Clinical Management of Field Worker Organophosphate Poisoning

JOHN E. MIDTLING, MD, MS, *and* PAUL G. BARNETT, *Salinas, California;* MOLLY J. COYE, MD, MPH, *San Francisco;* ANTONIO R. VELASCO, MD; PABLO ROMERO, MD; CHARLIE L. CLEMENTS, MD, MPH; MICHAEL A. O'MALLEY, MD; MICHAEL W. TOBIN, MD, *and* THEODORE G. ROSE, MD, *Salinas, California, and* IRA H. MONOSSON, MD, *Los Angeles*

A group of 16 cauliflower workers poisoned by residues of the organophosphate insecticides mevinphos and phosphamidon was followed in weekly clinics with interviews and determinations of plasma and erythrocyte cholinesterase levels. None had preexposure baseline values. Although six had initial erythrocyte cholinesterase values within the laboratory normal range, subsequent testing showed their erythrocyte activity had been significantly inhibited. While the most severe symptoms of the 16 subjects resolved after 28 days, their erythrocyte cholinesterase levels did not reach a plateau until an average of 66 days after exposure, after which most patients continued to report blurred vision, headache, weakness or anorexia. These findings support the view that the diagnostic utility of single cholinesterase levels is limited in the absence of baseline values.

(Midtling JE, Barnett PG, Coye MJ, et al: Clinical management of field worker organophosphate poisoning. West J Med 1985 Apr; 142:514-518)

California agriculture has a 30-year history of field worker poisonings caused by organophosphate pesticide residues. Incidents involving crews of as many as 100 or more vineyard and orchard workers have been reported.[1] There were 323 confirmed reports of pesticide residue-induced illnesses in 1983.[2] State health officials have estimated that as few as 1% of the residue-induced illnesses in field workers are reported.[1]

In the Salinas Valley of California, as in other agricultural districts, pesticides are used extensively. Local health officials received 350 physician reports of pesticide illness in 1983. Between 1980 and 1983 there were four incidents in which some 135 workers became ill from organophosphate pesticide residues on the foliage of cauliflower and lettuce plants. Since 1983 three incidents involving the drift of organophosphates resulted in 172 workers seeking emergency medical treatment.

The initial diagnosis and treatment of a cholinergic crisis are appropriately handled in most agricultural areas. In cases of pesticide applicator exposure to cholinesterase inhibitors, plasma and erythrocyte cholinesterase activities are ordinarily compared with preexposure baseline values, both to confirm the diagnosis and to decide when to release a patient for work involving possible reexposure to cholinesterase inhibitors.[3,4] However, other agricultural workers rarely have baseline cholinesterase tests. Because there is a wide variability in persons' normal cholinesterase values, the absence of baseline data makes the interpretation of single postexposure values difficult.

We followed a group of 16 field workers exposed to organophosphate pesticides to develop criteria for the diagnosis, management and return to work of organophosphate-poisoned persons who have no baseline cholinesterase values.

Report of Poisoning Event

A crew of 23 farm workers was exposed to pesticide residues in a cauliflower field in the Salinas Valley of California on July 10, 1980. The workers began their job of tying leaves over the head of the vegetable only six hours after the field had been sprayed with the organophosphate insecticides mevinphos (Phosdrin) and phosphamidon (Dimecron). The compounds are potent cholinesterase inhibitors. The oral median

From the Natividad Medical Center, Salinas, California (Dr Midtling, Mr Barnett, Drs Velasco, Romero, Clements, O'Malley, Tobin and Rose), and the Division of Family and Community Medicine (Drs Midtling, Coye, Velasco, Romero, Clements, O'Malley, Tobin and Rose) and the Department of Internal Medicine (Drs Coye and Rose), University of California, San Francisco, School of Medicine; the National Institute of Occupational Safety and Health, San Francisco (Dr Coye), and the Department of Internal Medicine, University of California, Los Angeles, School of Medicine (Dr Monosson).

Supported in part by grant No. 2-501704, Academic Senate, University of California, San Francisco.

Submitted, revised, July 9, 1984.

Reprint requests to John E. Midtling, MD, Natividad Medical Center, PO Box 1611, Salinas, CA 93902.

lethal dose (LD_{50}) of mevinphos is 6.1 mg per kg of body weight and the dermal LD_{50} is 4.7 mg per kg of body weight.[5] The oral and dermal LD_{50} values of phosphamidon are 24 and 143 mg per kg, respectively.[6] State regulations require a 72-hour interval between application of this combination of pesticides and reentry into the treated area.

