

## Dermatitis Among Stone Fruit Harvesters in Tulare County, 1988

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### Summary

In June, 1988 the Department of Food and Agriculture, Worker Health and Safety Branch, received a report regarding an outbreak of dermatitis among three crews of nectarine harvesters in Tulare County, California. On interview, 46 (80.7%) of 57 workers in the three affected crews reported experiencing a rash between June 13 and June 27. Of the 46 rashes reported on questionnaire, 42 (91.3%) were found to be contact dermatitis on medical examination. No cases were reported among members of a comparison crew employed by the same grower and none were identified on examination. Significant negative associations were noted between rash reported on questionnaire and exposure to *B. thuringiensis*, environmental heat, and work in untreated orchards; positive associations were noted for exposures to propargite and iprodione. The results of skin examinations performed on June 27 and 28 demonstrated a similar pattern of association between the rash score for individual workers and exposures between June 13 and June 27. Although exposures to iprodione and propargite were highly correlated and could not be separated on multivariate analysis, only 34 (74%) of the reported cases were preceded by exposure to iprodione whereas all of the cases were preceded by exposure to propargite. Propargite was thus the only exposure which could have accounted for all of the reported cases and also had a positive association with the occurrence of dermatitis. Contact dermatitis in the present episode was associated with levels of dislodgeable propargite residue ranging from 0.55 to 1.91  $\mu\text{g}/\text{cm}^2$ , with median values for the three affected crews equal to 0.61, 0.64, and 0.69  $\mu\text{g}/\text{cm}^2$  respectively. Median dislodgeable propargite residue to which the unaffected crew was exposed during the same time interval was 0.15  $\mu\text{g}/\text{cm}^2$ . This data thus yielded an estimated No-Observed-Effect-Level (NOEL) for repeated dermal exposure to propargite of approximately 0.2  $\mu\text{g}/\text{cm}^2$ .

## Introduction

In June, 1988 the Department of Food and Agriculture, Worker Health and Safety Branch, received a report regarding an outbreak of dermatitis among nectarine harvesters in Tulare County, California. Since initial information obtained from the County Agricultural Commissioner's Office indicated there was no violation of existing reentry intervals, investigators were sent to determine the cause of the incident. Numerous sources of skin disease known to be present in the agricultural work environment, including heat, exposure to irritating or allergenic plant material, and agricultural chemicals (Adams, 1983; Hogan and Lane, 1986), were considered as possible sources of the outbreak. Particular attention was paid to the possible role of excessive environmental heat, since this has previously been postulated to play a major role in the development of dermatitis in California agricultural workers (Winter and Kurtz, 1985). Dermatitis due to plant exposure was considered a priori to be a less likely cause of the outbreak since harvesting nectarines does not present an opportunity for contact with poison oak or other noxious weeds and the dermatitis due to nectarines or nectarine foliage has not previously been reported (Mitchell and Rook, 1979). This report presents the findings of the investigation.

## Methods

California physicians are required by law to report suspected cases of pesticide poisoning to the local county health officer and agricultural commissioner's office of each county for investigation (Edmiston and Maddy, 1987; Edmiston and Richmond, 1988). Episodes involving more than five individuals, or a single individual hospitalized for more than 24 hours, receive priority in investigation. The investigation conducted in this incident included: interviewing and examining workers, reviewing medical records, interviewing their employer, and collecting environmental exposure data.

Each employee in a crew reporting dermatitis was interviewed and examined. In addition, each employee in a reportedly unaffected crew was interviewed and examined. Interviews and exams were conducted in Spanish, using standardized questionnaires (Appendix 1). The purpose of the questionnaire was to identify affected workers and the day of onset of dermatitis. After completing the questionnaire, the face, neck, trunk, and upper extremities of each worker was examined to determine the distribution of skin lesions. In the exam, the severity of rash was scored on a scale from 0 to 3, with separate entries for erythema (redness), blistering, and postinflammatory changes in pigmentation. Eighteen separate anatomical regions were systematically examined, including the forehead and periorbital (region around the eyes) areas of the face, jaw, upper neck, "V" area of the neck, chest, and abdomen, and for each upper extremity the shoulder, upper arm, antecubital fossa (skin in front of the elbow), forearm, wrist, and hand. A subjective diagnosis was also recorded and specifically included codes for 1) contact dermatitis, 2) resolving dermatitis, and 3) normal examination or 4) abnormal examination secondary to other skin condition.

At the time of interview, medical records from the facilities that had treated the workers were requested and subsequently reviewed. For workers who had been treated, the recorded diagnosis and distribution of dermatitis was compared to

both questionnaire responses indicating the presence or absence of a rash in the previous two weeks and the results of our examinations performed at the time of the interview.

Several management employees, including the grower, were interviewed to obtain detailed records of work history for each of the four crews examined. Work histories were obtained for the period June 13 through June 27, 1988, including the specific orchard worked, variety picked and hours worked. In addition, pesticide spray records for each orchard worked were collected for the 1988 growing season to date. Spray records included application date, pesticide product used, amount used and dilution. This information was used with environmental sampling data to estimate exposure levels to workers at the time of their working in each field.

