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CORRESPONDENCE

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Amended Review of Paraquat Acute Illness Data

TO: Venus Eagle, Chemical Review Manager
Special Review and Reregistration Division (7508W)

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Please find below, the OREB review of:

| | |
|--------------------------|-----------------------|
| DP Barcode: | <u>D228285</u> |
| Pesticide Chemical Code: | <u>061601, 061603</u> |
| EPA Reg. No.: | <u>various</u> |
| EPA MRID No.: | <u>not applicable</u> |

I. INTRODUCTION

This document amends the review of paraquat acute illness data, dated December 19, 1995. The registrant has supplied additional data from Poison Control Centers and other information that permits changes in the recommendations from the previous review.

Paraquat is among the more toxic herbicides available for agricultural use (Morgan 1989, Stevens and Sumner 1991). For many years it has been a significant cause of death due to accidental and intentional ingestion. The manufacturer has introduced a

stenching agent, emetic (substance which induces vomiting) and blue dye starting in 1988 as a condition of registration to discourage its use by suicide victims and to help prevent accidental ingestions. Though it is much more difficult to be seriously poisoned by the dermal route or from inhalation, such incidents have occurred. Unlike the toxic organophosphate and carbamate insecticides, there is no effective antidotal treatment for paraquat ingestion, once a person has been over-exposed.

II. CONCLUSION

The following two paragraphs are recommended for inclusion in the Registration Eligibility Document:

There are a number of deaths resulting from oral ingestion of paraquat. Most of the fatal oral ingestions have been related to suicidal incidents. However, since 1988 when the manufacturer added a stenching agent, emetic (a substance that induces vomiting) and changed the color, the number of deaths and poisonings due to ingestion have declined markedly. U.S. Poison Control Center data, for example, show a decline of almost 50 percent when comparing the proportion of all pesticide exposures due to paraquat ingestion for the four years pre- and post-1988. Of the remaining accidental deaths, most occurred prior to 1980. During that time paraquat's end-use products were formulated into a brown liquid. This substance was easily mistaken for a type of soft drink. Reports of fatalities due to ingestion should continue to be monitored closely to assess the effectiveness of the preventive measures introduced by the manufacturer and to determine whether other measures (prohibiting concentrates to no more than 5-10%) might be warranted.

Dermal exposure to paraquat usually results in minor skin or eye irritation. Rarely, with heavier exposures resulting from misuse, more serious effects may occur such as blistered or ulcerated skin, loss of fingernails, skin burns, ulcers of the mouth, nosebleeds, and protracted or even permanent blindness. These more serious effects typically result when protective clothing is not worn, skin has abrasions or open cuts, and/or when extensive exposure is allowed to persist without washing. The label should warn against these hazards. Heavy, prolonged dermal exposure, as from a leaking knapsack type of sprayer, can result in severe poisoning and, rarely (outside the United States), even death. The labels should be checked to be sure they warn of the hazard from prolonged dermal contact and the importance of washing after dermal contamination. Based on problems with spray drift, the California Health Department has recommended that paraquat not be sprayed near residential areas. Such a statement is recommended for the paraquat label for all end-use products intended primarily for agricultural use.

III. DETAILED CONSIDERATIONS

California data

The California Department of Pesticide Regulation has provided a report of all paraquat cases reported since 1982 to their Pesticide Illness Surveillance System. 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, number of days off work and in hospital are provided.

California reported 33 cases of systemic occupational illness from 1982 through 1992 related to paraquat exposure and 26 cases of eye effects, 22 cases of skin effects and 4 combination eye/skin illnesses (California Department of Pesticide Regulation 1995). Five additional non-occupational cases of systemic poisoning were reported during this same time period and 3 of the 5 were fatal suicide ingestions. No accidental deaths were reported, though one case occurred when an application hose disconnected and required 17 days of hospitalization. Table 1 below gives the total number of cases per year in California for all agriculturally-related cases where a definite, probable, or possible causal relationship between exposure and illness were determined.

Ground application or other direct handling activities were associated with the overwhelming majority (76%) of systemic poisoning. There were 8 cases that related to exposure to drift (2 involving flaggers) and no cases related to field reentry. A variety of crops were reported associated with the 85 paraquat agricultural illnesses. Of the 49 cases where a crop was identified, 11 were associated with grapes, 10 with fruit (3 citrus and 7 other fruit), 9 with weeds, 7 with almonds, 5 with cotton, and 7 with other crops.

