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MEMORANDUM

SUBJECT: Review of Piperonyl butoxide Incident Reports
DP Barcode D302303, Chemical #067501

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BACKGROUND

The following data bases have been consulted for the poisoning incident data on the active ingredient piperonyl butoxide (PC Code: 067501):

- 1) 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. PCC data are coded so that pyrethrin/pyrethroid products with or without piperonyl butoxide can be examined

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separately.

Piperonyl butoxide is a synergist which is formulated with other pesticides. The analysis of poisoning data is difficult because it not usually possible to determine whether piperonyl butoxide or the other pesticides in the formulation are responsible for the adverse effects reported. However, for pyrethrins and pyrethroids, Poison Control Center data is coded according to whether or not piperonyl butoxide is present. This means it is possible to compare pyrethrin-based products with and without piperonyl butoxide present. Pyrethroid products were excluded because the wide variety of ingredients might confound the analysis. Other data bases do not have this capability and therefore are not a part of this review.

PIPERONYL BUTOXIDE REVIEW

I. Poison Control Center Data - 1993 through 1998

Results for the years 1993 through 1998 are presented below for occupational cases, non-occupational involving adults and older children, and for children under age six. Cases involving exposures to multiple products and cases with unrelated medical outcomes are excluded. Tables 1-5 present the hazard information for pyrethrins either with or without piperonyl butoxide as a synergist. Comparisons are made between these two categories and 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. Tables 1 and 2 report the number of cases on which the data derived in Tables 3-5 are based. Table 3 presents this information for occupational cases, Table 4 for non-occupational cases involving adults and older children (six years or older), and Table 5 for children under age six. High ratios suggested increased risk due to piperonyl butoxide are shown in **boldface type**.

Table 1. Number of pyrethrin exposures with piperonyl butoxide reported to the Toxic Exposure Surveillance System (AAPCC), number with determined outcome, number seen in a health care facility for occupational and non-occupational cases (adults and children six years and older) and for children under six years of age only, 1993-1998 .

Subgroup	Exposures	Outcome determined	Seen in Health Care Facility
Occupational: adults and older children	233	146	92
Non-occupational: adults and older children	8138	3992	1093
Children under age six	5492	2967	775

Table 2. Number of pyrethrin exposures without piperonyl butoxide reported to the Toxic Exposure Surveillance System (AAPCC), number with determined outcome, number seen in a health care facility for occupational and non-occupational cases (adults and children six years and older) and for children under six years of age only, 1993-1998.

Subgroup	Exposures	Outcome determined	Seen in Health Care Facility
Occupational: adults and older children	645	435	260
Non-occupational: adults and older children	4760	2652	865
Children under age six	2611	1402	337

Table 3. Comparison between pyrethrins (PY) formulated with and without piperonyl butoxide (PB) and with all pesticides for percent cases with symptomatic outcome (SYM), moderate or more severe outcome (MOD), life-threatening or fatal outcome (LIFE-TH), seen in a health care facility (HCF), hospitalized (HOSP), or seen in an intensive care unit (ICU) reported to Poison Control Centers, 1993-1998 for occupational cases only.

Pesticide	SYM*	MOD*	LIFE-TH*	HCF*	HOSP*	ICU*
PY + PB	87.7	25.3	0.685**	39.5	2.17	0.0
PY Alone	95.2	15.2	0.0	40.3	1.92	0.38
PY+PB to PY Alone Ratio	0.92	1.66	**	0.98	1.13	**
All Pesticides	86.0%	18.8%	0.621%	47.0%	6.08%	2.36%
Ratio PY+ PB to All Pesticides	1.02	1.34	1.10**	0.84	0.36	0.0**

* Symptomatic cases based on those cases with a minor, moderate, major, or fatal medical outcome. Denominator for SYM, MOD, and LIFE-TH is the total cases where medical outcome was determined. Denominator for HCF is all exposures. Denominator for HOSP and ICU is all cases seen in a health care facility.

** These estimates based on a single life-threatening case and a single case seen in a critical care facility.

Table 4. Comparison between pyrethrins (PY) formulated with and without piperonyl butoxide (PB) and with symptomatic outcome (SYM), moderate or more severe outcome (MOD), life-threatening or fatal outcome (LIFE-TH), seen in a health care facility (HCF), hospitalized (HOSP), or seen in an intensive care unit (ICU) reported to Poison Control Centers, 1993-1998 for non-occupational cases involving adults and older children.