Shortly after beginning work, crew members noticed the onset of blurred vision and eye irritation. They continued to work and over the next two hours additional symptoms of dizziness, weakness, disorientation, headache, nausea and vomiting developed. Several workers experienced cramps in their arms, legs and stomach. Two workers collapsed, one with loss of consciousness.

The two collapsed workers were driven by another exposed and symptomatic crew member to the emergency room of the Natividad Medical Center where all three were decontaminated and examined. The two collapsed workers presented with bradycardia, increased salivation, miosis and muscle fasciculations. Their serum cholinesterase values were 2.40 and 3.04 IU per liter (laboratory normal range of 8 to 18 IU per liter). The patient with the least cholinesterase activity received 1,000 mg of pralidoxime (Protopam) chloride intravenously. Both of these patients were given 2 mg of atropine sulfate intravenously and were admitted to the intensive care unit for observation. The patient who had driven these workers to the hospital received 1 mg of atropine and was admitted to the medical service for observation. His serum cholinesterase level was 6.06 IU per liter.

Thirteen other workers from this crew sought treatment on the same day from a physician recommended by the pesticide applicator. Two of these workers were admitted to hospital and the other 11 were released after plasma and erythrocyte cholinesterase determinations, with prescriptions for 2 grams of pralidoxime to be taken orally.

The remaining seven workers did not seek medical treatment on the day of the incident. One of this group, an elderly man, collapsed at home the day following his exposure and was taken to hospital. All but one of the other workers were seen by physicians during the following week.

Patients and Methods

All 23 members of the crew were invited to attend a series of follow-up clinics that began on July 21, 11 days after the incident. Initially 18 crew members joined the study but three were lost to follow-up. One additional crew member entered the study ten weeks after the poisoning.

The patients were all Hispanic and included six female and ten male subjects. Their ages ranged from 9 to 72 years, with ten patients between 18 and 26 years, three younger than 15 and three older than 34 years. One worker was five weeks pregnant at the time of exposure.

The patients had received antidotal therapy according to individual decisions of whether or not to seek medical care immediately after exposure. Pralidoxime had been administered orally to seven of the patients, pralidoxime and atropine intravenously to one person and atropine alone to two persons. The other six subjects received no antidotes.

All subjects were followed with weekly examinations. Symptoms reported by them were recorded, and blood specimens were analyzed for plasma and erythrocyte cholinesterase activity using the method of Michel.[7] Analyses were done at the same laboratory where most of the patients had

TABLE 1.—*Initial and Final Cholinesterase Values (Change in pH per Hour) of Patients Poisoned by Organophosphate Insecticide Residues.*

Patient Number	Admitted to Hospital	Received Pralidoxime	Plasma Cholinesterase Values			Erythrocyte Cholinesterase Values		
			Initial	Estimated Normal*	Percent Inhibited†	Initial	Estimated Normal*	Percent Inhibited†
Patients With First Comparable Analysis Within 1 Day of Exposure								
3	No	No	0.38	0.90	57.9	0.71‡	0.75	5.3
4	No	Yes	0.19	0.81	76.4	0.39	0.60	35.0
8	Yes	Yes	0.11	0.98	88.7	0.31	0.78	60.3
9	No	Yes	0.23	1.17	80.3	0.38	0.85	55.5
11	No	Yes	0.46‡	0.92	49.8	0.71‡	0.82	13.8
12	No	Yes	0.59‡	1.01	41.4	0.77‡	1.06	27.1
13	No	Yes	0.24	1.00	75.9	0.50	0.92	45.7
14	No	Yes	0.32	0.80	60.0	0.57	0.69	17.0
	Average Inhibition, 8 Patients				66.3§			32.5‖
Patients With First Comparable Analysis 11 Days After Exposure								
2	No	No	0.84‡	1.10	23.9	0.67‡	0.99	32.3
5	No	No	0.46‡	0.93	50.7	0.73‡	0.98	25.5
6	No	No	0.70‡	1.05	33.3	0.56	0.97	42.1
7	Yes	Yes¶	0.79‡	1.19	33.8	0.48	0.90	46.9
10	Yes	No¶	0.66‡	1.05	37.3	0.46	0.87	47.1
15	Yes	No¶	0.77‡	1.22	37.1	0.42	0.78	45.9
16	No	No	0.76‡	1.00	24.0	0.73‡	1.04	29.6
	Average Inhibition, 7 Patients				34.3§			38.5§
Patient With First Comparable Analysis 84 Days After Exposure								
1	No	No	0.63‡	0.75	16.0	0.83‡	0.87	4.6

