American Journal of Industrial Medicine 28:257–274 (1995)

Determinants of Disability in Illnesses Related to Agricultural Use of Organophosphates (OPs) in California

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Organophosphate (OP)-related illness data reported to the Worker Health and Safety Branch (WH&S) at the California Department of Food and Agriculture (CDFA, now Cal-EPA) in the years 1984–1988 were examined. Eight hundred and seventy-eight cases with systemic illness and 199 cases of skin disease or eye injury were identified. Systemic cases were divided into two outcome groups: (1) "severe," disability and/or hospitalization days (n = 361), and (2) "mild," no disability or hospitalization days (n = 372). For the remainder (n = 145) or 16.5% of the cases, illness severity could not be determined. Using multiple logistic regression, independent predictors of "severe" illness were identified among the systemic cases. Workers coming in contact with OP residue on commodities or in the field ("exposed to residue" or ER) (OR = 4.6, 95% CI = 3.03–7.07) and mixer/loaders/applicators (MLA) (OR = 4.1, 95% CI = 2.72–6.07) were at significantly increased risk of severe illness when compared with cases exposed to OP application drift. Cases with a Spanish surname were also at increased risk of severe illness (OR = 1.8, 95% CI = 1.25–2.73). Increased numbers of OPs per exposure were also associated with severe illness ($p < 0.001$).

Among cases who were exposed to only one OP, severe systemic cases were more likely than mild systemic cases to be associated with exposure to diethyl than dimethyl compounds (OR = 1.6, 95% CI = 1.09–2.38). Severe systemic cases were also more likely than severe skin/eye cases to be associated with exposure to OPs with high toxicity (OR = 5.5, 95% CI = 2.42–12.60) and with exposure to diethyl groups (OR = 4.8, 95% CI = 1.90–12.00). These findings suggest that reducing exposure to OP residues, to OPs with diethyl groups, and to multiple OPs, and exposure during mixer/loader/applicator activities would reduce the risk of OP-related illness.

Key words: organophosphates, disability, pesticide poisoning, Hispanics, risk factors, agriculture, occupation

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Accepted for publication September 29, 1994.

INTRODUCTION

The deleterious effects of pesticides on human health have been recognized since the large-scale introduction in the 1940s of major classes of synthetic organic pesticides that are currently used in agriculture [Hayes and Laws, 1991]. However, little is known about the amount and severity of disability associated with acute pesticide-related illnesses in agriculture.

Since 1973, physicians in California who treat illnesses that they suspect are associated with pesticide exposure have been required by law to report the cases to their county health officer in a Pesticide Illness Report and to the Department of Industrial Relations as a Doctor's First Report of Work Injury (DFRWI). The health officer notifies the County Agricultural Commissioner (CAC), the California Department of Food and Agriculture (CDFA), and the California Department of Health Services (CDHS). Subsequently, the CAC investigates the circumstances associated with the onset of illness and issues citations for violations of the California Administrative Code, when warranted. The Worker Health and Safety (WH&S) Branch at the CDFA (now in Cal-EPA) receives and compiles all reports of pesticide-associated illnesses [Maddy et al., 1990]. These reports are now part of the California Pesticide Illness Surveillance Program (PISP) [Mehler et al., 1992].

California regulates the possession and use of restricted pesticides known to be hazardous to human health, animals, bees, the environment, or crops. Medical supervision is also required to be provided by employers for all agricultural pesticide applicators exposed for 7 or more days in any 30-day period to organophosphates (OPs) or to carbamates in EPA toxicity category I (pesticides with LD_{50} of 50 mg/kg and under), or EPA toxicity category II (pesticides with LD_{50} >50 mg/kg and <500 mg/kg) [California Department of Health Services, 1988]. A recent study found that during the first 9 months of 1985, only 5% of pesticide applicators under medical supervision in California had red blood cell (RBC) or plasma cholinesterase values at or below the threshold indicated by California regulations for removal of workers from the workplace. One third of those with lower cholinesterase values also had a concurrent pesticide-related illness, as reported by physicians [Ames and Brown, 1989].

The purpose of the present study was to examine the severity of pesticide-related illness in California and the association of severe illness with demographic characteristics and circumstances of agricultural pesticide applications. We chose to restrict our analyses to OP-related illnesses because they comprise a large proportion of all pesticide-related cases, about 15% of those reported to the WH&S. In addition, cholinesterase testing information can be used as an objective measure in the assessment of the likelihood of systemic illness from OPs.

MATERIALS AND METHODS

Pesticide Illness Case Reports (PICRs)

The WH&S computerized agricultural OP-related data (years 1984–1988) were the primary source of information about cases in this study. The WH&S Branch classifies illnesses into: (a) skin or eye illnesses, which are topical injuries, and (b) systemic illnesses, for which the physicians report signs and symptoms indicative of internal absorption, such as in the digestive, neuromuscular, or respiratory systems.

TABLE I. Source of Variables Used in the Analysis: California, 1984–1988

Variable	WH&S computerized information	Manual abstraction (systemic cases only)
Demographics		
Gender		√
Hispanic surname		√
Age		√
Illness		
Type of illness (systemic, skin, eye)	√	
Circumstances of onset of illness		√
Symptoms		√
Signs		√
Cholinesterase measurement, if given		√
Date of onset of illness	√	
Days of disability—loss of work time	√	
Days of hospitalization	√	
Work/exposure		
County	√	
Crop	√	
Job activity	√	
Pesticides used	√	
Cluster affiliation with the index case[a]	√	
Noncompliance with California Ag. codes (notices of violation)		√
Detailed information of job activity (extracted from DFRWI)[b]		√
Likelihood of illness (definite, probable, possible, unlikely, unrelated)[c]	√	

[a]Two or more cases associated with a single applications exposure—usually one case; the index case carries most of the information about the incident.
[b]Doctor's First Report of Work Injury.
[c]See text.

