UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

August 16, 2005

MEMORANDUM

SUBJECT: Review of Pyrethrins Incident Reports - Second Revision
DP Barcode D320300, Chemical #069001

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BACKGROUND

The following data bases have been consulted for the poisoning incident data on the active ingredient Pyrethrins (PC Code:069001):

1) OPP Incident Data System (IDS) - reports of incidents from various sources, including registrants, other federal and state health and environmental agencies and individual consumers, submitted to OPP since 1992. Reports submitted to the Incident Data System represent anecdotal reports or allegations only, unless otherwise stated. Typically no conclusions can be drawn implicating the pesticide as a cause of any of the reported health effects. Nevertheless, sometimes with enough documentation risk mitigation measures may be suggested.

2) Poison Control Centers - as the result of a data purchase by EPA, OPP received Poison Control Center data covering the years 1993 through 1998 for all pesticides. Most of the national Poison Control Centers (PCCs) participate in a national data collection system, the Toxic Exposure Surveillance System which obtains data from about 65-70 centers at hospitals

and universities. PCCs provide telephone consultation for individuals and health care providers on suspected poisonings, involving drugs, household products, pesticides, etc.
3) California Department of Pesticide Regulation - California has collected uniform data on suspected pesticide poisonings since 1982. Physicians are required, by statute, to report to their local health officer all occurrences of illness suspected of being related to exposure to pesticides. The majority of the incidents involve workers. Information on exposure (worker activity), type of illness (systemic, eye, skin, eye/skin and respiratory), likelihood of a causal relationship, and number of days off work and in the hospital are provided.

4) National Pesticide Telecommunications Network (NPTN) - NPTN is a toll-free information service supported by OPP. A ranking of the top 200 active ingredients for which telephone calls were received during calendar years 1984-1991, inclusive has been prepared. The total number of calls was tabulated for the categories human incidents, animal incidents, calls for information, and others.

5) National Institute of Occupational Safety and Health's Sentinel Event Notification System for Occupational Risks (NIOSH SENSOR) performs standardized surveillance in seven states from 1998 through 2002. States included in this reporting system are Arizona, California, Florida, Louisiana, Michigan, New York, Oregon, Texas, and Washington. Reporting is very uneven from state to state because of the varying cooperation from different sources of reporting (e.g., workers compensation, Poison Control Centers, emergency departments and hospitals, enforcement investigations, private physicians, etc.). Therefore, these reports should not be characterized as estimating the total magnitude of poisoning. The focus is on occupationally-related cases not residential or other non-occupational exposures. However, the information collected on each case is standardized and categorized according the certainty of the information collected and the severity of the case.

Pyrethrins REVIEW

I. Incident Data System

The Incident Data System only had one case that could positively be identified as containing pyrethrins and no other active ingredient. The Office of Pesticide Programs has registered about 8,000 products containing pyrethrins over the years and nearly all contain a syngergist, principally piperonyl butoxide which contributes to its effects. Only about 120 products (nearly half are intermediates, intended for use in formulation) are registered containing just pyrethrins as the active ingredient. This complicates the determination of what effects, if any, are due to pyrethrin exposure alone. Only one incident of a pyrethrins powder is reported in the Incident Data System in Washington State in 1996 when eight employees where repackaging the powder into smaller containers. All eight cases were seen in an emergency department for unspecified symptoms. Seven of the illnesses were categorized as probably and one possibly due to their exposure. Please see the review by Blondell (2004) for a comparison of symptoms reported due to pyrethrins alone and pyrethrins with piperonyl butoxide.

II. Poison Control Center Data - 1993 through 2001

Results for the years 1993 through 2001 are presented below for occupational and non-occupational reports involving adults and older children and for children under age six. Cases involving exposures to multiple products or unrelated outcome are excluded. Tables 1-3 present the hazard information for pyrethrins compared with all other pesticides on six measures: percent with symptoms, percent with moderate, major, or fatal outcome, percent with major or fatal outcome, percent of exposed cases seen in a health care facility, and percent hospitalized and percent seen in a critical care facility. Table 1 presents the information for occupational cases, Table 2 for non-occupational cases involving adults and older children, and Table 3 for children under six.

Note that the majority of cases reviewed below probably involve lice shampoos, regulated by FDA, and intended for direct use on humans. Therefore, the evidence below likely overstates the risk of pyrethrin-only products. However, intentional use of pesticides on people are often one of the best sources of information on the potential for adverse effects. Most of the 100,000 pesticide exposures reported to Poison Centers each year are due to misuse resulting from direct application to skin, eyes, inhalation, or ingestion. Although these exposures are unintentional, they, like the intentional use of lice shampoo, can provide an indication of what types of effects are likely when misuse or inadvertent exposures occur. On the other hand, it should be acknowledged that percents and ratios presented in the table below largely reflect the use of lice shampoo rather than the typical pyrethrin product. The typical pyrethrin product contains more than one active ingredient and, given pyrethrins low toxicity, it is impossible to determine whether resultant effects are due to pyrethrins or some other ingredient.

Of the 1,447 products containing pyrethrins actively registered with EPA in 2004, only 66 (less than 5%) contain pyrethrins as the only active ingredient. Most of these are intermediate formulations, leaving only about 28 products (less than 2%) formulated for end use by the public. Of the 28 products only four were identified in the Poison Control Center's controlled list of product brand names. These four products were not responsible for enough cases to warrant a review, so instead the review below is largely dependent on FDA products used for head lice and the generic category "pyrethrins only (alone)". This generic category was responsible for over 4,000 exposures but it is not possible to determine what portion of this category was lice shampoos and what portion may have included products mixed with synergists and therefore, incorrectly coded.

To the extent that even direct application of lice shampoo does not cause higher rates of symptoms or requirements for health care, it reinforces the finding that pyrethrins are generally safer than other pesticides or, more specifically, other insecticides. An analysis of the symptoms occurring among the more serious exposures can be useful in identifying the primary risks from exposures to pyrethrins and suggesting warnings or label precautions for users.

Table 1. Comparison between pyrethrins and all insecticides and pesticides for percent cases

with symptomatic outcome (SYM), moderate or more severe outcome (MOD), life-threatening or fatal outcome (MAJ), seen in a health care facility (HCF), hospitalized (HOSP), or seen in an intensive care unit (ICU) reported to TESS, 1993-2001 for occupational cases only.

| Denominator measure | Severity of outcome (outcome determined) | | | Total exposed | Health care provided | |
|---|---|---|---|---|---|---|
| Denominator number | 269 | | | 420 | 123 | |
| Numerator measure | SYM* | MOD | MAJ | HCF* | HOSP* | ICU* |
| Numerator number | 257 | 38 | 0 | 123 | 5 | 1 |
| Pyrethrins percent | 95.5% | 14.1% | 0% | 29.3% | 4.06% | 0.81% |
| Insecticides percent | 86.7% | 20.1% | 0.737% | 42.0% | 8.18% | 3.84% |
| Ratio pyrethrins/insecticides | 1.10 | 0.70 | 0.0 | 0.70 | 0.50 | 0.21** |
| Pesticides percent | 86.1% | 19.6% | 0.681% | 45.6% | 6.14% | 2.40% |
| Ratio pyrethrins/pesticides | 1.11 | 0.72 | 0.0 | 0.64 | 0.66 | 0.34** |

* Denominator for HCF is total exposed. Denominator for HOSP and ICU are cases seen in health care facility.
** Ratio based on a single case.

