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BLOOD CHOLINESTERASE ACTIVITY IN WORKERS EXPOSED TO CHOLINESTERASES, A TEN-YEAR FOLLOW-UP

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The surveillance of workers exposed to anticholinesterase insecticides during their formulation has shown that the use of protective devices at work and observation of the hygienic and sanitary regulations provide a satisfactory protection and reduce significantly the absorption of anticholinesterase insecticides.

Our study has confirmed that a beweekly measurement of cholinesterase activity during a period of intense production is the only practicable method for determining the degree of absorption. With this method one can learn in time whether there are workers at risk, and thus prevent the danger of further absorption.

Without exception, the workers showing cholinergic symptoms had their blood cholinesterase inhibited 50% or more. However, complaints from workers were not always related to cholinesterase inhibition.

In agricultural workers exposed to insecticides cholinesterase inhibition rarely exceeded ten per cent. In several individuals who showed inhibition up to 40% subjective complaints were present.

It appears that long-term exposure to anticholinesterases had no effect on peripheral blood as revealed by blood cell counts.

The need for effective pest control is well recognized and the role of pesticides in agriculture, integrated pest or vector management and disease prevention is unquestionable. A variety of compounds, both very toxic and practically harmless are being used for these purposes.

It is known that the acute toxicity of most organophosphorus esters used as insecticides is mainly if not entirely, due to their inhibition of acetylcholinesterase. As a result of acetylcholinesterase inhibition in the nervous system, acetylcholine molecules accumulate at the synapse, initially causing excessive excitation and later leading to the blockage of

synaptic transmission (1). At present, the only practical way to evaluate the hazards of overexposure to anticholinesterase pesticides is to measure the activity of blood cholinesterase(s) in exposed people. Such measurement provide a valuable confirmation of the diagnosis of organophosphorus poisoning, since the early signs of intoxication with these substances are rather nonspecific. These measurements also permit to follow the process of recovery, and facilitate the decision of whether or not the patient is fit to return to work. Also, regular determination of blood cholinesterase serves as an early warning system for the recognition of excessive exposure (2—9).

The aim of this work was a case-control study in the workers occupationally exposed to a multitude of insecticides with emphasis upon subclinical effects. In order to determine the condition which precedes clinical poisoining, an assessment was made of cholinesterase activities in the blood of workers and this was correlated with exposure and with the cholinergic signs and symptoms of poisoning.

Since enzyme activities vary considerably within an individual (3, 10—13), it is important to establish the »normal values« of each individual. With this purpose plasma and whole blood cholinesterase activity was determined in a group of healthy human subjects with no previous exposure to anticholinesterase compounds.

SUBJECTS, METHODS AND MATERIAL

Non-exposed subjects

Plasma and whole blood cholinesterase activity was determined in a group of 408 subjects (257 males and 151 females). The group consisted of apparently healthy adults selected among factory office and research workers with no exposure to anticholinesterase compounds. The testing was done in all seasons over a period of two years. The degree of individual variation was studied in 34 subjects from the same group, by repetitive measurements of cholinesterase activities in plasma and whole blood over a period of 15 months.

Exposed subjects

Several groups of industrial and agricultural workers were examined.

A total of 567 industrial workers who worked at one time in any of the three different production lines in a pesticide formulating plant were examined. Only 170 of them were continuously employed in the production of pesticides for a number of years (2—14). The others were seasonal workers employed only during the periods of intense production.

The normal workday was eight hours, but periodically, because of intense production the workers worked overtime, up to 12 hours a day.

The technological process in the three lines differed (dust or wettable powder, emulsions and household sprays), so that the type of exposure also varied.

The greater demand for insecticides imposed by the market, especially in spring and summer, resulted in an increased production and therefore, in the first six months of the year the workers were exposed to organophosphorus and carbamate insecticides longer than usual. The active materials handled were various organophosphorus insecticides: azinphos-ethyl, bromophos, diazinon, dichlorvos, dimethoate, thiometon fenthion, methidation, monocrotophos, parathion, phorate, phosalone, and carbamate insecticides: carbaryl, dioxacarb, zineb. In addition 22 persons working with pesticides in a laboratory were also taken in the study. The workers were aged 21—60 years.

