

July 13, 2006

**MEMORANDUM**

**To: Cathryn O’Connell, Chemical Review Manager  
Special Review and Reregistration Division (MC 7508P)**

**From: Ruth H. Allen, PhD, MPH, Epidemiologist  
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**Through: David J. Miller, Chief  
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**Subject(s): Three Pyrethrin/Pyrethroid Health Effects Reviews  
DP Barcode: 326085                      PC Code: 069001**

**(A) “The Risk of Asthma Triggered by Pyrethrin/Pyrethroid Insecticides Determined by a Case-Control Study of Poison Control Data,” by JE Mosby (4-29-2003).**

**(B): “Human Exposures to Products Containing Pyrethrins and Piperonyl Butoxide Analysis of Poison Control Center Data (2001-2003)” by TG Osimitz, N Sommers and R Kingston (3-19-05), MRID Document # 466947-01.**

**(C) “Pyrethrins Allergic Contact Dermatitis in Man-- An Evidence-Based Dermatologic Review” by TG Osimitz, JA Franzosa, DR Maciver, HI Maibach (1-24-06), MRID Document # 467573-01.**

Chemistry and Exposure Branch (CEB) was requested by Special Review and Reregistration Division (SRRD) to review the three above-named reports concerning Pyrethrins and Pyrethroids. The Mosby report, review (A), was requested with DP# (324058) for the Pyrethrins RED. The purpose of this revisit is to highlight why US EPA is more concerned with pyrethrins than synthetic pyrethroid products. Synthetic pyrethroid incidents are being reviewed separately. The two industry reports, reviews (B) and (C), were requested with review (A).

Conclusions for each of the 3 reviews appear below:

**Conclusions for (A):** Mosby's thesis study highlights deaths in the literature and a scattered pattern of potentially preventable rapid deaths and serious illnesses in younger people and people with prior serious health conditions, including allergies/ asthma, diabetes and heart disease.

The Mosby report results are consistent for a statistically significant association between exposure to pyrethrin/ pyrethroid products and asthma symptoms in national poison control center data. The results are stronger for pyrethrins (Odds Ratio = 3.2) than pyrethroids (Odds Ratio = 1.8). The bottom line is a pattern of published clinical case reports over 12 years linking various pyrethrins/pyrethroids to rapid onset of multiple deaths and/or serious illnesses requiring hospitalizations. Most cases reviewed by Mosby were in young and middle- aged women with pre-existing disease.

It should be noted that: (1) national pesticide poisoning surveillance is poor, and potential cases can go undiagnosed. US General Accounting Office (GAO) has repeatedly identified under-reporting of diagnosed pesticide poisoning cases as a problem; and (2) disease causation is hard to prove, given competing environmental exposures, such as air pollution. In addition, as reflected in the government - wide Aging Initiative, this is a time when the median age of the US population is rising, and a greater fraction of the population is likely to have multiple pre-existing conditions.

**Conclusions for (B):** This industry review updates the Mosby Poison Control Center analysis by two years and raises a number of points. Rate calculation methods, as described in the submission, are non-standard and have been standardized in this review. Using the Symptoms by Organ System data from the industry report and the actual number of 40,000,000 units sold, the incident rate estimates are as follows:

- 1814 PY/ PBO dermal symptoms divided by 40,000,000 PY/PBO units sold x 100,000 yields a dermal symptoms rate of **4.5 /100,000** (dermal symptoms reported to PPCs in 2001-2003 per units of PY/PBO sold), and
- 1925 respiratory symptoms divided by 40,000,000 units sold x 100,000 yields a respiratory symptoms rate of **4.8/100,000** (respiratory symptoms reported in 2001-2003 per unit of PY/PBO sold).