Pesticide	SYM*	MOD*	LIFE-TH*	HCF*	HOSP*	ICU*
PY + PB	75.7	13.5	0.276	13.4	2.65	1.01
PY Alone	75.6	13.0	0.377	18.2	3.12	1.27
PY+PB to PY Alone Ratio	1.00	1.04	.732	0.74	0.85	0.80
All Pesticides	68.5%	10.5%	0.359%	16.5%	6.24%	2.67%
Ratio PY+ PB to All Pesticides	1.10	1.28	0.77	0.81	0.42	0.38

* Symptomatic cases based on those cases with a minor, moderate, major, or fatal medical outcome. Denominator for SYM, MOD, and LIFE-TH is the total cases where medical outcome was determined. Denominator for HCF is all exposures. Denominator for HOSP and ICU is all cases seen in a health care facility.

Table 5. Comparison between pyrethrins (PY) formulated with and without piperonyl butoxide (PB) and with symptomatic outcome (SYM), moderate or more severe outcome (MOD), life-threatening or fatal outcome (LIFE-TH), seen in a health care facility (HCF), hospitalized (HOSP), or seen in an intensive care unit (ICU) for adults and children six years and older reported to Poison Control Centers, 1993-1998 for children under six years old.

Pesticide	SYM*	MOD*	LIFE-TH*	HCF*	HOSP*	ICU*
PY + PB	41.2	5.93	0.168	14.1	2.71	0.90
PY Alone	33.0	4.56	0.143	12.9	4.45	1.48
PY+PB to PY Alone Ratio	1.25	1.30	1.17	1.09	0.61	0.61
All Pesticides	21.8%	1.40%	0.120%	16.4%	4.78%	1.36%
Ratio PY+ PB to All Pesticides	1.89	4.24	1.40	0.86	0.57	0.66

* Symptomatic cases based on those cases with a minor, moderate, major, or fatal medical outcome. Denominator for SYM, MOD, and LIFE-TH is the total cases where medical outcome was determined. Denominator for HCF is all exposures. Denominator for HOSP and ICU is all cases seen in a health care facility.

Two types of ratios are presented in tables 3-5. Ratios related to medical outcome include SYM, MOD, and LIFE-TH. MOD is a subset of SYM and LIFE-TH is a subset of MOD. In another words, these categories are not independent of one another. Of the 8 ratios (one ratio excluded based on insufficient numbers) of pyrethrins and piperonyl butoxide to pyrethrins alone, there were 5 ratios suggesting that piperonyl butoxide increased the likelihood of a given medical outcome and 3 ratios suggesting piperonyl butoxide might reduce the likelihood of a given medical outcome. None of the ratios were above 1.3, meaning the increased risk was always less than one-third more than the risk for pyrethrins alone. Such a finding may be due to chance. Compared to all pesticides, pyrethrins and piperonyl butoxides products always had a higher ratio, especially in the moderate medical outcome category. However, most of these increases appear to be due to the pyrethrins alone rather than pyrethrins combined with piperonyl butoxide. One exception to this appears in the moderate category which was somewhat increased for products containing piperonyl butoxide whether the comparison was with pyrethrins alone or all pesticides.

The second type of comparison presented in Tables 3-5 concerned type of medical care provided. Of the 8 ratios of pyrethrins and piperonyl butoxide to pyrethrins alone, there were 2 ratios suggesting that piperonyl butoxide increased the likelihood of a given medical outcome and 6 ratios suggesting piperonyl butoxide might reduce the likelihood of a given medical outcome. The increased ratio for hospitalization in the occupational category was based on just 7 total cases, too small a number to provide stable estimates of hazard. All of the ratios for products containing pyrethrins and piperonyl butoxide compared to all pesticides were below 1.0. This suggests that exposures to these products are less likely to require medical care. Generally, these ratios for more serious medical care (hospitalization, seen in a critical care facility) were quite low.