To assess the extent of exposure in workers who apply anticholinesterase insecticides in orcharding or farming, 129 agricultural workers were chosen. Their jobs were seasonal and lasted usually about two months. The working conditions were different from those of industrial workers since they worked in the open where the possibility of contamination was smaller, although in windy weather, or at higher temperature the exposure could increase considerably.

These workers were exposed mainly to phorate, and to a lesser extent to diazinon, methidation, fenthion and parathion.

Protective clothing

While working industrial workers wore overals, rubber gloves and rubber boots. For face and eye protection they occasionally used face shields and goggles, but no respirators or vapour filters.

Agricultural workers wore only protective clothing, and periodically gloves and respirators. In some orchards the spraying operation was highly mechanized. However, neither the drivers nor the mixers observed protective measures such as wearing gloves or a respirator. The mixing of concentrate was done in a most inappropriate way.

Blood cholinesterase determination

Blood samples were taken by a finger-prick. For determining whole blood cholinesterase activity 20 μl of blood was collected in the laboratory or in the field, in Sahli pipettes which had been heparinized by rinsing with a 2% heparin solution immediately before the collection of samples. For determining plasma cholinesterase activity blood samples were collected in dry, heparinized, glass capillaries as described by *Stubbs* and *Fales* (14).

The blood samples were collected from industrial workers at intervals which depended on the rate of production. When the rate of production was very high, the sampling was done every second week.

In workers handling anticholinesterase insecticides in farms or orchards, blood cholinesterase activities were measured before, in the middle, and at the end of the working season.

The measurements of cholinesterase activities were performed in the laboratory, while the sampling was done either in the laboratory or in the field in which case the samples were kept cool and transferred to the laboratory observing all the measures so as to reduce both further inhibition or spontaneous reactivation (15). Cholinesterase activity was measured by the spectrophotometric method of *Ellman* and co-workers (16) modified for plasma (17). The activity of whole blood cholinesterase measured by this method is primarily due to the activity of erythrocyte cholinesterase. If assumed that the haematocrit is 50%, erythrocyte cholinesterase contributes 92% and plasma cholinesterase only 8% to the total whole blood activity in uninhibited samples (18).

Medical data

Industrial workers were under regular medical control which included a general medical check-up twice a year, and routine analyses of blood and urine. Whenever necessary the workers were examined by a specialist. The history of illness related to occupational exposure was taken from each worker at intervals. All medical data both related or unrelated to occupation are kept in worker's medical files in the factory health unit which is headed by a specialist in occupational medicine. The relevant data from these records were used for the assessment of the effects of occupational exposure.

Agricultural workers, however, underwent no routine medical control. Therefore, the assessment of possible effects of occupational exposure on their health was based exclusively on the anamnestic data collected at the beginning and at the end of the working season.

For nine workers who worked with pesticides for more than 12 years (in one factory) the results of blood analyses performed oven a nine-years period were compiled from medical records and compared with 97 blood analyses performed in 48 transportation workers who had never been in contact with pesticides.

RESULTS AND DISCUSSION

Variation in enzyme activity in non-exposed people

The results of enzyme activities (expressed in μ-moles of thiocholine/ /min/ml) were distributed over a comparatively large range: 0.35—2.60 for plasma, and 2.70—7.70 for blood cholinesterase, with a mean of 1.34 and 5.10 respectively. (Fig. 1).

The coefficient of variation (S. D. $\times$ 100/Means) was 18% for erythrocyte and 25% for plasma cholinesterase. This is in accordance with the

