US Environmental Protection Agency
Office of Pesticide Programs

A Review of the Relationship between Pyrethrins, Pyrethroid Exposure and Asthma and Allergies

September 2009, corrected version

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Abstract

In the current review, EPA used a weight of evidence approach to determine whether an association exists between pyrethrins/pyrethroid exposure and asthma and allergies. More explicitly, the current review included data from both animals and humans. The Agency considered animal data regarding mode of action; target organ of toxicity; acute inhalation and dermal irritation; and sensitization. The Agency also considered human data including incident data from several sources and epidemiology studies. In the weight of evidence analysis, EPA considered consistency, reproducibility, temporal and dose concordance, and biological plausibility of the effects reported in each data set and across all data sets. Comparisons of health effects profiles were also conducted between pyrethrins/pyrethroid products and other insecticides when possible to determine whether exposure to this class of pesticides elicits a heightened or unique respiratory response compared to other insecticides. This approach is predicated on the premise that an integrative assessment is more informative than what any single dataset or study could provide; and that fundamental biological mechanisms of disease outcome are concordant across species.

Based on the current analyses, the Agency concluded there is no clear and consistent pattern of effects reported to indicate conclusively whether there is an association between pyrethrins/pyrethroid exposure and asthma and allergies. The Agency is not requiring additional warnings or label statements specific to asthmatic or allergic individuals on pyrethroids and pyrethrins end-use products, nor is the Agency requiring additional data from pyrethroid registrants at this time. However, in order to clarify the issue of possible correlation between use and incidents, the pyrethrins registrants have committed to a product stewardship program that will include a prospective in-depth follow-up of reported pyrethrins incident cases. The Agency will review the pyrethrins incident data as it is submitted. If the Agency identifies discrepancies or trends in the data that differ from the incident data considered in this review, the Agency will consider requiring additional or similar data from the pyrethroid registrants.

I. Introduction

On July 30, 2008 the Center for Public Integrity (CPI) published an article titled *'Safe' Pesticides Now First in Poisonings*, which focused on human incidents and exposure to pyrethroid and pyrethrins pesticide products. The article asserts that human incidents associated with pyrethroid and pyrethrins products have increased sharply over the past decade in both number and severity. CPI cites the Environmental Protection Agency's (EPA or Agency) Incident Data System in support of their assertion that 50 fatalities are associated with pyrethroids and pyrethrins since 1992, of which 20 occurred

between 2003 and 2007. The authors attribute the increase in pyrethroid and pyrethrins incidents largely to increasing use of the active ingredients since the phase-out of organophosphates in residential areas, beginning in 2000.

The article further states that "(d)espite the common belief that these insecticides are less toxic than organophosphates and that fatal incidents are rare, some scientists and physicians have begun to question their safety — especially for people with asthma or allergies."

The CPI report prompted EPA to conduct its most recent review of pyrethrins and pyrethroid incidents to identify any trends in the data. To determine whether there is an association between pyrethrins and pyrethroid products and asthma and allergy effects, EPA performed a thorough review of the animal and human incident and epidemiological data[1]. The process and conclusions of this evaluation are discussed in Sections III and IV below.

Before the recent review, various offices within EPA had considered the potential relationship between pyrethrum, pyrethrins, and pyrethroids and allergic/asthmatic effects. EPA's Office of Pesticide Programs' (OPP) "Recognition and Management of Pesticide Poisonings" manual states that crude pyrethrum is a dermal and respiratory allergen, probably due mainly to non-insecticidal ingredients. However, there are no pyrethrum end-use products currently registered with the Agency. The Agency does have over 1,200 registered end–use products containing pyrethrins, which is refined pyrethrum. In the production of pyrethrins, impurities such as sesquiterpene lactones (chemicals found in many plants that are known to cause allergic reactions) are removed from pyrethrum, which removes the allergic component (Osimitz, 2006). Pyrethroids are synthetic insecticides similar to pyrethrins, but have been modified to increase their insecticidal potency and their stability in the environment (Bradberry, 2005; Casida, 1980). There are approximately 2500 pyrethroid end-use products registered with the Agency. Neither pyrethrins nor pyrethroids have been characterized by EPA as allergens.

In 2000 the EPA's Office of Radiation and Indoor Air (ORIA) commissioned a review by the National Academy of Sciences' Institute of Medicine (IOM) of published data on the relationship between asthma and exposure to various substances commonly found in indoor air. Based on the results of this review, the Agency's risk reduction guidance for indoor asthma triggers focuses on secondhand smoke, dust mites, mold, cockroaches and other pests, household pets, and combustion byproducts. The IOM review considered pesticides as a potential asthma trigger, but found the information available to be inconclusive. Therefore the Agency has not listed pesticides as an indoor environmental trigger of asthma symptoms. The Agency has stated, however, that proper use of some pesticides as part of an exposure control program may yield benefits to some individuals with asthma, through the elimination or reduction of sources of allergens, such as cockroaches and other pests (IOM, 2000).

[1] The human studies described do not constitute "research involving intentional exposure of a human subject" under EPA's Rule for the Protection of Human Subjects.

The EPA does not require additional warning statements for individuals with respiratory allergies or asthma on registered pyrethrins or pyrethroid end-use pesticide products. However, in 1982 the Food and Drug Administration (FDA) required the following warning statement to appear on pediculicide products containing the combination of pyrethrum extract and piperonyl butoxide: "Use with caution on persons allergic to ragweed" (21 CFR § 358.601). According to FDA, the decision to add this statement was based on conflicting reports on the allergenicity of ragweed-sensitive individuals to pyrethrins formulations.

A scabicide cream product containing 5% permethrin (a type I pyrethroid) has been available with a prescription since 1989 and does not contain a specific asthma or allergy warning statement. It has a general statement warning of possible hypersensitivity to any of its components. A pediculicide cream product containing 1% permethrin is available over the counter (OTC). In 1990 when the product was changed from a prescription to OTC, labels warned consumers that the product may cause breathing difficulty or an asthmatic episode in susceptible persons but did not mention ragweed.

With the publication of the "Drug Facts Labeling" rule in 1999 (64 FR 13254), FDA standardized all OTC labels. In 2003, the allergy warning statements on all OTC pediculicide drug products was expanded and revised to the following: "Ask a doctor before use if you are allergic to ragweed. May cause breathing difficulty or an asthmatic attack" (68 FR 75414, published December 31, 2003).

The Reregistration Eligibility Document (RED) for pesticide products containing pyrethrins was published by OPP in 2006. During reregistration the association between pyrethrins products and allergy/asthma effects was considered. The Agency reviewed pyrethrins incidents to determine if they signaled a need for label language warning consumers of a possible association between exposure and allergy/asthma effects. Due to uncertainty in the data, label language similar to that required by the FDA was not considered necessary. Instead, as a condition of reregistration the EPA required the Pyrethrins Joint Venture (PJV), an industry task force, to institute a product stewardship program involving a prospective in-depth follow-up of reported pyrethrins incidents to clarify any possible correlation between pyrethrins product use and adverse health consequences. The product stewardship program also requires outreach to physicians and Poison Control Centers, and provides them with better guidance and diagnostic standards. As part of the PJV stewardship program, an annual report submitted to the Agency will be required for at least 5 years.