**Conclusions for (C):** The industry dermatology literature review highlights the evolution of product chemistry and makes conclusions not fully supported in the document submitted. The published papers on dermal and respiratory effects should correct this. The authors state that based on current chemistry and the current level of diagnostic standards, allergic contact dermatitis does not occur in response to pyrethrum/pyrethrin "at a significant incidence in either ragweed sensitive individuals or otherwise" but they do not provide the detailed evidence to support this conclusion. The authors report on an exhaustive search of the literature and attempted to score the papers

for the strength of the evidence. OPP believes that this is difficult to do given the variability in the literature over the last 200 years, and uncertainty on the purity and strength of material tested, appropriateness of the vehicle used in earlier patch testing, and number of persons tested.

## **DETAILED ANALYSIS**

Detailed analyses of each of the three above-cited reports are presented here.

### **(A) “The Risk of Asthma Triggered by Pyrethrin/Pyrethroid Insecticides Determined by a Case-Control Study of Poison Control Data,” by Jacqueline E. Mosby (4-29-2003).**

Protocol Approved by The George Washington University Medical Center Institutional Review Board IRB # UO40217EX. In Partial fulfillment of the Requirements for the Masters of Public Health Degree from The George Washington University School of Public Health and Health Services Department of Environmental and Occupational Health.

#### **General Comments:**

The Mosby document summarizes published clinical case reports on pyrethrins/pyrethroids for three separate fatalities and several serious allergic reactions, including asthma requiring hospitalization. For the Poison Control Center (PCC) cases described below, the primary route of exposure was from householder use of pet shampoo products without specific reference to shampoo formulation details. The Mosby report also analyzes poisoning incident data from the American Association of Poison Control Centers (AAPCC) using a case control study methodology.

#### **Specific Comments:**

See Mosby report and published articles referenced there for more details. This report refers to the Mosby thesis dated April 29, 2003 Revised Version.

#### **Poison Center Case Literature Reports:**

Case #1: In 1994, rapid death was reported in a 37-year old female with a history of mild asthma following use of a dog flea shampoo containing 0.06% pyrethrin and 0.6% piperonyl butoxide, plus other ingredients, including 54% non-pesticide inert ingredients.

Case #2: In 1998, emergency room treatment for acute asthma was reported in a 24-year old female after she returned home and slept 45 minutes in her residence that had been treated with Raid Fumigating Fogger. {This case was included by Mosby as relevant based on chemical content that is not specified in the summary document. }

Case #3 In 2000, a 48-year old woman with diabetes and severe asthma died of multi-system failures and complications. She was hospitalized 10 days following an allergic reaction to use of two products containing pyrethrins, permethrin and piperonyl butoxide.

Case #4 In 1998, a 39-year old woman with chronic asthma died from severe asthma, two 2 hours after treating her dogs with a dog shampoo containing 9.7% pyrethrin.

Case #5: In 2000, an 11-year old asthmatic girl with no history of hospitalization died after shampooing her dog with a product containing 0.2% pyrethrin. She had used the product twice before with mild increase in her asthmatic symptoms. She experienced severe breathing problems 10 minutes after starting to use the product. She received aggressive medical care, but died of “respiratory arrest secondary to acute asthmatic attack” 2 and 1/2 hours after the initial exposure.

**Additional Human Case Reports:** The Mosby report summarizes additional human case reports from the National Pesticide Medical Monitoring Program (NPMMP). For pyrethrins, two cases were classified as known (Type 1). The death of a 12-year old child was reported from acute asthma, without laboratory confirmation of pyrethrin exposure but with a clinical case history consistent with pyrethrin exposure. Also, of the cases classified as probable, three were diagnosed as asthma, three were hives, one was conjunctivitis, and one was possible neuropathy.

Mosby concludes that pyrethrins cases are most often related to respiratory or dermal effects. Crude pyrethrum is a respiratory allergen, and refined **pyrethrins** products, while less allergenic, appear to retain their irritant and sensitizing properties since cases exhibiting anaphylactic and pneumonia manifestations have been reported from shampoos containing pyrethrins. The speed of human death in the dog shampooing activity pattern cases suggests that inhalation as well as dermal exposure might be operating simultaneously, and that people previously sensitized may be more highly reactive at subsequent but much lower doses of the chemical.