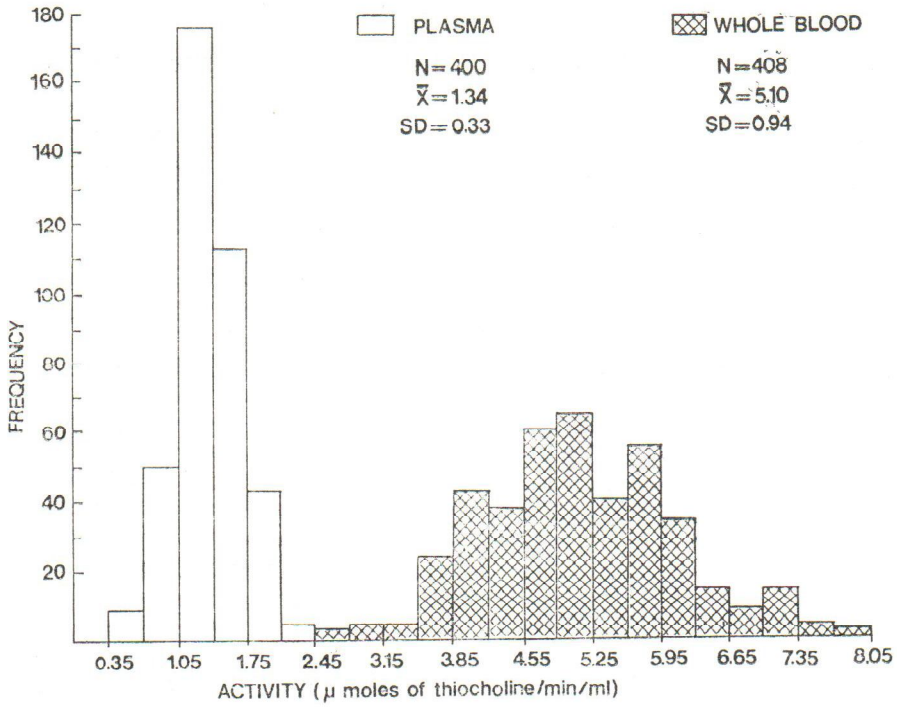

Fig. 1. *Distribution of plasma and whole blood cholinesterase activity in non-exposed humans*

results of other authors, who report coefficients of 10—15% for erythrocyte and 15—25% for plasma cholinesterase (3, 11, 13).

Figure 2 shows the distribution of values of plasma and whole blood cholinesterase activity for males and females. The difference in whole blood cholinesterase between the means of the male and female groups is statistically significant ($p < 0.005$, $t = 4.62$) and is probably caused by the difference in their haematocrit values (11).

The whole blood cholinesterase activity (y) was found to correlate well with the serum cholinesterase activity (x). The relationship between the two activities can be described by the empirical equation $y = (13.0 \pm 0.7) + (1.5 \pm 0.1)\,x$. This correlation was found valid for 400 samples.

The precision of the method was tested on a set of samples by two subsequent measurements of the activity of individual samples. The correlation between two pairs of measurements was $r = 0.99$ for plasma

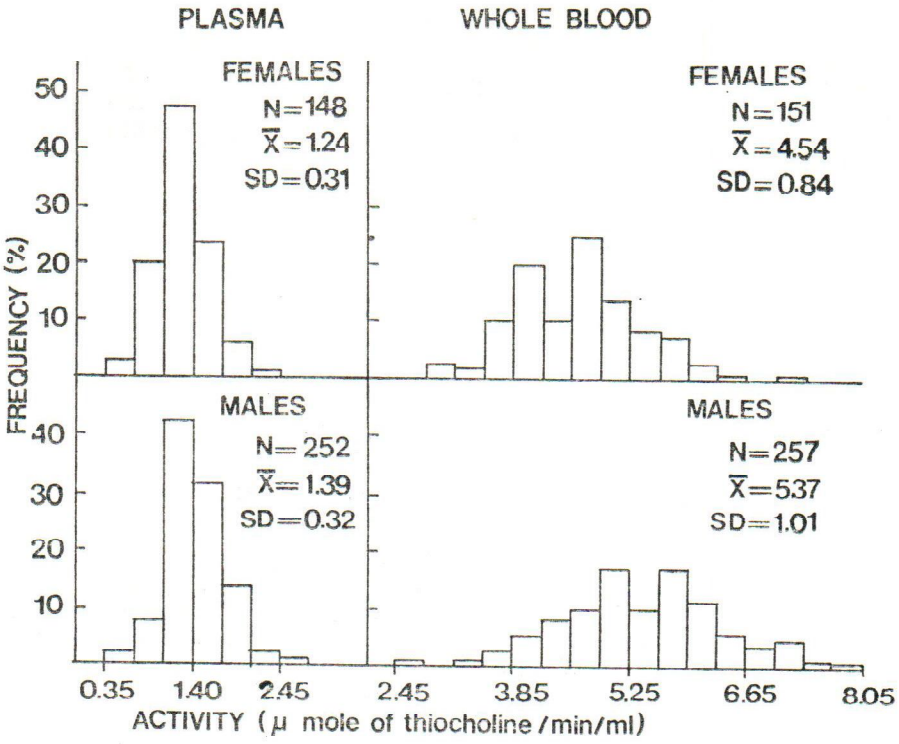

Fig. 2. *Distribution of plasma and whole blood cholinesterase activity in non-exposed humans by sex*