While the data collected by the PJV is expected to clarify whether pyrethrins exposure is associated with allergy and asthma effects, these new data won't be available for another 1-2 years. Therefore, the Agency has reviewed the current available animal studies, human incident data and epidemiological studies to evaluate whether there is a potential relationship between exposure to pyrethrins/pyrethroids and allergic/asthmatic responses.

II. Background

A. Definition of Asthma and Allergies

An allergy is an immunologically mediated adverse reaction to a particular substance, also called an allergen (common allergens include ragweed, peanuts, house dust mites). Allergic reactions can be expressed in many ways, such as a rash, an asthmatic response, swelling and/or shock. (NIH, 2006)

Asthma is a chronic inflammatory disease of the airways. Symptoms include wheezing, breathlessness, chest tightness and coughing (and are often episodic). Although research has indicated that there are both genetic and environmental components involved in the development of asthma, the etiology of asthma continues to be researched. Additionally, asthma lacks a universal definition, which adds to the overall complexity of evaluating this disease when there are such vast differences in medical diagnoses and multiple allergic triggers. Asthma triggers include pet dander from cats and dogs, cockroaches, house dust mites, environmental tobacco smoke, fungi/molds, rhinoviruses and nitrogen dioxide. (IOM, 2000; NIH 2007).

B. Prevalence of Asthma and Allergies

Based on statistics from the Centers for Disease Control and Prevention (CDC) in 2005 8% and 9.3% of U.S. non-institutionalized adults and children, respectively, were diagnosed with hay fever (a specific and widespread allergy), and 7.3% and 9.4%, respectively, were diagnosed with asthma (CDC, 2007b; CDC, 2007c). Overall the asthma rate in the U.S. increased towards the end of the 20th century, and the increase affected all ages, racial groups and geographic areas. However, more recently, evidence suggests asthma morbidity and mortality are leveling off or decreasing (CDC, 2007a; ALA, 2007). Regardless, asthma remains a public health concern. Public health surveillance indicates that the prevalence of asthma differs among various demographic subpopulations (e.g., blacks, Puerto Ricans, children, Northeasterners, those living below the federal poverty level) (CDC, 2007a).

C. Pyrethrum, Pyrethrins and Pyrethroids

Pyrethrum is an extract (and mixture of substances) derived from chrysanthemum flowers with insecticidal properties. Pyrethrins is a more refined pyrethrum extract, intended to further isolate the insecticidal components of pyrethrum. EPA regulates pyrethrins as one active ingredient, however, the refined extract contains a mixture of six isomers. Pyrethroids are a class of synthetic insecticides that are structurally similar to pyrethrins and act in a similar manner to pyrethrins, but have been modified to increase their environmental stability and their insecticidal properties (Bradberry, 2005; EPA, 1999; Casida, 1980). In general, pyrethrins/pyrethroids are less toxic to mammals and are considered good candidates for replacement of the more toxic organophosphate insecticides. As discussed in Section I, pyrethroids and pyrethrins are not expected to contain the allergic component found in pyrethrum. However, there have been reports

asserting a potential association between pyrethrins/pyrethroid exposure and allergic/asthmatic effects, based on human incident data.

D. Previous Reviews and Analysis

In 2005, the Agency reviewed pyrethrins incidents from the OPP Incident Data System (IDS), American Association of Poison Control Centers (PCC), Pesticide Telecommunications Network (NPTN), and the National Institute of Occupational Safety and Health's Sentinel Event Notification System for Occupational Risk (NIOSH SENSOR). The resulting report concluded that direct exposure to pyrethrins can cause skin, eye, or respiratory irritation. The literature review found evidence that persons may become sensitized or have cross-reactivity due to exposure to other allergens. Evidence that pyrethrins products may be involved in producing asthma-like reactions is suggested from a number of cases identified in the literature review. However, it was acknowledged that there is strong evidence for other causes of asthma, such as pet dander, cockroach allergens, and dust mites. Applications that can result in direct exposure to bystanders (e.g., automatic insecticide dispensers) can be expected to result in skin, eye, or respiratory effects in some sensitized individuals. (Blondell, 2005).

In 2004 the Agency reviewed Poison Control Center data covering the years 1993 through 1998, and concluded that there was a greater risk of moderate or major symptoms among those exposed to products containing pyrethrins and piperonyl butoxide (PBO) than those exposed to pyrethrins alone. PBO is a pesticide synergist, which is often co-formulated with the pyrethrins active ingredient to increase the insecticidal potency of the active ingredient. The data also indicated that respiratory symptoms (bronchospasm, coughing or choking, or dyspnea) and selected dermal symptoms (dermal irritation, pain, itching, or rash) were more likely if the exposure included PBO (Blondell, 2004).

In a Master's thesis (Mosby, 2003) analyzing PCC data, Jacqueline Mosby concluded that pyrethrins and pyrethroid exposure increased the likelihood of asthma or allergies. Mosby found that the effect is greater for pyrethrins than for pyrethroids. Mosby also noted that national pesticide poisoning surveillance is poor, and many cases may go undiagnosed or unreported.

In response to Mosby's work, Dr. Jerry Blondell acknowledged that there was some evidence of an association between dermal effects and exposure to pyrethrins/pyrethroid products. However, the associations were slight. Mosby concluded that EPA should "consider improving their labels to warn applicators and users with a history of ragweed allergy or asthma about the potential consequence of inhalation exposure when using products that contain pyrethrins/pyrethroids." (Mosby, 2003). Dr. Blondell supported similar label language.

During pyrethrins reregistration, EPA considered requiring a label warning for those with asthma or ragweed. However, due to uncertainty in pyrethrins incident data it was unclear whether those with asthma or ragweed allergies reacted more strongly to

products containing pyrethrins than the general population. Instead of adopting the suggested restrictions for these specific populations, the pyrethrins Reregistration Eligibility Decision (RED) includes precautions for all consumers, including requirements for ventilation when these products are used in enclosed areas. In addition, the RED requires registrants to conduct a stewardship program, cited above and described in detail in the RED[2].

III. Current Data Review and Analysis

In the current review, a weight of evidence approach was utilized to determine whether an association exists between pyrethrins/pyrethroid exposure and asthma and allergies. The current review considered animal studies addressing mode of action, target organ of toxicity, acute inhalation and dermal irritation, and sensitization. The review also considered human incident data from several sources and human epidemiology studies. In the weight of evidence analysis, several criteria are used to determine whether an association exists; they include consistency, reproducibility, temporal and dose concordance and biological plausibility of the effects/outcomes.

A. Animal Data

Animal studies show that pyrethrins and pyrethroids have low acute toxicity and the active components are rapidly and extensively metabolized with no significant accumulation, and they pose relatively low hazard to mammals. Available animal data do not indicate that pyrethrins or pyrethroids significantly affect organ systems other than the nervous system, although changes in liver weight and metabolism of chemicals have sometimes been used as an index of adverse effect levels for pyrethroids (Schoenig, 1995). Signs of respiratory irritation were reported in laboratory animals acutely exposed to aerosols of pyrethroids at lethal or near-lethal airborne concentrations (Curry and Bennett, 1985; Flucke and Thyssen, 1980; Hext 1987; Pauluhn and Thyssen, 1982). Intermediate-duration (90-day) repeated exposures of rats to mean analytical pyrethrins concentrations >30 mg/m3 resulted in clinical and microscopic evidence of respiratory irritation (Schoenig, 1995). These tested concentrations in animals are much higher than those to which humans are likely to be exposed.

