ABSTRACT

Monocrotophos (Azodrin®) is a cholinesterase inhibiting organophosphate, restricted use insecticide with systemic and contact action. Almost 90 percent of the California usage is on cotton. Between 1980 and 1986, there were 14 occupational illnesses reported as related to monocrotophos, 11 of which were systemic. Monocrotophos is rapidly metabolized and eliminated by mammals, predominately in the urine. Urine monitoring would likely be a feasible means to assess human exposures. The principal metabolite is dimethyl phosphate. The expected dermal absorption at 24 hours is reported as 13.2 percent. An acceptable surrogate study has been used to forecast worker exposures of 21 mg/day for ground mixer/loader applicators wearing standard work clothing and 35 mg/day for flaggers for aerial applications wearing cloth coveralls. Cotton scouts may receive as much as 70 mg/day.

This report was prepared as Appendix B to the Department's risk assessment document for monocrotophos.
APPENDIX B

California Department of Food and Agriculture
Worker Health and Safety Branch

Human Exposure Assessment

MONOCROTOPHOS

February 5, 1988

INTRODUCTION

Monocrotophos (Azodrin® dimethyl (E)-1-methyl-2-methylcarbamoylvinyl phosphate, C\textsubscript{7}H\textsubscript{14}NO\textsubscript{5}P, CAS 6923-22-4) is a cholinesterase inhibiting organophosphate insecticide with systemic and contact action. It is absorbed by leaves. The pure compound is produced as colorless crystals which are readily soluble in water, acetone and alcohol but are only slightly soluble in kerosene and diesel oil. Its vapor pressure is \(9 \times 10^{-5}\) mbar at 20 degrees C. The technical product is brown and melts at approximately 25 to 30 degrees Celsius. Monocrotophos is corrosive to iron and brass but not aluminum. It is slowly decomposed in water (\(t_{1/2}\) of approximately 22 days), but is rapidly hydrolyzed in alkaline media (1).

Azodrin® is a California and Federal Restricted Use Pesticide based on acute human oral toxicity and hazard to birds. Only one product, Azodrin® 5 is sold in California. The original registrant has sold their pesticide operations to a second company and labels for this product are currently active under both organizations although the old label should lapse at the end of 1987. The original registrant will no longer market the product at that time.

Azodrin® 5 is a water miscible liquid containing five pounds of active ingredient per gallon. The product is intended primarily for agricultural use, but some commercial horticultural usage might be allowed by old the label. At present, the new label only allows use on cotton, tobacco, sugarcane and peanuts, of which only cotton is a significant crop in California.

EPA STATUS

A Registration Standard was issued in September 1986 that contains EPA's regulatory position on products containing monocrotophos (2). Of primary interest are the requirement for protective clothing and equipment for mixers, loaders, flaggers and applicators (with high potential exposure), the continuance of the present 48-hour reentry interval and the prohibition of the use of backpack or Knapsack sprayers for application. Monocrotophos has been the subject of two recent Data Call In's, one for data pertaining to potential groundwater contamination, and a second as part of a general chronic data request for cotton insecticides.
An additional concern is the presence of trimethyl-phosphate (TMP) as a contaminant of the product. EPA has identified TMP as a potential mutagen and carcinogen, although its Theoretical Mean Residue Contribution is calculated by EPA to be 0.3 µg/day based on tolerances for monocrotophos. TMP is approximately one percent of the formulated product and could therefore be expected to result in worker exposure equal to approximately one percent of the exposure figures included later in this document. It is suggested that additional risk calculations for TMP be included in the final risk characterization.

**USAGE**

In 1985, 389,000 pounds of monocrotophos were sold in California (3) while 68,000 pounds were reported used by licensed Pest Control Operators (4). Use reports indicate that almost 90 percent of the monocrotophos used in California is applied to cotton. Past minor uses have included citrus, potatoes, roses and turf.

Azodrin® can be applied by air or by ground at from 0.2 to 1.0 pounds of active ingredient per acre. Applications to cotton can be repeated, but not more frequently than every five days. In the San Joaquin Valley, monocrotophos cannot be applied more than two weeks after bloom or after July 15 in order to protect wildlife. This restriction does not apply to the southern cotton growing districts of the State.