Table 2. Comparison between pyrethrins and all insecticides and all pesticides for percent cases with symptomatic outcome (SYM), moderate or more severe outcome (MOD), life-threatening or fatal outcome (MAJ), seen in a health care facility (HCF), hospitalized (HOSP), or seen in an intensive care unit (ICU) reported to TESS, 1993-2001 for non-occupational cases involving adults and older children.

| Denominator measure | Severity of outcome (outcome determined) | | | Total exposed | Health care provided | |
|---|---|---|---|---|---|---|
| Denominator number | 3087 | | | 5475 | 854 | |
| Numerator measure | SYM | MOD | MAJ | HCF* | HOSP* | ICU* |
| Numerator number | 2260 | 404 | 7 | 854 | 16 | 9 |
| Pyrethrins percent | 73.2% | 13.1% | 0.227% | 15.6% | 1.87% | 1.05% |

| Denominator measure | Severity of outcome (outcome determined) | | | Total exposed | Health care provided | |
|---|---|---|---|---|---|---|
| Denominator number | 3087 | | | 5475 | 854 | |
| Numerator measure | SYM | MOD | MAJ | HCF* | HOSP* | ICU* |
| Insecticides percent | 69.7% | 11.7% | 0.439% | 15.6% | 6.86% | 3.30% |
| Ratio pyrethrins/insecticides | 1.05 | 1.12 | 0.52 | 1.00 | 0.27 | 0.32 |
| Pesticides percent | 68.4% | 11.0% | 0.408% | 15.3% | 6.89% | 2.95% |
| Ratio pyrethrins/pesticides | 1.07 | 1.19 | 0.56 | 1.02 | 0.27 | 0.36 |

* Denominator for HCF is total exposed. Denominator for HOSP and ICU are cases seen in health care facility.

Table 3. Comparison between pyrethrins and all pesticides for percent cases with symptomatic outcome (SYM), moderate or more severe outcome (MOD), life-threatening or fatal outcome (MAJ), seen in a health care facility (HCF), hospitalized (HOSP), or seen in an intensive care unit (ICU) reported to Poison Control Centers, 1993-2001 for non-occupational cases involving children less than six years old.

| Denominator measure | Severity of outcome (outcome determined) | | | Total exposed | Health care provided | |
|---|---|---|---|---|---|---|
| Denominator number | 2280 | | | 4033 | 587 | |
| Numerator measure | SYM | MOD | MAJ | HCF* | HOSP* | ICU* |
| Numerator number | 926 | 157 | 5 | 589 | 12 | 4 |
| Pyrethrins percent | 40.6% | 6.88% | 0.219% | 14.6% | 2.04% | 0.68% |
| Insecticides percent | 26.1% | 1.96% | 0.216% | 9.94% | 8.76% | 3.50% |
| Ratio pyrethrins/insecticides | 1.56 | 3.51 | 1.01 | 1.47 | 0.23 | 0.19 |
| Pesticides percent | 21.6% | 1.41% | 0.127% | 14.8% | 4.85% | 1.46% |
| Ratio pyrethrins/pesticides | 1.88 | 4.88 | 1.72 | 0.99 | 0.42 | 0.46 |

* Denominator for HCF is total exposed. Denominator for HOSP and ICU are cases seen in health care facility.

The tables above are based on nearly 10,000 exposures, consistent with the widespread use of this insecticide and its use for head lice. From 1993-98 there were 4,164 exposures categorized as "Pyrethrins only (alone)" which accounted for 42% of the observations. However, this category was not used in the 1999-2001 data set.

Using the data for 1993-98, symptom prevalence was examined among the 485 reports of moderate or major medical outcome. The most common symptom was eye irritation/pain likely from getting pyrethrin-based lice shampoo in the eyes. Effect to the eyes accounted for five of the top ten symptoms reported: eye irritation, corneal abrasion, lacrimation, eye burns, and blurred vision. The application of pyrethrins as lice shampoo likely accounts for the overwhelming majority of these cases. The third most common symptom report was dyspnea or difficulty breathing. Coughing and bronchospasm were also among the top 20 reported symptoms. Five of the top 20 symptoms involved dermal effects including irritation, edema, erythema, rash, and itching. These findings are consistent with reports that "Crude pyrethrum is a dermal and respiratory allergen, probably due mainly to non-insecticidal ingredients. Contact dermatitis and allergic respiratory reactions (rhinitis and asthma) have occurred following exposures . . . The refined pyrethrins are probably less allergenic, but appear to retain some irritant and/or sensitzing properties" (Reigart and Roberts 1999).

Note that none of the ratios are above 1.2 with the exception of children under six years of age. This is likely due to the overwhelming use of lice shampoos in this age group where the pesticide is applied directly to the scalp and often gets into the eyes. The ratio for major medical outcome in children was based on four cases: three with severe eye effects and one with multiple seizures. As noted in the review of piperonyl butoxide (Review of Piperonyl butoxide Incident Reports, DP Barcode D302303, Chemical #067501, by Jerome Blondell), "Interestingly, five of the six lowest ratios [pyrethrins alone leads to more symptoms than pyrethrins combined with piperonyl butoxide] were all eye effects (blurred vision, burns to eye, corneal abrasion, eye irritation or pain, and lacrimation)." This may be due to pyrethrin products used as lice shampoos near the eyes or due to their formulation as powders and dusts which may be more likely to cause problems when they inadvertently get into eyes.

A more recent analysis examined of symptoms among reports categorized as moderate or major medical outcome for the years 1993 through 2003 due to pyrethrins and pyrethroids revealed that the most common symptom was dyspnea, present in 45% of 7,096 reports. Also reported in 15% or more of the 7,096 reports was bronchospasm (18%), cough/choke (35%), eye irritation (36%), corneal abrasion (15%), nausea (18%), and vomiting (18%). The prevalence of the respiratory symptoms, dyspnea, bronchospasm, and cough/choke, suggest that pyrethrins and pyrethroids may pose risks for persons with a history of respiratory illness, allergy, or asthma.

III. California Data - 1982 through 2002

Detailed descriptions of four cases submitted to the California Pesticide Illness Surveillance Program (1982-2002) were reviewed in which pyrethrins was used alone or was judged to be responsible for the health effects. Excluded from the review were 1,131 cases where pyrethrins were involved but not be determined to be the primary cause of the incident. Only cases with a definite, probable or possible relationship were reviewed. Excluded from the review were any cases where the primary cause of illness could not be determined. Among the four cases, all were considered possible but not probable or definite causes of the incidents reported. In a fogging incident, a worker experienced eye irritation. A dog groomer developed shortness of breath and chest pains from dermal contact with a dog dip. She had not received proper training for how to handle this pesticide. A stable worker was inadvertantly sprayed by someone treating a horse and experienced rash and productive cough. Finally, a 28 year-old man attempted suicide by spraying the pesticide inside his mouth. Initially he vomited and at the hospital it was found he had additional symptoms related to exposure to narcotics. It is not known what contribution the pyrethrins, synergists, or narcotics may have had to the resultant symptoms.