No animal studies were available in which inhalation exposure to pyrethrins or pyrethroids could be associated with immunological effects such as hypersensitivity (i.e., allergy or asthma). In contrast, immunosuppressive effects were observed in various pyrethroids via oral exposure such as decreased humoral immune response, reduced cell-mediated immune response and leukopenia (Lukowicz-Ratajczak and Krechniak, 1992; Demian, 1998; Varshneya et al., 1992).

The primary mode of action for pyrethrins and pyrethroid exposure is prolonging the open phase of the sodium channel gates of nerve cells (Casida et al., 1983; Coats, 1990; Narahashi, 1986; Sattelle and Yamamoto, 1988; Soderlund, 1995; Soderlund et al., 2002; Valentine, 1990; Vijverberg and van den Bercken, 1990). Using a variety of

[2] The pyrethrins RED can be found at http://www.epa.gov/pesticides/reregistration/pyrethrins/.

methods, including voltage clamp and patch clamp techniques, pyrethrins and pyrethroids have been shown to slow the closing of sodium channel gates following an initial influx of sodium during the depolarizing phase of an action potential, resulting in a prolonged sodium tail current (Narahashi 1986; Vijverberg and Van den Bercken 1982). The prolonged opening of the sodium channel in the nervous tissue causes repetitive firing of sensory nerve endings, resulting in a hyperexcitable state. In rodents, effects such as tremors are induced if the open state is prolonged for brief periods; effects such as sinuous writhing (choreoathetosis) and salivation occur if the open state is prolonged for longer periods.

There are two types of pyrethroids, types I and II, which differ in basic structure and in the symptoms of poisoning (Coats, 1990; Verschoyle and Aldridge, 1980). Type I pyrethroids do not include a cyano group, and their effects in rodents typically include rapid onset of aggressive behavior and increased sensitivity to external stimuli, followed by fine tremor, prostration with coarse whole body tremor, elevated body temperature, coma, and death. Type II pyrethroids include a cyano group in the alpha position, and their effects in rodents are usually characterized by pawing and burrowing behavior, followed by profuse salivation, increased startle response, abnormal hindlimb movements, and coarse whole body tremor that progresses to sinuous writhing (choreoathetosis). Almost all systemic effects of exposure to pyrethrins and their derivatives are targeted to the nervous system.

B. Human Incident Data

Human incident information is mainly self-reported, and typically neither exposures to a pesticide nor reported symptoms (nor the connection between the two) are easily verifiable or reliable. Incident information, however, does provide important feedback to the Agency. Incidents with severe outcomes, or other clear patterns or trends, can signal a need to further investigate a particular chemical or product.

The following table summarizes the strengths and limitations of various sources for human incident data for pesticides available to OPP. These sources differ in purpose, in scope, in key definitions, and in methods of data acquisition and database maintenance. These differences must be understood in order to accurately interpret the data.

Table 1: Strengths and Limitations of Human Pesticide Incident Data Sources			
Data Source	**Years**	**Strengths**	**Limitations**
OPP Incident Data System (IDS)	1992-present	-Centralized system -Incident reports from various sources -Case reports	-Uneven level of detail -Labor intensive; not fully automated -Largely anecdotal reports/allegations
American Association of Poison Control Centers (PCC)	1993-2005	-National scope -Able to summarize fields/organize information -Clinically oriented -Over 1.5 million records	-Focus on incidents in residential settings
National Pesticide Information Center (NPIC)	1978- present	-National scope	- Focus on incidents in residential settings -Limited scale; small sample size
Sentinel Event Notification System for Occupational Risk (SENSOR)	1998 - present	-Best available data for occupational incidents -Includes data from multiple sources - Provides detailed information -Standardized information	-Covers only 12 states -Reporting varies from state to state -Focus on occupationally-related cases (although approximately 50% of cases are non-occupational)
California Pesticide Illness Surveillance Program (PISP)	Standard collections from 1982; Methods revised 1992	-Unique infrastructure for follow-up -Strong baseline information; longest history -Includes all types of pesticides -Provides detailed information - Standardized information	-Limited to California -Occasional lag time between incident and report

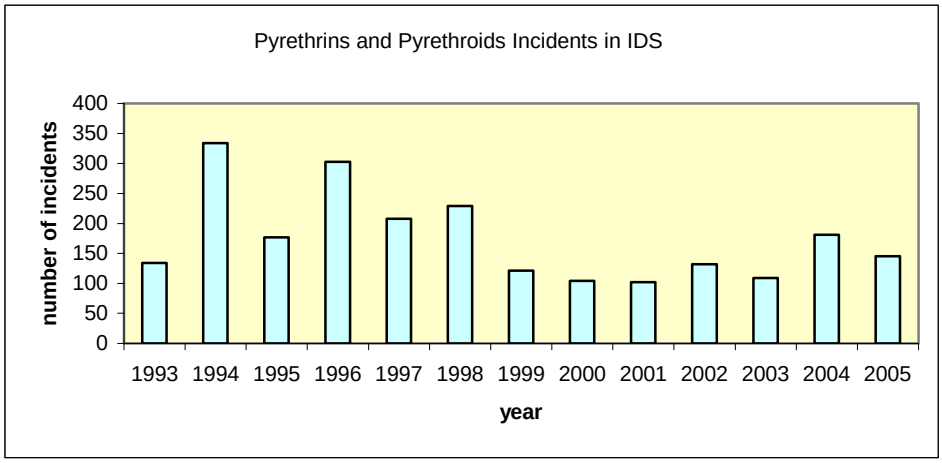
This review focused on the IDS, PCC, and NPIC databases, because their coverage is the most nearly national. To gain an additional regulatory perspective on pyrethrins and pyrethroid products we also considered FDA's incident database covering incidents associated with pharmaceutical use of pediculicides and scabicides containing pyrethrins and permethrin.

1. OPP Incident Data System (IDS) Data

OPP Incident Data System (IDS) contains incident reports submitted to OPP since 1992 from various sources including registrants, other federal and state health and environmental agencies, and individual consumers. These reports are typically anecdotal with low to moderate levels of detail. Often, it is difficult to draw clear conclusions implicating any pesticide as a cause of any of the reported health effects. Nevertheless, the data can be helpful in describing potential health effects from exposure to a pesticide.

The graph below shows the number of incidents reported to IDS each year from 1993-2005 involving products containing pyrethrins or pyrethroids. Among the total of 2,279 incidents there is no apparent temporal trend during this time period.

Figure 1



The Agency also examined reported deaths following exposure to products containing pyrethrins or pyrethroids from 2003 to May of 2008 to see if the information available about these incidents suggested a relationship between exposure to pyrethrins/pyrethroids and respiratory symptoms or allergic reactions. When available, the following information was extracted from IDS for each reported death associated with pyrethrins/pyrethroids: age and sex of the victim, the chemical the person was exposed to, time of exposure to initial onset of effects, the duration of exposure, symptoms, pre-existing conditions, and other circumstantial or exposure-related information.

Initially, 24 reports of deaths were identified in IDS appearing to be potentially related to exposure to pyrethrins and/or pyrethroids. Upon further examination, 16 of these reports were set aside for one or more of the following reasons:

1. Duplicate report of previously counted cases
2. The death was a suicide or homicide, or resulted from intentional misuse
3. Exposure was to other active ingredients as well as to pyrethrins/pyrethroids, and attribution to pyrethrins or pyrethroids is unclear.