*Estimated normal=average of last three analyses (see text).
†Percent inhibition=100−(initial value divided by estimated normal).
‡Initial value above the lower limit of laboratory normal (0.58 for erythrocyte and 0.44 for plasma).
§Inhibition was significant by paired *t*-test ($P<.001$).
‖Inhibition was significant by paired *t*-test ($P<.005$).
¶Received atropine.

cholinesterase determinations on the day of their exposure, so that the values could be appropriately compared with the initial results. They were followed until symptoms abated and three successive erythrocyte cholinesterase values showed no more than 0.02 Michel units (change in pH units per hour) increase. A case report published elsewhere presented partial data collected for workers' compensation insurance purposes.[8]

Clinical and Laboratory Findings

Cholinesterase Analyses

Normal plasma and erythrocyte cholinesterase activities were estimated for each person by averaging the last three values obtained. The initial and estimated normal activities for the 16 persons are given in Table 1. The eight persons in whom comparable cholinesterase levels were determined within 24 hours after exposure had plasma cholinesterase activity inhibited by an average of 66.3%. The difference between the initial and final plasma values for these subjects was statistically significant ($P < .001$). The erythrocyte cholinesterase activity in these subjects was, on the average, inhibited by 32.5%, a difference shown to be significant ($P < .005$).

The seven subjects for whom the first comparable cholinesterase determination was done 11 days after exposure had plasma cholinesterase depressed by an average of 34.3% and erythrocyte cholinesterase inhibited by an average of 38.5%. The fact that the initial plasma activity of these subjects was not more severely inhibited than their erythrocyte activity reflects the more rapid regeneration of plasma cholinesterase. Again, inhibition of both cholinesterases was statistically significant ($P < .001$).

The erythrocyte cholinesterase values for the 16 subjects over the course of the study are presented in Figure 1. This figure shows that the upward trend in values is apparent within the first three analyses. Regeneration was also apparent in the values of the subject enrolled in the study ten weeks after exposure.

Cholinesterase activities regenerated to 95% of the estimated normal values within an average of 57 days for plasma and 66 days for erythrocyte enzyme activity.

Rates of cholinesterase regeneration were calculated and expressed as the increase in percentage of the estimated normal activity per day. Regeneration rates for the persons followed during the first 11 days after exposure averaged 3.02% per day for plasma and 0.82% per day for erythrocyte cholinesterase. Pralidoxime had been administered to seven of these eight persons. Cholinesterase regenerated more slowly after the examination 11 days following exposure. The average rate of regeneration between this examination and the return to 95% of estimated normal activity was 0.96% per day for plasma and 0.56% per day for erythrocyte cholinesterase for the 15 subjects followed during this period.

Pralidoxime may have contributed to the higher initial rate of regeneration observed in this study; however, a more rapid rate of regeneration in the first 11 days following exposure was apparent even for the subject who had not received the antidote, indicating that there was a significant amount of spontaneous dephosphorylation of cholinesterase. There was no significant difference between the subgroups of persons who had received pralidoxime and those who had not in either the average regeneration rates or in the average number of days to recover 95% of estimated normal activity.

The slower regeneration of cholinesterase activity during the remaining convalescence is consistent with other reports that indicate that mevinphos becomes irreversibly bound to cholinesterase.[9]

The recovery of the patients' plasma cholinesterase, expressed as a percentage of individual estimated normal values, fits a logarithmic regression ($R = .91$). The regeneration of erythrocyte cholinesterase follows a linear model better than a logarithmic one ($R = .70$). These regressions are consistent with the observed recovery of cholinesterase in humans experimentally exposed to the organophosphate sarin, in whom the erythrocyte activity was restored at a rate that was constant during the period of recovery, whereas plasma cholinesterase returned at a rate that was more rapid at the outset and declined as recovery proceeded.[10]

Because subjects were followed beyond the recovery of plasma cholinesterase activity, until erythrocyte cholinesterase activity had reached a plateau of three weeks' duration,