**ILLNESS REPORTS**

Since 1980, there have been 14 occupational illnesses reported as related to monocrotophos. Eleven (80%) were systemic in nature. The remaining three were skin injuries.

**WORK PRECAUTIONS**

The new Azodrin® label meets the Federal requirements for protective clothing and equipment as outlined in the Registration Standard. For mixing and loading, and for ground application, the worker is instructed to wear a protective suit that affords full body protection in addition to impermeable gloves, a hat, boots, goggles and an approved pesticide respirator. The label provides additional recommendations for safe handling, such as washing contaminated clothing, along with thorough precautionary statements and statements of practical treatment as required for a Toxicity Category I material.

The Federal and California reentry interval for monocrotophos is 48 hours. Reentry prior to 48 hours is not allowed, by regulation, in California.
DERMAL TOXICITY

Acute dermal toxicity has been investigated in the rabbit for both the technical and formulated products. In the technical study, undiluted product was applied to the animals at 0, 125, 250, 500 and 1000 mg/kg body weight. Organophosphate intoxication was observed within 15 to 60 minutes of application depending upon the dose. Death occurred in the top two doses within six hours. Erythema was noted at the application site but was not apparent after 24 hours. Animals that survived appeared normal within 24 hours. The LD$_{50}$ calculated for this study was 354 mg/kg (5).

A similar study was conducted for Azodrin® 5. The test material was applied to a shaved portion of the animals back that was partially abraded. Some irritation at the application site was noted that was classified as slight. The dermal LD$_{50}$ was reported to be greater than 200 mg/kg (6).

There is apparently no data on dermal sensitization.

DERMAL ABSORPTION

One dermal absorption study was submitted in May 1987. $^{14}$C-Monocrotophos was provided to the contracting laboratory by the registrant as a stock solution in acetone. Dosages were applied in primarily acetone solutions. Treatment groups of four Harlan Sprague Dawley Wistar rats were dermally dosed at 0.2, 2.0 and 20.0 mg/rat dorsally on unabraded skin. A control group of eight rats was treated in the same manner with unlabeled monocrotophos. At the time of the study, the rats were seven to ten weeks old and weighed between 240 and 290 grams. The treatment groups were sacrificed at 0.5, 1, 2, 4, 10, 24 and 168 hours and the application site skin, the whole carcass and the blood were saved for liquid scintillation counting. Urine and feces were also collected and counted along with cage rinses and skin washes from the application site. Selected treatment groups were repeated. The 168-hour group rats were able to pry off the dosing template/protective cover and a new group of animals was tested. One group of 2.0 mg rats was retested as were five groups receiving 20.0 mg due to high variability in the results of the original set. No problems were reported during the repeat phases.

Monocrotophos was initially rapidly absorbed with the average rate of 32 µg/cm²/hour during the first half-hour following exposure. By 24 hours, the rate had dropped to an average of 2.3 for all three treatment levels. The registrant reports that the maximum dermal absorption at 24 hours averaged 13.2 percent, however, this figure includes the monocrotophos bound in application site skin and the monocrotophos not accounted for in the material balance. It may therefore overestimate the available dosage. If the monocrotophos bound in skin is not included in the calculation and only the compound found in the urine, feces, blood, carcass and cage rinses is counted, the average maximum dermal absorption at 24 hours would be 4.4 percent (7). Both figures (4.4 and 13.2) will be used in the exposure calculations.
BIOLOGIC FATE

Summaries of several metabolism studies, which include some information on kinetic disposition, have been submitted. In general, monocrotophos is rapidly metabolized and eliminated, predominately in the urine. The major metabolite in mammals is most often reported to be dimethyl phosphate, which is found in urine and should be stable enough to allow biological monitoring. Dimethyl phosphoric acid has been monitored in a previous study although the method of laboratory analysis used had not been used for monocrotophos before which caused the investigators some doubt about the validity of the urine monitoring results (8).