Of the eight deaths that may be attributable to exposure to pyrethrins and/or pyrethroid products, four victims showed respiratory symptoms, two showed other symptoms such as feeling ill and headaches, and burning hands, and no particular symptoms were reported for the remaining two victims. The eight deaths involved exposures to one or a combination of the following pyrethrins and pyrethroid active ingredients: pyrethrins, permethrin, cyfluthrin, cyhalothrin, bifenthrin, and esfenvalerate. No apparent link between the symptoms and the deaths, or between the type of pyrethrins and pyrethroids and the deaths, can be hypothesized.

2. American Association of Poison Control Centers (PCC) data

The American Association of Poison Control Centers database includes reports of over 200,000 pyrethrins and pyrethroid total incidents recorded from 1993-2005. Figures

2 and 3 below show pyrethrins and pyrethroid total incidents increasing gradually over time, both in crude count and as a percentage of all pesticide incidents.

Figure 2

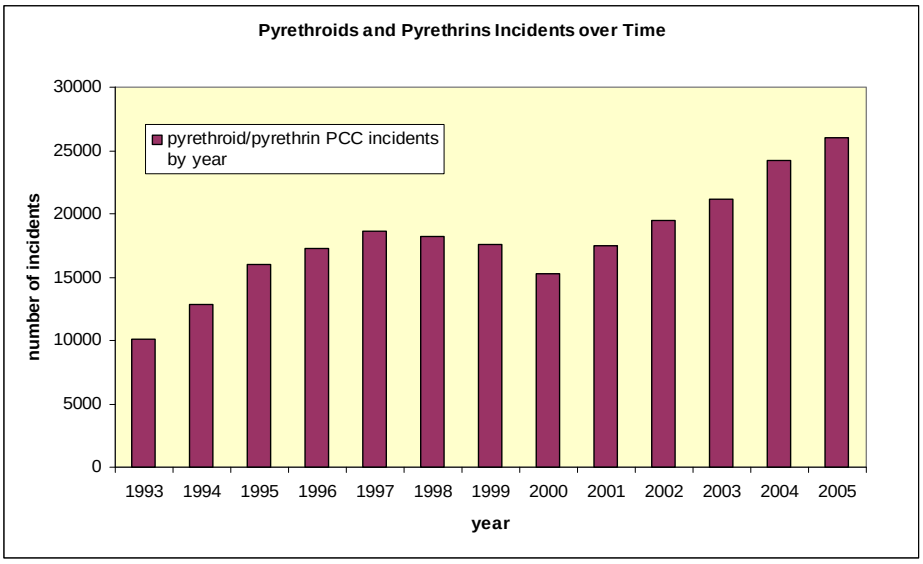
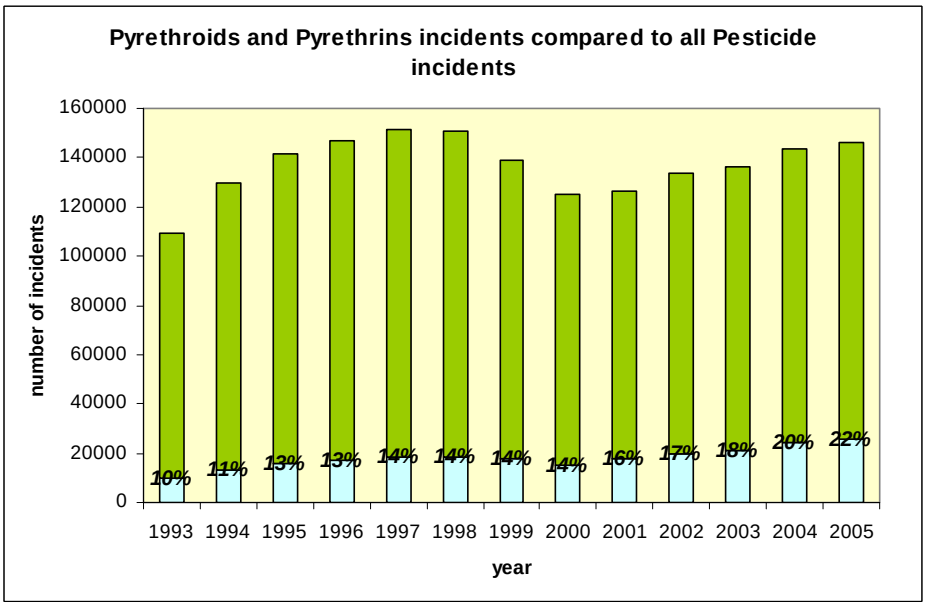


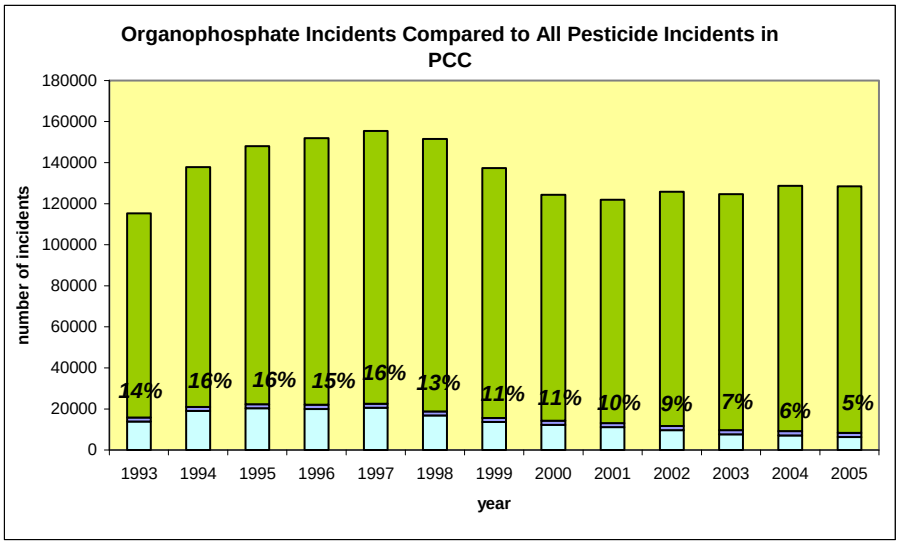
Figure 3



PCC information also shows total incidents involving organophosphates (OPs) decreasing over time, again both as crude counts and as a percentage of all pesticide

incidents. The decline in OP incidents coincides with an expected decline in usage following the phase-out of residential uses of OPs beginning in 2000 (Power, 2007).

Figure 4



PCC data support OPP hazard assessments showing OPs to be more toxic than pyrethrins and pyrethroid insecticides. The tables below report all deaths and "major" incidents, those in which the patient has exhibited symptoms as a result of the exposure which were life-threatening or resulted in significant adverse health effects for pyrethrins/pyrethroids, organophosphates, and carbamates. Although there were roughly a third more incidents overall from 1993-2005 involving pyrethrins/pyrethroids than involving OPs, more of the OP incidents resulted in serious health outcomes or death.