IV. National Pesticide Telecommunications Network

The National Pesticide Telecommunications Network does receive a large number of calls related to pyrethrins-containing products. In the most recent report for 2003, pyrethrin ranked sixth, with 74 incidents of which 45 involved humans, 40 involved animals, and nine involved other contamination-related problems. Of the 45 cases seen in humans, only 4 were designated as probable or a definite cause of the resulting adverse effects. This is because incidents are usually reported by telephone and documentation of exposure or health effects is seldom sufficient to establish a likely or definite cause and effect relationship. Also, most of these products also contain other ingredients and a large percentage are not specifically identified by product brand name. Therefore, extensive review of this information is not likely to add to our knowledge of the specific effects of pyrethrins.

V. NIOSH SENSOR reports 1998-2002

The NIOSH SENSOR reported 39 cases from 1998 through 2002. Of these, 10 occurred in California, seven in Florida, two in Louisiana, 10 in Oregeon, eight in Texas, and two in Washington. Note that the California reports come from the California Department of Health Services which use different criteria for listing an incident as due to pyrethins than the California Department of Pesticide Regulation (cited in section III above) which reported only 4 cases where pyrethrins was determined to be the primary pesticide responsible for the illness in their data from 1982 to 2002. All of the cases with one exception had a minor or unknown severity. Several cases may have involved other ingredients which were not clearly identified. The one case with moderate medical outcome experienced dermal and respiratory symptoms.

VI. Scientific Literature

**A. Hazardous Substances Data Base**

Maintained by the National Institutes of Health, this database provides comprehensive, scientifically reviewed highlights of the dermal and respiratory concerns related to pyrethrins. The following information was copied from the Hazardous Substances Databank (HSDB), a database of the National Library of Medicine's TOXNET system (http://toxnet.nlm.nih.gov) on April 2, 2003.
Query: The chemical name pyrethrins was identified.
**NAME: PYRETHRIN I**
CASRN: 121-21-1

**Human Toxicity Excerpts**:

The type I pyrethroids /including pyrethrin I/ produce the simplest poisoning syndrome & produce sodium tail currents with relatively short time constants. Poisoning closely resembles that produced by DDT & involves a progressive development of fine whole-body tremor, exaggerated startle response, incoordinated twitching of the dorsal muscles, hyperexcitability, & death. The tremor is assoc with a large incr in metabolic rate & leads to hyperthermia, which, with metabolic exhaustion, is the usual cause of death. Respiration & blood pressure are well sustained but plasma noradrenaline, lactate, & to a lesser extent adrenaline are greatly increased. [Hayes, W.J., Jr., E.R. Laws, Jr., (eds.). Handbook of Pesticide Toxicology. Volume 2. Classes of Pesticides. New York, NY: Academic Press, Inc., 1991. 589]**PEER REVIEWED**

Death occurred in a 2 yr old child following ingestion of approximately 14 g of pyrethrum powder (1-3% pyrethrins). Ingestion of 5-50 mg of pyrethrins reportedly produces no toxic effects.
[McEvoy, G.K. (ed.). American Hospital Formulary Service - Drug Information 2000.Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2000 (Plus Supplements). 3204]**PEER REVIEWED**

The most common adverse reaction results from the potent sensitizing properties of /SRP: inadequately purified/ pyrethrins. Clinical manifestations of exposure include contact dermatitis (erythema, vesiculation, bullae), anaphylactoid reactions (pallor, tachycardia, diaphoresis), and asthma. /Pyrethrins/
[Ellenhorn, M.J. and D.G. Barceloux. Medical Toxicology - Diagnosis and Treatment of Human Poisoning. New York, NY: Elsevier Science Publishing Co., Inc. 1988. 1081]**PEER REVIEWED**

When 200 people (177 women & 23 men) were patch tested with a 1% water dispersion of

pyrethrins, no evidence of primary irritancy or of sensitization was found. /Pyrethrins/
[Hayes, W.J., Jr., E.R. Laws, Jr., (eds.). Handbook of Pesticide Toxicology. Volume 2. Classes of Pesticides. New York, NY: Academic Press, Inc., 1991. 593]**PEER REVIEWED**

Formerly, contact allergy from pyrethrums was common & was caused by sensitizing sesquiterpene lactones contained in the crude extract (derived from a chrysanthemum species). Today, the extraction & purification process is such that the active insecticidal principle present in modern pyrethrum-containing insecticides should not contain any sensitizing sesquiterpene lactone. /Pyrethrums/
[Zenz, C., O.B. Dickerson, E.P. Horvath. Occupational Medicine. 3rd ed. St. Louis, MO., 1994 108]**PEER REVIEWED**

Caution: /Pyrethrum or inadequately purified pyrethrins/ can cause severe allergic dermatitis, systemic allergic reactions. Large amounts may cause nausea, vomiting, tinnitus, headache, & other CNS disturbances. /Pyrethrins/
[Budavari, S. (ed.). The Merck Index - Encyclopedia of Chemicals, Drugs and Biologicals. Rahway, NJ: Merck and Co., Inc., 1989. 1267]**PEER REVIEWED**

The clinical manifestations of inhalation exposure to pyrethrins can be local or systemic. Localized reactions confined to the upper respiratory tract include rhinitis, sneezing, scratchy throat, oral mucosal edema, and even laryngeal mucosal edema. Localized reaction of the lower respiratory tract include cough, shortness of breath, wheezing, and chest pain. An asthma like reaction occurs with acute exposures in sensitized patients. Hypersensitivity pneumonitis characterized by chest pain, cough, dyspnea, & bronchospasm may occur in an individual chronically exposed. /Pyrethrum and synthetic pyrethroids/
[Ellenhorn, M.J., S. Schonwald, G. Ordog, J. Wasserberger. Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning. 2nd ed. Baltimore, MD: Williams and Wilkins, 1997. 1626]**PEER REVIEWED**

A 36 yr old woman with a history of asthma developed severe shortness of breath 5 min after she began to wash her dog with an insecticide shampoo containing 0.05% pyrethrin. She soon developed gasping respiration. In 5 min she was in cardiopulmonary arrest. Despite resuscitative efforts she died. Postmortem findings were considered to be compatible with asthma. /Pyrethrin/
[Ellenhorn, M.J., S. Schonwald, G. Ordog, J. Wasserberger. Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning. 2nd ed. Baltimore, MD: Williams and Wilkins, 1997. 1626]**PEER REVIEWED**

Superficial corneal abrasions have been reported after use of a 0.17% synergized pyrethrin shampoo to control head lice in children, although this may have been the result of ingredients other than pyrethrins.
[Hayes, W.J., Jr., E.R. Laws, Jr., (eds.). Handbook of Pesticide Toxicology. Volume 2. Classes of Pesticides. New York, NY: Academic Press, Inc., 1991. 593]**PEER REVIEWED**

**Skin, eye, and respiratory irritations**:

... Pyrethrin I ... in pure form /is/ ... irritating to eyes & mucous membranes.
[Grant, W.M. Toxicology of the Eye. 3rd ed. Springfield, IL: Charles C. Thomas Publisher, 1986. 774]**PEER REVIEWED**

**Drug warnings:**

Individuals sensitive to ragweed have shown cross-sensitivity to unrefined but not to refined pyrethrins; however, manufacturers of pyrethrins combinations warned that these products should not be used by ragweed-sensitive patients. /Pyrethrins/
[McEvoy, G.K. (ed.). American Hospital Formulary Service - Drug Information 2000.Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2000 (Plus Supplements). 3204]**PEER REVIEWED**