Foliar samples were taken in each orchard picked by the four crews interviewed and treated with pesticides. Samples were collected for propargite analysis in each of the orchards worked by the four crews during the period June 13 through June 27 that had been treated with Omite<sup>R</sup>. Several fields treated with Carzol<sup>R</sup> and considered suspect of causing the dermatitis cases were sampled for formetanate hydrochloride. One suspect field, treated with Rovral<sup>R</sup> was sampled for dislodgeable iprodione. Follow-up samples were taken approximately weekly in suspect orchards with particularly high residues.

Samples were collected from the nectarine foliage by cutting leaf discs with a five cm<sup>2</sup> punch. Each sample consisted of four discs from each of ten trees. Two samples were taken from each treated field.

Chemical analyses for propargite, formetanate hydrochloride, and iprodione were run in the Worker Health and Safety Laboratory Section of Chemistry Laboratory Services in Sacramento following the standard method for dislodgeable residue (Gunther, 1973). Dislodgeable residue samples were extracted by adding to each jar containing 40 leaf punches 50 milliliters (mls) of distilled water and two drops of dioctyl sodium sulfosuccinate (Sur-ten<sup>R</sup>) two percent surfactant solution. The jar was rotated for twenty minutes and the liquid phase decanted into a 500 ml separatory funnel. Dislodgeable residue remaining on the leaf was removed by repeating this step twice. A total of 150 mls of distilled water, plus surfactant and dislodged pesticide, was then extracted using 50 mls of either methylene chloride (propargite and formetanate hydrochloride) or ethyl acetate (iprodione) and dried using sodium sulfate. The solvent was then evaporated using a rotary evaporator and the residue redissolved in hexane (propargite and iprodione) or methanol (formetanate hydrochloride). For propargite and iprodione samples, the redissolved material was then analyzed by gas chromatography, using either an electron capture (propargite) or nitrogen-phosphorous detector (iprodione). Formetanate hydrochloride samples were analyzed by liquid chromatography using a ultraviolet spectrographic detector. For all analyses quantitative results were obtained by comparison to standard solutions of the relevant compound.

Where sufficient residue data were available, exposure was quantified by calculating residue-hours of exposure (Saunders et al, 1987). Residue-hours



at the time of initial treatment or at the time of the CDFA examination. Three cases of contact dermatitis among members of the three affected crews were identified on examination in individuals who had not reported a rash during the interview. The specificity of the questionnaire in identifying a rash confirmed to be contact dermatitis on medical examination was thus 82% (19/23) and the sensitivity was 42/45 = 93%).

Comparison of the results of the medical examinations performed by treating physicians and those performed during the CDFA investigation demonstrated good agreement. The predominant lesions noted on both examinations were fine erythematous papules of the antecubital fossae, with the right arm typically more severely affected than the left. More severe cases involved other areas including the forearm, upper arm and shoulder, neck and face. At time of the examination on June 27, no cases had demonstrable lesions on the chest, but five (16%) of thirty-two workers who sought medical treatment had at least minimal involvement of the chest recorded on the physical examination. One worker, who reported wearing a short sleeved shirt while working rather than the long sleeved shirts typical of the majority of crewmembers, had a rash on the forearm which resembled sunburn or acute photodermatitis.

Rash scores differed significantly among crew members with active cases of contact dermatitis on examination and those with resolving contact dermatitis (Figure 2). All cases subjectively recorded as normal skin examinations had zero rash scores except four individuals who had mild erythema confined to the neck. Since the degree of erythema was slight and could possibly have been attributed to sun exposure, these individuals were not felt to have definite cases of contact dermatitis.

When rash scores were compared by crew, there were significant differences between the three crews involved in the outbreak and the comparison crew which did not have any cases of contact dermatitis reported on the questionnaire (Figure 2). Two members of the control crew had extensive cases of vitiligo. The first case reported that the lesions had been present for two years prior to the examination and the second case reported that the lesions had been present for ten years. It was thus considered unlikely that either case was related to the worker's current employment. A third worker in the control crew was found to have mild acne over the chest.

#### Work History and Environmental Sampling Data

Work histories and results of analysis of all environmental samples taken for fields worked by the four crews between June 13 and June 27 are shown in Table 1. For chemicals where reliable decay rate data were available, estimated residue levels on the day of exposure are shown as well as the actual level of residue measured on the day of sampling. Measured levels of formetanate hydrochloride ranged from 0.30 to 1.26 ug/cm<sup>2</sup> at the time of sampling for affected crews. No residue results were available for iprodione because of an interference peak which precluded both qualitative and quantitative analysis. The estimated levels of propargite range from 0.55 to 1.91 ug/cm<sup>2</sup> for affected crews. The unaffected crew worked in treated orchards for three days;

the estimated level of propargite dislodgeable residue ranged from 0.14 to 0.82 ug/cm<sup>2</sup>. They also worked in ten orchards treated either with formetanate hydrochloride or *B. thuringiensis* but no residue samples were available from these fields. Between June 13 and June 27 the high daily temperature ranged from 90 degrees (June 21) to 103 degrees (June 19).

