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NEUROTOXIC EFFECTS IN WORKERS EXPOSED TO LEPTOPHOS (PHOSVEL®)

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ABSTRACT

NIOSH was advised by a Federal EPA official of potential health problems at Velsicol's Bayport, Texas plant among employees who were involved in the manufacture and packaging of leptophos. Twelve cases of serious neurological disorders had been identified by a medical consultant to the company. This plant also manufactured a resin called Klyrvel, at about the time they produced leptophos. n-Hexane, a known neurotoxic solvent that can cause neurologic effects, was used in considerable quantities in the production of the resin during the period 1971–1975. The plant had experienced a high rate of employee turnover and many workers who had been exposed to leptophos and other chemicals were no longer employed by the Velsicol Company. NIOSH considered it essential that a health study be conducted of all current and former workers.

Between January and April, 1977, 155 persons reported for comprehensive examinations that evaluated general physical status, neurological status, and measures of neuromuscular, ophthalmological, psychological, and biochemical function. Additionally, industrial and medical records were reviewed and case studies compiled to define the circumstances that led to reported serious neurological disturbances in certain workers.

NIOSH's medical evaluation showed that a substantial number of those examined were found to have neurological, electromyographic, electroneurographic, and psychological performance abnormalities ranging from slight to serious. A causal association of these findings with worker exposure to leptophos is difficult to establish in individual cases because of the presence of other neurotoxic agents such as n-hexane. A comparison, however, of the medical findings with available "normal values" suggests a worker population whose health has been adversely affected.

The National Institute for Occupational Safety and Health (NIOSH) is responsible for helping ensure that every person in the Nation has safe and healthful working conditions. To accomplish this end, the Institute engages in research on occupational safety and health problems including evaluation of hazards and toxicity determinations. One of the many hazards considered for investigation by the Institute's Division of Surveillance, Hazard Evaluations, and Field Studies (DSHEFS) is multiple exposure of workers to neurotoxic chemicals.

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In late January, 1976, NIOSH was advised by a Federal EPA official of potential health problems among employees at the Velsicol Chemical Company's Bayport Plant in Houston, Texas; a plant involved in the manufacture and packaging of leptophos [0-(4-bromo-2,5-dichlorophenyl) 0-methyl phenylphosphonothioate], also known by the trade name "Phosvel". At that time leptophos was registered by EPA primarily for export with only limited experimental use allowed in this country. Velsicol, however, was applying to EPA for full domestic use of leptophos on several crops and for further experimental use. The increased domestic use was being questioned because of scientific reports that leptophos was neurotoxic to mammals and birds.

A NIOSH health hazard evaluation team visited the plant and conducted a walk-through inspection which included interviews and medical screening examinations of current employees. During this visit only two of the twenty-six workers NIOSH examined displayed signs and symptoms of mild neurological dysfunction. However, 12 cases of serious neurological disorders had been identified in June, 1975, by a medical consultant to the company.

A number of other potentially toxic chemicals were used in the manufacture of leptophos. One of these, toluene, is a neurotoxic solvent. This plant also manufactured a resin called Klyrvel, about the time they produced leptophos. n-Hexane, a solvent that can cause neurologic effects, was used in considerable quantities in the production of the resin during the period 1971–1975.

Since the plant had experienced a high rate of employee turnover, many workers who had been exposed to leptophos and other chemicals were no longer employed by the Velsicol Company. For example, 11 of the 12 workers previously reported to be seriously affected were not employed at the time of our visit. For these reasons, when NIOSH announced on December 1, 1976, that we would conduct a medical study of all present employees at the Bayport plant, we included former employees as well.

Nearly all of the 301 current and former employees were notified of the availability of medical examinations. A contract was awarded to the Kelsey-Seybold Clinic in Houston, Texas, to conduct a comprehensive medical examination based on an extensive protocol developed by NIOSH. Between January and April, 1977, 155 persons reported for the comprehensive examinations that evaluated general physical status, neurological status, and measures of neuromuscular, ophthalmological, psychological, and biochemical function (Part I – Medical Examination).