Local irritation incl erythema, pruritus, urticaria, edema, eczema, & slight corneal erosion & stromal edema may occur & ... contact with face, eyes, mucous membranes, & urethral meatus should be avoided. ... Pyrethrins with piperonyl butoxide should not be applied to acutely inflamed skin or raw, weeping surfaces. ... The drug should not be used more than twice in 24 hours. /Pyrethrins/
[McEvoy, G.K. (ed.). American Hospital Formulary Service - Drug Information 2000.Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2000 (Plus Supplements). 3204]**PEER REVIEWED**

Chronic respiratory disease: In persons with chronic respiratory disease, especially asthma, the inhalation of /pyrethroids/ might cause exacerbation of symptoms due to its sensitizing properties. Skin disease: /Pyrethroids/ can cause dermatitis which may be allergic in nature. Persons with pre-existing skin disorders may be more susceptible to the effects of this agent. Any employee developing the above-listed conditions should be referred for further medical examination. /Pyrethrum/
[Mackison, F. W., R. S. Stricoff, and L. J. Partridge, Jr. (eds.). NIOSH/OSHA - Occupational Health Guidelines for Chemical Hazards. DHHS(NIOSH) PublicationNo. 81-123 (3 VOLS). Washington, DC: U.S. Government Printing Office, Jan. 1981. 1]**PEER REVIEWED**

In persons with chronic respiratory disease and especially asthma, the inhalation of pyrethrum /and inadequately purified pyrethrins/ might cause exacerbation of symptoms due to its sensitizing properties. Skin disease: Pyrethrum can cause dermatitis which may be allergic in nature. Persons with preexisting skin disorders may be more susceptible to the effects of this agent. /Pyrethrum/
[Mackison, F. W., R. S. Stricoff, and L. J. Partridge, Jr. (eds.). NIOSH/OSHA - Occupational Health Guidelines for Chemical Hazards. DHHS(NIOSH) PublicationNo. 81-123 (3 VOLS). Washington, DC: U.S. Government Printing Office, Jan. 1981. 1]**PEER REVIEWED**

The following information was copied from the Hazardous Substances Databank (HSDB), a database of the National Library of Medicine's TOXNET system (http://toxnet.nlm.nih.gov/cgi-bin/sis/search) on January 27, 2005.
Query: The chemical name pyrethrins was identified.
**NAME: PYRETHRUM**
CASRN: 8003-34-7

**Human Toxicity Excerpts**:

Since the pyrethrin concentration of pyrethrum powder is about 1-3% & of insecticide sprays is usually 1-2%, serious poisoning are highly improbable, but death of a 2 yr old child has been attributed to ingestion of 1/2 oz (15 g) of pyrethrum concentrate. Kerosene & naphtha, the common solvents in pyrethrum sprays, are generally more hazardous than the "active ingredients".
[Gosselin, R.E., R.P. Smith, H.C. Hodge. Clinical Toxicology of Commercial Products. 5th ed. Baltimore: Williams and Wilkins, 1984., p. III-353]**PEER REVIEWED**

An 11 mo old infant was playing with a box of pyrethrum powder when the top came off & the child's mouth, nostrils, & entire face were covered with the powder. Within moments, the baby suffered pallor, intermittent convulsions, & then vomiting. As soon as physician arrived, he found the child collapsed, reddened by pain when pulled up by the hands, & refusing to nurse. Heart sounds were feeble & slow & resp was labored. The face & mucous membranes were washed carefully. Two doses of syrup of ipecac (10 g each at interval of 5 min) produced abundant vomiting. Except for slight inflammation of conjunctivae & extreme reddening of lips & tongue, the child was essentially recovered in 1.5 hr & resumed nursing.
[Hayes, Wayland J., Jr. Pesticides Studied in Man. Baltimore/London: Williams and Wilkins, 1982., p. 79]**PEER REVIEWED**

Injury to humans ... has most frequently resulted from allergic properties ... rather than ... direct toxicity. Although the allergy usually has been assoc with occupational or therapeutic contact, it is impossible to exclude the possibility of injury assoc with other kinds of exposure. Pyrethrum sensitivity may manifest itself in several forms. ... Contact dermatitis is by far the most common. The usual ... /outbreak/ is a mild erythematous vesicular dermatitis with papules in moist areas, & intense pruritus. In few cases, bullae appear. Edema & cracking develop in severe cases. Pyrethrum dermatitis may be made worse by exposure to sun. Several cases have shown ... "local anaphylaxis", characterized by dermatitis & sudden severe swelling of face, sometimes incl eyes & lips. A mild form accompanied by tachycardia, pallor, sweating, & fever was produced in ... experiments. Some individuals show manifestations of pyrethrum sensitivity similar to those seen in pollinosis, incl sneezing, serous nasal discharge, & nasal stuffiness.
[Hayes, Wayland J., Jr. Pesticides Studied in Man. Baltimore/London: Williams and Wilkins, 1982., p. 79]**PEER REVIEWED**

Although pyrethrins are reported to be contact allergens, occasional incidents of sensitization characterized by dermatitis were probably due to impurities from the pyrethrum flowers. Commercially avail prepn of pyrethrins are refined ... & usually only very mild skin sensitization occurs.
[American Hospital Formulary Service-Drug Information 85. Bethesda, MD: American Society Hospital Pharmacists, 1985. (Plus supplements A & B, 1985)., p. 1604]**PEER REVIEWED**

Inhalation of dust or spray mists can cause headache & nausea.
[Hartley, D. and H. Kidd (eds.). The Agrochemicals Handbook. Old Woking, Surrey, United Kingdom: Royal Society of Chemistry/Unwin Brothers Ltd., 1983., p. A357/Oct 83]**PEER REVIEWED**

... Only 1 case of pneumonitis due to pyrethrins has been reported. The patient was hospitalized because of fatigue, chest pain, coughing, & shortness of breath. X-ray revealed coarse, reticular, diffuse, bilateral interstitial pattern in lung. Lung biopsy showed interstitial fibrosis with eosinophilic infiltration & large aggregates of histiocytic cells. No pathogen grew on culture. A pulmonary challenge test with the insecticide was positive as was a skin test with pyrethrum alone. The patient admitted using about 2.5 aerosol cans of pyrethrum-based insecticide in her home each week.
[Hayes, Wayland J., Jr. Pesticides Studied in Man. Baltimore/London: Williams and Wilkins, 1982., p. 79]**PEER REVIEWED**

With massive doses ingested orally, nervous system symptoms may occur, which incl excitation & convulsions leading to paralysis & accompanied by muscular fibrillation & diarrhea. Death is due to resp failure.
[Doull, J., C.D.Klassen, and M.D. Amdur (eds.). Casarett and Doull's Toxicology. 3rd ed., New York: Macmillan Co., Inc., 1986., p. 553]**PEER REVIEWED**

SYMPTOMATOLOGY: (largely inferred from animal studies): 1) Numbness of lips and tongue, sneezing, nausea, vomiting, and diarrhea. 2) Headache, restlessness, tinnitus, incoordination, clonic convulsions, stupor, and prostration. 3) Death due to respiratory paralysis. 4) Skin contact may cause dermatitis, sometimes with an associated eosinophilia. 5) Hydrocarbon solvents such as kerosene may produce pulmonary edema.
[Gosselin, R.E., R.P. Smith, H.C. Hodge. Clinical Toxicology of Commercial Products. 5th ed. Baltimore: Williams and Wilkins, 1984., p. III-354]**PEER REVIEWED**

Crude pyrethrum is a dermal and respiratory allergen, probably due mainly to non-insecticidal ingredients. Contact dermatitis and allergic respiratory reactions (rhinitis and asthma) have occurred following exposures. Single cases exhibiting anaphylactic and pneumonitic manifestation have also been reported. The refined pyrethrins are probably less allergenic, but appear to retain some irritant and/or sensitizing properties.
[U.S. Environmental Protection Agency/Office of Prevention, Pesticides, and Toxic Substances. Reigart, J.R., Roberts, J.R. Recognition and Management of Pesticide Poisonings. 5th ed. 1999.