cholinesterase and r = 0.91 for the whole blood cholinesterase activity. Such a high correlation permits a precise determination of sample activity by only one measurement.

Variation in enzyme activity in an individual

The measurements were carried out under the conditions as identical as possible. The temperature of the buffer ranged from 18 to 25° C. For the temperature correction factors the data published by *Reiner* and co-workers (19) were used.

The factor of variation was 5.95 for the activity of whole blood cholinesterase and 8.77 for the activity of plasma cholinesterase. The coefficients of variation agree with the data of other authors; they were 7.2 for whole blood and 11.9 for plasma cholinesterase activity (3).

Enzyme activity in workers from a pesticide manufacture

The production of organophosphorus insecticides increased during the ten-year period of observation. It was expected that with the increased exposure the number of blood samples with diminished enzyme activities would also increase. However, Table 1. shows that the greatest number of blood samples with the enzyme activity lower than 50% was recorded in the first two years. The accompanying symptoms or signs of poisoning were also most numerous in the same years.

In the first two years the workers were exposed to and handled mainly dimethoate and chlorfenvinphos, both very dangerous insecticides which are extremely toxic to mammals. Certain technological procedures and working conditions provided inadequate protection, and in addition there was a great deal of overtime work during the peak of the season. After the cases of poisoning were analysed the working conditions were considerably improved. Therefore, although the extent of work remained the same, there were no cases of occupational poisoning in 1972, except for one accidental intoxication at work. In 1973 the situation did not change. Only two exposed workers had blood cholinesterase activities lower than 50% which is below the limit for occupational exposure.

In the following years there has been an increase in the production of insecticides. The number of seasonal workers with no previous experience with insecticides also increased. From the results presented in Table 1, the number of reduced enzyme activities again seems to have become higher. If however, the accompanying symptoms observed in some workers are expressed as percentages they varied between 7 and 17% (Table 1).

Table 2 relates to the poisoning of a few workers during the period of observation. The poisonings were recorded mostly in 1971 (N = 7). Only those workers are listed for whom it was possible to ascertain that the accompanying symptoms were due to excessive exposure to anticholinesterase compounds.

After a two-week removal from the place of exposure cholinesterase activity increased in all these workers. The workers were exposed to various organophosphorus or even carbamate insecticides so that the spontaneous reactivation of the inhibited enzyme was not identical in all workers.

The workers were exposed to organophosphorus compounds containing dimethoxy or diethoxy radicals. The acetylcholinesterase of human erythrocytes inhibited by a dimethoxy organophosphorus compound is known to reactivate quickly ($t^1/_2 = 51$ min) while for the plasma cholinesterase inhibited by the same group of organophosphorus compounds the half time reactivation is $\geq$ 83 hours (20). Erythrocyte acetylcholinesterase inhibited by diethyl organophosphorus compounds also reactivates faster ($t\ ^1/_2 = 2.4$ days) than plasma cholinesterase ($t\ ^1/_2 = 30$ days) (21).

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Table 1

The relationship between whole blood cholinesterase activity and complaints in workers manufacturing anticholinesterase insecticides in one plant

Inhibition of cholinesterase activity in whole blood (%)	Number of workers (Without complaints/with complaints)										Total
	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	
0— 25	46/1	59/1	99/0	47/4	56/0	83/1	89/3	167/3	155/3	183/4	984/20
25— 50	10/6	18/14	6/0	19/1	37/14	71/9	26/4	7/1	9/1	34/6	237/56
50— 75	11/13	5/6	0/1	1/1	9/2	6/8	2/2	0/5	1/12	6/16	41/66
75—100	1/5	0/3	0/0	0/0	0/1	1/1	0/0	0/3	0/6	0/6	2/25
Total	68/25	82/24	105/1	67/6	102/17	161/19	117/9	174/12	165/22	223/32	1264/167
Complaints (%)	37	29	1	9	17	12	8	7	13	14	13