**Mosby Thesis Study Case - Control Results:** Poison Control Center (PCC) data for pyrethrums, pyrethrins and pyrethroids were analyzed using a case control study design for n= 13,485 subjects among 650,000 persons reporting exposure to all types of pesticides from 1993-1999. Findings from analysis of the PCC data are as follows, and all are statistically significant with a *p-value* of 0.001: (Odds ratio\* and confidence intervals\*\* are defined further in Appendix A.)

(1) For combined pyrethrin, pyrethroid and “insect\_py” variables, an odds ratio (OR) of 2.5 with 95% confidence limits (CI) (2.3 to 2.7) means a 2.5 times higher likelihood that persons exposed to both pyrethrins or pyrethroid products experience dermal or respiratory symptoms compared to persons exposed to other types of pesticides. This odds ratio value of 2.5 is significantly different from 1 which indicates that there is a statistically significant increase in the likelihood.

(2) For pyrethrins only, an OR of 3.2, and (CI) of 2.7 to 3.8 means a **3.2 times** higher likelihood that persons exposed to products containing pyrethrins experience dermal or respiratory symptoms than persons exposed to other types of pesticides. This odds ratio value of 3.2 is significantly different from 1 which indicates that there is a statistically significant increase in the likelihood.

(3) For pyrethroids only, an OR of 1.8 means a **1.8 times** higher likelihood that persons exposed to products containing pyrethroids experience dermal or respiratory symptoms than persons exposed to other types of pesticides. This odds ratio value of 1.8 is significantly different from 1 which indicates that there is a statistically significant increase in the likelihood.

**Bottom Line Conclusions for (A):** The Mosby report results are consistent for a statistically significant association between exposure to pyrethrin/ pyrethroid products and asthma symptoms in national poison control center data. The results are stronger for pyrethrins (3.2) than pyrethroids (1.8).

The bottom line is a pattern of published clinical case reports over 12 years, linking various pyrethrins/pyrethroids to rapid onset of multiple deaths and/or serious illnesses requiring hospitalizations. Most cases reviewed by Mosby were in young and middle-aged women with pre-existing disease.

It should be noted that: (1) national pesticide poisoning surveillance is poor, and potential cases can go undiagnosed. US General Accounting Office (GAO) has repeatedly identified under-reporting of diagnosed pesticide poisoning cases as a problem; and (2) disease causation is hard to prove, given competing environmental exposures, such as air pollution. In addition, as reflected in the government - wide Aging Initiative, this is a time when the median age of the US population is rising, and a greater fraction of the population is likely to have multiple pre-existing conditions.

**(B): “Human Exposures to Products Containing Pyrethrins and Piperonyl Butoxide Analysis of Poison Control Center Data (2001-2003)” by TG Osimitz, N Sommers and R Kingston (3-19-05), MRID Document # 466947-01.**

A duplicate registrant submission from Pyrethrins Joint Venture and PBO Task Force II (one report) regarding their independent analysis of poison center data (2001-2003) is reviewed below. The same document has 2 MRID numbers for two chemicals as follows:

MRID: 466948-01 - Pyrethrins PCC Review

MRID: 466947-01 - PBO PCC Review.

**Purpose:** The report entitled “Human Exposures to Products Containing Pyrethrins (PY) and Piperonyl Butoxide (PBO) Analysis of Poison Control Center (PCC) Data (2001-2003)” was prepared by Safety Call International - Science Strategies Consulting Group

for the Piperonyl Butoxide (PBO) Task Force II (PBTF II) under the auspices of the Consumer Specialty Products Association. The purpose of the report is to support reregistration and to address issues in three EPA/OPP reviews on PBO and Pyrethrins Incident Report Memoranda prepared by Jerry Blondell on April 6, 2005 and August 16, 2005). One specific issue is language for precautionary labeling warning users and the medical community about the potential of asthma or allergic reactions in sensitized individuals, especially those with preexisting respiratory disease. Thus, special attention is paid to dermal and respiratory effects.