When the relationship between cases and the prior exposures was evaluated graphically, it was apparent that all of the cases reported on the questionnaire were preceded by exposure to both propargite and formetanate hydrochloride, and 34 (74%) were preceded by exposure to iprodione and only one case had any prior exposure to *B. thuringiensis* (Figure 3). Statistical evaluation of the work histories and residue sampling data demonstrated a significant positive association (with the cases demonstrating a higher mean rank than non-cases using the Mann-Whitney U test) between the occurrence of rash reported on questionnaire and the exposures prior to the onset of the rash for propargite and iprodione. There was a significant negative association between the occurrence of rash and days worked in untreated fields and fields treated with and *B. thuringiensis*. Evaluation of the relationship between the heat exposure index, degree-days, and reported occurrence of rash also demonstrated a significant negative association (Table 2).

The results of skin examinations performed on June 27 and 28 demonstrated a significant positive association between the rash score for individual workers and exposures between June 13 and June 27 to propargite and iprodione. There was no significant association for exposure to formetanate hydrochloride and the heat exposure index, degree-days. Significant negative associations were found for exposures to untreated fields and to fields treated with *B. thuringiensis* (Table 3). When the propargite residue hours and iprodione-days were analyzed simultaneously in a multiple linear regression model, the results showed that propargite-residue hours had a slightly stronger association with the rash score. However, a high degree of correlation existed between propargite-residue hours and iprodione; neither exposure could be demonstrated to be significant separate risk factors in the multivariate analysis (Table 4).

#### Discussion

Because of the wide variety of potential causes of contact dermatitis in the agricultural work place, it has frequently been difficult to identify the source of individual cases (Edmiston and Richmond, 1988). In the outbreak reported here a high incidence of dermatitis was reported among three crews of stone fruit harvesters exposed to persistent pesticide residues during two weeks in June, 1988. The character and distribution of the skin lesions found on examination were consistent with the dermatitis arising from contact with pesticide residues on foliage. Lesions were found on predominantly on the upper extremities, shoulders and neck. Only 5 (16%) of the 32 workers who sought medical treatment had lesions on the chest, the area characteristically affected by heat rash (*miliaria rubra*) (Domonkos et al, 1982). Heat rash could also have been excluded as a cause of the outbreak by the complete absence of dermatitis in a comparison crew which worked throughout the same time period. Other factors associated with the nature of the work itself, such as contact with plant foliage, were excluded by the significant negative association

between the occurrence of contact dermatitis and work in orchards which had not been treated with pesticides. The high cumulative incidence in the three affected crews further suggests that the contact dermatitis was irritant rather than allergic in nature.

The principal limitation of the analyses conducted was the necessity to rely on group exposure data as an approximate measure of individual exposure. The effect of this limitation is demonstrated in Figure 2, which shows the marked variation in rash score among members of the three affected crews. Although individual susceptibility may explain part of the variation in rash score, individual variation in exposure must also be an important underlying factor. Our data, which represents individual high and low exposures by the same group estimate of exposure, therefore has a significant degree of random misclassification. This misclassification of exposure produces a strong bias towards the null hypothesis, i.e. that there is no association between exposure and effect (Kleinbaum et al, 1982; Lilienfeld and Lilienfeld, 1980). In our study, this would have the effect of reducing the apparent association between exposure to various pesticides and the subsequent occurrence of dermatitis.

Of the pesticides encountered by the four crews evaluation of work histories revealed that exposure to both propargite and iprodione were positively associated with the occurrence of dermatitis (Tables 2 and 3). Because exposures to these materials were highly correlated, it was not possible to ascertain from multivariate analysis whether either was a separate risk factor (Table 4). However, of these two compounds, only propargite could have conceivably accounted for all of the reported cases (Figure 3). In addition to propargite, all of the cases had previous exposure to fometanate hydrochloride, but this compound was not statistically associated with the occurrence of rash. The apparent cause of the high incidence of dermatitis in the three crews was thus determined to be residues of propargite which persisted well beyond the one day reentry interval (CDFA, 1987) which was in effect at the time of the incident. This conclusion is supported by both animal toxicity studies, which indicate that propargite is a far more potent skin irritant than either fometanate hydrochloride or iprodione (Appendix 1) and use experience with propargite in California (Maddy, 1976; Maddy, 1980; Nishioka et al, 1970; O'Malley et al, 1989; Saunders et al, 1987; Smith et al, 1982).

To estimate what amount of propargite residue might be considered a no-observable-effect-level (NOEL) for periods of prolonged exposure, one must consider data from previous episodes of fieldworker dermatitis. Although published descriptions of the 1986 dermatitis outbreak involving propargite exposure to orange harvesters, do not include details of residue exposure (Saunders et al, 1987), CDFA files (Appendix 3) indicate that six affected crews worked from one to four days picking oranges in orchards with dislodgeable residues ranging from 0.82 to 5.49 ug/cm<sup>2</sup>. Median residue levels to which the six crews were exposed were 1.65, 1.52, 2.47, 1.51, 3.33 and 1.88 ug/cm<sup>2</sup>. Using the work-task-residue-transfer-factors of 9,400 cm<sup>2</sup>/hr for harvesting of navel oranges in propargite treated orchards reported by Thongsinthusak et al (1989), the range of dislodgeable residue levels seen in the 1986 incident represent Potential Daily Dermal Exposure (PDDE) (Thongsinthusak and Krieger, 1989) from 61 mg to 413 mg of propargite per eight hour work day, with a median level (combining all six crews) of 133 mg per eight hour day.