The computerized information was supplemented by manual abstraction of data from Pesticide Illness Case Report (PICR) records for systemic cases only. According to WH&S records, some OP-related illnesses also included exposures to other pesticides.

Variables extracted from the PICRs for this study are listed in Table I. "Likelihood of illness" is a WH&S evaluation of the relationship of the exposure, the circumstances of the exposure, and the outcome (categorized as definite, probable, possible, unlikely, and unrelated illness) [Maddy et al., 1990]. Job activities that were coded by WH&S were "mixer/loaders," defined as workers who mixed and/or loaded or diluted pesticide concentrates during exposure, and "applicators," defined as workers who were exposed to pesticides during applications. Other job activities involving potential exposure to pesticides were "flaggers," "workers cleaning/fixing machinery," "workers exposed to residue on commodities or in the fields," and "coincidental"—people who were exposed to drift of pesticide applications.

Counties in which illnesses were reported were grouped for analysis into six geographical regions corresponding to agricultural regions of the state: (1) North Coast (Del Norte, Humboldt, Mendocino, Napa, Sonoma); (2) Sacramento Valley

(Butte, Colusa, Glenn, Lassen, Placer, Sacramento, Solano, Sutter, Tehama, Yolo, Yuba); (3) San Joaquin Valley (Calaveras, Fresno, Kern, Kings, Madera, Merced, San Joaquin, Stanislaus, Tulare); (4) Central Coast (Alameda, Contra Costa, Monterey, San Benito, San Mateo, Santa Clara, Santa Cruz); (5) South Coast (Los Angeles, Orange, San Diego, San Luis Obispo, Santa Barbara, Ventura); and (6) Desert (Imperial, Riverside) [Employment Development Department, 1991].

Systemic Cases

Classification protocol for systemic illnesses. To obtain maximum standardization of the certainty that a case had a systemic OP-related illness, a computerized evaluation replaced the original WH&S (1984–1988) likelihood evaluation. The decision tree for the computerized evaluation of cases with corresponding work and application history followed the recent 1989 WH&S guidelines [O'Malley, 1991] with a few minor changes. "Definite" cases were defined as those with one or more symptoms or signs compatible with OP poisoning (Table II) and with a depressed or decrease from baseline (RBC or plasma) cholinesterase. Since cholinesterase testing was reported from different laboratories that used different methods, cholinesterase inhibition was considered present if reported values were lower than the laboratory's reported lower normal range of cholinesterase if no baseline cholinesterase was reported. If baseline cholinesterase values were reported, values lower than 80% of baseline were designated as cholinesterase inhibition. "Probable" cases were defined as cases with missing or ambiguous cholinesterase values exhibiting signs of OP-related illness (miosis, salivation, sweating, involuntary urination, lacrimation, or bradycardia). "Possible" cases were defined as cases with information about compatible symptoms only. Single isolated cases were required to have two symptoms to qualify as possible cases, while cases belonging to a cluster (i.e., two or more cases associated with a single application exposure) qualified as possible cases if only one symptom was reported. The rest of cases were considered "unlikely" (Fig. 1).

Notices of violations and warnings. Noncompliance with or violations of the California Code of Regulations (title 3, division 6) were determined from the CACs reports of their investigation into the circumstances of illness onset. Warning letters and verbal descriptions of violations were also included. The presence of notices ("yes" or "no") and the subsection of the regulations violated were coded and entered into the database.

Other variables. Spanish surname was coded using the 1980 census list of Spanish surnames [Census list of Spanish Surnames, 1980]. Since Spanish surname correlates highly with Hispanic ethnicity (Dr. James Beaumont, UCD, personal communication), we refer to cases with Spanish surname as Hispanics in this paper. Clusters were identified by the presence of an index case number and involved two or more cases presenting themselves for treatment after a common exposure. The WH&S "coincidental" job activity category was recoded to indicate separately persons exposed to drift while working in agriculture and persons exposed to drift who were not working in agriculture.

Skin/Eye Cases

Only information derived from the WH&S computerized data, including the likelihood of illness, was used in the analysis of skin/eye cases, since we did not have objective means for further evaluation of these cases. Assessment of these cases was

TABLE II. Signs and Symptoms Associated with Organophosphate-Related Illnesses

Symptoms	Signs
Abdominal pain	Bradycardia
Blurred vision	Diaphoresis
Bronchial secretions	Lacrimation
Chest pain	Miosis
Confusion	Salivation
Convulsion	Uncontrolled urination or defecation
Cough	
Diarrhea	
Dizziness	
Fainting	
Fasciculations	
Incoordination	
Irritation of nose, mouth, eyes	
Headaches	
Loss of appetite	
Muscle weakness	
Nausea	
Nervousness	
Numbness	
Palpitations	
Shaking	
Sleepiness	
Slurred speech	
Sweating	
Unconsciousness	
Vomiting	
Wheezing	

not as rigorous as the assessment of the systemic cases. Therefore, only descriptive statistics of the skin/eye group are reported here. Furthermore, skin/eye cases were also exposed to other irritant chemicals. Since propargite and sulfur are known skin and eye irritants, it was assumed that they were causal when they were noted to be involved in exposure resulting in skin/eye illness, and OP-related cases also exposed to these two pesticides were excluded from the analysis.

