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ORGANOPHOSPHATE–INDUCED CHRONIC TOXICITY IN OCCUPATIONALLY EXPOSED WORKERS

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ABSTRACT

Organophosphate chronic toxicity has been evaluated in this study. Biological screening for organophosphate insecticide-exposed workers is mostly recommended for mixers, loaders, formulators and spraymen. We have studied 17 occupationally exposed persons to pesticides. Using Ellman's colorimetric method, their plasma cholinesterase activities have been measured. Results show that the appearance of some of the symptoms of chronic organophosphate toxicity depends on the extent of plasma cholinesterase activity reduction. Our results also indicate that headache, weakness, nervousness, memory difficulty, tremors, insomnia and dizziness are the main problems demonstrated in these workers.

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INTRODUCTION

An estimated 4 to 5 million persons work in agriculture; among them mixers, loaders, applicators and other workers who directly handle agricultural chemicals are at highest risk for pesticide-related illnesses.

Poisoning with organophosphate insecticides (OP) is common among pesticide workers.[1] Measurement of plasma cholinesterase (ChE) is of value in monitoring low levels of exposure to OP esters.[4] Routine monitoring of OP exposed workers
used for many years to identify workers at risk for poisoning before the occurrence of clinical symptoms.[1] Thus poisoning can be prevented by improving working conditions and removing those workers with low ChE activity from exposure.[1] Measurement of pre-exposed ChE levels is also important, because sometimes there may be persons who have mild symptoms similar to OP poisoning (e.g., headache, nausea, lightheadedness) and low normal ChE activity, making the diagnosis difficult.[1] In addition, clinicians supervising ChE screening programs for workers exposed to OPs who have no baseline measurements are faced with the dilemma of allowing over-exposed workers at risk of poisoning to continue to be exposed to OPs.[1] In this study we have measured plasma ChE activity in three separate assays and evaluated the relationship between ChE reduction and occurrence of symptoms of OP chronic toxicity.

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MATERIAL AND METHODS

Dithionitrobenzoic acid was purchased from Merck, Germany, and KH_2PO_4, K_2HPO_4 and acetylthiocholine iodide from Sigma, USA.

The study population consisted of 17 pesticide-exposed male workers from whom six were OP formulators. These workers were active in 5 work shifts weekly starting at 7:30 am and ending at 4 pm. The factory produces aproximately 20 organo phosphate and 6 non-organophosphate compounds as pesticide. Thirty healthy males who had never been exposed to OPs were selected as the control group. None of

Table I. Mean plasma ChE activity in insecticide formulators, obtained in each sampling.

Monitoring No.	N	Mean plasma ChE activity (KU/L)	SD	SE	CV (%)	Normal range (KU/L)	Depression of ChE (as % of lower normal limit)
1	6	2.46*	0.73	0.3	26.7	2.66-4.75	8
2	6	1.57*	1.17	0.48	67.8	"	41
3	6	2.65*	0.85	0.35	29	"	1

* Reduction of ChE activity is statistically significant, $P < 0.05$.
SD = Standard deviation.
SE = Standard error.
CV = Coefficient of variation.

Table II. Mean plasma ChE activity in non-formulator workers, obtained in each sampling.

Monitoring No.	N	Mean plasma ChE activity (KU/L)	SD	SE	CV (%)	Normal range (KU/L)	Depression of ChE (as % of lower normallimit)
1	11	3.20*	0.87	0.26	26.1	2.66-4.75	-
2	11	3.04*	0.90	0.27	26.6	"	-
3	11	2.73*	0.79	0.23	26.9	"	-

* Reduction of ChE level is not statistically significant.