Table 1. Number of agricultural illnesses reported due to Paraquat in California, 1982-1992.

| YEAR | SYSTEMIC | EYE | SKIN | EYE/SKIN | TOTAL |
|-------|----------|-----|------|----------|-------|
| 1982 | 5 | 6 | 2 | 1 | 14 |
| 1983 | 3 | 6 | 2 | 0 | 11 |
| 1984 | 3 | 4 | 4 | 1 | 12 |
| 1985 | 3 | 2 | 3 | 1 | 9 |
| 1986 | 1 | 1 | 1 | 0 | 3 |
| 1987 | 6 | 1 | 3 | 0 | 10 |
| 1988 | 1 | 3 | 0 | 0 | 4 |
| 1989 | 6 | 0 | 0 | 1 | 7 |
| 1990 | 2 | 2 | 4 | 0 | 8 |
| 1991 | 3 | 1 | 1 | 0 | 5 |
| 1992 | 0 | 0 | 2 | 0 | 2 |
| TOTAL | 39 | 27 | 22 | 4 | 92 |

The ratio of systemic poisonings (1982-89) for agricultural workers per 1,000 applications was 0.17 (California Department of Food and Agriculture 1983-89). For just workers handling paraquat the ratio was 0.13 per 1,000 applications. This ratio is not high when compared to the median reported for 29 insecticides (.41 for all agricultural workers and .21 for handlers), but may be high when compared to other herbicides. It should be noted that there appears to be a downward trend in California agricultural illness with an average of 10 per year from 1982 through 1987 and an average of 5 per year from 1988 through 1992.

National hospital data

Earlier data on hospitalized pesticide poisoning permit comparisons with national usage data. An estimated 4.2 occupational cases were hospitalized each year from 1977 through 1982 (Keefe, Savage, and Wheeler 1990). This estimate is based on 3 observed cases in a 6% sample of the nations hospitals. Compared to an estimated 2.84 million pounds in use in 1982, this gives a ratio of 1.5 cases per million pounds in use (Gianessi 1986). This was slightly higher than the average of 1.2 per million pounds, the average for all pesticides. The only herbicide responsible for more occupational hospitalization than paraquat was 2,4-D with an estimated 25 cases per year, but a much lower ratio of 0.6 hospitalized cases per million pounds reported in use.

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National Poison Control Center data

Starting in 1989 the American Association of Poison Control Centers reported separately on number of paraquat associated exposures (Litovitz et al. 1990, 1991, 1992, 1993, 1994). Zeneca, the leading registrant for paraquat products, purchased data prior to 1989 from the AAPCC to permit comparisons. A total of 615 reports were received during the five-year period 1989-93. Most of these cases, 84%, were adults and 93% were deemed accidental exposures (7% were intentional suicides or homicides). A total of 73% of all cases were seen at a health care facility. In 55% of the 615 cases a medical outcome was determined. Twenty-nine percent of cases had exposure with no symptoms, 52% had minor symptoms which would not usually require significant medical treatment, 12% had moderate outcome, and 3.6% (12 cases) had major medical outcome indicating life-threatening effects or permanent disability.

There were 9 deaths including 6 that were suicides, 2 accidental, and 1 unknown. One of the accidental deaths likely involved ingestion and one case involved only dermal or inhalation exposure. Further examination of the dermal/inhalation case suggested that other causes of death besides paraquat should be considered. From 1985 through 1988 when Poison Centers also reported individual deaths there were 7 deaths reported including 5 suicides and 2 accidental ingestions. According to Morgan (1989) any adult receiving more than about 1-2 swallows of 20% paraquat concentrate (7.5-15 ml) is likely to have a fatal prognosis. On this basis one author has recommended that concentrates of 20% or more should not be sold (Tinoco et al. 1993). On average there were only 3 accidental deaths reported due to herbicides each year from 1980 through 1989 (National Center for Health Statistics 1983-1993): Another 3.3 deaths per year was reported due to unknown type of pesticide. Given 0.62 paraquat deaths per year from Poison Control Centers, it appears likely that paraquat accounts for between 0.6 and 3-6 accidental deaths per year or perhaps 5-15% of the 22.5 accidental pesticide-related deaths reported annually. Given this number and percentage, the steps taken by the manufacturer in 1988 to prevent accidental ingestion were justified. Continued monitoring of poisoning incident data is recommended to assess the success of these steps.

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Table 2. Human Paraquat Exposures Reported to Poison Control Centers, 1989-1993.

| YEAR | MEDICAL OUTCOME* | | | | | TOTAL EXPOSED |
|-------|------------------|-------|----------|-------|-------|---------------|
| | NONE | MINOR | MODERATE | MAJOR | DEATH | |
| 1989 | 24 | 36 | 7 | 2 | 1 | 134 |
| 1990 | 19 | 47 | 11 | 2 | 3 | 129 |
| 1991 | 27 | 38 | 5 | 3 | 4 | 134 |
| 1992 | 19 | 35 | 6 | 0 | 1 | 114 |
| 1993 | 9 | 21 | 13 | 5 | 0 | 104 |
| TOTAL | 98 | 177 | 42 | 12 | 9 | 615 |

* Medical outcome was determined in about 55% of the total cases, so the rows do not add to the totals given in the right-hand column. Five of the deaths are known to be suicides. The number of attempted suicides in other categories of medical outcome is not known, but does not exceed 40 cases over the these four categories.