In a rat study, a 5 mg/kg dose was administered by intraperitoneal injection. During the first six hours after administration, 45 percent of the dose was excreted in the urine and feces. More than 60 percent had been eliminated after 24 hours, with 58.4 percent found in the urine and 5.1 percent found in the feces. The principle metabolite was dimethyl phosphate, with o-dimethyl-Azodrin and hydroxy-methyl-Azodrin found in smaller amounts (9). In a second study, oral doses of 1 mg/kg of $^{32}$P-labeled Azodrin® were given to rats of both sexes. After 48 hours, 63-71 percent of the dose had been excreted in the urine and five percent in the feces. The major metabolites in the urine were dimethyl phosphate and 3-hydroxy-N-methyl-cis-crotonamide (10).

In a goat study, a single oral dose of 1 mg/kg of $^{32}$P and N-methyl-$^{14}$C labeled Azodrin® was given. By 72 hours, 90 percent of the $^{14}$C and 67 percent of the $^{32}$P had been excreted in the urine. Dimethyl phosphate and methyl hydrogen phosphate of 3-hydroxy-N-methyl-cis-crotonamide were the major metabolites (10).

$^{32}$P-labeled Azodrin® was fed to cows in rations containing 45 ppm for 14 days. Urine and feces were collected at unscheduled times. Milk was sampled both morning and evenings. At the end of the study the animals were sacrificed and tissue samples were also taken. While traces of various metabolites were found in milk and sampled tissues, the predominate metabolites in urine were dimethyl phosphate and salts of methyl hydrogen phosphate of 3-hydroxy-N-methyl-cis-crotonamide (11).

APPLICATION RELATED EXPOSURE

Three registrant conducted studies have been submitted. The first two are relatively old studies (1964, 1968) that do not accurately and fairly assess true exposure as compared to more recent, more complete exposure studies (12,13). Both studies attempt to measure exposure for aerial application. While there some are useful measurements of cholinesterase values, those parts of the two reports that deal with actual exposure are not sufficiently refined to allow accurate estimates of long term risk. The following are important shortcomings of the first two studies:

1. Neither study contains or will allow an extrapolation of total body exposure since neither study includes hand exposure or inhalation exposure data. There is actually only one replication per participant, which for some work categories means only one replication.
2. No controls or storage blanks or storage correction factors were included in the studies. No storage conditions or times to analysis are included.

3. The time that the workers were monitored is too short to adequately assess exposure. In one study the monitoring period was roughly 40 minutes, in the second, the exposure period was less than one hour.

4. There does not appear to be, in either study, an accurate and reliable measurement of final patch area. Patches consisted of only one gauze pad with no backing foil or paper. There is, therefore, no way to estimate the protective factor from clothing. Only five patch locations were used in one study.

5. The formulation and percent active ingredient are not specified in one study.

6. Cholinesterase activity data for some work categories could be confounded by immediate prior exposure to cholinesterase inhibiting pesticides.

For the above reasons, our exposure assessments did not use the 1964 and 1968 studies.

The third study was submitted by the new registrant. It contains mixer/loader/applicator data for Bidrin® (dicrotophos) for ground and aerial application and was submitted specifically for use as a surrogate to replace monocrotophos data (14). For several reasons, this study is an appropriate surrogate.

The vapor pressures of the two active ingredients are roughly the same with dicrotophos being slightly more volatile. However, there should not be enough difference in volatility to affect the outcome of a comparison for this kind of data. Likewise, their solubility and stability in solution are comparable. Both are absorbed by the leaf and have systemic as well as contact activity. Both have an acute oral LD$_{50}$ in the rat of 20-22 mg/kg. The study for Bidrin® was conducted as used on cotton and is therefore appropriate since almost 90 percent of the Azodrin® used in California is applied to cotton. When formulated, both products contain volatile solvents as inerts, which are different, but Azodrin® contains a greater percentage.