Table 2: Total Incidents in PCC Database by Insecticide Class, 1993-2005

Insecticide Class	Total Incidents in PCC*	Ratio
Pyrethrins/Pyrethroids (P/P)	234,206	P/P:C ~ 3
Organophosphates (OP)	178,705	OP:C ~ 2.3
Carbamates (C)	78,085	C:C = 1

*See Appendix I for further information about queries

Table 3: Annual Deaths and Major Incidents by Insecticide Class						
Major Incidents			Year	Incidental Deaths		
P/P	OP	C		P/P	OP	C
16	39	11	1993	1	0	0
20	43	8	1994	0	2	0
19	46	10	1995	0	1	0
18	35	9	1996	1	3	2
22	48	10	1997	0	3	0
28	31	12	1998	0	2	0
33	61	8	1999	1	2	0
21	61	5	2000	0	1	0
23	46	11	2001	0	0	0
30	43	14	2002	0	4	0
24	30	6	2003	1	3	1
35	35	7	2004	0	0	0
35	26	7	2005	3	2	0

A chemical's 'related-effect profile' or symptom signature refers to the different symptoms or effects that are reported to be related to exposure to the chemical. The Agency reviewed all reported incidents in the PCC database for pyrethrins and eight pyrethroid active ingredients (bifenthrin, cyfluthrin, cypermethrin, deltamethrin, permethrin, resmethrin, sumithrin, and tetramethrin) selected based on their usage information and use patterns. The Agency considers these eight to be representative pyrethroids since they are among the most commonly used and encompass the full range of approved residential uses for pyrethroids. Results of this analysis are shown in Table 4 below.

The reported related effects are summarized by category, such as cardiovascular, dermal, gastrointestinal, etc., in Table 4 for each of the nine active ingredients. Although PCC does not capture information about asthma or allergies directly, EPA believes the PCC categories of respiratory and dermal effects may be correlated to potential asthmatic or allergic responses.

Table 4: Analysis of Related Clinical Effects Reported in PCC for Pyrethrins and Select Pyrethroids									
Category of Effects	**Bifenthrin**	**Cyfluthrin**	**Cypermethrin**	**Deltamethrin**	**Permethrin**	**Pyrethrins**	**Resmethrin**	**Sumithrin**	**Tetramethrin**
	Type I*	**Type II***	**Type II***	**Type II***	**Type I***		**Type I***	**Type I***	**Type I***
	% (Count)	**% (Count)**	**% (Count)**	**% (Count)**	**% (Count)**	**% (Count)**	**% (Count)**	**% (Count)**	**% (Count)**
Cardiovascular	2% (49)	2% (234)	2% (265)	1% (19)	2% (446)	1% (811)	2% (83)	2% (197)	2% (224)
Dermal	26% (506)	25% (2623)	16% (2328)	37% (627)	21% (5619)	16% (9359)	16% (679)	19% (2109)	17% (2382)
Gastrointestinal	18% (361)	22% (2349)	27% (3980)	17% (300)	24% (6301)	23% (13199)	24% (992)	23% (2557)	24% (3355)
Heme/Hepatic	0% (5)	0% (11)	0% (15)	0% (1)	0% (14)	0% (14)	0% (3)	0% (2)	0% (3)
Neurological	15% (285)	12% (1323)	10% (1476)	11% (195)	13% (3394)	10% (5556)	13% (557)	11% (1261)	12% (1665)
Ocular	21% (403)	19% (2008)	14% (2117)	14% (232)	18% (4904)	26% (14935)	22% (918)	21% (2324)	19% (2736)
Renal	0% (1)	0% (10)	0% (17)	0% (0)	0% (14)	0% (37)	0% (3)	0% (15)	0% (11)
Respiratory	7% (141)	12% (1246)	22% (3284)	9% (148)	13% (3437)	14% (8071)	12% (514)	14% (1576)	17% (2416)
Miscellaneous	11% (212)	8% (870)	9% (1306)	11% (193)	10% (2611)	8% (4819)	9% (381)	11% (1186)	10% (1469)
Total Related Effects	1,963	10,674	14,788	1,715	26,740	56,801	4,130	11,227	14,261
Total Incidents	2,827	9,462	12,039	2,396	47,422	94,337	6,127	17,830	21,414

*Type I and type II indicates the absence or presence of a α-cyano moiety, respectively. An α-cyano moiety is not present in any of the pyrethrins isomers.

The reported health effects associated with these chemicals do not show a disproportionate number of respiratory or dermal effects reported for pyrethrins or pyrethroid exposures compared to other categories of effects. Overall, the three most frequently reported related effects are gastrointestinal, dermal and ocular effects. Exceptions include cypermethrin, where respiratory effects are the second most frequently reported effect, and tetramethrin where respiratory effects are the third most frequently reported effect (along with dermal). The percentages calculated for the three most frequently reported effect categories for each chemical are fairly similar, and fall within 11% of each other, except for deltamethrin, where dermal effects are reported 20% more than the next most frequently reported effect (gastrointestinal). The Agency is aware that pyrethroids can cause paresthesia, which is characterized by a temporary burning, stinging, itching and tingling of the skin (Bradberry, 2005; EPA 1999). This is more common in pyrethroids containing a cyano group (i.e., type II pyrethroids). Typically, the labels of pyrethroid products potentially associated with paresthesia effects inform users about the possibility and advise users to wash their hands immediately following contact.

To put those individual chemical 'related effects profiles' in Table 4 into a larger context, the effects reported for the pyrethrins/pyrethroids class as a whole were compared to reported effects for other major classes of insecticides, organophosphates

(OPs) and carbamates. As shown in Table 5 below, the symptom profiles for these three insecticidal classes are fairly similar. The most frequently reported related effect for all three insecticide classes is gastrointestinal. The second most frequently reported related effect is ocular (although for OPs neurological effects, and for carbamates dermal effects were reported as frequently as ocular effects). Even though there are slight differences among the classes between the frequency of related effects (e.g., gastrointestinal effects are reported more frequently for OPs and carbamates [29% and 30%, respectively] than for pyrethrins/pyrethroids [23%]), these differences are secondary to their similar symptom signatures (i.e., gastrointestinal is reported most frequently, ocular/neurological/dermal is reported second frequently, dermal/neurological is reported third frequently, and respiratory/miscellaneous is reported fourth frequently).

Table 5: Analysis of Related Clinical Effects Reported in PCC for Pyrethroid/Pyrethrins, OPs and Carbamates[3]

Related Effects	Pyrethroid/Pyrethrins	Organophosphates	Carbamates
	% (Count)	% (Count)	% (Count)
Cardiovascular	2% (2178)	3% (3563)	3% (941)
Dermal	19% (27141)	13% (15792)	16% (5269)
Gastrointestinal	23% (32222)	29% (33445)	30% (9529)
Heme/Hepatic	0% (44)	0% (91)	0% (24)
Neurological	11% (14810)	17% (20724)	15% (4869)
Ocular	21% (29907)	17% (20267)	16% (5291)
Renal	0% (87)	0% (328)	0% (64)
Respiratory	15% (20884)	10% (11832)	10% (3241)
Miscellaneous	9% (12680)	11% (13129)	10% (3266)
Total Related Effects	139953	119171	32494

3. National Pesticide Information Center (NPIC) data

In addition to IDS and PCC, the NPIC database was also evaluated. Unlike IDS and PCC, NPIC can be searched for the key terms "allergy" and "asthma". NPIC queried their database for pyrethroids, pyrethrins, OP, and carbamate incidents from 1995-2007, and found these key terms within the case descriptions of about 14% of the NPIC pyrethroid incidents, about 17% of the pyrethrins incidents, 7% of OP incidents, and 8% of carbamate incidents.

[3] These percentages are not absolute values, and reflect the lack of certainty associated with self- reported human incident data. For example, a difference of 5% should not be interpreted as an absolute value given the lack of precision and reliability of the underlying data.