EPA Document No. EPA 735-R-98-003, and available in electronic format at: http://www.epa.gov/pesticides/safety/healthcare, p. 68]**PEER REVIEWED**

Prepn containing synthetic pyrethroids are less likely to result in allergic reactions.
[Doull, J., C.D.Klassen, and M.D. Amdur (eds.). Casarett and Doull's Toxicology. 3rd ed., New York: Macmillan Co., Inc., 1986., p. 553]**PEER REVIEWED**

Death occurred in a 2-yr-old child following ingestion of approx 14 g of pyrethrum powder (1-3% pyrethrins). Ingestion of 5-50 mg of pyrethrins reportedly produces no toxic effects.
[McEvoy, G.K. (ed.). American Hospital Formulary Service - Drug Information 2000.Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2000 (Plus Supplements)., p. 3204]**PEER REVIEWED**

Exposure to the natural pyrethrum mixture is known to cause contact dermatitis, and descriptions of the effects range from localized erythema to a severe vesicular eruption.
[Klaassen, C.D., M.O. Amdur, Doull J. (eds.). Casarett and Doull's Toxicology. The Basic Science of Poisons. 5th ed. New York, NY: McGraw-Hill, 1995., p. 667]**PEER REVIEWED**

Accidental and Intentional Poisoning. Very little injury by pyrethrum has been the result of recognized accidents. There is one report of a 2-yr-old girl in Montreal who died after eating about half an of ounce of insect powder.
[Hayes, W.J., Jr., E.R. Laws, Jr., (eds.). Handbook of Pesticide Toxicology. Volume 2. Classes of Pesticides. New York, NY: Academic Press, Inc., 1991., p. 593]**PEER REVIEWED**

Mammalian toxicity is extremely low, in part because of poor bioavailability and a large first-pass extraction by the liver. Fatalities have not been associated with pyrethrin ingestion in this century. The estimated lethal dose of pyrethrum in humans is over 1 g/kg.
[Ellenhorn, M.J. and D.G. Barceloux. Medical Toxicology - Diagnosis and Treatment of Human Poisoning. New York, NY: Elsevier Science Publishing Co., Inc. 1988., p. 1081]**PEER REVIEWED**

In a study of workers engaged in processing pyrethrum powder, 30% had erythema, skin roughening, & pruritus, which subsided on cessation of exposure. One of these workers had an anaphylactic type of reaction; shortly after entering a dust-laden room, the facial skin turned red & the person felt a sensation of burning & itching; the cheeks & eyes rapidly became swollen; the pruritus became severe. The entire condition disappeared in 2 days after removal exposure. Some persons exhibit sensitivity similar to pollinosis, with sneezing, nasal discharge, & nasal stuffiness. A few cases of asthma due to pyrethrum mixtures have been reported; some of the individuals involved had a previous history of asthma, with allergy to a wide spectrum of substances.
[Zenz, C., O.B. Dickerson, E.P. Horvath. Occupational Medicine. 3rd ed. St. Louis, MO., 1994, p. 641]**PEER REVIEWED**

The chief effect in humans from exposure to pyrethrum is dermatitis. The usual lesion is a mild erythematous dermatitis, with vesicles, papules in moist areas, and intense pruritus; a bullous dermatitis may develop.
[Geiger D.L., Poirier S.H., Brooke L.T., Call D.J., eds. Acute Toxicities of Organic Chemicals to Fathead Minnows (Pimephales Promelas). Vol. III. Superior, Wisconsin: University of Wisconsin-Superior, 1986., p. 687]**PEER REVIEWED**

The case of a 43 yr old woman with a history of asthma and ragweed allergy, who experienced an anaphylactoid reaction after self medicating with a shampoo containing pyrethrins for the treatment of head lice, is presented. Periorbital edema appeared within one hour of application of pyrethrins. The following morning, the patient developed increasing signs of shortness of breath, chest tightness and numbness and became unresponsive. Treatment included naloxone, epinephrine, dextrose, aminophylline, albuterol, methylprednisolone and prednisone. It was concluded that patients who are sensitive to airborne allergens may develop anaphylaxis when exposed to pyrethrins based products. /Pyrethrins/
[Culver CA et al; Clin Pharm 7 (Nov): 846-49 (1988)]**PEER REVIEWED**

The most common adverse reaction results from the potent sensitizing properties of /SRP: inadequately purified/ pyrethrins. Clinical manifestations of exposure include contact dermatitis (erythema, vesiculation, bullae), anaphylactoid reactions (pallor, tachycardia, diaphoresis), and asthma. /Pyrethrins/
[Ellenhorn, M.J. and D.G. Barceloux. Medical Toxicology - Diagnosis and Treatment of Human Poisoning. New York, NY: Elsevier Science Publishing Co., Inc. 1988., p. 1081]**PEER REVIEWED**

When 200 people (177 women & 23 men) were patch tested with a 1% water dispersion of pyrethrins, no evidence of primary irritancy or of sensitization was found. /Pyrethrins/
[Hayes, W.J., Jr., E.R. Laws, Jr., (eds.). Handbook of Pesticide Toxicology. Volume 2. Classes of Pesticides. New York, NY: Academic Press, Inc., 1991., p. 593]**PEER REVIEWED**

Formerly, contact allergy from pyrethrums was common & was caused by sensitizing sesquiterpene lactones contained in the crude extract (derived from a chrysanthemum species). Today, the extraction & purification process is such that the active insecticidal principle present in modern pyrethrum-containing insecticides should not contain any sensitizing sesquiterpene lactone. /Pyrethrums/
[Zenz, C., O.B. Dickerson, E.P. Horvath. Occupational Medicine. 3rd ed. St. Louis, MO., 1994, p. 108]**PEER REVIEWED**

The allergenic properties of pyrethroids /with early pyrethrum preparations/ are marked in comparison with other pesticides. Many cases of contact dermatitis and respiratory allergy have been reported. Persons sensitive to ragweed pollen are particularly prone to such reactions. Preparations containing synthetic pyrethroids are less likely to cause allergic reactions than are the preparations made from pyrethrum powder. /Pyrethroids/
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman

and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1687]**PEER REVIEWED**

Cause transient conjunctival edema & hyperemia. The constituents Pyrethrin I & II in pure form are ... irritating to eyes & mucous membranes. No persistent ocular disturbance from pyrethrum or its derivatives appears to have been reported. /Pyrethrin I & II/
[Grant, W.M. Toxicology of the Eye. 3rd ed. Springfield, IL: Charles C. Thomas Publisher, 1986., p. 774]**PEER REVIEWED**