There is, however, a difference in application rate. The Bidrin® study was conducted at maximum label rate for cotton which is 0.2 pounds of active ingredient (ai) per acre. The maximum label rate for Azodrin® on cotton in California is 1.0 pound ai. However, when diluted in a tank mix, the percentage of active ingredient in the solution is the same since the Azodrin® label calls for five times the water for both aerial and ground applications than does the Bidrin® label. There would still need to be a five-fold adjustment in the measured exposure values as workers handle five times the compound. Also, while the study was not conducted in California, and closed systems were not used, it is doubtful that an additional study conducted specifically with Azodrin® would show substantially different exposure values than those reported after the five-fold adjustment has been made.
Six individuals were monitored in the Bidrin® exposure study. Two were pilots for aerial application, two were mixer/loaders for those same applications and two were ground applicators that did their own mixing and loading. Dermal exposure was measured in the traditional method using patch dosimeters and handwashes. Inhalation exposure was measured using sampling pumps and sorbent tubes in the breathing zone of the worker. Length of exposure monitoring ranged from two hours and 20 minutes to six hours and thirty minutes. The application rate for each replicate was 0.2 pounds of active ingredient per acre. All workers wore standard work clothing. Chemically resistant gloves were worn during mixing but not during application. Respirators were worn during all mixing and loading (14).

The total exposure based on average micrograms dicrotophos found per replicate ranged from a low of 1.5 µg/pound of ai applied for a pilot to a high of 212 µg/pound ai applied for a ground M/L/A. Based on the assumption that an aerial applicator can apply 600 acres or 120 pounds ai/day and 100 acres or 20 pounds ai/day can be treated by ground equipment, maximum expected total exposure for each work category is shown in the following table. The final column reports expected exposure for Azodrin® as calculated from Bidrin® data.

Table 1 - Expected Azodrin® Exposure as Extrapolated From Measured Values From the Submitted Surrogate Study

<table>
<thead>
<tr>
<th></th>
<th>Max. Exposure per lb. ai applied (µg)¹</th>
<th>Est. lbs. applied/day²</th>
<th>mg/day Surrogate³</th>
<th>mg/day Azodrin⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aerial Application</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M/L</td>
<td>13.8</td>
<td>120</td>
<td>1.7</td>
<td>8.5</td>
</tr>
<tr>
<td>Pilot</td>
<td>22.7</td>
<td>120</td>
<td>2.7</td>
<td>13.5</td>
</tr>
<tr>
<td><strong>Ground Application</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M/L/A</td>
<td>212</td>
<td>20</td>
<td>4.2</td>
<td>21.2</td>
</tr>
</tbody>
</table>

WH&S, 1987

1. Includes inhalation exposure.

2. For aerial application, 600 acres per day is estimated which at 0.2 lbs ai/acre equals 120 pounds. For ground application an average estimated acreage treated per day is 100, resulting in handling of 20 pounds ai.


4. Estimated Azodrin® exposure is based on five times the measured Bidrin® exposure.

When compared to data from a 1981 study conducted by Worker Health and Safety on the products DEF® and Folex® as applied to cotton by air at rates of one to 1.5 pounds of active
ingredient per acre, the estimated Azodrin® exposures are solidly within the expected range (15). Further, if the maximum measured exposure for flaggers from the DEF/Folex study is normalized to eight hours and is substituted for missing flagger data from the Bidrin® study, the estimated exposures and Lifetime Average Daily Doses would be as found in Table 2.

Table 2 - Expected Daily Exposure and Lifetime Average Daily Dosage for Workers Applying Azodrin® to Cotton in California

<table>
<thead>
<tr>
<th></th>
<th>Exposure</th>
<th>Daily Dosage</th>
<th>Days Exposure</th>
<th>LADD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg/day</td>
<td>µg/kg/day</td>
<td>per Year</td>
<td>µg/kg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13.2%</td>
<td>4.4%</td>
<td>13.2%</td>
</tr>
<tr>
<td>Aerial Application</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pilot</td>
<td>14</td>
<td>34</td>
<td>11</td>
<td>40</td>
</tr>
<tr>
<td>Mixer/Loader</td>
<td>9</td>
<td>22</td>
<td>7</td>
<td>40</td>
</tr>
<tr>
<td>Flagger</td>
<td>35</td>
<td>84</td>
<td>28</td>
<td>40</td>
</tr>
<tr>
<td>Ground Application</td>
<td>21</td>
<td>51</td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td>Reentry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cotton Scout</td>
<td>72</td>
<td>173</td>
<td>58</td>
<td>40</td>
</tr>
</tbody>
</table>

