raw data.

The 1993 NAS report *Pesticides in the Diets of Infants and Children* and passage of the FQPA in 1996 channeled focus among scientists and the public on the impacts of chlorpyrifos on children's neurodevelopment. For this reason, there was intense interest in the results of the first guideline-DNT study conducted by Dow on chlorpyrifos in rats.

The Hoberman DNT study in rats was submitted to EPA in 1998, right in the midst of intense focus on the implementation of the FQPA. Dow had reported the high dose level in Hoberman as the LOAEL, rendering the mid-dose as the NOAEL and basis for setting the chlorpyrifos DNT aRfD and aPAD. The end result would have been little or no change in chlorpyrifos tolerances and uses, because the Dow-identified, DNT-based aPAD would have been about the same as the then-current aPAD based on AChE inhibition.

The EPA's scientists recognized problems with Dow's statistical analysis and conclusions. The Agency rejected Dow's analysis. The EPA was unable to determine the LOAEL and NOAEL for DNT effects in the Hoberman study and the Agency's reviewer was sharply critical of decisions Dow had made in carrying out the statistical analysis.

Even a hint of DNT effects at either the mid-dose or lowest dose tested would have been regarded within Dow as unwelcomed.

The Mie et al. analysis of the Hoberman raw data identifies the lowest dose tested in Hoberman as the LOAEL. The statistical tests conducted by Mie et al. are aligned with EPA guidelines and adhere to widely acceptable scientific practice. In addition, and as EPA had expected, Mie et al. conclude that all treatment groups in the Hoberman displayed treatment-oriented DNT effects, and hence the study did not identify a NOAEL. Had the EPA done the same analysis as Mie et al., the Agency would have reached basically the same conclusion. It would have set a DNT-

based aPAD for chlorpyrifos orders of magnitude lower that the existing aPAD based on suppression of AChE. This would have almost certainly led to an end of all chlorpyrifos food uses by the end of the 2000s.

Dow's successful masking of adverse findings in the Coulston et al. and Hoberman studies prevented much more substantial restrictions on chlorpyrifos's agricultural uses than occurred as a result of the Dow-EPA deal in 2000.

If EPA and DPR regulators had understood what these studies actually show, few if any uses of chlorpyrifos would have remained on the market beyond the late 2000s.

Were There Effective and Affordable Alternatives to Chlorpyrifos?

In the two decades after the passage of the FQPA, the pesticide industry discovered and gained registrations of 59 OP alternatives. Many had gained accelerated registration as a result of EPA classification as a reduced risk, safer or biochemical insecticide.

Of these 59 newly registered insecticides since 2000, at least one-half are registered for many or most of the same crops as chlorpyrifos. More than a dozen have earned market shares in multiple crops that dwarfs the market share of chlorpyrifos.