Statistical Analysis

All analyses, unless otherwise specified, were performed by multiple logistic regression. Data were processed by Statistical Analysis Systems (SAS Institute, version 6, 1990) and by BMDP [BMDP Statistical Software Manual, 1990]. Model fit was evaluated either by Hosmer-Lemeshow or C.C. Brown goodness-of-fit statistics in a stepwise logistic regression using BMDP LR. PROC LOGISTIC, PROC REG, and PROC CATMOD (SAS) [SAS Institute, 1990] were used to identify influence points, to test for collinearity diagnostics according to the recommendations of Slinker and Glantz [1985] and Kleinbaum et al. (1987), and to test for dose-response trends. Since carbamates cause health effects similar to the OPs, a dummy variable controlling for their presence was included in logistic regression analyses.

Reported days of disability (lost work days) and of hospitalization were used as indicators of the severity of systemic OP-related illness. Cases were categorized by the severity of outcome resulting from exposure: (A) "mild" cases with no disability or hospitalization days; (B) "severe" cases resulting in disability or hospitalization

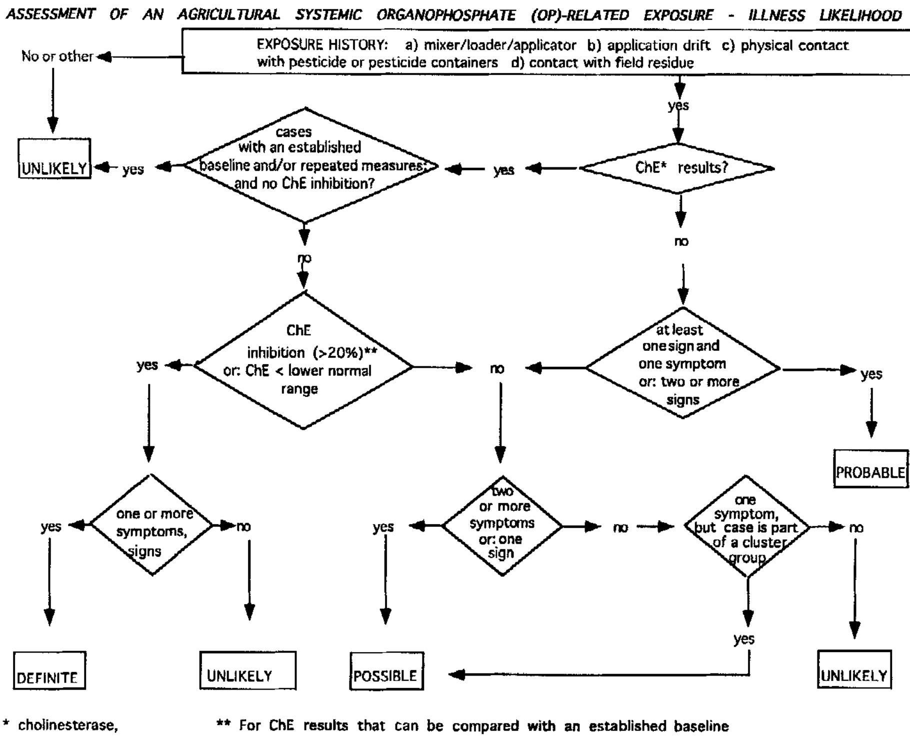

Fig. 1. Algorhythm used for classifying likelihood of systemic OP-related illness.

days (this group also included one individual who collapsed in a previously sprayed field and who died subsequently); and (C) cases with missing information on both disability and hospitalization days or cases that had a report of no disability or hospitalization days and were missing information on the other variable (n = 145; 16.5% of all cases). Group C was excluded from most analyses, except as specifically noted.

In the logistic regressions, the dependent variable was hospitalization and/or disability days (severe) as compared with no disability and no hospitalization days (mild). This is a comparison of two groups with different health outcomes. The study may thus be viewed as similar to a proportional mortality ratios (PMR) (or proportional morbidity ratios) study, using case-control methodology, as explained by Breslow and Day [1987] and Rothman [1986]. Discussion of risk therefore refers to the probability of the illness being severe (proportional rate for severity) rather than to the probability that an individual will develop a severe illness.

Independent variables tested were (a) demographics (gender, Hispanic surname, age with missing values substituted by the median age); and (b) determinants of OP applications (number of OPs used per exposure, season, and job activities of the cases). The job activity variable was grouped into three categories for the analysis: (1) "other" used as a reference group (90% of this group were cases exposed to OP

TABLE III. Chemical Properties of Organophosphates Associated With Illnesses

Organophosphate	Structure[a]	Toxicity category[b]	Restricted use pesticide[c]
Acephate	1	III	
Azinphos-Methyl	1	I	√
Bensulide	3	III	
Chlorpyrifos	2	II	
DDVP	1	I	√
DEF	3	II	√
Demeton	2	I	√
Diazinon	2	II	
Dimethoate	1	II	
Disulfoton	2	I	√
Ethion	2	II	√
Fenamiphos	3	I	√
Fonofos	3	I	√
Malathion	1	III	
Merphos	3	II	√
Methamidophos	1	I	√
Methidathion	1	I	√
Mevinphos	1	I	√
Monocrotophos	1	I	√
Naled	1	I	
Oxydemeton-Methyl	1	II	√
Parathion	2	I	√
Parathion-Methyl	1	I	√
Phorate	2	I	√
Phosalone	2	II	
Phosmet	1	II	
Phosphamidon	1	I	√
Profenofos	3	II	√
Tetrachlorvinphos	1	III	
Trichlorfon	1	II	

[a]1—dimethyl R group. 2—diethyl R group. 3—not applicable, was excluded from the chemical properties analysis.
[b]EPA toxicity categories [Farm Chemicals Handbook, 1992].
[c]Years 1984–1988.

application drift); (2) mixer/loaders/applicators (MLA); and (3) exposed to residue on crops and commodities (ER). The two outcome groups (mild and severe) were compared separately for their associations with the computerized assessment of certainty of illness and with violations of California regulations.