To evaluate the circumstances that allegedly led to workers experiencing serious neurological disorders and to fully document the medical findings in these workers, an evaluation was made of their medical files, production data for the Velsicol Chemical plant and other information made available through workers' compensation files. Several of the more seriously affected workers participated in NIOSH's medical examination study. Therefore, the current health status of these workers and the possibility of permanent damage could be evaluated. The results of this comparison are included in the medical findings of Part I – Medical Examination. The findings of the case studies of alleged

leptophos exposure are reported in Part II of this report. Recommendations resulting from NIOSH's health survey comprise Part III of this study and focus on early detection and prevention, industrial hygiene practices, medical surveillance and monitoring and medical examinations for evaluating reversibility of effects.

I – MEDICAL EXAMINATION

METHODOLOGY

At the Clinic, the participating individuals were received and identified. The medical examination was explained to him (her) and the informed consent to participate voluntarily was obtained. A detailed occupational history, with particular emphasis on exposure to pesticides and other chemicals, a health history that emphasized neurological symptoms, and a history of smoking and drinking habits were obtained[19].

Physical examination

The participants were examined by one of the two physicians conducting medical examinations to assess their general physical status. Height, weight, pulse rate, and blood pressure were measured. The head, eyes, ears, nose, mouth, and throat were examined. Chest sounds (heart and lungs) were noted and the abdomen was palpated. The general condition of the skin and the limbs was also checked[19].

Ophthalmological examination

The ophthalmological examination was done by one of the two participating ophthalmologists. The eye lids, cornea, lens, retina, pupillary reflex, and other cardinal items were examined. The visual field was tested on two axes using a perimeter. The ocular pressure was checked for glaucoma using a noncontact tonometer[19].

Chest X-ray

A 36-X-43 cm PA (posterior-anterior) chest X-ray was taken and read by a radiologist.

Laboratory tests

The laboratory tests that were run included urinalysis, complete blood count (CBC), serology, sequential multiphasic analysis (SMA), and red blood cell cholinesterase (RBC-ChE) determination. Included in the SMA were analyses for glucose, sodium, potassium, chloride, carbon dioxide, blood urea nitrogen (BUN), creatinine, calcium, phosphorus, uric acid, total protein, albumin, globulin, iron, total bilirubin, alkaline phosphatase, serum glutamic pyruvic transaminase (SGPT), lactic dehydrogenase (LDH), cholesterol, and triglycerides.

Neurological examination

A neurological examination was done by one of the three participating neurologists. Tests for the following were included in the examination: mental status (orientation, memory, and alertness), cranial nerves, deep tendon reflexes, plantar reflex (Babinski's sign), general motor survey (walk on toes and heels), muscle coordination, gait and stance, muscle tone and strength, tremor, and sensory survey.

The evaluation of each participant's mental status included the following tests of memory: Serial 7's, 6 Digits Forward, 5 Digits Backward, and Sentence Retention. Criteria used to assess a satisfactory result in these tests were: greater than 11 correct for Serial 7's, more than 3 correct in 6 Digits Forward, more than 2 correct in 5 Digits Backward, and success in one of three trials in Sentence Retention.

The results of the aforementioned mental status evaluation were *not* used to classify participants into abnormal or slightly abnormal categories.

Criteria for classification

For the purpose of the neurological examination, each individual was classified as follows:

1. Neurologically abnormal if:
1.1 plantar reflex (Babinski's sign) was positive (extensor), or
1.2 spastic gait was observed, or
1.3 increased deep tendon reflex was present and accompanied by an EMG abnormality (altered insertional activity) of the extensor digitorum brevis or tendon reflex was noted and accompanied by abnormal motor unit potentials of the extensor digitorum brevis muscle or abductor hallucis muscle, or
1.4 decreased deep tendon reflex was noted and accompanied by abnormal motor unit potentials of the extensor digitorum brevis muscle or abductor hallucis muscle, or
1.5 decreased sensorium was noted and accompanied by abnormal latency in median, ulnar or sensory nerve, or
1.6 any three of the following four were positive – increased or decreased deep tendon reflex, nystagmus, decreased sensorium, and muscle weakness.

2. Neurologically slightly abnormal if any abnormality not qualifying for the "abnormal category" was noted in:
2.1 deep tendon reflex, or
2.2 muscle strength or tone, or
2.3 sensory testing.