**General Comments/Highlights:** The report summarizes PCC data for a narrower and more recent time period than the Mosby report, and it uses a descriptive analysis methodology. It raises a number of relevant points, and contains useful information on product use and usage patterns.

**Specific Comments:** Background on poison center operations described in (B) is not repeated here. The point of this review is to determine which products are currently causing the most concern, i.e., the incidents with the highest number and severity.

**(1) Classification of Cases:** Registrants who market end use products state that for the period of the EPA data review (1993-2001) no products were marketed with pyrethrins (PY) only and thus label their analysis of pyrethrins and piperonyl butoxide (PY/PBO) products. PCC Toxic Exposure Surveillance System (TESS) data classification for the 1990s makes it difficult to separate natural PY (the focus of the Pyrethrin Joint Venture) from pyrethroids. Around 2000, TESS changes eliminated this false distinction so the industry 2001-2003 analysis makes no distinction between the different chemicals.

**(2) Exclusions:** The industry analysis excludes pediculicide use (intentional administration to the skin) because FDA, not EPA, regulates them now. The analysis also excludes multiple substance products, which is reasonable given the report purpose. For public health education purposes, it would be helpful to know how many case calls were excluded for these reasons.

**(3) Wide Usage:** For 2001-2003, household insecticide sales were 40,000,000 units, according to the industry reports. Further extrapolation by the industry report to number of uses per units sold ( $n=4$ ) and the number of people per household to ( $n=3$ ) are not necessary, as 40,000,000 units is a valid large number.

**(4) Overall PCC Call Volume and PY/PBO Rates:** For 2001-2003, there were 7,043,589 human exposure cases to chemicals of all kinds reported to participating PCCs nationwide with a mean of 38,388 or 8.1 per 1000 individuals per year.

Specifically, of that total of over 7 million calls to PCCs across the USA, there were 15,427 calls related to PY/PBO with a mean of 5,142 per year. The industry report (B) description of the PCC classification scheme, caller characteristics, caller ages and medical outcome details and not repeated here.

**(5) Exposures:** Residential exposure accounted for 94% of exposure sites, and 3.6% occurred at a workplace. Eighty-one percent of cases were managed onsite; 12 % were treated en route to a health care facility, and 6% were treated at a health care facility. Most exposures were classified as unintentional cases, 11% were due to misuse situations, and 1% was intentional suicide or abuse cases. Routes of exposure for PY were: ingestion (34.2%), inhalation/nasal (27.6%), and dermal (27.2%). Some cases could not be classified as to route of exposure.

**(6) Severity of Outcome (Dermal and Respiratory):** For all cases, whether followed to completion or not, 59.4% were classified as minor effects. Of cases followed to completion, 23.4% were classified as minor. Taking account non-toxic and presumed non-toxic cases, 96% were coded minor. Moderate outcomes were seen in 381 (7.7% of all dermal calls) exposed by inhalation with 11 (0.2%) of all dermal calls experiencing major outcomes. Dermal exposure to PY/PBO resulted in 163 callers (5.3%) and 2 were major outcome cases (0.1% of all dermal calls). Ocular irritation was the most frequently reported symptom overall, and gastrointestinal (GI) symptoms were most common for ingestion cases.