Table 2

Symptoms of poisoning and cholinesterase activities of exposed workers

Worker	Exposure to compound	Duration of exposure	Signs and symptoms recorded	Whole blood ChE activity (%)	
				while having symptoms	two weeks later
M. B.	dimethoate phosalone	2 months	loss of appetite, weakness	55	70
S. DJ.	„	40 days	tiredness, exhaustion, tightness in chest, cough	59	65
S. V.	„	2 months	stomach discomfort	49	69
T. Z.	„	15 days	hand-sweating, headache	56	76
J. Z.	„	7 days	vomiting, weakness, salivation, tiredness, abdominal cramps	24	48
G. R.	„	33 days	vomiting, slower pupillary reaction	37	66
K. J.	„	30 days	weakness, exhaustion	44	62
J. B.	„	21 days	weakness, headache, exhaustion	40	53
K. M.	„	15 days	tiredness, sleepiness, myosis	9	22
R. Z.	„	12 days	abdominal cramps, vomiting	21	38
C. J.	dimethoate phosalone dichlorvos	34 days	tiredness, sleepiness, headache	54	72
D. B.	dimethoate phosalone dichlorvos	7 days	weakness, headache, vomiting	24	42
N. Z.	dimethoate phosalone	3 months	weakness, headache, sweating, sickness	37	68
M. K.	„	3 months	headache, sickness, dizziness	53	63
K. M.	dioxacarb	4 months	tightness in chest, stiff extremities	78	83
	carbaryl	4 months			
K. S.	„	20 days	dizziness, sickness, vomiting	42	87
V. J.	phosalone		headache, sickness	51	81
B. V.	OP and carbamate insecticides	Continuous laboratory work	sweating, tiredness, vomiting	48	71
B. J.	„	„	weakness, vomiting, suffocation	44	71

Further, most organophosphorus insecticides inhibit, to a greater extent, plasma cholinesterase (22). The emulsion-production workers had a lowered plasma cholinesterase activity in most measurements which is in accordance with the literature data about the slow spontaneous reactivation and higher inhibition of serum cholinesterase. Still, we did not consider this as too important, for plasma cholinesterase can be highly inhibited without any consequence to health. In the workers exposed to dimethoxy organophosphorus compounds such as dichlorvos, dimethoate and other, the phenomenon of ageing of the inhibited human erythrocyte cholinesterase should be borne in mind since it occurs relatively fast (half-time of ageing about four hours) in contrast to diethyl organophosphorus compounds with a half-time of ageing of about 40 hours (23). The aged cholinesterase is irreversibly inhibited and cannot be reactivated even by oximes. In the workers exposed to carbamate insecticides it was difficult to assess the actual degree of exposure because of the already well-known property of carbamylated cholinesterase to reactivate spontaneously in a very short time (25, 26). *Aldridge* and *Reiner* showed that the half-time of reactivation for monomethyl carbamates is only 30 minutes, and for dimethyl carbamates 76 minutes if the cholinesterase of purified bovine erythrocytes was carbamylated (21, 23, 24). Some of the workers from the production of insecticidal powder had blood cholinesterase activities lower than 60% at the time of sampling, but a 24-hour interruption of exposure was sufficient for cholinesterase activity to return to normal. Since the duration of exposure had no lasting effect on cholinesterase activity and on workers' health, the cholinesterase activities in these workers were monitored only 2—3 times a year, during the peak of production.

In order to determine the degree of exposure in the course of one working day, blood and plasma cholinesterase activities in workers were measured before and after the work shift. The results are presented in Table 3. In ten workers from the group engaged in the formulation and packing of phosalone, cholinesterase activity was measured at 6 a. m. and at 1 p. m. After cessation of exposure in five workers the measured blood cholinesterase activity was the same, while in the other five it was reduced by 6—10%. Plasma cholinesterase activity in these workers was reduced by 10—15%.