There was an increase in moderate to more serious symptoms among those exposed to pyrethrins plus piperonyl butoxide products when compared to pyrethrins alone or with all pesticides. To determine why this was so, a more detailed analysis was performed on the 120 plus symptoms reported to Poison Control Centers. Only symptoms reported among 30 or more people that had a moderate, major, or fatal outcome were considered. Thirty was selected as a cutoff because it was judged as the minimum number needed to avoid effects due to chance. Table 6 presents the results of this analysis. There were a total of 479 persons with moderate to fatal outcome to pyrethrins products that included piperonyl butoxide and a total of 760 persons with moderate to fatal outcome due to pyrethrins alone. Similarly, the number of cases with medical outcome determined was 4532 persons exposed to pyrethrin products that included piperonyl butoxide and 7175 persons with medical outcome determined exposed to pyrethrins alone. The two ratios ($479/760$ and $4532/7175$) equal exactly 0.63. Odds of getting a symptom was based on using the number of persons with moderate outcome or above in the denominator. Evidence of hazard for a particular symptom increases, the higher the odds ratio and/or the higher the number of people affected. Consistency among symptoms might also lend support to the finding that piperonyl butoxide was a cause of a particular group of symptoms rather than just a chance finding.

Table 6. Odds* of moderate, major, or fatal cases reporting a symptom for those exposed to products containing pyrethrins and piperonyl butoxide to pyrethrins alone and the odds ratio for increased risk when piperonyl butoxide is present in the formulation (Number observed with symptoms in parentheses),

Symptom	PY and PB Odds (N)	PY alone Odds (N)	PY and PB to PY alone odds ratio*
Chest pain	0.0459 (22)	0.0303 (23)	1.51
Dermal edema	0.0584 (28)	0.0724 (55)	0.81
Erythema/flushed	0.0772 (37)	0.0605 (46)	1.28
Hives/welts	0.0167 (8)	0.0355 (27)	0.47
Dermal irritation/pain	0.1106 (53)	0.0645 (49)	1.71
Pruritis (itching)	0.0626 (30)	0.0368 (28)	1.70
Rash	0.0918 (44)	0.0553 (42)	1.66
Nausea	0.0835 (40)	0.0697 (53)	1.20
Throat irritation	0.0584 (28)	0.0645 (49)	0.90
Vomiting	0.0939 (45)	0.0579 (44)	1.62
Dizziness/vertigo	0.0584 (28)	0.0434 (33)	1.35
Headache	0.0689 (33)	0.0553 (42)	1.24
Blurred vision	0.0313 (15)	0.0658 (50)	0.48
Burns to eye	0.0418 (20)	0.0724 (55)	0.58
Corneal abrasion	0.0939 (45)	0.2447 (186)	0.38
Eye irritation/pain	0.2651 (127)	0.4289 (326)	0.62
Lacrimation (tearing)	0.0647 (31)	0.1000 (76)	0.65
Bronchospasm	0.0710 (34)	0.0513 (39)	1.38
Cough/choke	0.1628 (78)	0.1092 (83)	1.49
Dyspnea	0.2818 (135)	0.1460 (111)	1.93

* PY = pyrethrins, PB = piperonyl butoxide. Odds = number with symptoms/number with moderate, major, or fatal outcome (479 for PY+PB and 760 for PY alone).

Out of 20 symptoms with a total of 30 or more persons with moderate outcome or higher, there were 12 symptoms with odds ratios above 1.0 suggesting some additional risk from exposure to piperonyl butoxide and 8 symptoms with ratios below 1.0 suggesting a protective effect. Interestingly, five of the six lowest ratios were all eye effects (blurred vision, burns to eye, corneal abrasion, eye irritation or pain, and lacrimation). This unexpected finding suggests that something about products containing piperonyl butoxide makes them less injurious than products containing pyrethrins alone. This may be due to the fact that products with pyrethrins alone may be more likely to be formulated as dusts, granules or other solid formulations which are more irritating to eyes than products containing piperonyl butoxide which may be more likely formulated as liquids. More research would be needed to confirm this suspicion.

The three ratios due to respiratory symptoms (bronchospasm, cough/choke, and dyspnea) were higher for pyrethrin products that contained piperonyl butoxide. This may mean that piperonyl butoxide has respiratory irritant properties that are more likely to lead to asthma-like symptoms. This was especially true for dyspnea (difficulty breathing) which was reported in 135 cases. This was the highest number for any symptom involving those with moderate or major outcome exposed to PY and PB and the highest ratio (1.94). The next three highest ratios (all about 1.7) were dermal irritation/pain, itching, and rash, suggesting these reactions were more likely if piperonyl butoxide was present in the formulation.