**(7) Sensitive Populations with Pre-Existing Disease:** Dermal symptoms, including dermal irritation, were seen in 14% of cases. Serious dermal symptoms (moderate or major) were rare and seen in 2 cases. Respiratory symptoms were reported in 1,925 cases (12% of all cases). The duration of respiratory symptoms was 24 hours in 87% of the cases. Ten callers received bronchodilator treatment associated with symptoms. Four were classified as minor and 6 had moderate outcomes. No major (i.e. life-threatening) outcomes were seen in the time period of study. See the report for a summary of TESS data limitations, such as lack of narrative, no pre-existing condition information, lack of quantitative information on exposure and limited cause and effect information. The authors note that in spite of their limitations, the TESS data do provide important clues and safety findings for PY/PBO products.

**(8) Prevalence of Allergic Sensitization and Asthma:** As summarized in industry report (B), the Third National Health and Nutrition Examination Survey (NHANES III) reported on 10,508 individuals tested for common allergens and half were positive for one or more allergens. For short ragweed, positive test results were seen in 26.2% of those tested. In the National Health Interview Surveys (NHIS) from 1997 data, 26.7 million people (96.6/1000) reported having a physician diagnosis of asthma, and 11.1 million asthmatic individuals (40.7/1000) reported having an asthma attack or episode in the last 12 months.

The industry report authors argue that if PCC callers are evenly distributed among asthma sufferers, then there should be more PY/PBO calls and more severe cases requiring treatment. Alternately, asthma sufferers may be less likely to use products a second time , if they were previously exposed and sensitized. Or, the gap in PCC data reporting follow-up treatment may be too great to capture the outcomes of interest. PCC data are known to be an incomplete window on rare serious cases or mortality.

**(9) Relative Risk:** The industry report authors compute rates of exposure using the higher 300,000,000 people exposed estimate as a denominator and they derive 1 per 20,000 exposures for PY/PBO calls and 1 per 156,000 exposures or 1 per 165,000 exposures for reported respiratory and dermal effects, based on the breakdown for 15,427 reported calls related to PY/PBO in 2001-2003.

**Part (B) Bottom Line/ Conclusions:** Using the Symptoms by Organ System data from the industry report and their actual number of 40,000,000 units sold, and converting to a more standard rate /100,000 changes the rate calculation as follows:

- 1814 PY/ PBO dermal symptoms divided by 40,000,000 PY/PBO units sold x 100,000 yields a dermal symptoms rate of **4.5 /100,000** (dermal symptoms reported to PPCs in 2001-2003 per units of PY/PBO sold), and
- 1925 respiratory symptoms divided by 40,000,000 units sold x 100,000 yields a respiratory symptoms rate of **4.8/100,000** (respiratory symptoms reported in 2001-2003 per unit of PY/PBO sold).

**(C) “Pyrethrins Allergic Contact Dermatitis in Man-- An Evidence-Based Dermatologic Review” by TG Osimitz, JA Franzosa, DR Maciver, HI Maibach (1-24-06), MRID Document # 467573-01.**

**General Comments:** This descriptive study covers 61 literature references on pyrethrum/pyrethrins botany, chemistry, refining process, allergic reactions and contact dermatitis. According to the authors interpretation, the evidence is lacking for allergic contact dermatitis resulting from exposure to pyrethrum in man and for cross reactions in ragweed sensitive people.

Moreover, they note that since 1967 use of refined pyrethrins has lowered the level of putative sensitizers compared to the ground chrysanthemum flowers or less refined extracts used earlier in the twentieth century. The flowers for commercial production of pyrethrins are grown mainly in East Africa and Australia, and solvent extraction to produce a resin for further commercial refining, production and formulation is also done overseas. See Appendix B for a description of EPA/ SRRD pyrethrins and related terminology.

**Part (C) Specific Comments:**

The following points are of note:

**(1) Terminology:** Pyrethrins are the insectically active ingredient in pyrethrum. Not all authors use the same terminology, so unless there is a distinction made the terms are consider synonymous.

**(2) Known History of Sensitization:** Sensitization for pyrethrum exposure has been known in the medical literature for 100 years, and according to the industry report are products used to treat head lice are so labeled when regulated by FDA.