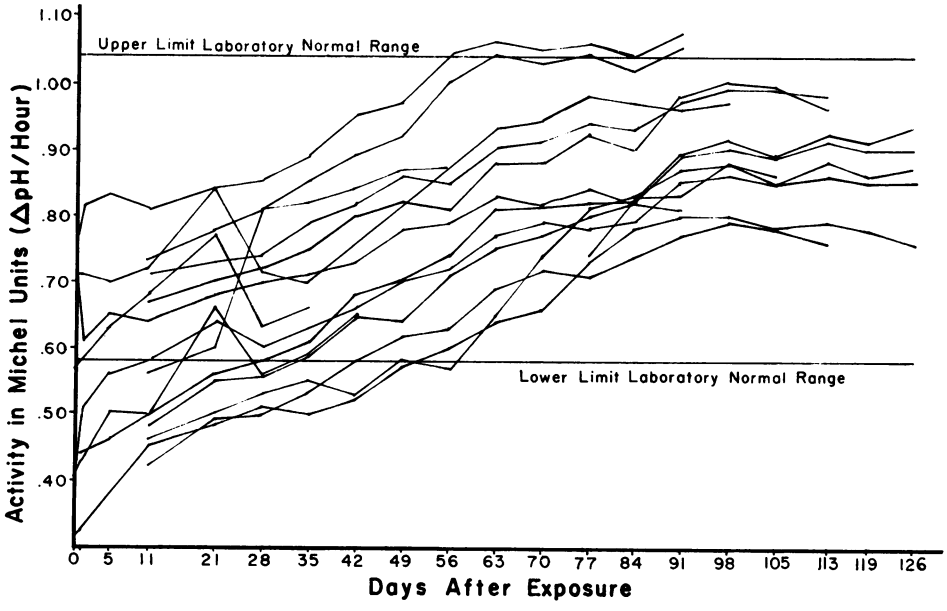

Figure 1.—Erythrocyte cholinesterase values for 16 subjects following poisoning by organophosphate insecticides.

the data allow evaluation of the postexposure period for a possible rebound effect in plasma cholinesterase activity. Some researchers have reported a rebound of 10% to 20% above normal baseline in studies of animal and human subjects exposed to organophosphates; the effect seems to occur most prominently in plasma cholinesterase levels.[11-13] This phenomenon was not apparent in the pattern of plasma cholinesterase regeneration in our study. The greatest plasma cholinesterase activity measured was no more than 3% greater than the final plasma value in any of the subjects, well within the margin of analytic error.

Clinical Findings

The symptoms most frequently reported by the patients are presented in Figure 2. Symptoms commonly associated with organophosphate-induced cholinergic excess such as nausea, dizziness, vomiting, abdominal pain and ataxia were reported by many patients initially but abated within 28 days. Other symptoms persisted throughout the entire study period in a significant number of patients. Blurred vision was one of the most common initial complaints, and reports of it persisted throughout the 18 weeks of the study. Headache, weakness and anorexia were also reported late in the study.

Prescribing the oral form of pralidoxime appears to have been ill-advised in this case. Most of the persons were nauseated or vomiting. The patient discovered to be five weeks pregnant at the time of exposure had an uneventful pregnancy and was delivered of an apparently healthy infant. A second person became pregnant during the follow-up period, had a normal pregnancy and was delivered of a healthy baby as well.

Discussion

It is commonly stated that organophosphate-poisoned persons must suffer about a 50% inhibition of plasma or erythrocyte cholinesterase activity before symptoms appear.[14] In this case, moderately severe symptoms were suffered by a group of workers whose erythrocyte cholinesterase activity appears to have been only 30% inhibited. This concurs with observations that the suddenness of decline in cholinesterase activity is more important than the absolute amount of the decline in determining whether symptoms will be manifest.[15]

It has been reported that the symptoms of patients with mild or moderately severe poisoning disappear within 24 hours and that patients with mild poisoning recover complete blood cholinesterase activity within two weeks.[14] In this case, most of the patients continued to report symptoms 70 days or more after exposure. They had regenerated 95% of their plateau plasma activity after an average of 57 days and 95% of erythrocyte activity after an average of 66 days.

It has also been reported that erythrocyte cholinesterase regenerates at a rate of 1% per day, an estimate based on the replacement rate of erythrocytes.[3] A similar rate of regeneration was observed only during the first 11 days following the poisoning; most of these persons had received pralidoxime. Erythrocyte cholinesterase from day 11 to plateau regenerated at a much slower rate, less than 0.5% per day.