Dermatitis in the 1988 episode was associated with levels of propargite ranging from 0.55 to 1.91  $\mu\text{g}/\text{cm}^2$ , with median values for the three affected crews equal to 0.61, 0.64 and 0.69  $\mu\text{g}/\text{cm}^2$ . Based on the work-task-residue-transfer-factor of 9,400 for harvesting peaches (Thongsinthusak et al, 1989), the range of PDDE associated with contact dermatitis in the 1988 episode ranged from 41 mg to 142 mg of exposure per eight hour work day, with a median level equal to 48 mg of exposure per eight hour work day. The propargite residue to which the unaffected crew was exposed during three days of the same time interval ranged from 0.14  $\mu\text{g}/\text{cm}^2$  to 0.82  $\mu\text{g}/\text{cm}^2$ , with a median level of 0.15  $\mu\text{g}/\text{cm}^2$ . These represent PDDE ranging from 10 mg to 75 mg per eight hour work day, with a median value of 11 mg per eight hour work day.

#### Conclusions

Dislodgeable foliar residue and PDDE data from the 1986 and 1988 dermatitis episodes demonstrate a continuum of exposure and effect. While one or two days of harvesting in orchards with propargite residues greater than 1.0  $\mu\text{g}/\text{cm}^2$  (75 mg PDDE) can produce severe dermatitis, lower levels of residue can also produce dermatitis, generally of a less severe nature, in crews exposed continuously over a one to two week period. A (NOEL) for prolonged exposure while hand harvesting stone fruit, can be estimated based on the 0.15  $\mu\text{g}/\text{cm}^2$  median dislodgeable foliar residue to which the unaffected crew was exposed to be approximately 0.2  $\mu\text{g}/\text{cm}^2$  (15 mg PDDE). A similar figure might be arrived at by taking the median exposures which produced dermatitis in the three affected crews, and dividing by a factor of two. This estimate of the NOEL should be considered in conjunction with the existing data on the dissipation of propargite residue (Saiz and Schneider, 1987; Smith, 1989) in evaluating the reentry interval for propargite. In setting reentry intervals for other combinations of crops and work tasks associated with transfer factors substantially different than harvesting stone fruit (Thongsinthusak et al, 1989), appropriate adjustments in the estimated NOEL should be considered.

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Table 1

## Dislodgeable Residue Sampling Results for Fields Worked 6/13-6/27/88

Crew/ Date-hrs	Ranch	Crop Variety	App. Date	Propargite Residue:		Formetanate	Bac.	High Temp.	
				Meas.	Est.	HCl Residue	Ipro- dione		Thurin- qiensis
Crew 79									
13 9.5	Belak/Reb	StR Plum		U		U	U	96	
14 7.7	Belak/Reb	StR Plum		U		U	U	100	
15 4.5	IO Harrel	BlB Plum		U		U	U	101	
15 5.0	IO Harrel	StR Plum		U		U	U	101	
16 4.0	IO Harrel	StR Plum		U		U	U	93	
17 7.0	Belak/Reb	StR Plum		U		U	U	93	
18 2.5	Cradd	StR Plum		U		U	U	98	
19		No work						103	
20 9.5	Trav	SpR Nect	6/1	0.46	0.58	0.89	U	U	91
21 9.5	Trav	SpR Nect	6/1	0.46	0.55	0.89	U	U	90
22 9.5	Trav	FBr Nect	6/1	0.58	0.64	1.26	6/14	U	93
23 9.5	Trav	Fla Nect	6/1	1.29	1.91	-	U	U	98
24		No work						96	
25		No work						92	
26		No work						94	
27		No work						95	
Crew 80									
13 7.5	Peack	StR Plum		U		U	U	96	
13 2.5	Jones	K97 Plum		U		U	U	96	
14 9.5	Dub Lusk	JG1 Plum		U		U	U	100	
15 0.7	Dub Lusk	MiG Plum		U		U	U	101	
15 2.5	Dub Lusk	JG1 Plum		U		U	U	101	
15 6.7	Peacock	StR Plum		U		U	U	101	
16 2.05	Keltner	StR Plum		U		U	U	93	
16 7.5	Sultana	SpR Nect	5/24	0.79	1.40	0.38	U	U	93
17 8.0	Trav	SpR Nect	6/1	0.56	0.62	0.26	U	U	93
18		No work						98	
19		No work						103	
20 9.5	Trav	SpR Nect	6/1	0.46	.58	0.89	U	U	91
21 9.5	Trav	SpR Nect	6/1	0.46	.55	0.89	U	U	90
22 9.5	Trav	FBr Nect	6/1	0.58	.64	1.26	6/14	U	93
23 9.5	Trav	Fla Nect	5/30	1.29	1.91	U	U	U	98
24		No work						96	
25 9.5	Trav	Fla Nect	5/30	0.69	.69	U	U	5/26	92
26		No work						94	
27		No work						95	