them had been sampled for ChE assay before exposure. Sampling was done at three time intervals: when production had diminished to its minimum, when it had increased to its maximum capacity and when production was low. Eleven non-formulator workers were also sampled. Two different questionnaires were prepared[5] and all of the workers were asked about their history of diseases, poisoning and symptoms of chronic OP toxicity. Their plasma ChE activity was measured using Ellman's colorimetric method.[3] Each worker was sampled and blood specimens were centrifugated and the plasma phase was separated. For all of the samples, 10 µl of plasma was added to 3 ml of solution containing the indicator, dithionitrobenzoic acid (0.25 mmol) and buffer. KH_2PO_4 and K_2HPO_4 (75 mmol). Finally, 10 µl of substrate, acetylthiocholine iodide (Sigma, USA) was added to them and the changes in absorbance (reflecting ChE activity) were read using a Shimadzu model UV-160 double beam ultraviolet-visible spectrophotometer. The results have been expressed as mean ± SE and the statistical differences assayed according to Student's t-test. The accepted level of significance was from $P < 0.05$.

RESULTS

The mean age of the workers was 30, and duration of employment ranged from 3 months to 7 years. 35% of the workers reported poisoning at some time in the past, although no one had required treatment during the 6 months before this study. Mean plasma ChE activity in insecticide formulators and non-formulators has been shown separately for each group (Tables I, II). Mean plasma ChE levels of controls were from 2.66 to 4.75 KU/L (SD = ± 1.044, n = 30). The mean plasma ChE level among exposed formulators in each monitoring was clearly lower than that of non-formulators (Table III). Reduction of ChE activity in formulators with respect to its level in controls was noticeable.

Table III. Comparison of the mean plasma ChE activity in pesticide formulator and non-formulator workers.

Monitoring No.	Mean plasma ChE activity (KU/L)	SE
1	F: 2.46 nF: 3.20	0.3 0.26
2	F: 1.57 nF: 3.04	0.48 0.27
3	F: 2.65 nF: 2.74	0.35 0.24

(F) formulators
(nF) non-formulators
* $P < 0.05$.

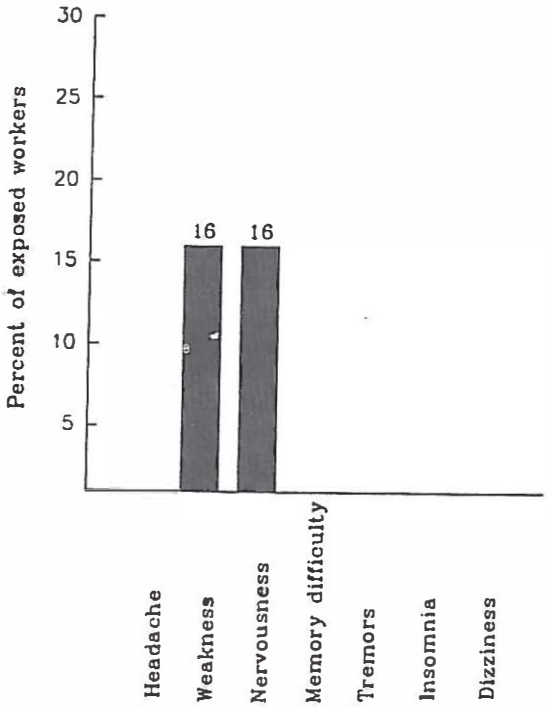

Fig. 1. The appearance of symptoms of chronic OP toxicity, when the ChE level = 2.46 ± 0.3 KU/L.