In another pesticide formulating plant, workers were engaged in the production of pesticides containing thiometon or dichlorvos. Since for most of the workers no preexposure values were recorded, it was not possible to calculate the actual degree of cholinesterase inhibition. However, in comparison with the normal values determined by the same method in non-exposed workers enzyme activities were sometimes low. Only the tendency of a further recovery or diminution of enzyme activity could be registered.

The results of measurements of enzymes activities in the workers whose preexposure values were taken are presented in Table 4. The

Table 3

Blood and plasma cholinesterase activity measured at the beginning and at the end of a work shift in workers from the production of emulsion (exposure to phosalone)

Worker	Enzyme preparation	Blood and plasma cholinesterase activity (%)	
		measured at 6 a. m.	measured at 1 p. m.
1	blood	90	81
	plasma	72	65
2	blood	90	83
	plasma	100	100
3	blood	98	97
	plasma	90	90
4	blood	87	82
	plasma	100	100
5	blood	78	71
	plasma	82	74
6	blood	93	93
	plasma	83	83
7	blood	96	90
	plasma	92	78
8	blood	88	87
	plasma	90	90
9	blood	95	94
	plasma	99	97
10	blood	93	94
	plasma	100	98

mean activities of a group of workers engaged in the formulation of thiometon or dichlorvos are given for a period of six years. Very often enzyme activities were low. Almost always these low values were accompanied by symptoms of poisoning such as headache, fatigue, giddiness and sweating.

Workers employed in the application of insecticides in agriculture

Preexposure values were determined for each worker in the course of the working season and cholinesterase activity was measured twice or once during the exposure period. The results of measurements are given in Table 5. In the first year of testing, the group as a whole did

Table 4

The mean value of blood cholinesterase activity in workers engaged in the formulation of thiometon and dichlorvos (expressed in percent of the preexposure values)

Year	Date	Mean	± SEM	N
1970	4 February	85	2.41	20
	20 March	74	3.89	22
	8 April	72	2.21	19
	20 May	62	2.67	14
	1 September	79	3.81	18
	30 October	92	2.67	14
1971	19 April	72	5.76	9
	10 June	67	6.58	12
	17 June	63	3.20	12
1972	13 April	91	3.27	10
	19 April	80	7.51	9
1973	11 July	47	6.47	12
	16 July	63	4.77	18
	23 July	65	6.87	7
1974	9 April	91	2.44	19
1975	20 February	72	3.34	22
	3 March	75	7.74	8
	10 July	68	2.98	17
	21 July	66	3.18	19
	10 November	92	1.60	24

not show the reduced mean values of cholinesterase activity. The lowest blood cholinesterase activity was 84% of the preexposure value.

In the second year, of the 44 tested workers, six had blood cholinesterase activity between 60% and 70%, six between 70% and 80% and the rest over 80%. This decrease indicated that the workers absorbed a certain amount of organophosphorus insecticides in the course of work.

The group of orchard spraymen was exposed to a greater variety of compounds. In one farm in 1973 phorate (5%), parathion (46.5%), diazinon (20%) and fenthion (10%) were used. The results are given in Table 6. The conditions of work were poor — work was not mechanized and protective devices were used infrequently. The exposure to anticholinesterase compounds was about 60 days over four months. The measurements were done after approximately 20 days of exposure. Cholines-

Table 5

The mean value of whole blood and plasma cholinesterase activity in agricultural workers expressed in percent of the preexposure values

	April, 1973 After 10 days of exposure		May, 1973 After 20 days of exposure	
	Whole blood	Plasma	Whole blood	Plasma
Mean	100	99	98	98
SEM	± 2.57	± 3.12	± 3.25	± 4.20
N	10	9	8	8

	April, 1974 After 16 days of exposure		April, 1975 After 16 days of exposure	
	Whole blood	Plasma	Whole blood	Plasma
Mean	87	89	95	93
SEM	± 1.49	± 1.47	± 1.08	± 1.65
N	44	43	34	33

terase activities showed no significant trend to decrease, although the lowest activity was obtained in the third measurement (mean = 86% for blood cholinesterase and 75% for plasma cholinesterase). In 1975 the exposure of people employed in another orchard who used Azinphos-ethyl (25%), phosalone (30%) and carbaryl (50%) as insecticides was followed. The agricultural work was completely mechanized except in places where the mixing and dilution of the compounds took place. The workers were exposed to anticholinesterase compounds continuously for only two to three days with fortnight breaks. Table 6 shows that their cholinesterase was practically undiminished, particularly when data are compared with the former group.