WH&S, 1987

1. From "Bidrin® Field Exposure Study in Post-Emergent Application on Cotton" Shell Development Co., 1986 and "Monitoring of Potential Exposures of Mixer-Loaders, Pilots and Flaggers During Application of DEF® and Folex® to Cotton Fields in the San Joaquin Valley of California, 1979" CDFA WH&S, Rev. 1981. The Bidrin® data is based on the estimated amount of acreage that could be treated in an eight-hour day. The flagger DEF®/Folex® data is from a seven-hour workday normalized to eight hours. Workers in the Bidrin® study wore standard work clothing, chemically resistant gloves were worn during mixing and respirators were worn during mixing and loading. Flaggers in the DEF®/Folex® study wore coveralls with no other protection. Cotton scout data is from "Establishment of Reentry Intervals for Organophosphate Treated Cotton Fields Based on Human Data: III." Cotton scout clothing not specified in study. Exposure includes inhalation exposure at 100 percent retention of compound by the lungs.

2. Daily dosage is calculated based on a 54.8 kg worker and is listed for both 13.2 and 4.4 percent dermal absorption. Inhaled dose absorption is treated, as is the dermal dose.

3. Estimated days exposure per year is for commercial applicators working for 10 days each for four months for aerial application and five days each for four months for ground application. Estimated days per year for cotton scouts is based on 80 total hours of exposure per month for four months.

4. Lifetime Average Daily Dosage is calculated for both dermal absorption rates over 24 hours assuming a 40-year working lifetime.
There is also the possibility that there may be limited exposure for workers planting monocrotophos treated cotton seed, although extent of the problem is undocumented and the potential exposure remains unmeasured.

**EXPOSURE AT REENTRY**

Reentry is of concern for cotton scouts. The registrant has submitted two studies that apply specifically to field reentry. In the first, two separate groups of five volunteers entered a cotton field, treated with one pound of monocrotophos active ingredient, at 48 and 72 hours post treatment and remained for five hours of exposure. Moderate plasma ChE inhibition was noted in the 48 and 72 (up to 40 percent) hour reentry subjects. Similar depression was found for the RBC ChE of workers reentering at 48 hours (up to 30 percent) (16). Dislodgeable residue analysis showed that by the 48 hour exposure period, residue samples collected from the top, middle and bottom of plants and then composited was reduced from 12.8 to 6.3 µg/cm². By 72 hours, residue was reduced to 4.3 µg/cm². This corresponds to levels of monocrotophos extracted from shirts and pants and washed from hands after five hours of exposure at the same time intervals totaling 35.8 mg and 45.1 mg, respectively. Adjusting the 72-hour potential dermal exposure data from five hours to eight hours results in an expected exposure to hands and clothes of 72.2 mg, which is greater than the measured exposure for 48 hours. Inhalation exposure would add an additional 1.0 µg when normalized to eight hours if 100 percent retention is assumed. Additional residue accumulating at locations such as the face and neck, the wrists and the ankles would increase the expected exposure by an unknown amount. The Zweig-Popendorf Transfer Coefficient (17) would indicate an exposure of approximately 172 mg/day, possibly overestimating true exposure by a factor of two, however the residue found in the subject study was highly variable, increasing by 20 percent between the 48 and 72 hour samples.

We would prefer to use the study data rather than the Zweig-Popendorf figure to estimate reentry exposure. In either case, expected exposure for a cotton scout is expected to be high.

The second study measured dislodgeable foliar residue for tobacco treated with 0.5 lb. ai/acre Azodrin® 5 and evaluated ChE activity for workers reentering fields for eight-hour periods. Dimethyl phosphoric acid was measured in urine of the workers (8).