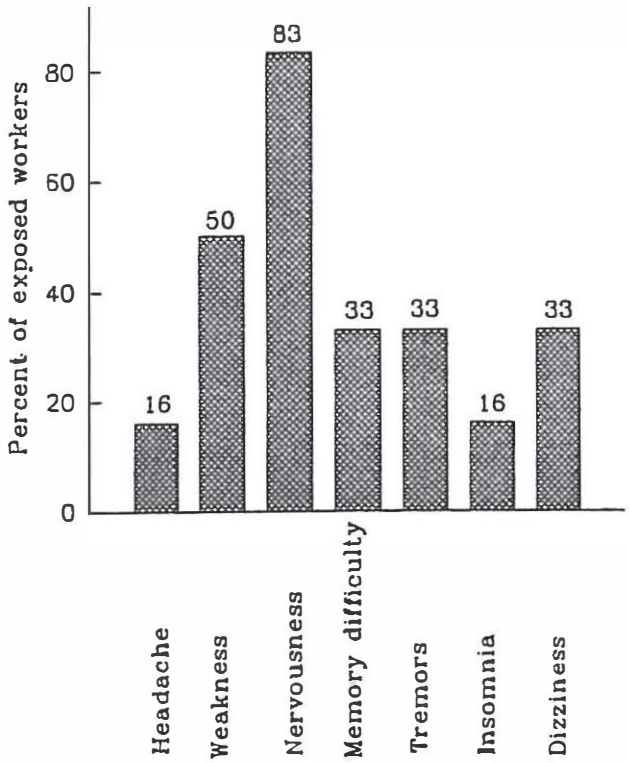

Fig. 2. The appearance of symptoms of chronic OP toxicity, when the ChE level = 1.57 ± 0.48 KU/L.

Table IV. Occurrence of symptoms[5] of chronic OP poisoning in pesticide formulators (n = 6).

Symptoms	First Monitoring (%)	Second Monitoring (%)	Third Monitoring (%)
Headache	-	16	33
Weakness	16	50	16
Nervousness	16	83	33
Memory difficulty	-	33	16
Tremors	-	33	-
Insomnia	-	16	-
Dizziness	-	33	50

Table V. Occurrence of symptoms of chronic OP poisoning in pesticide non-formulators (n=6).

Symptoms	First Monitoring (%)	Second Monitoring (%)	Third Monitoring (%)
Headache	9	18	18
Weakness	18	36	27
Nervousness	18	27	18
Memory difficulty	-	18	9
Tremors	-	18	18
Insomnia	-	-	9
Dizziness	-	18	18

In Tables IV and V the extent of symptoms of chronic OP toxicity in formulator and non-formulator workers are shown. These results suggest that the appearance of chronic toxicity symptoms is accompanied by reduction of the ChE level (Fig. 4, r = -0.99).

The relationship between chronic OP toxicity manifestations and ChE activity among formulators are shown in Figures 1,2, and 3.

DISCUSSION

ChE activity determination has been used since the 1950s to document acute poisonings and patterns of chronic

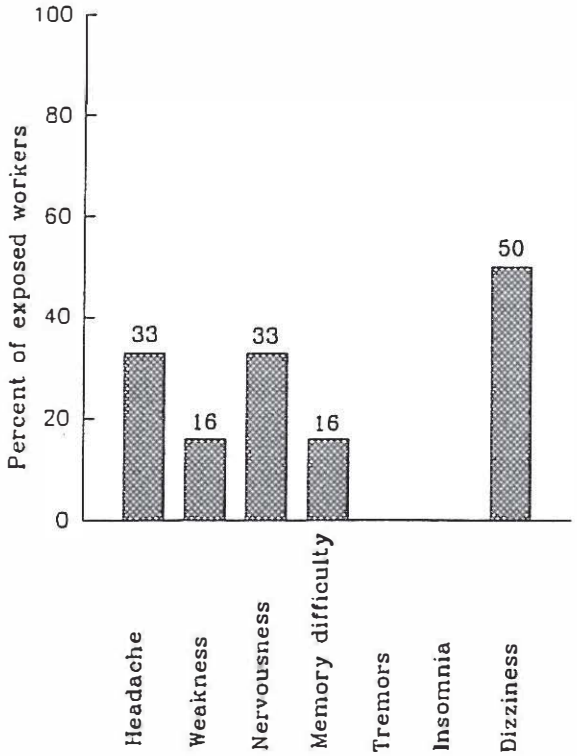

Fig. 3. The appearance of symptoms of chronic OP toxicity, when the ChE level = 2.65 ± 0.35 KU/L.