To evaluate the contribution of chemical structure to severity of systemic illness, a chemical properties analysis was conducted on a subset of cases associated with only one OP exposure (n = 553). The EPA toxicity categories [Farm Chemicals Handbook, 1992] and "R" groups (dimethyl and diethyl) of the two outcome subgroups were compared by logistic regression, adjusting for the presence of carbamates. Toxicity categorization was based on the EPA toxicity categories: (a) category I (most toxic), (b) category II, and (c) category III (least toxic) (Table III).

RESULTS

Descriptive Analysis of Systemic Illnesses

From the 1159 OP-related cases evaluated by WH&S from 1984 to 1988, 281 (24.2%) were excluded from the analysis because they were either asymptomatic

(39.5% of excluded), their illnesses were not pesticide related as indicated by physicians (33.1%), or they were missing critical information (missing work history or CACs investigation, or OP names) (27.4%). The remaining 878 cases fulfilled the computerized evaluation requirements for definite, probable, or possible OP-related illnesses and formed the study group. No person was associated with more than one case.

In the study group, 660 cases (75.2%) had Hispanic surnames, and 200 cases (22.8%) were females (Table IV). Ages of cases ranged from 1 to 73 years, (median, 30 years); 6.2% of the cases were missing information about age. Not all cases were agricultural workers: 86 (9.7%) of cases were residents of areas sprayed with OPs, school employees and students, utility workers, or passengers in cars passing by areas of OP applications.

A total of 67 clusters were identified, ranging from 2 to 43 cases per cluster (total cases in clusters were 61.5% of all cases) (Table V). The percentage of females was somewhat higher in clusters (31.1% of all clusters) than in the overall group (22.8%). Most of the cases in clusters were exposed to agricultural drift (41.6%) or to field residue (40.4%), and were working with vegetables or melons (45.6%) or nuts and fruits (23.6%). Thirty-one percent of the cases were associated with notices of violations, which ranged from 1 to 14 violations per case.

About 20% of the cases were associated with exposure to more than one OP (Table V). The largest numbers of illnesses associated with more than one OP were reported from Monterey (52.0% of cases with more than one OP).

Among the 61 hospitalized cases, days of hospitalization ranged from 1 to 48 (median, 2 days). OPs associated with the highest number of hospitalized cases were Mevinphos (19 cases), Phosalone (14 cases), Methamidophos (7 cases), and Parathion (7 cases). Reported days of disability ranged from 1 to 71, (median, 2 days).

Cases that were missing disability and hospitalization information (group C) were similar to severe cases (group B) with regard to the proportion of females and the proportion with Hispanic surnames (Table IV). The age distributions of the three case groups were quite similar. The groups varied somewhat on location: While most (46.3%) of the cases in group C originated in the Central Coast, most of the severe and mild cases originated in the San Joaquin Valley (Table IV). Discriminant analysis using variables tested in the logistic regression (Hispanic surname, season, job activity, and number of OPs exposed) suggested that among group C cases, 47% could be classified as mild and 53% as severe. Using logistic regression, a significantly higher number of Group C cases occurred in summer and fall, and had a smaller number of OPs per exposure compared with the combined mild and severe groups.

Comparison of Systemic Cases With Disability and Hospitalization Days (Severe) to Systemic Cases With No Disability or Hospitalization (Mild)

Results of logistic regression analyses. Crops in which cases worked and the region where exposure occurred did not differ significantly between the severe and mild groups, and thus were not tested as covariates in subsequent analyses. Model fit was obtained by including job activity, Hispanic surname, and number of OPs per exposure (Table VI). A higher likelihood of severe compared to mild OP-related illness was observed in a dose-response fashion when more than one OP was involved in the (exposure chi-square for trend = 30.35, $p < 0.001$).

Evaluation of illness likelihood. Both the original WH&S assessment and our

TABLE IV. Characteristics of the Population With Organophosphate-Related Systemic Illnesses, by Severity: California, 1984–1988

	Mild (A) zero disability/zero hospitalization N = 372		Severe (B) disability and/or hospitalization N = 361		(C) missing disability and hospitalization data N = 145		Total N = 878	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Gender								
Males	253	(68.0)	304	(84.2)	121	(83.4)	678	(77.2)
Females	119	(32.0)	57	(15.8)	24	(16.6)	200	(22.8)
Surname								
Hispanic	239	(64.3)	290	(80.3)	131	(90.3)	660	(75.2)
Non-Hispanic	130	(34.9)	71	(19.7)	14	(9.7)	215	(24.5)
Missing	3	(0.8)					3	(0.3)
Age								
0–10	20	(5.4)	0	(0.0)	0	(0.0)	20	(2.3)
11–15	9	(2.4)	1	(0.3)	1	(0.7)	11	(1.3)
16–24	64	(17.2)	101	(28.0)	33	(22.8)	198	(22.6)
25–34	124	(33.3)	130	(36.0)	54	(37.2)	308	(35.1)
35–44	75	(20.2)	61	(16.9)	29	(20.0)	165	(18.8)
45–54	35	(9.4)	30	(8.3)	13	(9.0)	78	(8.9)
55–64	16	(4.3)	17	(4.7)	6	(4.1)	39	(4.4)
>65	2	(0.5)	1	(0.3)	2	(1.4)	5	(0.6)
Missing	27	(7.3)	20	(5.6)	7	(4.8)	54	(6.2)
Age								
Mean	32		32		32		32	
Median	31		30		30		30	
Job classification								
Drift—worked in ag.	111	(29.8)	87	(24.1)	55	(37.9)	253	(28.8)
Field residue (ER)	68	(18.3)	133	(36.8)	54	(37.2)	255	(29.0)
Mix/load/apply (MLA)	70	(18.8)	120	(33.2)	27	(18.6)	217	(24.7)
Drift—did not work in ag.	105	(28.2)	5	(1.4)	5	(3.5)	115	(13.1)
Clean/fix	3	(0.8)	7	(1.9)	0	(0.0)	10	(1.1)
Other	15	(4.0)	9	(2.5)	4	(2.8)	28	(3.2)
California regions								
San Joaquin Valley	172	(46.2)	203	(56.2)	59	(40.7)	434	(49.4)
Central coast	132	(35.5)	97	(26.9)	68	(46.9)	297	(33.8)
Sacramento Valley	29	(7.8)	10	(2.8)	5	(3.5)	44	(5.0)
South coast	25	(6.7)	34	(9.4)	2	(1.4)	61	(7.0)
Desert	8	(2.2)	13	(3.6)	2	(1.4)	23	(2.6)
North coast	6	(1.6)	4	(1.1)	9	(6.2)	19	(2.2)