3. Neurologically normal if none of the above symptoms/signs were evidenced.

Psychological performance measures

Exposure of humans to neurotoxic chemicals can result in degraded performance on tests psychological function. Indeed, such behavioral observations are often among the earliest indications of the effects of a neurotoxic

agent[18]. In order to evaluate the extent to which Velsicol employees might exhibit impaired psychological performance, a battery of eight tests was administered to each participant in the study. This battery of tests was chosen to evaluate, in an objective manner, each individual on cognitive, psychomotor, and perceptual-motor performance and included the following tests: 1) Santa Ana Dexterity (dexterity and eye-hand coordination), 2) Choice Reaction Time (response speed), 3) Time-Shared Performance (divided attention), 4) Digit Span (memory), 5) Digit Symbol (memory efficiency), 6) Block Design (perceptual organization), 7) Neisser Letter Search (visual filtering), and 8) Raven Progressive Matrices (visual organization).

At the time of the examination, each worker was made familiar with each of the eight psychological performance tests through instruction by a psychological aid[19]. Following instruction in performance of a particular test, the worker was given one training trial, following by an actual data collection trial. A tape recorder containing instructions for each test was used to standardize the instructions given to the workers. Instructions were given in either English or Spanish, depending upon the worker's choice.

Criteria for classification

The psychological performance results for each worker were compared to the results from the total study population of 130. Group means were calculated for each psychological performance test. Each worker's results from each psychological test (e.g., Digit Span) were then compared with the group mean score. If the worker's performance was one or more standard deviations different from the group mean and in the direction of impaired performance, then the worker was defined as having failed the particular test under consideration.

As discussed previously, eight psychological performance tests were administered to each worker. Due to an equipment malfunction, however, the data from the Time-Shared Performance test were not recorded for all workers. The psychological performance results from the remaining seven tests were reviewed, and the following classifications established with criteria below:

1. *Abnormal*–any worker who failed five or more of the seven psychological performance tests.
2. *Slightly* abnormal–any worker who failed four of the seven tests.
3. *Normal*–all workers with fewer than four failures.

Visual function measures

Three additional tests of visual function were added to the clinical ophthalmological examination given to each worker. These additional tests were added to provide as complete a picture as possible of each person's visual function and in recognition of the fact that mild to moderate exposure to organophosphate compounds can produce blurred vision and marked miosis[8].

Results of these tests were recorded on the ophthalmological examination form. Tests of visual function included: visual field, critical flicker frequency (CFF) and color vision.

Electroneurography and electromyography

Electroneurography (ENG) and electromyography (EMG) provide sensitive and objective methods of detecting impairment of nerve and muscle function. Since Velsicol employees were reported to have worked with neurotoxic chemicals known to cause peripheral neuropathy, an ENG/EMG examination was administered to each participant in the study to determine the degree and permanency of peripheral nervous system impairment. One hundred and thirty-six participants were administered ENG/EMG tests at the Kelsey-Seybold Clinic, Houston, Texas. Because of scheduling problems, nineteen participants were sent to the St. Luke's Episcopal Hospital for ENG/EMG tests. A description of the ENG/EMG examination and the criteria used by NIOSH to classify ENG/EMG results as normal, slightly abnormal or abnormal follows:

Electroneurography

For the ENG examination sensory and/or motor nerve conduction studies were carried out on the following nerves: 1) median motor/sensory, 2) ulnar motor/sensory, 3) peroneal motor, 4) posterior tibial motor and 5) sural sensory. Although not routinely measured by the laboratories selected for the study, skin temperatures were recorded at proximal and distal stimulation points with surface thermocouples manufactured by the Yellow Springs Instrument Company and supplied to the clinics by NIOSH. Proximal and distal latency, amplitude of the sensory or motor action potential, and distance from stimulation to recording site were recorded on a standardized form. The sural sensory nerve response was recorded at 7, 14 and 21 cm.

For classification of each subject into a normal or abnormal category, the "normal values" used were provided to NIOSH by Kelsey-Seybold and St. Luke's Episcopal Hospital[19]. The NCV data were corrected according to DeJesus' temperature correction formula[3]. A few subjects with low limb temperatures were critically reviewed to avoid any misclassification resulting from an abnormally low limb temperature.

Electromyography

For the EMG examination, electrical activity was recorded from the following muscles: 1) extensor digitorum brevis, 2) abductor hallucis, 3) tibialis anterior, 4) gastrocnemius, 5) quadriceps, 6) abductor pollicis brevis, and 7) first dorsal interosseous. For each muscle tested, information was recorded on a standardized format for the following: insertional activity, positive waves, fasciculations, fibrillations, abnormal motor unit potentials (amplitude, duration, polyphasics), and firing patterns.