Zeneca purchased additional data on paraquat from the AAPCC and provided it to EPA. This data permits a specific analysis on those exposures involving paraquat and no other products. It turns out that 29% of the 615 cases involved in Table 2 did involve exposure to two or more products, typically paraquat and some other pesticide. Table 3 below presents, the data for the 71% of cases involving paraquat without concomitant exposures. Table 4 presents the same information by route of ingestion.

As stated above, the manufacturer introduced measures to reduce the likelihood of ingestion of paraquat in 1988. A comparison of numbers of ingestions (reported in Table 4) before and after that time must take into account the increased coverage and number of Poison Control Centers reporting annually. One way to do this is to assume that total number of pesticide cases should be stable over this time period. An analysis (not shown here) of pesticide cases as a proportion of total poison exposures shows that this is the case. Therefore a comparison of proportion of paraquat cases before and after 1989 when preventive measures went fully into effect should reveal a decline in ingestions. For the four prior years, 1985 through 1989, there were 52 paraquat ingestions and 215,464 exposures to pesticides (disinfectant excluded) or a percentage of 0.024 for paraquat ingestions. For the four years 1990 through 1993 there were 43 paraquat ingestions and 326,879 exposures to pesticides or a percentage of 0.013. This figure represents a decline of 46% from the 1985 through 1989 time period, which suggests that preventive measures introduced in 1988 have markedly reduced paraquat ingestions.

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Table 3. Human Paraquat Exposures Reported to Poison Control Centers by medical outcome, 1985-1993.

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

Table 4. Human Paraquat Exposures Reported to Poison Control Centers by route of exposure, 1985-1993.

| YEAR | ROUTE OF EXPOSURE | | | TOTAL |
|-------|-------------------|--------|------------|-------|
| | INGESTION | DERMAL | ALL OTHER* | |
| 1985 | 12 | 16 | 42 | 70 |
| 1986 | 19 | 28 | 47 | 94 |
| 1987 | 11 | 20 | 39 | 70 |
| 1988 | 10 | 36 | 52 | 98 |
| 1989 | 7 | 31 | 40 | 78 |
| 1990 | 9 | 23 | 37 | 69 |
| 1991 | 20 | 35 | 32 | 87 |
| 1992 | 4 | 22 | 33 | 59 |
| 1993 | 10 | 20 | 24 | 54 |
| TOTAL | 102 | 231 | 346 | 679 |

Incident Data System

The Office of Pesticide Programs has maintained a computer database of all incidents reported to EPA since June 1992. Reports come from various sources including registrants, other federal and state agencies, and environmental groups and individuals. Approximately 20 paraquat incidents have been reported to date. Only 10 of these involve humans and 7 of the 10 were suicide ingestions (6 of which were fatal). None of the 3 accidental human exposures was well enough documented to provide evidence that paraquat was responsible for the adverse effects reported.

Review of pertinent literature

Two articles have been published which review evidence of paraquat poisoning due to dermal exposures (Smith 1988, Garnier et al. 1994). A total of 16 cases are reported including 13 cases which were fatal. In all of these cases the evidence linking the exposure to the adverse effects was deemed convincing. Six of the 13 deaths involved deliberate application to the skin. Another five cases involved prolonged contact with dilute (2 cases) or high concentration (28g/l or 40g/l in 2 cases, likely greater than 1.5% in a third case) paraquat applied from a knapsack type sprayer. Two fatal cases reported contact with dilute spray and previous skin damage from dermatitis or scratches from branches. One of these involved exposure all day to a leaking knapsack sprayer and unknown level of dilution. The second case involved exposure for many days and an apparent misdiagnosis at the hospital. The time course in this case (fatality 8 weeks after exposure) is unusual suggesting some other cause of death may be responsible. Taken together this evidence suggests that excessive, prolonged exposure or excessive exposure involving damaged skin can be fatal. Therefore, protective clothing is necessary for handlers of this product whether it be concentrate or dilute.

According to Stevens and Sumner (1991) there are a number of reports of severe skin and eye injury resulting from dermal exposures. Although most exposures result in only mild irritant effects, severe effects to the skin and eyes have been reported when treatment has been delayed (e.g., first degree burns, loss of nails, scarring, blindness). A recent study by Ames et al. (1993) reported on a community exposed to paraquat spray drift. The study reported elevated symptom incidence rates for cough, diarrhea, eye irritation, headache, nausea, rhinitis, throat irritation, trouble breathing, unusual tiredness, and wheezing. Elevated rates of fever and nausea were reported based on an internal comparison among those who reported odors after application. The authors felt the results provided some evidence of paraquat-related symptoms. The authors concluded "This incident reinforces the necessity for proper aerial application, including maintaining proper aircraft height and observing wind velocity restrictions. However,

mitigation of paraquat drift exposures may best be accomplished by not spraying near residential communities."

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