Caution: /Pyrethrum or inadequately purified pyrethrins/ can cause severe allergic dermatitis, systemic allergic reactions. Large amounts may cause nausea, vomiting, tinnitus, headache, and other central nervous system disturbances. /Pyrethrins/
[Budavari, S. (ed.). The Merck Index - Encyclopedia of Chemicals, Drugs and Biologicals. Rahway, NJ: Merck and Co., Inc., 1989., p. 1267]**PEER REVIEWED**

About 50% of persons sensitive to ragweed exhibit cross-sensitivity to pyrethrum (ragweed and chrysanthemum are in the same botanical group).
[Ellenhorn, M.J., S. Schonwald, G. Ordog, J. Wasserberger. Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning. 2nd ed. Baltimore, MD: Williams and Wilkins, 1997., p. 1626]**PEER REVIEWED**

The clinical manifestations of inhalation exposure to pyrethrins can be local or systemic. Localized reactors confined to the upper respiratory tract include rhinitis, sneezing, scratchy throat, oral mucosal edema, and even laryngeal mucosal edema. Localized reaction of the lower respiratory tract include cough, shortness of breath, wheezing, and chest pain. An asthma like reaction occurs with acute exposures in sensitized patients. Hypersensitivity pneumonitis characterized by chest pain, cough, dyspnea, & bronchospasm may occur in an individual chronically exposed. /Pyrethrum and synthetic pyrethroids/
[Ellenhorn, M.J., S. Schonwald, G. Ordog, J. Wasserberger. Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning. 2nd ed. Baltimore, MD: Williams and Wilkins, 1997., p. 1626]**PEER REVIEWED**

Pyrethrum generally is rated as the safest insecticide because its primary toxicity is low. The low toxicity of pyrethroids in mammals is due largely to their rapid biotransformation by ester hydrolysis and/or hydroxylation.
[Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996., p. 1687]**PEER REVIEWED**

Sensitivity was produced in 10-26% of unselected test populations by repeated application of pyrethrum ointment.
[Hayes, W.J., Jr., E.R. Laws, Jr., (eds.). Handbook of Pesticide Toxicology. Volume 2. Classes of Pesticides. New York, NY: Academic Press, Inc., 1991., p. 593]**PEER REVIEWED**

**Skin, Eye and Respiratory Irritations**:

The chief effect from exposure ... is skin rash particularly on moist areas of the skin. ... May irritate the eyes.
[Mackison, F. W., R. S. Stricoff, and L. J. Partridge, Jr. (eds.). NIOSH/OSHA - Occupational Health Guidelines for Chemical Hazards. DHHS(NIOSH) Publication No. 81-123 (3 VOLS). Washington, DC: U.S. Government Printing Office, Jan. 1981., p. 1]**PEER REVIEWED**

... Pyrethrin I ... in pure form /is/ ... irritating to eyes & mucous membranes.
[Grant, W.M. Toxicology of the Eye. 3rd ed. Springfield, IL: Charles C. Thomas Publisher, 1986., p. 774]**PEER REVIEWED**

**Drug Warnings**:

Commercial /liq/ formulations /such as A-200 pyrinate, RID/ are irritating to eyes & mucous membranes & ... should not be used to treat Phthirus pubis infestations of the eyelashes ... .
[American Medical Association, Department of Drugs. Drug Evaluations. 6th ed. Chicago, Ill: American Medical Association, 1986., p. 1436]**PEER REVIEWED**

Individuals sensitive to ragweed have shown cross-sensitivity to unrefined but not to refined pyrethrins; however, manufacturers of pyrethrins combinations warned that these products should not be used by ragweed-sensitive patients. /Pyrethrins/
[McEvoy, G.K. (ed.). American Hospital Formulary Service - Drug Information 2000.Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2000 (Plus Supplements)., p. 3204]**PEER REVIEWED**

Local irritation incl erythema, pruritus, urticaria, edema, eczema, & slight corneal erosion & stromal edema may occur & ... contact with face, eyes, mucous membranes, & urethral meatus should be avoided. ... Pyrethrins with piperonyl butoxide should not be applied to acutely inflamed skin or raw, weeping surfaces. ... The drug should not be used more than twice in 24 hours. /Pyrethrins/
[McEvoy, G.K. (ed.). American Hospital Formulary Service - Drug Information 2000.Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2000 (Plus Supplements)., p. 3204]**PEER REVIEWED**

**Medical Surveillance**:

Employees should be screened for history of certain medical conditions which might place the employee at increased risk from pyrethrum exposure. Chronic respiratory disease: In persons with chronic respiratory disease and especially asthma, the inhalation of pyrethrum might cause exacerbation of symptoms due to its sensitizing properties. Skin disease: Pyrethrum can cause dermatitis which may be allergic in nature. Persons with preexisting skin disorders may be more susceptible to the effects of this agent.
[Mackison, F. W., R. S. Stricoff, and L. J. Partridge, Jr. (eds.). NIOSH/OSHA - Occupational

Health Guidelines for Chemical Hazards. DHHS(NIOSH) Publication No. 81-123 (3 VOLS). Washington, DC: U.S. Government Printing Office, Jan. 1981., p. 1]**PEER REVIEWED**

Initial medical screening: Employees should be screened for history of certain medical conditions ... which might place the employee at increased risk from /pyrethroid/ exposure. Chronic respiratory disease: In persons with chronic respiratory disease, especially asthma, the inhalation of /pyrethroids/ might cause exacerbation of symptoms due to its sensitizing properities. Skin disease: /Pyrethroids/ can cause dermatitis which may be allergic in nature. Persons with pre-existing skin disorders may be more susceptible to the effects of this agent. Any employee developing the above-listed conditions should be referred for further medical examination. /Pyrethrum/
[Mackison, F. W., R. S. Stricoff, and L. J. Partridge, Jr. (eds.). NIOSH/OSHA - Occupational Health Guidelines for Chemical Hazards. DHHS(NIOSH) Publication No. 81-123 (3 VOLS). Washington, DC: U.S. Government Printing Office, Jan. 1981., p. 1]**PEER REVIEWED**

**Populations at Special Risk**:

Cases of asthmatic-like reactions have been reported in some individuals who had previous history of asthma with broad allergic background.
[Doull, J., C.D.Klassen, and M.D. Amdur (eds.). Casarett and Doull's Toxicology. 3rd ed., New York: Macmillan Co., Inc., 1986., p. 553]**PEER REVIEWED**

Sensitivity as judged by skin tests occurs in over 40% of persons who are sensitive to ragweed. However, patch tests were positive in only 1.3% of patients with various skin diseases, incl some with allergic contact dermatitis of unspecified cause.
[Hayes, Wayland J., Jr. Pesticides Studied in Man. Baltimore/London: Williams and Wilkins, 1982., p. 79]**PEER REVIEWED**

In persons with chronic respiratory disease and especially asthma, the inhalation of pyrethrum /and inadequately purified pyrethrins/ might cause exacerbation of symptoms due to its sensitizing properties. Skin disease: Pyrethrum can cause dermatitis which may be allergic in nature. Persons with preexisting skin disorders may be more susceptible to the effects of this agent.
[Mackison, F. W., R. S. Stricoff, and L. J. Partridge, Jr. (eds.). NIOSH/OSHA - Occupational Health Guidelines for Chemical Hazards. DHHS(NIOSH) Publication No. 81-123 (3 VOLS). Washington, DC: U.S. Government Printing Office, Jan. 1981., p. 1]**PEER REVIEWED**