U=untreated; T=treated, N=residue data not available

Table 1, Continued

## Dislodgeable Residue Sampling Results for Fields Worked 6/13-6/27/88

Crew/ Date-hrs	Ranch	Crop Variety	App. Date	Propargite Residue:		Formetanate	Bac.	High Temp.
				Meas.	Est.	HCl Residue	Ipro- dione	
Crew 86								
13 9.5	Jones	K97 Plum		U		U	U	96
14 9.5	Garispe	FCr Plum		U		U	U	100
15 5.0	Garispe	MaG Plum	5/10	U		T,N	U	101
15 4.5	Dreo	StR Plum		U		U	U	101
16 9.5	3-R-W	BlA Plum		U		U	U	93
17 9.5	Garispe	MaG Nect	5/10	U		T,N	U	93
18 4.5	Garispe	FCr Nect		U		U	U	98
18 5.0	Garispe	FBr Nect		U		U	U	98
19		No work						103
20 9.5	Dreo	BlA Plum		U		U	U	91
21 3.0	Dreo	BlA Plum		U		U	U	90
21 6.5	Liebau	StR Plum		U		U	U	90
22 4.5	Liebau	StR Plum		U		U	U	93
22 5.0	Sultana	Fla Nect	5/26	0.69	0.82	U	U	T,N 93
23 5.0	Garispe	MaG Nect	5/10	U		T,N	U	98
23 4.5	M Geor	MaG Nect	5/19	0.12	0.15	T,N	U	98
24 9.5	M Geor	MaG Nect	5/19	0.12	0.14	T,N	U	96
25		No work						92
26		No work						94
27		No work						95
Crew 89								
13 9.5	Jones	BlB Plum		U		U	U	96
14 3.0	Trav.	SpR Nect	5/30	0.46	0.76	0.89	U	U 100
14 6.5	Trav.	BlB Nect	6/1	U			U	U 100
15 8.5	Trav	SpR Nect	6/1	0.46	0.72	0.89	U	U 101
16 9.5	Trav	SpR Nect			0.69		U	U 93
17 8.0	Trav	SpR Nect	6/1	0.39	0.66	0.39	U	U 93
18 7.0	Trav	FBr Nect	6/1	0.58	0.76	1.26	6/14	U 98
19		No work						103
20 9.5	Trav	SpR Nect	6/1	0.46	0.58	0.89	U	U 91
21 9.5	Trav	SpR Nect	6/1	0.46	0.55	0.89	U	U 90
22 9.5	Trav	FBr Nect	6/1	0.58	0.64	1.26	6/14	U 93
23 9.5	Trav	Fla Nect	6/1	1.29	1.91	U	U	U 98
24		No work						
25 9.5	Sulta	Fla Nect	6/1	0.69	0.69	U	U	5/26 92
26		No work						94
27		No work						95

U=untreated; T=treated, N=residue data not available

Table 2

Comparison of Prior Exposures Cases  
and Non-Cases Reported on Questionnaire: Mann-Whitney U Test

<u>Variable</u>	<u>Mean Rank</u>		<u>U</u>	<u>P</u>
	<u>Non-Cases</u>	<u>Cases</u>		
Propargite-Residue-Hrs	29.0	46.8	399.5	.0005
Propargite-Days	33.13	43.93	532.0	.0330
Formetanate HCL-Days	40.23	38.99	712.5	.8032
Days in				
Untreated Fields	54.17	29.29	266.5	.0000
Iprodione-Days	29.39	46.53	412.5	.0003
B. thuringiensis-Days	56.25	27.85	200.0	.0000
Degree-Days	59.59	25.52	93.0	.0000

Table 3

Correlation of Exposure Variables with Rash Score on Exam

<u>Variable</u>	<u>Correlation Coefficient</u>	<u>P</u>
Propargite-Res. Hours	.44370	.0000
Propargite-Days	.38683	.0003
Formetanate HCL Days	.17825	.0605
Days in Untreated		
Fields	-.35348	.0008
Iprodione-Days	.43624	.0000
B. thuringiensis-Days	-.04767	.3403
Degree-days	-.15052	.0957

Table 4

Multivariate Analysis of Relationship between Rashscore and Exposure Variables

Correlation Between Variables

	<u>Propargite Residue Hours</u>	<u>Iprodione Days</u>	<u>Rash Score</u>
Propargite Residue-Hours	1.000	0.930	0.444
Iprodione Days	0.930	1.000	0.436
Rash Score	0.444	0.436	1.000

Multivariate Linear Analysis

<u>Variable</u>	<u>Beta*</u>	<u>Significance Value</u>
Propargite Residue-Hours	0.28134	0.3234
Iprodione Days	0.17455	0.5393

\* Standardized Regression Coefficient

Appendix 1

Date \_\_\_\_\_, Name \_\_\_\_\_ Crew Leader: \_\_\_\_\_

Questions regarding your history of allergies:

As a child did you have a problem with rashes or eczema?

At any age did you have a problem with allergies? itching in the eyes or nose, or sinusitis?

Was this provoked by dust? feathers? cat or dog hair? Something else?

Urticaria or hives? Asthma? Other allergy?