independent computerized evaluation of diagnosis certainty showed similar patterns in the relationship between certainty of illness and probability of disability (severity). The closer to "definite" the assessment became, the higher the likelihood of disability or hospitalization compared with "possible" cases (for definite cases OR, 4.9; 95% CI, 3.21–7.55 and for "probable" cases OR, 2.6; 95% CI, 1.26–5.51). These results lend support to the validity of our criteria definitions of definite, probable, and possible, which were made independently of disability information.

Mixer/loaders/applicators (MLA). MLA were significantly more likely to have severe than mild illness (crude OR = 1.9, 95% CI = 1.38–2.70 and adjusted OR = 4.1, 95% CI = 2.72–6.07). When the data were stratified by job activity and number

TABLE V. Circumstances Surrounding Organophosphate-Related Systemic Illness, by Severity: California, 1984–1988

	Mild (A) zero disability/zero hospitalization N = 372		Severe (B) disability and/or hospitalization N = 361		(C) missing disability and hospitalization data N = 145		Total N = 878	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Commodities								
Vegetables and melons	129	(34.7)	100	(27.7)	77	(53.1)	306	(34.9)
Nuts and fruit	97	(26.1)	94	(26.0)	21	(14.5)	212	(24.2)
Grapes	31	(8.3)	39	(10.8)	30	(20.7)	100	(11.4)
Field crops	10	(2.7)	10	(2.8)	2	(1.4)	22	(2.5)
Cotton	20	(5.4)	42	(11.6)	2	(1.4)	64	(7.3)
Greenhouse, nurseries, other	30	(8.1)	22	(6.1)	0	(0.0)	52	(5.9)
Missing/NA	55	(14.8)	54	(15.0)	13	(9.0)	122	(13.9)
Number of OPs per exposure								
One OP	313	(84.1)	253	(70.1)	139	(95.9)	705	(80.3)
Two OPs	51	(13.7)	74	(20.5)	4	(2.8)	129	(14.7)
Three and more OPs	8	(2.2)	34	(9.4)	2	(1.4)	44	(5.0)
Presence of violation notices or warnings by season								
	Violations/ illnesses		Violations/ illnesses		Violations/ illnesses		Violations/ illnesses	
Winter	24/68 = 0.35		17/62 = 0.27		0/7 = 0.00		41/137 = 0.30	
Spring	9/91 = 0.10		13/39 = 0.33		0/12 = 0.00		22/142 = 0.15	
Summer	41/166 = 0.25		90/166 = 0.54		21/58 = 0.36		152/390 = 0.39	
Fall	16/47 = 0.34		14/94 = 0.15		36/68 = 0.53		66/209 = 0.32	
Clusters								
Yes	245	(65.9)	186	(51.5)	109	(75.2)	540	(61.5)
No	127	(34.1)	175	(48.5)	36	(24.8)	340	(38.5)

of OPs, the proportion of severe illnesses among the MLA did not change between those with only one OP exposure and those with multiple OP exposures; however, the "other" and ER job activity groups had an increase in proportion of severe illnesses with multiple OP exposures.

Notices of violation and warnings. Notices of violation (yes or no) were associated with severe cases (OR, 1.9; 95% CI, 1.33–2.60). A brief evaluation of the notifications indicated that for the severe cases, the largest proportion of violations (49.9%) was associated with procedures (violations of the pesticide use permit system, of pesticide use regulations, or of requirements regarding storage of pesticides), followed by violations of field worker safety (employer responsibility for the safety of employees, field work during pesticide application, inadequate field reentry time after pesticide application, working in hazardous areas) (19.9%), and failure to provide appropriate medical care (7.2%). Procedural violations occurred most frequently among the mild cases (69.8%), followed by nonspecific (unclear—incomplete information) violations (15.6%), field worker safety violations (4.9%), and failure to provide appropriate medical care (2.7%). Summer was the season with the largest

TABLE VI. Odds Ratios (ORs) and 95% Confidence Intervals (CI) for Organophosphate-Related Systemic Illnesses Resulting in Severe Illnesses Compared With Mild Illnesses: California, 1984–1988[a]

Variable	OR	95% CI
Others (reference group)	1.0	
Mixer/loaders/applicators (MLA)	4.1	2.72–6.07
Exposed to residue (ER)	4.6	3.03–7.07
One OP (reference group)	1.0	
Two OPs	3.2	2.02–5.04
Three and more OPs	4.1	1.74–9.49
Hispanic surname	1.8	1.25–2.73

[a]Multiple logistic regression adjusted for age and presence of carbamates.

proportion of illnesses associated with violations (Table V) (chi-square = 12.21, $p < 0.01$). Field worker safety violations were also associated with severe cases in the summer (24.1% of all summer violations vs. 6.5% of all summer violations for the mild cases).