Note that the above reference refer to the risk of effects due to pyrethrins with little or no reference to piperonyl butoxide. Pyrethrin-based powders typically contain 1-3% pyrethrum. From the *Hazardous Substances Data Base,* pyrethrum (unrefined plant derivatives from which pyrethrin are extracted) sensitivity may manifest in several forms, including:

$ Contact dermatitis with papules in moist areas and intense pruritus and sometimes bullae appear;

$ Edema and skin roughening develop in severe cases;
$ "Local anaphylaxis" characterized by dermatitis and sudden severe swelling of face eyes and lips;
$ Mild form characterized by tachycardia, pallor, sweating and fever produced in experiment.
$ In some instances, reactions similar to pollinosis including sneezing, serous nasal discharge and stuffiness

The Hazardous Substances Data Base (HSDB) report includes additional case reports of adverse health outcomes following exposure to pyrethrin. In a study of workers in pyrethrum powder processing facility, 30% of workers experienced erythema, skin roughening and pruritus which subsided upon cessation of exposure. One worker had anaphylactic type reaction shortly after entering a dust laden room, the facial skin turned red and the person felt a sensation of burning and itching, cheeks and eyes became swollen, and severe pruritus developed. Among workers, a few cases of asthma due to pyrethrum mixtures have been reported some of the individuals involved had a previous history of asthma with allergy to a wide spectrum of substances. Additionally, a 43-year old woman with a history of asthma and ragweed allergy experienced anaphylactic reaction after self medicating with a shampoo containing pyrethrin for the treatment of head lice. Periorbital edema occurred within 1 hour. Other symptoms included: shortness of breath, chest tightness and numbness, unresponsiveness.

**B. Master's Thesis comparing asthma-like symptoms among pyrethrins and other pesticides**

Under the partial supervision by the author of this review, a master's thesis was completed using Poison Control Center data. The master's thesis by Mosby (2003) concluded that "this study shows significant association between exposure to pyrethrins and pyrethroids to asthma. This association is much stronger for pyrethrins than pyrethroids.." Asthma itself is not diagnosed by Poison Control Centers. Rather the thesis identified cases of respiratory distress as persons having 1)dyspnea, 2) bronchospasm, 3) respiratory depression, or 4) therapy from a bronchodilators, or antihistamines. Controls were identified and included if they reported to PCC symptoms of drowsiness, burns, abdominal pains, bullae, hypertension, hypotension, tachycardia, anorexia, agitated, syncope, visual defects, bleeding and fever. A possible confounder in this study is the dermal symptoms were excluded from controls because they may be related to pyrethrin/pyrethroid exposure. Using 1993-98 data there were 8,267 cases and 5,218 controls. The pyrethrins case-control study Odds Ratio for asthma like symptoms or treatment was 3.2 with 95% confidence Limits of 2.7 to 3.8. This suggests that person exposed to pyrethrin-containing products are three times more likely to have respiratory-related problems than person exposed to other types of pesticides. The effect of adding age and sex to the analysis lowered the odds ratio minimally. After adjusting the analysis for age and sex, the odds ratio of 3.18 for pyrethrins went to 3.16.

Mosby (2003) noted the following limitation:

The cases were people who called into the PCC with asthma like symptoms, and the controls were people who called into the PCC with all other symptoms that were not related to asthma or pyrethrin/pyrethroid exposure. The selection of control symptoms may be questioned. However, the controls also have health concerns, but not asthma or pyrethrin/pyrethroid related. One possibility is that people who have been exposed to pyrethrins/pyrethroids could also have skin aliments, and since we are just looking at respiratory problems associated with asthma, leaving this group of people out of the study might bias the results. However, this was addressed by examining the percent of controls that had different skin aliments to determine if in fact these people had been exposed to pyrethrin/pyrethroids. There was some evidence of an association between dermal effects and exposure to pyrethrin/pyrethroid. However, the associations were slight with odds ratio ranging from 1.1 to 1.2 and statistically significant. So there was some evidence that excluding dermal effects from the control group may have resulted in increased odds ratio. Nonetheless, the majority of the association between pyrethrins/pyrethroids and asthma can not be explained by this factor.

Mosby made the following recommendation based on her research:

The 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 pyrethrin/pyrethroids. An example of label change could be “Caution: This product may cause difficulty breathing and /or bronchospasm in susceptible individuals. Do not use this product if you are known to be allergic to chrysanthemum or ragweed”. Patients with a history of asthma or ragweed allergy should consult their physician prior to use.” Also precautionary statements should be considered for the product labels that say “these products should only be used when there is proper ventilation, and avoid inhaling spray”.

She also recommended the following data requirements:

I recommend that EPA gather more information on the toxicity of this active ingredient during the registration process. . . I believe that more current scientific methods for immunotoxicity should be considered (e.g. ELISA method to predict IgE changes). Also, data that measures human or animal mast cells is needed to determine if pyrethrins or pyrethroids are in fact associated with asthma. Further study is needed in this area of mast cells, and how the change in the mast cells may be a indicator of asthma. Also, the use of a provocation test should be considered as a tool to determine if asthma occurred. This would allow researchers to look at the ability of the test species to move air to see if there is a change in airflow and if asthma occurred based on exposure to pyrethrin or pyrethroids. While the fundamental purpose of this paper was to determine if there was a relationship between respiratory complaints (asthma like symptoms) from the PCC data and exposure to pyrethrins or pyrethroids, this paper does not go far enough. It does not make a distinction between anaphylaxis, allergies, or asthmatic responses in those with reactions to pyrethrins and pyrethroids mainly because of the limitations in the PCC

data. However, further research is needed this area to better define the exact cause of the respiratory complaints (asthma-like symptoms) associated with the pyrethrin and pyrethroid class of insecticides. Additional work is needed to build on my analysis to determine what role the synergist and the inert play in the occurrence of asthma.

**C. Additional Scientific Literature**

Wax and Hoffman (1994), reported a 37-year old woman died after washing a pet dog with insecticide shampoo containing 0.06% pyrethrin, 0.6% piperonyl butoxide, 42% detergents (sodium laurel sulfate, sodium myristyl sulfate, lauric diethanolamide, lauric-myristic diethanolamide), and other ingredients. The post-mortem included the following findings: severe thickened basement membranes, goblet cell hyperplasia, prominent mucous gland, smooth muscle hypertrophy, and mucous plugging, and eosinophilic infiltrates. These findings are consistent with "the natural history of fatal asthma. . . . Pyrethrin exposure is the probable trigger although the act of dog grooming could have also played a role. The fact that the patient had never had a problem with the dog prior to this episode and that she had not previously used this insecticide shampoo suggests that the shampoo was the etiologic agent. The temporal relationship, however, does not establish causality." The case-report discussion included a warning that some allergic patients may experience extreme manifestations of hypersensitivity and fatal outcome as a result of pyrethrin exposure. Authors recommended that label warnings should be improved and suggested "Caution: This product may cause bronchospasm in susceptible individuals. Patients with a history of asthma or ragweed allergy should consult their physician prior to use."

