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PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

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MEMORANDUM

SUBJECT: Review of Paraquat Incident Reports Involving Inhalation
DP Barcode D260797, Chemical #061601

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BACKGROUND

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 Nation's Poison Control Centers (PCCs) participate in the Toxic Exposure Surveillance System (TESS) which obtains data from 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. PCCs are staffed by Poison Information Specialists who are available 24 hours a day, 365 days a year to provide poison information, telephone management and consultation, and collect pertinent data on each exposure. Certified centers require their specialists to be trained and certified and account for 83% of the cases submitted to TESS. Until the training is completed, some calls at certified centers may be answered by individuals who have not yet completed their training and passed their certification examination. The majority of centers have a board certified physician on-call at all times with expertise in medical toxicology. The PCCs participating in TESS complete a form or computer record describing each case with standard data elements (e.g., age, route of exposure, symptoms, medical care received, and medical outcome).

Poison Control Center Data is subject to both under- and over-reporting. Many cases seen by health care providers are not reported to PCCs, especially if the clinician is comfortable with their management. Health care providers account for about 13% of all calls to PCCs. The majority of calls come from the lay public some of whom may call when exposure is assumed but not confirmed (e.g., infant next to an open container). Lay persons may report symptoms less accurately which must be translated into specific medical terminology by Poison Information Specialists. In the discussion provided below, exposures include cases where exposure was suspected but not confirmed. Cases classified as symptomatic are those cases followed up to determine outcome with a symptom or clinical effect deemed to be related to the exposure based on the information collected by the Poison Information Specialist.

Poison Control Center Data - 1993 through 1998

The initial analysis below compare paraquat with all other pesticides for all routes of exposure (Tables 1-3). The subsequent section (Tables 4-6) makes the same comparison but only for exposures involving inhalation as the route of exposure. 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 or intentional exposures (e.g., suicide attempts) are excluded. Tables 1-3 present the hazard information for paraquat 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 reports the number of cases on which the data derived in Tables 2-4 are based. Table 2 presents this information for occupational cases and Table 3 for non-occupational cases involving adults and older children (six years or older). Too few cases are reported for children under age six to warrant a detailed analysis of their exposures.

Table 1. Number of paraquat exposures 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	322	151	184
Non-occupational: adults and older children	461	180	198
Children under age six	39	17	15

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Table 2. Comparison between paraquat and 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*
Paraquat	66.2%	23.8%	1.99%	57.1%	10.33%	5.98%
All Pesticides	86.0%	18.8%	0.62%	47.3%	7.18%	2.85%
Ratio	0.77	1.26	3.21	1.21	1.44	2.10

* 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 3. Comparison between paraquat and 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 non-occupational cases involving adults and older children.

Pesticide	SYM*	MOD*	LIFE-TH*	HCF*	HOSP*	ICU*
Paraquat	65.0%	27.2%	2.78%	43.0%	11.1%	6.56%
All Pesticides	68.5%	10.5%	0.36%	18.1%	7.35%	3.24%
Ratio	0.95	2.59	7.72	2.38	1.51	2.02

* 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.

As would be expected for a highly toxic herbicide, paraquat has a higher likelihood of moderate and serious effects and greater requirement for health care than do other pesticides. The ratio of increased hazard tends to get higher with greater severity and with greater health care requirements. Life-threatening cases were three times more likely among occupational cases (based on 3 cases) and 8 times more likely among non-occupational cases (based on 5 reported cases). The same information reported above is repeated below for just those exposures where inhalation (but not the oral route) was a route of exposure and when inhalation was the only route of exposure.

Table 4. Number of paraquat exposures **by inhalation route*** reported to the Toxic Exposure Surveillance System, number with determined outcome, number seen in a health care facility for occupational and non-occupational cases (adults and children six years and older), 1993-1998 .

Subgroup	Exposures	Outcome determined	Seen in Health Care Facility
Occupational: adults and older children	96/48	45/17	69/30
Non-occupational: adults/older children	137/86	47/27	65/40

* First number is inhalation combined with other non-oral routes of exposure/second number is where inhalation was the only reported route of exposure.

Table 5. Comparison between paraquat and all pesticides **due to inhalation*** 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 in an intensive care unit (ICU) reported to Poison Control Centers, 1993-1998 for occupational cases.

Pesticide	SYM*	MOD*	LIFE-TH*	HCF*	HOSP*	ICU*
Paraquat	60.0/64.7	22.2/17.6	4.44/5.88	71.9/62.5	13.0/13.3	5.80/6.67
All Pesticides	85.8/84.3	21.1/19.9	0.73/0.56	47.2/44.4	9.50/7.19	3.66/2.50
Ratio	0.70/0.77	1.05/0.88	5.92/10.5	1.52/1.41	1.37/1.85	1.58/2.67

* 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 6. Comparison between paraquat and all pesticides **due to inhalation*** 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 non-occupational cases involving adults and older children.