Questions dealing with your work:

During the last two weeks have you had a rash (redness, itching or burning of the skin? (If yes: On what day or date did it begin ? \_\_\_\_\_)

Did you go to the doctor? Yes no (If yes, when did you go? \_\_\_\_\_)

Did you receive medicine? Yes no (If yes: Cream ? Injection? Pills?)

Exam: 1=slight 2=moderate 3=severe blank=normal Crossed out=not examined

Periorbital:	erythema _____	blistering _____	postinflammatory _____
Jaw:	erythema _____	blistering _____	postinflammatory _____
Upper Neck:	erythema _____	blistering _____	postinflammatory _____
V of neck:	erythema _____	blistering _____	postinflammatory _____
Chest:	erythema _____	blistering _____	postinflammatory _____
Abdomen:	erythema _____	blistering _____	postinflammatory _____
L Shoulder:	erythema _____	blistering _____	postinflammatory _____
Upper arm:	erythema _____	blistering _____	postinflammatory _____
Antecubital:	erythema _____	blistering _____	postinflammatory _____
Forearm:	erythema _____	blistering _____	postinflammatory _____
Wrist:	erythema _____	blistering _____	postinflammatory _____
Hand:	erythema _____	blistering _____	postinflammatory _____
R Shoulder:	erythema _____	blistering _____	postinflammatory _____
Upper arm:	erythema _____	blistering _____	postinflammatory _____
Antecubital:	erythema _____	blistering _____	postinflammatory _____
Forearm:	erythema _____	blistering _____	postinflammatory _____
Wrist:	erythema _____	blistering _____	postinflammatory _____
Hand:	erythema _____	blistering _____	postinflammatory _____

Diagnosis: Contact Dermatitis Other: \_\_\_\_\_

## Appendix 2

### Review of Dermal Irritation and Sensitization Data on Formetanate Hydrochloride, Propargite, and Iprodione in Reference to 31-Tul-88

Work and application histories from the 31-Tul-88 indicated that the three affected work crews were exposed to Omite<sup>R</sup> 30W, Carzol<sup>R</sup> and Rovral<sup>R</sup>. The experimental data in CDFA files on the three compounds are reviewed below:

#### Formetanate hydrochloride

##### Study # 1

Summary data were available from a primary skin irritation test was performed on albino rabbits using 500 mg of technically pure formetanate hydrochloride slightly moistened with water. The skin irritation index was 3.9, compared to a maximum possible score of 8. No irritation occurred on intact skin.

##### Study # 2

Slight skin irritation occurred on abraded rabbit skin during a subacute rabbit dermal toxicity test using 80% technical material at 1000 and 2000 mg/kg/day. No irritation occurred on intact skin. Complete data from the study were not available in the cited volume.

##### Study # 3

No dermal sensitization occurred in a human study using the Repeated Insult Patch Technique (RIPT) using a 0.1% concentration, although slight irritation was noted in one of the 50 subjects.

#### Iprodione

##### Study # 1

Data from a modified Draize test using 50% wettable powder demonstrated a primary skin irritation index of 2.50 in the albino rabbit. A slight degree of irritation was noted for both intact and abraded skin. No other dermal irritation or sensitization studies are available for this compound.

##### Study # 2

This study was submitted by the registrant of propargite and compared the dermal sensitization potential of the active ingredients iprodione and propargite using a modified version of the Buehler method. While the study had some technical deficiencies (i.e. lack of a positive control group and the use of the same animals to test both products), a number of the findings were of significance. In the range finding portion of the study it was determined that iprodione could be applied during the challenge tests at the maximum concentration allowed by the protocol (5%); propargite could only be applied at concentrations of 0.1%. During the challenge portion of the study both materials produced less reaction than during the induction phase, indicating neither material was a sensitizer under the conditions tested.

## Propargite

### Study # 1

Dermal patches containing 0.5 ml of a 0.4% weight/volume suspension of Omite<sup>R</sup> 30 W were applied to 69 human subjects. Study subjects removed the patches after 24 hours and application sites were read at 48 hours. Following the first reading a second and third patches were applied and read according to the same procedure. The results indicated that 0.4% Omite<sup>R</sup> 30W produced no irritation under the study conditions in about 2/3 of the subjects and erythematous responses in the remainder.

### Study # 2

Repeated dermal study (Leary Protocol in Rabbits) - Omite<sup>R</sup> 30W. Two studies were run. In the first study, dosage levels were 1000 and 2000 mg/kg. As noted in the cited data volume, "the severe corrosive type dermal response and toxic effect made it unfeasible to continue." At a 0.36% dilution the skin changes observed were characterized as moderate.

### Study # 3

Omite<sup>R</sup> technical was applied to intact and abraded skin of albino rabbits for 24 hours. The chemical was washed off and the rabbits observed for an additional 48 hours. Second degree skin burns were observed in all animals.

### Study # 4

Paper discs, soaked in 2% solutions of either Omite<sup>R</sup> 30W or Omite<sup>R</sup> 57E were applied to the forearms of adult volunteers and left in contact with the skin for 24 hours. Omite<sup>R</sup> 30W appeared to cause minimal irritation in this test. Any reactions disappeared within 96 hours after the paper disc was removed. Omite<sup>R</sup> 57E caused more intense reactions which persisted up to a week following the removal of the disc.