4. FDA Adverse Event Reporting System (AERS)

Information from FDA was obtained on incidents related to the use of pediculicide and scabicide products they regulate. FDA provided EPA with a report from their AERS incident database for permethrin and pyrethrum extract (i.e., pyrethrins-related incidents). The summary table of symptoms (Table 6 below) provided by FDA indicates a low incidence of respiratory effects and anaphylactic reactions, despite the more direct application of pediculicides, which may increase the likelihood of exposure via the dermal and inhalation routes. The table includes information on permethrin prescription cream (5%) for scabies and over-the-counter cream (1%) for lice, and pyrethrins over-the-counter shampoos (0.33%) for lice.

Table 6: Crude Counts of Selected Adverse Event Terms for Pediculicide and Scabicide Products

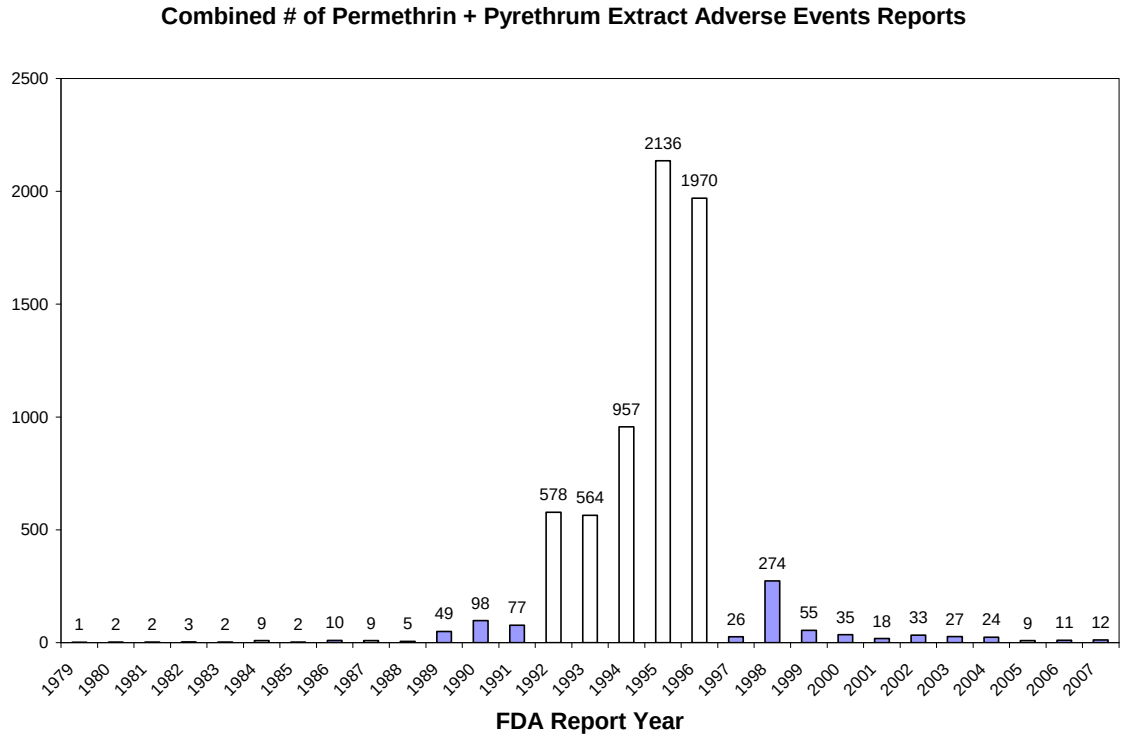
System Organ Class	Preferred Term	Permethrin Drug Products (n=340)	Pyrethrum Extract Products (n=8)
Immune System Disorders	Anaphylactic Reaction	0	1
	Anaphylactoid Reaction	2	0
	Drug Hypersensitivity	3	0
	Hypersensitivity	23	0
	Multiple Allergies	2	0
Respiratory, Thoracic, and Mediastinal Disorders	Asthma	18	0
	Hyperventilation	1	1
	Laryngospasm	2	0
	Respiratory Disorder	1	0
	Respiratory Distress	1	1
	Respiratory Failure	0	1
	Throat Tightness	1	0
	Wheezing	1	0
Skin and Subcutaneous Tissue Disorder	Angioedema	2	0
	Dermatitis	181	3
	Dermatitis Bullous	25	0
	Dermatitis Contact	5	0
	Dermatitis Exfoliative	23	0
	Photosensitivity Reaction	3	0
	Rash	4	0
	Rash Erythematous	7	0
	Rash Generalized	1	0
	Rash Maculo-Papular	40	0
	Rash Papular	2	0
	Rash Pruritic	3	0
	Rash Vesicular	1	0
	Skin Exfoliation	2	0
	Stevens Johnson Syndrome	1	0
	Toxic Epidermal Necrolysis	2	0
	Urticaria	30	1

The "preferred terms" listed in Table 6 were selected by FDA reviewers as those keywords in the AERS system best describing the adverse events of concern to EPA in this review. One or more of these adverse events of interest was reported for 348 of the

total 6,998 reports for permethrin and pyrethrum products—just under 5%. Summation of the columns would exaggerate the number of incidents, because one report may have been assigned more than one of the coded terms.

Figure 5 shows the distribution by FDA receipt year of the total of 6,998 reports for permethrin (6,908) and pyrethrins (90) products.

Figure 5



As outlined in the introduction, FDA first included a warning statement on pyrethrins labels in 1982, added language warning of breathing difficulty for asthmatics handling permethrin products in 1990, and expanded asthmatic and allergy warnings to all over the counter pediculicide products in 2003. If the changes in required warning labels in 1982 and 2003 had an effect, it cannot be identified from this data, which is overwhelmed by the dramatic peak in incident reporting during the mid-1990s.

C. Other Human Incident and Epidemiological Data Available in Published Literature[4]

There are many human studies available in the literature related to the health effects of pyrethrins and pyrethroids. Although multiple human studies were considered,

[4] The Agency is aware of published studies involving human subjects intended to explore the relationship between exposure to pyrethroids or pyrethrins and allergic and asthmatic responses. The Agency will submit these studies to the Human Studies Review Board for review and consideration. Pending the outcome of review, the Agency will determine whether to include those studies in the weight of the evidence consideration.

the following studies are highlighted, as they reflect the information most relied on in this analysis.

1. Review of Human Pyrethrins and Pyrethroid Incidents in Pacific Northwest (Walters et al., 2009)

This study reviewed pesticide surveillance data from 2001 through 2005 for the Washington State Department of Health and Oregon Public Health Division. Based on this evaluation, the report concluded that of the 407 total reported incident cases, 92% were categorized as low severity illnesses, while 8% fit into the moderate/high category with 1 death potentially attributable to pyrethrins/pyrethroid exposure. Similar to EPA's analyses, this article acknowledges that the increase in incidents reported for pyrethrins/pyrethroids could potentially be explained by the phase-out of the organophosphates beginning in 2000/2001. While the article notes that 52% (of the 407 cases) were reported with symptoms of respiratory illnesses (210 cases), these symptoms include a majority of coughing (n=112), dyspnea (n=88) and respiratory irritation (n=98), but only a small number (n = 45) of asthmatic attacks. There were also a high proportion of neurological symptoms (n=162) and gastrointestinal cases (n=134). Multiple symptoms could be from the same individual, which could contribute to double counting of effects. The article states that "there is also a potential for false positives because nonspecific symptoms may have been coincidental and not actually caused by pesticide exposure" (Walters et al., 2009). The authors also conclude that there is a significant association between pre-existing conditions (asthma, allergy, multiple chemical sensitivity) and case severity, but state that incident data are usually incomplete, with limited documentation in the literature.