Pesticide	SYM*	MOD*	LIFE-TH*	HCF*	HOSP*	ICU*
Paraquat	74.5/85.2	36.2/33.3	2.13/3.70	47.4/46.5	6.15/10.0	1.54/2.50
All Pesticides	80.9/80.5	16.5/15.8	0.48/0.41	20.8/19.5	8.75/8.07	3.94/3.59
Ratio	0.92/1.06	2.19/2.11	4.44/9.02	2.28/2.38	0.70/1.24	0.39/0.70

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Table 4. Number of paraquat exposures **by inhalation route*** reported to the Toxic Exposure Surveillance System, number with determined outcome, number seen in a health care facility for occupational and non-occupational cases (adults and children six years and older), 1993-1998 .

Subgroup	Exposures	Outcome determined	Seen in Health Care Facility
Occupational: adults and older children	96/48	45/17	69/30
Non-occupational: adults/older children	137/86	47/27	65/40

* First number is inhalation combined with other non-oral routes of exposure/second number is where inhalation was the only reported route of exposure.

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Pesticide	SYM*	MOD*	LIFE-TH*	HCF*	HOSP*	ICU*
Paraquat	60.0/64.7	22.2/17.6	4.44/5.88	71.9/62.5	13.0/13.3	5.80/6.67
All Pesticides	85.8/84.3	21.1/19.9	0.75/0.56	47.2/44.4	9.50/7.19	3.66/2.50
Ratio	0.70/0.77	1.05/0.88	5.92/10.5	1.52/1.41	1.37/1.85	1.58/2.67

* 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 6. Comparison between paraquat and all pesticides **due to inhalation*** 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 non-occupational cases involving adults and older children.

Pesticide	SYM*	MOD*	LIFE-TH*	HCF*	HOSP*	ICU*
Paraquat	74.5/85.2	36.2/33.3	2.13/3.70	47.4/46.5	6.15/10.0	1.54/2.50
All Pesticides	80.9/80.5	16.5/15.8	0.48/0.41	20.8/19.5	8.75/8.07	3.94/3.59
Ratio	0.92/1.06	2.19/2.11	4.44/9.02	2.28/2.38	0.70/1.24	0.39/0.70

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* 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.

For the most part, the excess hazard seen for all routes of exposure also applies to inhalation exposures. One notable exception to this was the likelihood of symptoms and moderate effects among occupational cases. Note that sometimes information on route of exposure may be incorrectly reported and incorrectly coded. An audit of 512 pesticide records did find that route of exposure was correctly coded in 96% of all cases. It would be desirable to conduct a study to confirm that inhalation really was significant factor in the reported Poison Control Center cases. Still the pattern of increased hazard for paraquat when compared to other pesticides generally remains high, even if only exposures involving inhalation are considered.

Zeneca purchased Poison Control Center data for the years 1985 through 1993 which was reported in the "Amended Review of Paraquat Acute Illness Data" (Jerome Blondell, DP Barcode D228285, August 5, 1996). The following table summarizes the information obtained on those cases that received follow-up to determine medical outcome.

Table 7. Human paraquat exposures (including intentional and unintentional exposures) reported to Poison Control Centers where medical outcome was determined, 1985-1993.

YEAR	MEDICAL OUTCOME					TOTAL
	NONE	MINOR	MODERATE	MAJOR	DEATH	
1985	17(3)	19(6)	2(2)	1(0)	1(0)	40(11)
1986	28(0)	31(12)	3(0)	0(0)	3(0)	65(12)
1987	15(1)	32(11)	6(2)	0(0)	1(0)	54(14)
1988	29(3)	34(6)	8(1)	0(0)	1(0)	72(10)
1989	21(2)	24(6)	4(1)	2(1)	0(0)	51(10)
1990	11(1)	29(6)	7(1)	2(1)	2(0)	51(9)
1991	21(1)	31(5)	2(0)	3(1)	4(0)	61(7)
1992	9(0)	23(3)	4(1)	0(0)	1(0)	37(4)
1993	6(0)	17(2)	9(2)	5(0)	0(0)	37(4)
TOTAL	157(11)	240(57)	45(10)	13(3)	13(0)	468(81)

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% Inhalation	7.0%	23.8%	22.2%	23.1%	0.0%	17.3%

The information reported in Table 7 is repeated below for more recent years in Table 8. Note that this Table (unlike Table 7) includes only unintentional exposures.

Table 8. Human paraquat exposures (excluding intentional exposures) reported to Poison Control Centers where medical outcome was determined, 1993-1998. Numbers in parentheses are exposures due to inhalation (may include dermal or ocular exposures) but not including oral exposures.

YEAR	MEDICAL OUTCOME					TOTAL
	NONE	MINOR	MODERATE	MAJOR	DEATH	
1993	7(2)	13(2)	6(1)	3(0)	0(0)	29(5)
1994	24(6)	19(4)	13(3)	0(0)	0(0)	56(13)
1995	21(1)	31(12)	29(11)	0(0)	0(0)	81(24)
1996	27(6)	32(8)	3(3)	0(0)	0(0)	62(17)
1997	35(15)	25(3)	16(3)	1(1)	2(0)	79(22)
1998	14(1)	19(6)	10(3)	2(2)	0(0)	45(12)
TOTAL	128(31)	139(35)	77(24)	6(3)	2(0)	352(93)
% Inhalation	24.2%	25.2%	31.2%	50.0%	0.0%	26.4%

Both Tables 7 and 8 suggest that about one-quarter of paraquat exposures, including those with significant medical outcome (minor, moderate, and major) are due to inhalation. If inhalation was less of a risk than other routes of exposure, a drop off in the percent cases would be expected in moderate and major categories. However, this is not the case, suggesting that inhalation can be a significant risk for symptoms of paraquat intoxication.