### Study # 5

Omite<sup>R</sup> 30W and Omite<sup>R</sup> technical were both tested for skin sensitization using a procedure modeled after that of E.V. Buehler. Neither material proved to be a sensitizer under the test conditions.

### Study # 6

Undiluted Omite<sup>R</sup> 30W caused moderate erythema, eschar formation, and edema to intact and abraded skin of 6 albino rabbits when applied and held in place for 24 hours. The irritation score for the test was not reported.

A modified Buehler test was performed on the Omite<sup>R</sup> CR formulation. The induction concentration was 33% w/v of Omite<sup>R</sup> CR; animals subsequently had a primary challenge with 5% Omite<sup>R</sup> CR and then 5 days later were rechallenged with the same concentration. The incidence of grade 1 or greater responses in the rechallenge test groups (5 Omite<sup>R</sup> 30W 259-015 of 20) was greater than

that of the naive control group (0 of 10). The test was interpreted to mean that this material is a weak to moderate sensitizer.

Conclusions: A comparison of dermal irritation caused by technical formulations of propargite (Omite<sup>R</sup>) and formetanate hydrochloride (Carzol<sup>R</sup>) showed that the former caused 2nd degree burns in contrast to moderate degrees of irritation produced by the latter. A skin irritation test on iprodione (Rovral<sup>R</sup>) technical material was not available, but the 50% wettable powder formulation appeared to be less irritating than the technical material used in the studies of formetanate and propargite. Omite<sup>R</sup> 30W appeared to be less irritating in the rabbit bioassay than propargite technical material, producing only "moderate" degree of irritation. Direct comparison could not be made to the Rovral<sup>R</sup> study since the data contained in the summary of the Omite<sup>R</sup> 30W study did not include a skin irritation index score.

The subacute dermal toxicity study for Omite<sup>R</sup> 30W showed that repeated applications of this material produced severe skin reactions in the test animals. A comparable study using 80% formetanate hydrochloride produced only slight degree of irritation. An inference can thus be drawn from the available data that Carzol<sup>R</sup> is a much less potent skin irritant than Omite<sup>R</sup> 30W. The limited data available on the Rovral<sup>R</sup> formulation of iprodione (50% wettable powder) indicate that the material is a weak to moderate skin irritant. In the comparative dermal sensitization study reported by the registrant of propargite, the maximum tolerated concentration of propargite at challenge testing was 0.1% compared to 5% for iprodione. Although the study had some minor technical inadequacies, iprodione did not appear to be a sensitizer under the conditions tested.