In addition to reviewing incident data, the authors also point out that there are inconsistencies between human studies available in the literature. They mention the West Nile virus study discussed below (Karpati et al., 2004), and note there was no association between mosquito control spraying of pyrethroids for West Nile virus and emergency department asthma visits in New York City in 2000. However, the authors also describe a report on flight attendants who experienced health effects after aircraft deinsection, some of which were respiratory effects (Sutton et al, 2007).[5] Subsequently, the authors state that the inconsistencies in the available human studies may be reconciled through the collection of more robust incident data for pyrethrins/pyrethroid exposure and asthma, better public education on the appropriate use of pesticides, and heightened awareness that many aerosols and foggers may be respiratory irritants of potential health concern for those with hyper responsive respiratory airways like asthmatics (Walters et al., 2009).

[5] Other effects experienced by the flight attendants after pyrethroid spraying on airplanes included confusion, weakness and heart palpitations. The respiratory effects were no more frequent than other health symptoms. Additionally, the flight attendant study was limited as it included only six completed interviews out of 17 flight attendants; eight declined participation, and three could not be reached.

2. Population Based Case Study of West Nile Virus Treatment (Karpati et al., 2004)

The analysis conducted by Karpati et al. (2004) showed that spraying a product containing 10% sumithrin (a type I pyrethroid) and 10% PBO for West Nile Virus control in New York City was not followed by population-level increases in public hospital emergency department (ED) visit rates for asthma. Possible associations between exposure to this pyrethroid product and increased rates of asthma-related public hospital ED visits in vulnerable populations were also examined. No association between the spraying of this pesticide and an increased rate of asthma-related ED visits was seen in children or in those with chronic obstructive pulmonary disease in this study population. This study did find an association between known asthma triggers (ozone levels, particulate matter [PM_{10}] and temperature) and asthma-related ED visits.

3. Agricultural Health Study (Hoppin et al., 2002, 2006, and 2008)

The Agricultural Health Study (AHS) is an ongoing prospective cohort study involving over 89,000 private and commercial pesticide applicators and their spouses. The goals of the project are to investigate the effects of environmental, occupational, dietary, and genetic factors on the health of the agricultural population. In a cross-sectional analysis of the AHS cohort 1993-1997, Hoppin et al. explored the association between 40 individual pesticides, including OPs, carbamates, and permethrin (a type I pyrethroid), and respiratory outcomes (wheeze) by studying both farmers and commercial applicators. Among approximately 20,000 farmers and 2,000 commercial applicators, incidence of increased wheeze was associated with individual OP and carbamate pesticides. Permethrin use on crops was not associated with increased wheeze in farmers or commercial applicators. However, permethrin use on poultry was associated with wheeze (permethrin was the only insecticide reported separately for crop and animal use in the AHS data). Among asthmatic subjects, however, five chemicals, including permethrin [poultry] showed significantly lower odds ratio of wheeze (2002, 2006).

Further, in their analysis of 25,814 farm women in the Agricultural Health Study, Hoppin et al. (2008) used self-reported history of doctor-diagnosed asthma with or without eczema and/or hay fever to create two case groups: patients with atopic asthma and those with nonatopic asthma. Atopic asthma, or allergic asthma, occurs when an individual is exposed to items in their environment to which they have an allergy. Other individuals with nonatopic asthma have no allergies, and the cause of their airway inflammation is unclear. Hoppin et al. found pesticide use overall (any pesticide use) was associated with atopic or allergic asthma (2006, 2008). A total of 7 of 16 insecticides, 2 of 11 herbicides, and 1 of 4 fungicides were significantly associated with atopic asthma; only permethrin use on crops was associated with nonatopic asthma (2008).

IV. Conclusion

A. Weight of Evidence Data Conclusion

Unlike previous reviews, this assessment used a weight-of-evidence approach, integrating both animal and human incident and epidemiological data, seeking to determine whether exposure to products containing pyrethrins and/or pyrethroids is associated with asthma and allergies. This approach was selected because an integrative assessment with animal and human data is more informative than an analysis of any single dataset or study, and because fundamental biological mechanisms of disease outcome are assumed to be concordant across species.

The animal data show that pyrethrins and pyrethroids have low acute toxicity to mammals via oral, dermal and inhalation routes of exposure and are not skin sensitizers. While these animal studies were not specifically designed to identify potential asthmatic responses, it does provide dose response information and severity of acute responses via the inhalation route of exposure. Animal data taken alone, however, does not form the bases of the overall conclusion.

The IDS incidents did not indicate an association between exposure to pyrethrins/pyrethroids and asthma/allergies. No causal relationship between exposure to pyrethrins or pyrethroids and asthma or allergic effects can be established using IDS incident data alone. PCC pyrethrins/pyrethroid incident data do not demonstrate a heightened respiratory or dermal response compared to other symptom categories. Furthermore, the PCC data show effects profiles for pyrethrins and pyrethroids—e.g., the distribution of reported effects by category—quite similar to those for organophosphates and carbamates. NPIC data reports higher frequencies of incidents indexed for "allergy" or "asthma" for pyrethrins and pyrethroids as compared to OPs and carbamates. FDA adverse event data did not support an association between use of pyrethrins or permethrin pharmaceutical pediculicide and scabicide products and allergic or asthmatic responses, despite the more direct method of application and associated high human exposure levels.

Incident databases do not consistently show trends or patterns potentially indicative of allergies/asthma consequent to exposure to pyrethrins or pyrethroids. If there were a strong relationship, the Agency would expect to find a clear and consistent pattern of increased respiratory and allergic effects reported across multiple human incident databases.

The review article by Walters et al. (2009) articulates some of the limitations of human incident data: incomplete information, lack of information about pre-existing health conditions, potential for misclassification or false positives and underreporting. These limitations make it difficult to assess a causal relationship between asthma and exposure to pyrethroids or pyrethrins using incident data. Although human incident databases provide useful feedback to the Agency on registered pesticides, they may be inadequate to identify a relationship between exposure to pyrethrins or pyrethroids and allergy or asthma responses. These databases vary in quality, level of detail, and type of information.

Human data are inconsistent. Although there are studies indicating an association between asthma/allergies and pyrethrins and/or pyrethroids exposure, there are also

similar studies that do not indicate an association. Better designed and executed studies, such as the population-level study (Karpati et al., 2000) did not find a higher number of hospital visits for subjects with asthma following wide-area exposure to pyrethroids. The cross-sectional Agricultural Health study did not report a clear association between respiratory symptoms (wheezing) and exposure to permethrin (Hoppin, 2002 & 2006), but follow-up investigation of this potential relationship is ongoing.

Based on its assessment of the available animal experimental data, human incident data, and human epidemiology studies, EPA concludes that there does not appear to be a clear relationship between exposure to products containing pyrethrins or pyrethroids and allergic or asthma responses.