Literature reported relative to inhalation of paraquat

NIOSH performed a Health Hazard Evaluation (HHE Report 94-0413-2560, February 1996, by Steven W. Lenhart) of witchweed applicators in North Carolina. This evaluation was requested to establish by air sampling measurements, when respirators were needed during

knapsack application. The application rate was reported to be 0.5 pounds of paraquat cation per acre for periods ranging from 14 to 144 minutes. Five workers had breathing zone samples taken in eight applications. No paraquat was detected in any of the samples. However, the minimum detectable level of paraquat ranged from 70 ug/m^3 to 700 ug/m^3, depending on the duration of air sampling. Nevertheless, NIOSH concluded "the overall results of this air sampling survey suggest that" workers "have essentially no risk for inhalation exposure to paraquat during witchweed eradication activities". The HHE suggested that the low inhalation risk was due to the relatively large size of droplets created by knapsack sprayers which settle quickly and have low volatility. Despite these low risks, NIOSH did recommend that a full facepiece shield be worn to protect the eyes, face, and mouth from spills and splashes during mixing, loading, knapsack application, and maintenance activities. However, during paraquat application using all-terrain vehicles or tractors, no specific personal protective equipment was recommended, but should be available, in the event that application equipment needed repair.

In a letter to the editor, a New Zealand medical school lecturer questioned whether inhalation of paraquat could be a risk for human poisoning (Howard 1983). He cited two trials of spraying equipment which found a maximum airborne concentration in the breathing zone of 12 mg/m^3. He noted that this was a fraction of the current TLV and that no organ accumulation would be expected at these low levels. He then cited two of his own studies in England and Malaysia that showed no evidence of respiratory effects in person exposed to paraquat.

In contrast to the literature cited above, Ames et al (1993) studied a community exposed to drift from a helicopter application in California. Comparisons of reported symptoms suggested that "residents probably did experience an increase in health symptoms from the drift." Symptoms more commonly reported included diarrhea, unusual tiredness, cough, headache, nausea, stuffy/runny nose, tearing eyes, and throat irritation. The authors acknowledged that there was a potential for bias in the results because some community members were upset about the drift and may have exaggerated their symptoms.

A report on 15 unintentional fatalities in Costa Rica found two cases apparently due to inhalation (Wesseling et al. 1997). The two workers did not report any exceptional exposure circumstances and no oral or skin lesions were observed. The clinical course of their illness and the gross and histological changes in the lungs supported a clinical diagnosis of paraquat poisoning. The authors note that there are no other reports of fatal paraquat poisonings (though one nonfatal case was reported by Garnier 1995) and that exposure studies have concluded that the small amounts available in the breathing space and large droplet size mean exposure by inhalation should be negligible. However, they then cite the Ames et al. (1993) study above which suggest "the possibility of intoxications from inhalation of droplets from other types of spraying". They note that nosebleeds are frequently observed among paraquat sprayers "which indicates nasal retention of non-respirable-size particles." They suggest that absorption through the nasal mucosa and gastrointestinal absorption after swallowing may have contributed to an internal dose sufficient to contribute to lethality in their two cases. In addition, there may have been unobserved absorption through minor skin lesions.

Conclusion

The evidence that paraquat can cause poisoning by the inhalation route is contradictory. The Poison Control Center data and the reports by Ames et al. (1993) and Wesseling et al. (1997) suggest that inhalation of paraquat is not uncommon and can result in life-threatening and perhaps even fatal poisoning. On the other hand, assessments of exposure by NIOSH (1996), Howard (1983) and others suggest that respirable levels sufficient to cause poisoning cannot occur under normal circumstances. Both the Wesseling et al. (1997) and the NIOSH (1996) reports suggest that large droplets that could get into the nasal mucosa may pose a serious hazard. These droplets may be swallowed or absorbed across the nasal membrane. This latter scenario is especially likely if there are nosebleeds which are known to occur through prolonged exposure to spray droplets of paraquat (Howard 1979, Castro-Gutierrez et al. 1997). Nasal exposure to non-respirable droplets of paraquat could cause serious and perhaps fatal poisoning by paraquat.

Recommendation

The face shield recommended by NIOSH should be considered minimum protection for any applicator of paraquat. Some type of mask to keep droplets away from the mouth and nose should be recommended and workers should be advised of the danger of lethal effects if paraquat is absorbed into the bloodstream through open cuts or nosebleeds. Careful follow-up with inhalation cases reported to Poison Control Centers would be desirable to confirm the reported route of exposure and subsequent adverse effects.

References

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