**(3) Chemistry of Commercial Pyrethrins:** Pyrethrins are a mixture of biologically active esters that vary in composition and sensitizing properties. Of those compounds, terpenoids are of interest as putative dermal sensitizers.

**(C) Bottom Line Conclusions:**

The authors state that based on current chemistry and the current level of diagnostic standards, allergic contact dermatitis does not occur in response to pyrethrum/pyrethrin “at a significant incidence in either ragweed sensitive individuals or otherwise” but they do not provide the detailed evidence to support this conclusion.

The authors report on an exhaustive search of the literature and attempted to score the papers for the strength of the evidence. OPP believes that this is difficult to do given the variability in the literature over the last 200 years, and uncertainty on the purity and strength of material tested, appropriateness of the vehicle used in earlier patch testing, and number of persons tested.

The Pyrethrin Joint Venture (PJV) provision of known standards for future diagnostic testing is a worthwhile initiative.

## Appendix A: Odds Ratio and Confidence Intervals Defined

[\*An odds ratio, cross product ratio or relative odds is defined differently according to the situation under discussion.]

Consider the following example:

	Used pyrethrins	No use of pyrethrins
Asthma	a	b
No asthma	c	d

The odds ratio (cross product ratio) is  $ad/bc$ .

\*\*Confidence intervals, or confidence limits are the range of values determined by the degree of presumed random variability in the data, within which the value of a parameter (e.g., a mean) is thought to lay, with a specified degree of confidence, often 95%. The boundaries of a confidence interval are the confidence limits. JD Last (1983) *A Dictionary of Epidemiology*, p. 73 and p. 21.]

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## Appendix B: Pyrethrins and Related Terminology from EPA/SRRD

Pyrethrins are botanical insecticides that come from the pyrethrum flower, *Chrysanthemum cinerariaefolium*. Pyrethrins have limitations because of the cost of production and instability in sunlight; therefore, many synthetic pyrethrins-like compounds were developed to be more stable in sunlight and cost effective. These compounds are referred to as synthetic pyrethroids.

There are no active end-use product registrations that contain pyrethrum. All end-use products contain the refined chemical pyrethrins.

The term “pyrethrins” refers to all six isomers found in pyrethrum, extracts which are obtained from the dried and ground flowers of the pyrethrum plant, *Chrysanthemum cinerariaefolium*. The CAS Registry No. for the mixture is 8003-34-7.

The individual isomers are referred to by the common names of the acid followed by an Arabic number 1 or 2 (i.e., pyrethrin 1, pyrethrin 2, cinerin 1, cinerin 2, jasmolin 1, jasmolin 2). If the term pyrethrin is followed by a roman numerical designation, than it refers to all of the isomers of that number in the pyrethrum extract (e.g., pyrethrins I includes pyrethrin 1, cinerin 1, and jasmolin 1). See Table 12 for a summary of terms.

<b>Table 1: Pyrethrins Terms</b>	
Pyrethrum	Plant extract from <i>Chrysanthemum cinerariaefolium</i> , containing all 6 isomers
Pyrethrins	pyrethrin 1, pyrethrin 2, cinerin 1, cinerin 2,

	jasmolin 1, jasmolin 2
Pyrethrins I	pyrethrin 1, cinerin 1, and jasmolin 1

**Partial List of synthetic pyrethroids:** (Case chemicals \* in the Mosby report (A) and related NIOSH SENSOR OR documents \*\* were reviewed separately and excluded from the final version of this review of pyrethrin only, and other pyrethroids

allethrin  
 bioresmethrin  
 \*cyfluthrin  
 \*cypermethrin  
 cyphenothrin  
 deltamethrin  
 d-phenothrin  
 \* \*esfenvalerate  
 fenvalerate  
 fluvalinate  
 \*permethrin  
 resmethrin  
 sumethrin  
 tetramethrin

cc: Hans Allender, HED  
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 HED pyrethrin/ pyrethroids/ piperonyl butoxide files