B. Regulatory Conclusion

As discussed in Section II above, previous evaluations of incident data have recommended warning statements on pyrethrins/pyrethroid product labels such as "Ask a doctor before use if you are allergic to ragweed. May cause breathing difficulty or an asthmatic attack for sensitive subpopulations." However, our evaluation of the FDA's data indicated that the inclusion of similar warning language on labels of FDA-regulated pyrethrins products was unrelated to the frequency of reported incidents. Although the nature of the use of the FDA-regulated pyrethrins products generally results in relatively high direct human exposure, the symptoms reported to the FDA Adverse Events Reporting System do not suggest an association between exposure and respiratory effects.

Based on the weight of the evidence discussed above, the Agency concludes there is not a clear relationship between pyrethrins/pyrethroid exposure and asthma and allergies. Therefore, the Agency is not requiring additional warnings or label statements specific to asthmatics on pyrethroids and pyrethrins end-use product labels at this time.

As noted above, during pyrethrins reregistration the Agency required the Pyrethrins Joint Venture to institute a product stewardship program involving a prospective in-depth follow-up of reported pyrethrins incidents to clarify any possible correlation between pyrethrins pesticide product exposures and adverse health incidents. The Agency will review the pyrethrins incident data as it is submitted. If these new data provide new insights or evidence of trends in the data that differ from the incident data considered in this review, the Agency may consider imposing a similar stewardship requirement on registrants of products containing pyrethroids.

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Appendix I: Incident Databases

1. Incident Data System (IDS)

IDS is maintained by OPP and incorporates data submitted by registrants under FIFRA section 6(a)(2), as well as other incidents reported directly to EPA. FIFRA allows the aggregation of individual events in some circumstances. IDS includes information on incidents involving humans, plants, wild and domestic animals where there is a claim of an adverse effect, as well as detects of pesticides in water. The vast majority of reports are received in paper format. IDS entries act as a pointer to copies of original reports, retained on microfilm and scanned images in OPP's Information Service Center. Many companies use standardized, industry-developed Voluntary Incident Reporting Forms. While IDS reports are broad in scope, the system does not consistently capture detailed information about incident events, such as occupational exposure circumstances or medical outcome. In most cases data going into IDS is not validated or verified, though some reports are collected from calls to contract poison control centers.

2. American Association of Poison Control Centers (PCC)

The National Poison Data System (NPDS), formerly the Toxic Effects Surveillance System (TESS), is maintained by the American Association of Poison Control Centers (PCC), with funding from several federal agencies. NPDS is a computerized information system with geographically specific and near real-time reporting (for bioterrorism detection purposes). While the main mission of Poison Control Centers is helping callers respond to emergencies, and not collecting specifics on incidents, NPDS data helps identify emerging problems in chemical product safety. Hotlines at 61 PCC's nationwide are open 24/7, 365 days a year, with many bilingual centers in high Spanish speaking areas, and the capability to translate 80 languages. Hotlines are staffed by specially trained nurses to provide poisoning information and clinical care recommendations to callers with a focus on triage to give patients appropriate care. Using computer assisted data entry, standardized protocols, and strict data entry criteria, local callers report incidents that are retained locally and updated in summary form to the national database. Since 2000 nearly all calls in the system are submitted in a computer-assisted interview format by the 61 certified Poison Control Centers, adhering to clinical criteria designed to provide a consistent approach to evaluating and managing pesticide and drug related adverse incidents. Information calls are tallied separately and not counted as incidents. The PCC system covers nearly all the US and its territories and is undergoing major computer enhancements post 9/11.

- There are 1,546,503 records of "incidents" in the PCC database for pesticides, algicides and disinfectants. Not all of these records are complete

- Some analyses were conducted searching by chemical, but the broader queries were done using the Major_Category and/or Minor_Category fields, searching for all records that identified *pyre*, *organophosphate* or *carbamate* in one of these two fields.

- ***Major/Minor Category queries***

Major_Category	Minor_Category	Associated # of records
organophosphate	*pyre*	0
carbamate	*pyre*	0
pyre	*organophosphate*	0
pyre	*carbamate*	5709[§]
organophosphate	*organophosphate*	178,705
carbamate	*carbamate*	78,085
pyre	*pyre*	234,206

[§]These 5,709 records of incidents are called up due to the Minor_Category designation "PIPERONYL BUTOXIDE & PYRETHRINS (WITHOUT CARBAMATE OR O.P.)"; not because they involve exposure to both a pyrethrins/pyrethroid product and a carbamate

- **Table 3 – Query details**
  - ***Major/Minor Categories – queried for pyre/pyre, organophosphate/organophosphate, carbamate/carbamate***
    (see table above)
  - ***Medical outcome – queried for designation 4 and 3***
    4 – death [definition: the patient died as a result of the exposure or as a direct complication of the exposure where the complication was unlikely to have occurred had the toxic exposure not preceded the complication. Only include those deaths which are probably or undoubtedly related to the exposure.]
    3 – major [definition: the patient has exhibited symptoms as a result of the exposure which were life-threatening or resulted in residual disability or disfigurement. Follow-up is required to make this determination unless the initial poison center call occurs sufficiently long after the exposure that you are certain the clinical effect(s) will not get worse. Symptomatic patients must be followed until symptoms have resolved or nearly resolved, unless the symptoms are anticipated to be long-term or permanent.]
  - ***Reason for Exposure – excluded designations 9-14***

Reason_for_exposure	Code
Unintentional-General	1
Unintentional-Environmental	2
Unintentional-Occupational	3
Unintentional-Therapeutic error	4
Unintentional-Misuse	5
Unintentional-Bite/sting	6
Unintentional-Food poisoning	7
Unintentional-Unknown	8
Intentional-Suspected Suicide	**9**
Intentional-Misuse	**10**
Intentional-Abuse	**11**
Intentional-Unknown	**12**
Other-Contamination/tampering	**13**
Other-Malicious	**14**
Adverse_rxn-Drug	15
Adverse_rxn-Food	16
Adverse_rxn-Other	17
Unknown_reason	18
Other-Withdrawal	19

- **Table 4 – Query details**
  - ***PC_Code – queried for record of incidents with particular pc codes associated with them***
    (done using EPA/OPP generated table associated PDX_ID with PC codes)
  - ***Total incidents:*** the total number of incidents represents all incidents associated with a particular PC code. The total related effects can be lower or higher than the total incidents because some incidents have no clinical effects reported and some incidents have multiple clinical effects reported.

- **Table 5 – Query details**
  - ***Major/Minor Categories – queried for pyre/pyre, organophosphate/organophosphate, carbamate/carbamate***
    (see table above)

3. National Pesticide Information Center (NPIC)

NPIC is funded by EPA to serve as a source of objective, science-based pesticide information in response to inquiries and to respond to incidents. NPIC functions nationally during weekday business hours, under a cooperative agreement between Oregon State University and EPA. Similar to Poison Control Centers, NPIC's primary purpose is to provide information and not to collect incident data. NPIC does collect information about incidents from inquirers and reports that information to EPA (about 10% of NPIC's annual calls are considered "incident" related). The Center's main role is to provide information to inquirers on a wide range of pesticide topics, and direct callers for pesticide incident investigation and emergency treatment.

4. FDA Adverse Effect Reporting System (AERS)

The FDA AERS provides crude count data. For any given report, there is no certainty that a suspected drug/biologic product caused the reported event, because physicians are encouraged to report suspected events. However, the event may have been related to the underlying disease being treated, may have been caused by some other drug/biologic product being used concomitantly, or simply may have occurred by chance at that time.