Frequency of reported symptoms. The number of reported symptoms per case ranged from 1 to 10, with a mean of 3.5 in the severe group and a mean of 2.9 in the mild group. About 18% of the severe cases were associated with signs of OP poisoning (range 1–4) vs. 8.1% in the mild group (range 1–2) (Table VII). Most of the symptoms occurred in similar frequencies among mild and severe cases. Headache was the most frequent symptom reported in both severe and mild cases (55.7%), followed by nausea (50.6%), eye/nose/mouth irritation (39.3%), dizziness (33.3%), and vomiting (27.4%). Infrequent symptoms or signs that were more common among the severe illness group were fasciculations (muscle twitching; 4.7% of severe vs. 1.6% of mild cases), fainting (4.2% in severe vs. 0.5% in mild cases), bradycardia (slow heart rate; 4.4% in severe vs. 0.0% in mild cases), shaking (3.6% in severe vs. 0.8% in mild cases), diaphoresis (profuse sweating; 9.4% in severe vs. 3.2% in mild cases), and miosis (constriction of pupil of the eye; 6.4% in severe vs. 1.0% in mild cases).

Twenty-four percent of the reported cholinesterase (ChE) values in the severe group (reported for 72% of the cases in this group) had values indicating 20–50% inhibition and an additional 20% had ChE values indicating 50% and more inhibition. In the mild group (ChE values reported for 54% of the cases), values indicating inhibition were 6% and 4%, respectively.

Chemical structure and toxicologic properties. Analysis of the effect of OP chemical structure and toxicologic properties was carried out on the subgroup of cases associated with only one OP exposure. No association was observed between the severity of the illness and toxicity category (OR, 1.1; 95% CI, 0.75–1.56) (Table VIII). However, a modest but statistically significant association was observed for severe illness with exposure to diethyl OPs (OR, 1.6, 95% CI, 1.09–2.38). Job categories were also analyzed separately because an interaction was observed between the job activity and the toxicity categories ($p < 0.01$). While the MLA and the "other" group did not show increased severity with higher toxicity of the OP, in the ER group severity of disease was associated with exposure to more toxic compounds. Compared with mild cases, in the ER subgroup the severe cases were significantly

TABLE VII. Frequency of Reported Organophosphate-Related Signs and Symptoms California, 1984–1988

	Mild group N = 372		Severe group N = 361	
	n	(%)	n	(%)
Number of signs per case[a]				
0	342	(91.9)	297	(82.3)
1–2	30	(8.1)	56	(15.5)
3–4	0	(0.0)	8	(2.2)
Number of symptoms per case[a]				
0	0	(0.0)	2	(0.6)
1–2	171	(46.0)	97	(26.9)
3–4	159	(42.7)	180	(49.9)
5–6	31	(8.3)	66	(18.3)
7+	11	(3.0)	16	(4.4)

[a]See Table II.

associated with violations of regulations, such as early reentry (43.4% of violations) or lack of medical supervision (22.6%), but not with clusters, gender, or surname. Clustering, therefore, could not explain the relationship of severity with higher OP toxicity in the ER group. Overall, for those exposed to only one OP, we observed no significant differences in the median number of disability or hospitalization days by the chemical properties of the OP.

Skin/Eye Illnesses

A total of 199 cases of skin or eye illnesses were identified as definite, probable, or possible by WH&S. Most of the skin/eye cases were associated with Dimethoate (13.6%) and Acephate (12.2%) (Table IX). The highest proportion of these cases worked in nut and fruit crops (22.1%) (Table X). MLA had the highest proportion of these cases (53.8%). This was in contrast to the systemic cases, which occurred most frequently with exposure to Mevinphos (23.5%), while working with vegetable and melon crops (34.9%) and exposed to application drift (41.9%) (Tables IV and V). None of the skin/eye cases was reported to have been hospitalized, but disability days (18.4% of all skin/eye cases) ranged between 1 and 30, with a median of 3 days. Systemic cases were significantly more likely to be hospitalized or to have disability days than skin/eye cases (OR, 3.9; 95% CI, 2.72–5.70). For the subset of severe cases exposed to single OPs, severe systemic cases were more likely than severe skin/eye cases to be associated with toxicity category I OPs (OR = 5.5, 95% CI = 2.42–12.60) and with diethyl groups (OR = 4.8, 95% CI = 1.90–12.00).

DISCUSSION

The WH&S database is a unique source of information on acute pesticide-related illnesses and disability. We identified several factors associated with systemic OP-related illness of greater severity: Hispanic surname, job activity, increasing number of OPs in the exposure, violations of California regulations, and chemical structure of the OP. Chemical structure was also associated with the type of illness outcome (systemic vs. skin/eye).

TABLE VIII. Odds Ratios (ORs) for the Association of Organophosphate Chemical Properties With Severe Illness: California, 1984–1988[a]

Category	ORs (95% CI)			
	ER[b] (N = 174)	MLA[c] (N = 128)	Others (N = 251)	Total (N = 553)
EPA toxicity category I vs. EPA toxicity category II and III	35.3 (11.00–113.00)	1.7 (0.76–3.62)	0.3 (0.14–0.60)	1.1 (0.75–1.56)
Diethyl vs. dimethyl group	19.1 (5.24–69.70)	0.5 (0.22–1.00)	2.2 (1.11–4.34)	1.6 (1.09–2.38)

[a]Multiple logistic regression adjusting for the presence of carbamates, Spanish surname, sex, and age.
[b]Exposed to Residue.
[c]Mixer/loaders/applicators were males only.