This report shows many of the problems inherent in using postexposure cholinesterase values in the absence of baseline data either for diagnosing organophosphate pesticide poisoning or for determining when patients have recovered enough to return to work that may involve reexposure to organophosphate or carbamate pesticides. The laboratory normal range may not always be a useful standard for estimating cholinesterase inhibition. Because the range of normal is so wide, patients whose normal values are at the upper end of the range may lose half of their cholinesterase activity and still have values above the lower limit. As can be seen in Table 1, the initial erythrocyte cholinesterase value for 6 of the 16 patients was above the lower limit of the laboratory normal range. Subsequent testing showed that the erythrocyte cholinesterase activity in these persons was inhibited by an average

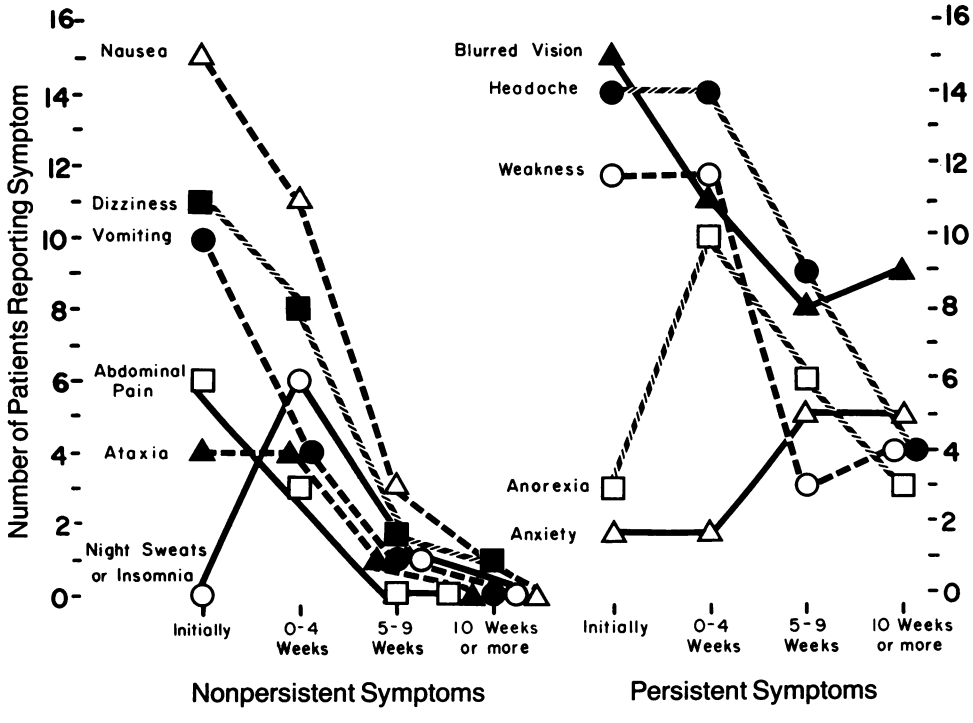

Figure 2.—Persistent and nonpersistent symptoms most frequently reported by 16 organophosphate-poisoned patients.

of 22.3%, which a paired t test found significantly different from their final erythrocyte activity ($P < .005$). This concurs with other observations that patients who suffer moderately serious organophosphate poisoning may have cholinesterase values within the lower limits of the laboratory normal range.[15]

If these workers, most of whom had nonspecific symptoms, had presented to separate physicians without a dramatic history of group poisoning (if, for example, only one worker had entered the field), the diagnosis might have been missed. Indeed, this is the dilemma that clinicians in agricultural areas routinely confront.

We suggest that sequential postexposure cholinesterase determinations may be a feasible and useful alternative to reliance on the laboratory normal range as a means to confirm cholinesterase inhibition. Sequential postexposure testing may improve the accuracy of diagnosis, provide evidence of the work relatedness of the illness for compensation and guide a physician in determining a patient's ability to work. Patients who have no baseline cholinesterase values and present with a history of exposure, cholinergic symptoms and values at the lower limits of normal should be kept from work involving any additional exposure until their cholinesterase level is retested in three to five days. Our experience in this case suggests that upon retesting, the plasma cholinesterase level should increase 15% to 20% if a significant organophosphate-induced cholinesterase inhibition has occurred. Regeneration of plasma activity is more likely to be seen over this short period because of the more rapid rate of recovery of this enzyme. Further increases on subsequent determinations would confirm the diagnosis.