The exposure of workers employed in the agricultural application of insecticides is essentially different from that of industrial workers. Work is done in the open with interruptions, and finished products are used.

Four of eight examined workers employed in the orchard spraying (1973) showed and reported some signs and symptoms of poisoning, such as sweating, headache, and nausea. The same symptoms were observed in farm spraymen whose cholinesterase activity was below 70%. Although the symptoms were not typical cholinergic symptoms, it was concluded that they were due to the absorption of a certain amount of anticholinesterase compounds. The workers were in good health and the symptoms cannot be ascribed to any other cause.

Table 6

The mean value of whole blood and plasma cholinesterase activity in orchard spraymen expressed in percent of the preexposure values

	27 April, 1973		26 May, 1973	
	Whole blood	Plasma	Whole blood	Plasma
Mean	100	100	93	89
SEM	± 1.13	± 3.44	± 5.35	± 3.36
N	8	8	8	8

	2 July, 1973		26 May, 1975*	
	Whole blood	Plasma	Whole blood	Plasma
Mean	86	75	94	95
SEM	± 3.82	± 7.24	± 1.35	± 1.47
N	6	6	33	32

	30 May, 1975*	
	Whole blood	Plasma
Mean	97	94
SEM	± 1.26	± 2.35
N	20	20

* after 2—3 days of exposure

Blood picture and exposure to organophosphorus compounds

According to literature data (27, 28), it was expected that increased exposure of the workers employed in the production of organophosphorus insecticides would reduce the total number of leucocytes, and increase the number of lymphocytes in response to a possible allergic reaction of the worker to the insecticide in question. Our results are shown in Table 7. No significant differences in the same workers were noted in the period before and after exposure to organophosphorus compounds. Also, no differences were observed between the exposed and the control group. The results agree with those of *Warnick* and *Carter* (5) and *Ensberg* and co-workers (6), but do not agree with those of *Davignon* and co-workers (27) and *Paccaganella* and co-workers (28).

Table 7

Mean number of leucocytes and lymphocytes in workers exposed to organophosphorus compounds and in control group

Workers (number)	Mean values			
	1966—1969		1970—1973	
	leucocytes	lymphocytes per 100 leuc.	leucocytes	lymphocytes per 100 leuc.
Exposed workers (9)	7270	35	6964	32
Control group (48)	—	—	6164	35

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Sažetak

AKTIVNOST KOLINESTERAZA KRVI U RADNIKA EKSPONIRANIH ANTIKOLINESTERAZAMA. REZULTATI DESETGODIŠNJEG PRAĆENJA

Kontrola radnika zaposlenih u formulaciji antikolinesteraznih insekticida pokazuje da upotreba propisanih zaštitnih sredstava pri radu i pridržavanje higijenskih i sanitarnih odredaba omogućuje zadovoljavajući stupanj zaštite i značajno smanjuje apsorpciju antikolinesteraznih insekticida.

Naša proučavanja potvrđuju da mjerenje aktivnosti kolinesteraze svakog drugog tjedna za vrijeme trajanja intenzivne produkcije pruža jedinu praktičnu mjeru za određivanje stupnja apsorpcije. Na taj način može se na vrijeme uočiti potencijalna opasnost za svakog pojedinog radnika i tako spriječiti opasnost od daljnje apsorpcije.

Bez iznimaka, radnici u kojih su se pojavili kolinergični simptomi otrovanja imali su kolinesterazu pune krvi inhibiranu oko ili više od 50%. Međutim, pritužbe radnika nisu uvijek bile u skladu s inhibicijom kolinesteraze.

U poljoprivrednih radnika eksponiranih insekticidima u pravilu inhibicija kolinesteraze nije premašila deset posto. U nekoliko osoba kojima je inhibicija kolinesteraze premašila 40% bile su prisutne i subjektivne smetnje.

Čini se da dugotrajna ekspozicija antikolinesteraznim spojevima nema učinka na broj krvnih stanica u perifernoj krvi.

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