Wagner (2000) presented a case report of an 11-year old female who suffered a fatal asthma attack after use of an animal shampoo containing pyrethrin (0.2%). Within 10 minutes, the girl experienced shortness of breath and wheezing. Upon receipt of medical attention, the girl was apneic and unresponsive and experiencing bracycardia. Treatment failed and the girl expired. Autopsy report indicated mucous plugging of secondary and tertiary bronchioles, pulmonary edema and congestion. Cause of death was respiratory arrest due to an acute asthmatic attack Oleoresin is a suspected allergenic impurity in the pyrethrin formulation. The author posits this impurity from the pyrethrum extract (1-3% of the pyrethrin formulation) may the responsible mechanism of action in this case. Limitations in this case report include: no knowledge as to whether the girl was truly atopic (elevated IgE antibody); not known if allergic to ragweed or other compounds; opportunity for sensitization from previous exposure to pyrethrin not documented because this incident may have been the first use of pyrethrin product; and, possibility of allergic reaction to both pyrethrin and/or dog dander should be considered in this case.

An earlier review by Wagner (1994) cited a case of a 45 year old school teacher who had an episode of acute asthma and continued having problems with breathing, tearing, and itching and redness of the skin when she was in the classroom which was treated regularly with pyrethrum insecticide. He concluded "it is clear that allergy to these compounds can occur". In his discussion he commented that "many reports of skin or respiratory reaction to pyrethrins or

pyrethrum have been recorded. This includes not only acute contact dermatitis or severe and recurrent urticaria but also respiratory complaints." A report from the Centers for Disease Control and Prevention (1994) noted a list of occupational "agents associated with reported cases of occupational asthma and related conditions". Included on the list was pesticides/herbicides with the footnote "such as malathion and pyrethrins".

Paton and Walker (1988) detail the case of acute poisoning following cutaneous and inhalation exposure to pyrethrin product Controller Flea and Tick Mist (0.15% pyrethrin). The patient applied the product to the floor in an unventilated room and to a pet without gloves. Symptoms included: cutaneous parenthesis, upper respiratory tract irritation, dyspnea with productive cough, and repetitive vomiting and diarrhea. The patient recovered with therapy.

Contact dermatitis usually limited to mild paresthesia has resulted in severe erythema and vesciculations and is the most common adverse effect of pyrethrin exposure upon dermal contact. Clinical manifestations of inhalation exposure to pyrethrin can be local or systemic. Localized effects of the upper respiratory tract include rhinitis, sneezing, scratchy throat, oral mucosal edema, laryngeal mucosal edema and of the lower respiratory tract include cough, shortness of breath, wheezing and chest pain. Hypersensitivity pneumonitis, characterized by chest pain, cough, dyspnea and bronchospasms has occurred to chronically exposed persons (Paton and Walker, 1988).

Many researchers believe that although pyrethrin are reported to be contact allergens, sensitization characterized by dermatitis is probably due to impurities from the pyrethrum plant products (unrefined). Blondell (2004) analyzed reported incidents to Poison Control Centers and found evidence suggesting that piperonyl butoxide increases the risk of dermal irritation/pain, itching, and rash by about 1.7 times. Perhaps, less purified pyrethrum products contain allergenic substances that induce attacks of allergic rhinitis and asthma in humans (Wagner, 2000). In 1934, Feinberg demonstrated that among 225 patients with known (allergic) reactions to ragweed pollen, 104 also had cutaneous reactions with pyrethrum. This cross-sensitivity is recognized as a common phenomenon among individuals with hay fever. These data illustrate the importance of alerting allergic/sensitive persons to the presence of pyrethins in the environment.

**D. <u>Automatic pyrethrin dispensing units</u>**

Another use of the insecticide is to control indoor flying insects in restaurants and other businesses through use pyrethrin and pyrethroid insecticides sprayed from automatic dispensing units. Often placed near entrances, these units are designed to kill flying insects in food service or work areas. A number of adverse health events have been reported as a result of this use. The Morbidity and Mortality Weekly Report has detailed these incidents (Centers for Disease Control (CDC) and Prevention, 2000). The following three incidents occurred in the same restaurant. In 1999, a 42-year-old cook working at a Florida restaurant developed a sore throat, dyspnea, headache, and dizziness after a several-hour exposure to mist released from insecticide dispensers in the food preparation area. A 40-year-old male customer developed headache and

shortness of breath within 1 hour of entering the restaurant. These symptoms lasted approximately 4 hours. A 47-year-old male customer experienced a sharp burning sensation in his left eye and noted swelling, redness, and irritation of the eyelid that persisted approximately 24 hours. The implicated pesticide dispenser was within 6 feet of the booth where this customer had been sitting, and it faced his left eye. None of the three persons sought medical attention for their symptoms. The active ingredients released by these dispensers were pyrethrin and piperonyl butoxide. In a fourth incident included in the article, a 17-year-old male restaurant employee in California was changing the cartridge of an automatic insecticide dispenser. When he closed the dispenser panel, the firing mechanism was activated and discharged a pyrethrin-containing mist into his right eye. The employee immediately experienced burning in the eye and promptly sought medical attention at the emergency department of a local hospital. He was diagnosed with chemical conjunctivitis and treated symptomatically.

In addition to the documented cases above, the CDC report noted 54 cases of pesticide-related illnesses reported to Poison Control Centers from 1993 through 1996, 32 cases reported to the California Department of Pesticide Regulation, and reports from other sources. Among the 94 pyrethrin/piperonyl butoxide cases in the combined surveillance 38% experienced signs or symptoms involving the eye, 36% had neurological symptoms (typically headache, dizziness), 24% had gastrointestinal symptoms (typically nausea), and 21% had respiratory symptoms (typically cough, difficulty breathing). The editorial note in the CDC publication concluded "given the dispensers' widespread use and potential for malfunction and /or improper use or maintenance, these units may pose a public health hazard". The CDC report recommended that effective flying insect control could be achieved by nonchemical integrated pest management practices such as proper sanitation and installation of air curtains and screens. "However, if automatic insecticide dispensers are used, they should be installed according to manufacturer labeling instructions. Warning stickers on dispensers should be considered" so that persons passing nearby would not be directly exposed. Dispensers installed in locations frequented by the public should be set to dispense insecticide during nonbusiness hours and be serviced by commercial pest control operators who use person protective equipment to avoid unintended exposure. The primary concern with these products is that they should not be allowed to be used in a manner that allows bystanders to be sprayed directly in the face.

## VI. Conclusions

Pyrethrins can be a skin, eye, or respiratory irritant from direct exposure. Among the most widely used insecticides among the general public, pyrethrins are generally much less likely to cause signs or symptoms of poisoning. There is some evidence that persons may become sensitized or have cross-reactivity due to exposure to other allergens. Evidence that pyrethrin products may be involved in producing respiratory irritation, allergy- or asthma-like reactions is strongly suggested from a number of reports. However, it should be acknowledged that the evidence for other causes of asthma (pet dander, cockroach allergens, and dust mites) is much stronger. 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.

VII. Recommendations

Pyrethrins products should include label warnings of their risk to skin, eye, or respiratory effects if used in enclosed spaces. A warning along the lines suggested by Wax and Hoffman (1994) "Caution: This product may cause bronchospasm in susceptible individuals. Patients with a history of asthma or ragweed allergy should consult their physician prior to use" should be considered. Such warnings should only apply to products used in enclosed spaces. For example, "Avoid contact with skin or eyes. Susceptible individuals may experience irritant or allergic-type reactions. Persons with respiratory illness may experience difficulty breathing and should avoid use in enclosed spaces and consult their physician prior to use." No pyrethrin product should be used in a manner that would permit spraying bystanders directly in the face.

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