Cholinesterase inhibition for any individual did not exceed 18 percent and no symptoms or clinical signs of illness were seen. Urine monitoring did not show a significant difference in dimethyl phosphoric acid before vs. after exposure. Dislodgeable foliar residue results showed low levels of monocrotophos ranging from 0.3 µg/cm² at 48 hours to 0.03 µg/cm² at 96 hours. Based on Zweig/Popendorf, the estimated dermal exposure at reentry into cotton would be 12 mg/person/day at 48 hours. This study recommended a 72-hour reentry interval for tobacco.
LITERATURE CITED


12. Shell data: Dermal Exposure to Azodrin® Insecticide Resulting from Aerial Application. 1968. CDFA Vol. 296-001.


Appendix 1

Quality and Availability of Data for Use in the Evaluation of Monocrotophos as Used in California

We are currently reviewing data as part of the Department's risk assessment process for compounds that have shown potential adverse effects that was submitted in 1982 by the Shell Chemical Company in support of the registration of Azodrin® (monocrotophos) in California. This includes worker exposure studies for both application and reentry.

There are two studies available that attempt to measure exposure during aerial application. Both fall short of what will be required to accurately and fairly assess the true exposure of workers in California. The studies were conducted in 1964 and 1968, which is very early in the science of workplace monitoring in the agricultural setting. While one includes measurements of cholinesterase activity which may be useful for some work categories in our estimate of acute risk, those parts of the reports that deal with actual exposure are not sufficiently refined to allow accurate estimates of long term risk. The following are reasons why these studies are not acceptable:

1. Neither study contains or will allow an extrapolation of total body exposure since neither study includes hand exposure or inhalation exposure data. There is actually only one replication per participant, which for some work categories means only one replication.

2. No controls or storage blanks or storage correction factors were included in the studies. No storage conditions or times to analysis are included.

3. The time that the workers were monitored is too short to adequately assess exposure. In one study the monitoring period was roughly 40 minutes, in the second, the exposure period was less than one hour.

4. There does not appear to be, in either study, an accurate and reliable measurement of final patch area. Patches consisted of only one gauze pad with no backing foil or paper. Therefore, there is no way to estimate the protective factor from clothing. Only five patch locations were used in one study.

5. The formulation and percent active ingredient are not specified in one study.

6. Cholinesterase activity data for some work categories could be confounded by immediate prior exposure to cholinesterase inhibiting pesticides.

There is also no dermal absorption data for this compound. Studies will be needed for both worker exposure (worst case) and dermal absorption to replace our worst case estimates for this product. We would ask that this document be forwarded to the new registrant of this compound and that at your earliest convenience you arrange a conference call or provide for us a contact person to discuss the needed data.
Appendix 2

Suitability of Surrogate Worker Exposure Data for Monocrotophos

We have discussed the possibility of using mixer/loader/applicator exposure data, collected for dicrotophos (Bidrin®) in a study conducted in Mississippi by the Shell Development Company, during the evaluation of worker exposure to monocrotophos (Azodrin®). This report was submitted specifically for use as a surrogate study in response to the Department's earlier letter requesting data for the compounds under SB 950 review. The study was submitted by Du Pont, the new registrant of monocrotophos. It includes data for personnel involved in both aerial and ground application. For several reasons this study may be suitable for use as a surrogate.

The vapor pressures of the two active ingredients are roughly the same with dicrotophos being slightly more volatile. However, there should not be enough difference in volatility to affect the outcome of a comparison for this kind of data. Likewise, their solubility and stability in solution are comparable. Both are absorbed by the leaf and have systemic as well as contact activity. Both have an acute oral LD50 in the rat of 20-22 mg/kg. The study for Bidrin® was conducted as used on cotton and is therefore appropriate since almost 90 percent of the Azodrin® used in California is applied to cotton. When formulated, both products contain volatile solvents as inerts that are different, but Azodrin® contains a greater percentage.

Possible objections to overcome include the difference in application rate. The Bidrin® study was conducted at maximum label rate for cotton, which is 0.2 pounds of active ingredient per acre. The maximum label rate for Azodrin® on cotton in California is 1.0 pound ai. However, when diluted in a tank mix, the percentage of active ingredient in the solution is the same since the Azodrin® label calls for five times the water for both aerial and ground applications than does the Bidrin® label. There would still need to be a five-fold adjustment in the measured exposure values. While the study was not conducted in California, and closed systems were not used, it is doubtful that an additional study conducted specifically with Azodrin® would show much lower exposure values than those reported (the highest exposure measured was for a ground M/L/A at approximately 4.4 mg/day). Even though the five-fold adjustment would raise the expected exposure, it appears at this time as though the risk could be mitigated.