TABLE IX. Leading Organophosphates Associated With Systemic and Skin/Eye Cases: California, 1984–1988[a]

Mild (A) zero disability/ zero hospitalization			Severe (B) disability or hospitalization			All cases[b]		
OP	No.	(%)	OP	No.	(%)	OP	No.	(%)
Systemic cases								
Mevinphos	83	(18.8)	Mevinphos	116	(22.8)	Mevinphos	259	(23.5)
Parathion	56	(12.7)	Oxydemeton-Methyl	57	(11.2)	Parathion	108	(9.8)
Azinphos-Methyl	49	(11.1)	Methamidophos	46	(9.1)	Methamidophos	83	(7.5)
Methamidophos	30	(6.8)	Azinphos-Methyl	40	(7.9)	Oxydemeton-Methyl	77	(7.0)
Acephate	29	(6.6)	Parathion	39	(7.7)	Dimethoate	72	(6.5)
Others	194	(44.0)	Others	210	(41.3)	Others	503	(45.7)
Skin/eye cases								
Dimethoate	22	(13.6)	Acephate	6	(15.8)	Dimethoate	29	(13.6)
Acephate	20	(12.4)	Dimethoate	6	(15.8)	Acephate	26	(12.2)
Chlorpyrifos	20	(12.4)	Chlorpyrifos	4	(10.5)	Chlorpyrifos	25	(11.7)
Diazinon	17	(10.5)	Malathion	4	(10.5)	Diazinon	18	(8.5)
Naled	13	(8.0)	Naled	4	(10.5)	Naled	17	(8.0)
Others	70	(43.1)	Others	14	(36.8)	Others	100	(46.0)

[a]Illnesses are counted more than once, depending on the number of OPs which are associated with each illness.
[b]Includes illnesses with missing disability and hospitalization information, systemic (n = 155), skin/eye (n = 13).

Job activity was significantly associated with illness severity. The MLA group had more severe illness (OR = 4.1, 95% CI = 2.72–6.07), as did the ER group (OR = 4.6, 95% CI = 3.03–7.07) in this population. In the ER group, illness severity was also strongly associated with high toxicity OPs. It is possible that as a consequence of the medical monitoring of the MLA group and its having more protection and education about OP exposures, the association with illness severity in this group was reduced. Another possible interpretation is that of detection bias: Since MLA have more access to physicians, milder cases of illnesses are evaluated and reported, while the ER illnesses will be only recognized in more severe cases.

Mixing of more than one OP increased the likelihood of severe illness, especially if no protective gear was worn (the non-MLA subgroups). Some studies suggest

TABLE X. Factors Associated With the Organophosphate-Related Skin/Eye Cases California, 1984–1988

	Mild (A) zero disability/zero hospitalization N = 149		Severe (B) disability and/or hospitalization N = 37		(C) missing disability and hospitalization data N = 13		Total N = 199	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Job activity								
Mix/load/apply (MLA)	77	(51.7)	24	(64.9)	6	(46.2)	107	(53.8)
Field residue (ER)	51	(34.2)	11	(29.7)	5	(38.5)	67	(33.7)
Coincidental	17	(11.4)	2	(5.4)	2	(15.4)	21	(10.6)
Other	4	(2.7)	0	(0.0)	0	(0.0)	4	(2.0)
Commodities								
Nuts and fruit	35	(23.5)	7	(18.9)	2	(15.4)	44	(22.1)
Vegetables and melons	24	(16.1)	8	(21.6)	3	(23.1)	35	(17.6)
Greenhouse, nurseries, other	29	(19.5)	5	(13.5)	0	(0.0)	34	(17.1)
Grapes	22	(14.8)	6	(16.2)	0	(0.0)	28	(14.1)
Cotton	14	(9.4)	2	(5.4)	4	(30.8)	20	(10.1)
Field crops	3	(2.0)	2	(5.4)	0	(0.0)	5	(2.5)
Missing/NA	22	(14.8)	7	(18.9)	4	(30.8)	33	(16.6)
Seasons								
Winter	24	(16.1)	3	(8.1)	0	(0.0)	27	(13.6)
Spring	51	(34.2)	11	(29.7)	1	(7.7)	63	(31.7)
Summer	60	(38.9)	17	(46.0)	11	(84.6)	86	(43.2)
Fall	16	(10.7)	6	(16.2)	1	(7.7)	23	(11.6)
Clusters								
No	138	(92.6)	36	(97.3)	8	(61.5)	182	(91.5)
Yes	11	(7.4)	1	(2.7)	5	(38.5)	17	(8.5)
Number of OPs per exposure								
One OP	136	(91.3)	36	(97.3)	13	(100.0)	185	(93.0)
Two OPs	13	(8.7)	1	(2.7)	0	(0.0)	14	(7.0)

potentiation or additiveness of different OPs [Hayes and Laws, 1991]. This suggests that the practice of mixing pesticides that are acting on the same biologic target site needs to be reevaluated to reduce OP-related illnesses. Decreasing the recommended concentrations of OPs when mixing, or using only single OP formulations in each application, might also reduce the number of severe OP illnesses.

Hispanic surname also was associated with illness severity. This finding suggests that the more severe cases among Hispanics were reaching medical authorities and being reported to the state, while milder cases were not reported, that is, there may have been a bias resulting in greater reporting of severe cases but less reporting of mild cases among Hispanics. It also suggests that Hispanics may have had more severe exposures, as was demonstrated with the ER subgroup with only one OP exposure, most of whom were Hispanics.

Not unexpectedly, violation of California regulations was significantly associated with illness severity. The largest number of safety violations occurred in the summer, with a 0.39 ratio of notices per illness. Several explanations for the greater rate of summer violations are possible. First, environmental conditions, such as heat or dryness, may have a differential effect on the pesticide degradation in the fields [Nigg et al., 1978] or on workers [Nunneley, 1989], by limiting them from functioning freely with their protective gear, and making them less likely to use or wear such protection. Second, it is possible that the production demands of summer agricultural activities prevent workers and employers from adhering to precautionary measures when working with hazardous pesticides. Further, it is possible that more temporary workers who are not trained in proper handling of hazardous materials are employed in the summer. The importance of training and education is also reflected in a recent study of mixer/loaders in Nicaragua [McConnell et al., 1992]. In that study, mixer/loaders with previous training had higher cholinesterase levels (closer to normal) than untrained workers. The PICRs information on citations was probably not reflective of all citations issued, but there is no obvious reason that the information reaching the WH&S would be biased towards specific seasons or citations.