Because persons with depressed cholinesterase values are especially vulnerable to poisoning by organophosphate and carbamate pesticides, it would be prudent to keep them from work involving exposure to these chemicals until their erythrocyte cholinesterase has regenerated. Erythrocyte rather than plasma values are recommended as the end point because the former better reflects cholinesterase levels in nerve tissue and, therefore, physiologic effect.[3] It is difficult to ascertain when cholinesterase activity of a patient has regenerated when there is no baseline value, however. In estimating when regeneration has been completed, consideration should be given to the fact that the erythrocyte cholinesterase activity of a healthy person may normally vary by 10% on retesting.[16] If a value increases by less than 10% over the previous value, the plateau may have been reached. Other factors that should be considered in deciding when to release such patients for work include the likelihood of reexposure to a cholinesterase inhibitor, the persistence of symptoms, whether values are at the lower limit of normal and the economic impact on patients of prolonged absence from work. This impact is only somewhat mitigated by temporary disability benefits provided by workers' compensation insurance in some states. Once patients' symptoms have abated, physicians may feel compelled to release them to work to minimize the impact of this loss of earnings, especially when the risk of reexposure is small. Patients should be advised that additional exposure before recovery is complete will entail serious risks. They should also be advised to seek medical care promptly should symptoms recur.

A more conservative approach should be taken when there is a high potential for reexposure, as was observed in this study. The work of cauliflower tying involves substantial dermal exposure to crop foliage during a time in the season when organophosphate insecticides are intensively used. The possible hazards of this occupation were underscored when a second tying crew was poisoned in September 1982. Of the 36 persons poisoned in this second incident, 6 were among the patients included in this report. A third cauliflower crew was poisoned in the Salinas Valley in April 1983.

In response to the problem of residue-induced illness, Monterey County has adopted a unique regulation requiring that warning signs be posted in fields where a worker safety reentry interval of 24 hours or greater is in effect.

REFERENCES

1. Kahn E: Pesticide related illness in California farm workers. J Occup Med 1976; 18:693-696
2. Occupational Injury Report HS-1186. Sacramento, Calif, Dept of Food and Agriculture, Mar 1984
3. Durham WF, Hayes WJ: Organic phosphorus poisoning and its therapy. Arch Environ Health 1962; 5:21-43
4. Namba T, Nolte CT, Jacrel J, et al: Poisoning due to organophosphate insecticide: Acute and chronic manifestations. Am J Med 1971 Apr; 50:475-492
5. Gaines TB: The acute toxicity of pesticides to rats. Toxicol Appl Pharmacol 1960; 2:88-99
6. Gaines TB: Acute toxicity of pesticides. Toxicol Appl Pharmacol 1969; 14:515-534
7. Michel HO: Electrometric method for determination of red blood cell and plasma cholinesterase activity. J Lab Clin Med 1949; 34:1564-1568
8. Whorton MD, Obrinsky DL: Persistence of symptoms after mild to moderate acute organophosphate poisoning among 19 farm field workers. J Toxicol Environ Health 1983; 11:347-354
9. Rider JA, Pulletti EJ, Swader JI: The minimal oral toxicity level for mevinphos in man. Toxicol Appl Pharmacol 1975; 32:97-100
10. Grob D, Harvey JC: Effects in man of the anticholinesterase compound sarin (isopropyl methyl phosphonofluoridate). J Clin Invest 1958; 37:350-368
11. Frawley JP, Hagan EC, Fitzhugh OG: A comparative pharmacological and toxicological study of organic-phosphate anticholinesterase compounds. J Pharmacol Exp Ther 1952; 105:156-165
12. Frawley JP, Fuyat HN: Pesticide toxicity: Effect of low dietary levels of parathion and systox on blood cholinesterase of dogs. J Agric Food Chem 1957; 5:346-348
13. Rider JA, Moeller HC, Swader J, et al: The effect of parathion on human red blood cell and plasma cholinesterase: Section II. AMA Arch Ind Health 1958; 18:441-445
14. Namba T: Cholinesterease inhibition by organophosphorus compounds and its clinical effects. Bull WHO 1971; 44:289-307
15. Summerford WT, Hayes WJ, Johnson JM, et al: Cholinesterase response and symptomatology from exposure to organic phosphorus insecticides. Arch Ind Hyg Occup Med 1953; 7:383-398
16. Yager J, McLean H, Hudes M, et al: Components of variability in blood cholinesterase assay results. J Occup Med 1976 Apr; 18:242-244