II. Scientific Literature

Pegus Research, Inc. completed a study titled "Human exposures to consumer products containing pyrethrins, pyrethroids & piperonyl butoxide reports to the American Association of Poison Control Centers 1994-1999." This report, completed Nov. 8, 2001, was submitted to EPA by the Piperonyl Butoxide Task Force II/Consumer Specialty Products Association. This review did not provide a comparison of products with and without piperonyl butoxide. In addition, this review included pyrethroids, so it was not possible to perform the type of comparison presented above. Detailed information was obtained on three deaths, however, exposure to something other than pesticides was a more likely cause of death in each case. Information was also abstracted from the medical record in about half of the cases classified as major medical outcome. However, these abstracts generally do not contain sufficient information to draw conclusions about the effects specific to piperonyl butoxide. Therefore, no attempt is made to review this document in detail.

Pegus Research, Inc. pointed out important limitations of using Poison Control Center data, including

- inability to determine rates of adverse events because the number of persons exposed (population at risk) is unknown.
- difficulty determining causal relationship with the limited information collected by the poison specialist at the Poison Control Center.

- Lack of information on medical history, circumstances of exposure, susceptibility due to age or medical condition, etc.
- Varying quality of data due to coding and recording errors.
- Questionable exposures reported, especially in the case of young children, where exposure is not documented.
- inability to attribute to single ingredient when even single product exposures may include exposure to several ingredients in one formulation.

Osimitz and Breathnach (2001) summarized the risks of piperonyl butoxide in a chapter in the "Handbook of Pesticide Toxicology Second Edition". Very few human studies were reported that included an assessment of health effects from exposure. One study they cited reported application of 3.3 mg pyrethrum extract and 13.2 mg piperonyl butoxide applied to the backs of six volunteers. No clinical signs were noted. Another study involved two men ingesting capsules containing increasing amounts of piperonyl butoxide (5, 10, 20, and 50 mg) at consecutive intervals of about 1 week. No signs of toxicity were seen. Assuming a 70 kg body weight, this suggests a 0.71mg/kg body weight no-effect-level in humans. However, this finding is greatly limited since only two healthy adult men were tested. A third study in Italy was cited that examined 11 workers employed at a piperonyl butoxide manufacturing facility for periods of 15 to 26 years. Workers received x-rays and spirometric evaluations every three years and annual clinical chemistry analysis. No adverse clinical signs or symptoms related to piperonyl butoxide were reported. Similar findings were also reported for a manufacturing facility in Scotland. Details of these reviews are not available to the current reviewer.

The following excerpts from the Hazardous Substances Data Base maintained by the National Institutes of Health provide comprehensive, scientifically reviewed highlights of the dermal and respiratory concerns related to pyrethrins:

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**

Note that the above reference refer to the risk of effects due to pyrethrins with little or no reference to piperonyl butoxide.

III. Conclusion

Based on data from Poison Control Centers, there appears to be a greater risk of moderate or major symptoms among those exposed to products containing pyrethrins and piperonyl butoxide than those exposed to pyrethrins alone. A detailed review of symptoms found that respiratory symptoms (bronchospasm, cough/choke, and dyspnea) and selected dermal symptoms (dermal irritation/pain, itching, and rash) were more likely if the exposure included piperonyl butoxide. These symptoms are likely the reason for increased risk of moderate effects which typically would require medical attention.

Other literature suggests that pyrethrin-based products may pose a hazard to asthmatics (Ellenhorn et al. 1997, Reigart and Roberts 1999, Wagner 2000). The findings from analysis of symptoms from Poison Control Centers suggests that piperonyl butoxide adds to that risk.

IV. Recommendations

Labeling should advise handlers using products containing piperonyl butoxide that respiratory irritation, rash, and itching can occur in sensitive individuals and that protective clothing is recommended. Persons with asthma or other respiratory impairments should be advised to use extra caution to avoid inhalation or other exposure to the product.

References

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Wagner SL. 2000. Fatal asthma in a child after use of an animal shampoo containing pyrethrin. *West J Med* 173:86-87.

cc: Piperonyl butoxide file (067501)
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