Figure 1

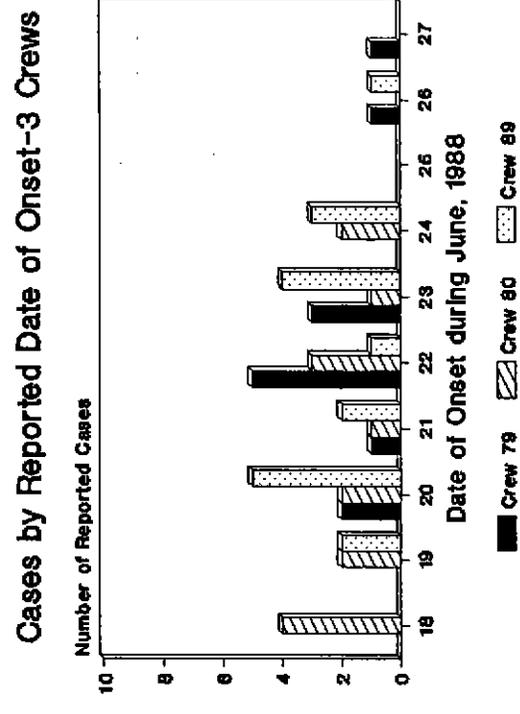
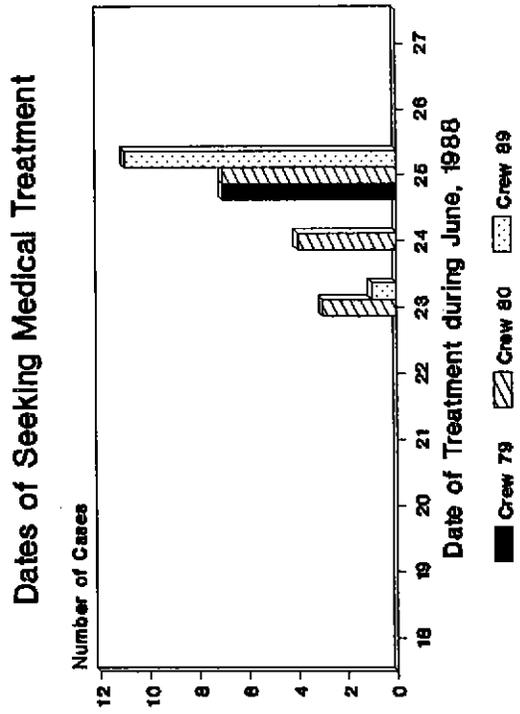
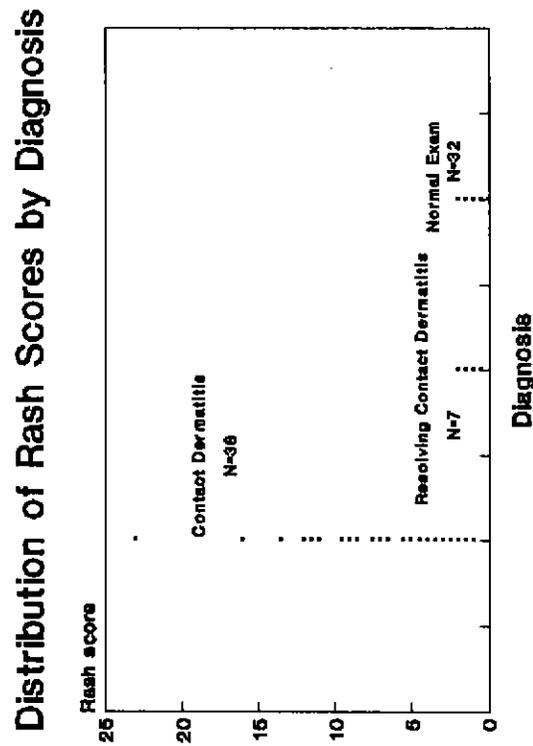
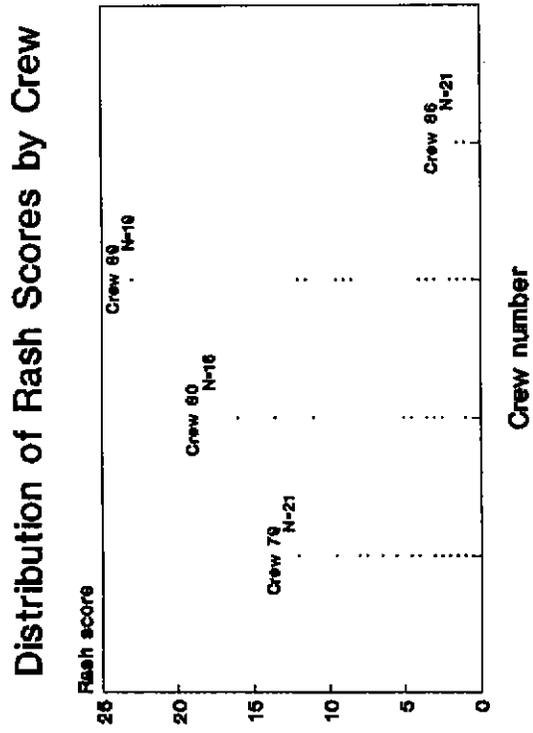
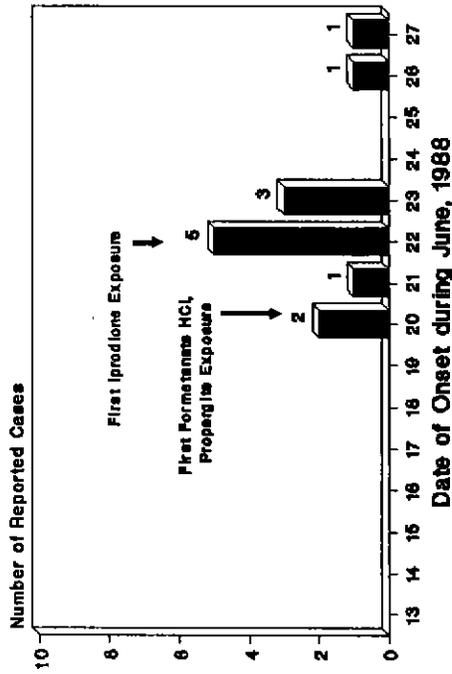


Figure 2

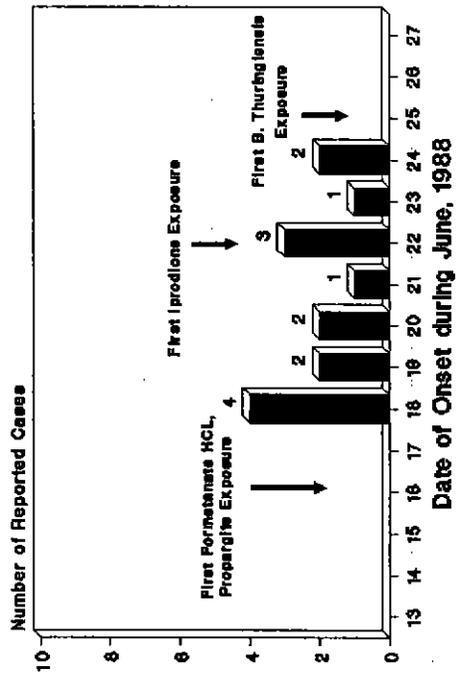


**Figure 3** Dates of Rash Onset vs. Previous Exposures

**Cases by Reported Date of Onset Crew 79**



**Cases by Reported Date of Onset Crew 80**



**Cases by Reported Date of Onset Crew 89**