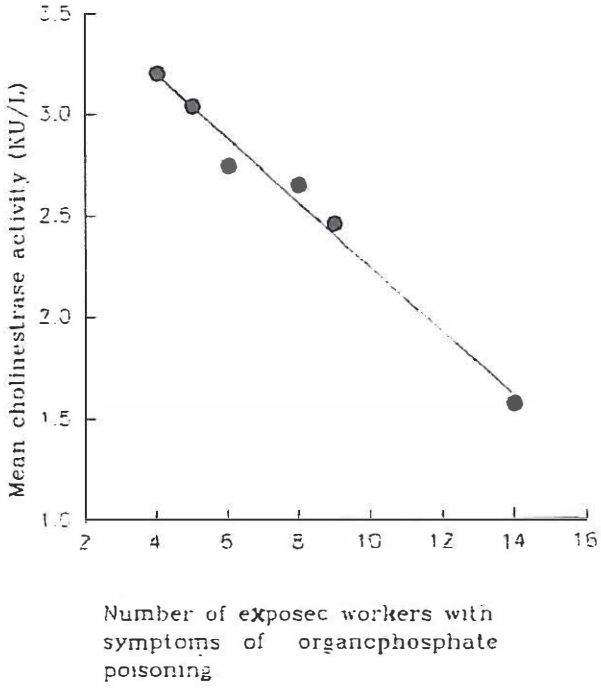

Fig. 4. Correlation between plasma ChE activity and the extent of OP-induced toxic symptoms among exposed workers (r = - 00.99).

exposure among pesticide applicators.[2] The appearance of symptoms depends mostly upon the rate of fall in ChE activity, not the absolute level of activity reached.[2] Workers may exhibit 70% to 80% inhibition of both ChE enzymes after several weeks of moderate exposure without manifesting cholinergic symptoms.[2] Both plasma and erythrocyte ChE levels have been used as indices of exposure for assessment of low level chronic residue exposure among field workers.[2] But inhibition of erythrocyte ChE is a better indicator of biological effects than serum ChE, since it is analogous to the enzyme found in nervous system tissues.[2] Regeneration of plasma activity is more likely to be seen during short periods (because of its more rapid rate of recovery)[2] and its measurement may be of value in monitoring low levels of exposure to OP esters.[4] Therefore, we chose plasma ChE measurement for evaluation of chronic OP toxicity in exposed workers. Since the workers did not have baseline values, normal ChE activity (2.66-4.75 KU/L, measured in healthy non-exposed control groups) was estimated for each subject. With respect to our results, after 54 days plasma ChE activity decreased to 59% of its level and after 45 days regenerated to 99%. From the symptoms of chronic OP toxicity (headache, weakness, nervousness, memory difficulty, tremors and dizziness) only weakness and nervousness were reported by 16% of workers initially. When enzyme activity was depressed to 41% (at the second monitoring), appearance of many symptoms increased in workers. In the third monitoring (99% of normal ChE activity), the extent of complained symptoms had diminished. Comparison of obtained results shows that the appearance of symptoms of chronic OP toxicity depends on the extent of enzyme activity depression (Fig. 4). Also, the appearance of toxic symptoms in formulators (persons who are directly exposed to OP insecticides) was much more common than non-formulators and their enzyme activity was lower. Depending upon the conditions of the work area, the workers' own attention to hygiene, the toxicity of insecticides used and the actual duration of exposure, the ChE tests were performed. The workers of this factory were using proper gloves, masks and clothing and other standard safety facilities. All of the production lines had standard ventilation systems operating throughout the whole work shift, but the odor of poisons was distributed in every direction. The workers were using showers daily and at the end of the work shift. Due to high exposure to pesticides and their ability to be readily absorbed through intact skin, ChE activity depression and symptoms of chronic toxicity were obviously confirmed in some of the workers.

In many cases where various routes of exposure have been quantified, skin absorption has a much greater potential for exposure than inhalation.[6] Therefore, care must be taken to minimize the frequency and duration of skin exposure with these materials.

Suitable work safety clothing must be provided, with

employers responsible for its laundering. Routine washing of hands, face and neck prior to breaks or lunch must be emphasized. Daily showers at the end of the work shift are required. Employee training should be designed to influence employees to comply with appropriate work practices.[6] Such training should be conducted for all newly-hired persons and periodically for all employees.[6]

It seems that one of the most important responsibilities of an agricultural chemical manufacturer is to provide periodic toxicity evaluation programs and facilities to control employees' health and hygienic conditions.

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