The chemical properties analyses were conducted separately for the different job activity categories. When job activity was held constant, the structure of the R group appeared to be most highly associated with illness severity. Confirming previous findings in animals [Hayes and Laws, 1991], a stronger association of the diethyl OPs than dimethyl OPs was observed with severity of systemic illness (for the two unprotected exposure groups—''others'' and ER). Hayes argued that cholinesterase inhibited by dimethoxy compounds shows faster spontaneous reactivation than that inhibited by diethoxy compounds [Hayes and Laws, 1991].

While larger numbers of OP-related illnesses among pesticide applicators in California were reported for category I OPs than category II OPs during 1982–1985 [Brown and Ames, 1989], our data did not show a similar pattern for OP-related illness severity. In our study the more toxic compounds were highly associated with severity of systemic disease only for the ER group. While these findings could be due to chance, small sample size, or presence of clusters (in the non-MLA groups), they may also be explained by MLAs taking greater safety precautions with more toxic pesticides. This would not be the case, however, with workers entering previously sprayed fields, where it is assumed that the pesticides have already dissipated and do not pose any hazard. Another possibility is that the MLA may be less cautious with less toxic materials, therefore increasing the chance of severe illness with less toxic materials. In the ER group, violations of reentry interval regulations occurred frequently, underscoring the importance of adherence to those regulations for disease prevention.

When comparing the severe systemic cases to the severe skin/eye cases, we found an association of systemic illness with more toxic compounds; the less toxic compounds were associated with skin/eye illness. However, it is important to note two issues related to the skin/eye cases: (1) The quality of the criteria for designating skin/eye cases was not as rigorous as for systemic cases, and (2) presence of other irritant chemicals (benomyl, captan, fenbutatin-oxide, zineb) in the exposure may be a potential confounder, making the conclusions of this comparison less certain.

The analysis conducted here was hypothesis-generating with no a-priori hypotheses regarding risk factors for disease severity. Thus, since multiple comparisons were made, we cannot eliminate the possibility that some findings occurred by chance alone, but we accept the notion put forward by Rothman [1990] that to reduce the chance for type II error, no adjustments are needed. In addition, comparisons of proportions (rather than rates) were made, which subjects these to the characteristic limitations of PMR studies [Breslow and Day, 1987], since proportionate excess may reflect either a significant excess or a deficit in absolute rates of other causes (which in our data are represented by the mild cases).

The question of underreporting of agricultural pesticide-related illnesses in California has been a subject of much controversy and discussion [Kahn, 1976; Shor, 1987; Moses, 1989; Blanc et al, 1989]. Also, the CACs operate under a priority code that requires them to spend more time investigating illness episodes that are associated with deaths, five or more cases, or individual cases hospitalized for more than 24 hr. The assumption underlying the present analysis is that underreporting of illnesses and the priority code investigations do not severely bias the variables of interest in this study.

In 1987, 26% of the reported pesticide-related illnesses in California (n = 398) were associated with disability, and 2.3% of the reported cases were hospitalized [Maddy et al, 1990]. Among lost-work claims for skin disease in California agriculture in the years 1978–1983, 20.4% were associated with agricultural chemicals [O'Malley and Mathias, 1988]. Comparison of California pesticide-related disability information to other published reports of disability studies is difficult because the definitions of disability vary from loss of 1 day of work or school [National Center for Health Statistics, 1971] to chronic conditions that impair a person's lifelong ability to work [Kraus and Stoddard, 1991; Wolfe and Haveman, 1990]. Worldwide information about pesticide-related illnesses is also very limited because estimates generally rely on outbreak investigations and not on surveillance data [Levine and Doull, 1992], and they frequently include mostly severe cases and suicide attempts [Maddy et al., 1990]. Maddy et al. [1990] suggest that the WH&S California data are probably more complete than any other surveillance data in the world.

Our criteria for evaluating certainty of diagnosis differed from the original WH&S, but we still observed that with knowledge of the likelihood of exposure, of cholinesterase inhibition, and of the symptoms, it was possible to evaluate by computer algorithm the probability that an illness was OP related. The computer algorithm did not consider the disability/hospitalization information, but cases with evaluation of definite illness were nonetheless more likely to be associated with hospitalization and disability than cases designated as probable or possible illnesses.

The results of this study show that the chemical structure of the OPs is associated with severity of illness. They also underscore the importance of knowing the circumstances of pesticide application when physicians evaluate an OP-related illness. We have identified factors that can be targeted in prevention of OP-related illnesses or in reducing their severity, and preventing or reducing exposures of unprotected workers or populations. While education of populations exposed to pesticides about the health effects of pesticides could be implemented to reduce pesticide-related illnesses, growers and local government personnel also need to assume responsibility for reduction of pesticide exposures to workers and to local populations.

ACKNOWLEDGMENTS

This study was supported by University of California Agricultural Health and Safety Center at Davis, NIOSH Cooperative Agreement U07/CCU906162, and NIEHS Agrochemical Center Grant E505707. We thank Dr. Louise Mehler, Don Richmond, Cliff Smith, and Sue Edminston from the Worker Health and Safety

(WH&S) Branch at the CDFA for their continuous assistance, advice, and discussion during the execution of this project. We also thank Mark Hansen from the Department of Environmental Toxicology at UCD for helpful discussions about the categorization of the chemical structure of OPs.

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