Criteria for classification. The following criteria were used by NIOSH to classify the electrophysiological measures as normal, abnormal, or slightly abnormal.

1. Electromyography

1.1 Normal: Motor unit potentials, firing pattern, insertional activity, positive waves, fasciculations, and fibrillations were all normal.

1.2 Slightly abnormal: Motor unit potentials were normal but the EMG revealed an altered firing pattern (other than full interference), decreased or increased insertional activity, increased positive waves, increased fasciculations, or increased fibrillations.

1.3 Abnormal: Abnormal motor unit potentials detected in one or more of the seven muscles examined (this measure reflects the degree of peripheral sprouting of terminal nerve fibers and is the single most important way in which the nervous system attempts to compensate for loss of motor units. Altered firing pattern, insertional activity, increased positive waves, fasciculations, or fibrillations may have been present in addition to abnormal motor unit potentials).

2. Electroneurography

2.1 Normal: All nerve conduction velocities, distal latencies and amplitudes of the motor nerves, and latencies of the sensory nerves tested were within the normal ranges provided by the Kelsey-Seybold Clinic and St. Luke's Episcopal Hospital[19].

2.2 Slightly abnormal: Values in 2.1 were normal, but out-of-range values were reported for one or more of the eight measurements of the distal latency or amplitude of the median, ulnar, peroneal or posterior tibial nerves.

2.3 Abnormal ENG: Nerve conduction velocities for the median, ulnar, peroneal or posterior tibial motor nerves were classified abnormal if they were lower than the normal values reported by the Kelsey-Seybold or St. Luke's Episcopal Hospital. Latencies for the median, ulnar or sural sensory nerves were considered abnormal if the latency values were higher than the normal values reported by the two clinics noted above. An increase in latency is the single most important pathological change in the sensory electroneurogram. An ENG result was thus classified as abnormal if one or more of these seven measures was found abnormal.

3. Effects of temperature and age on conduction velocity

Studies indicate that the conduction velocity may be lowered 2–2.4 m/sec for each drop in temperature of 1 °C[5]. As noted earlier, all participants were required to wait in the clinic (temperature equilibration) before ENG/EMG testing. Additionally, surface skin temperatures were measured and used to identify participants with extremely low or high limb temperatures.

Previous NIOSH studies have shown age to be a factor which influences conduction velocity[7]. Therefore, statistical comparisons of Velsicol participants were performed with age as a covariate.

DATA ANALYSIS AND RESULTS

The questionnaire results and laboratory results for each of the 155 participants were coded and entered into the computer. Although the summary tables include results for all 155 participants, 25 of these (including four female participants) were excluded from the statistical analyses. Twenty-one males were excluded because of a "confounding factor". A "confounding factor" was defined to be 1) diagnosed diabetes or 2) high blood glucose, or 3) excessive alcohol consumption. Of these 21, 15 were diabetic or had high blood glucose (or both) and six reported excessive alcohol consumption. The following criteria were used to identify diabetics, those having high blood glucose values, and those with excessive consumption of alcohol:

Diabetics: Affirmative response to the directed question "Have you been told by a doctor you have this condition?"

Blood glucose: Any value greater than 135 mg/100 ml.

Excessive alcohol: A response greater than that shown for any of the following questions from the questionnaire:

a) "On the average, how many beers do you drink per day?" 6
b) "About how many bottles of wine do you drink per week?" 10
c) "About how many cocktails or drinks of other liquor do you have per week?" 42

A significance level of 5% was used to determine statistical significance in all of the following statistical analyses.

Work history

The Velsicol work history was provided by the company and verified by the study participant at the time of the interview. Pre– and post– Velsicol occupational histories, as reported by the participants, were taken by the interviewer. These occupational histories were used to classify each participant into one of three exposure groups according to three time periods. These groups were:

Group I: Worked at Velsicol (or was sub-contractor to Velsicol) before October, 1971, only.

Group II: Worked at Velsicol (or was sub-contractor to Velsicol) all or part of the time between October, 1971, and March, 1976.

Group III: Worked at Velsicol (or was sub-contractor to Velsicol) after March, 1976, only.

Group I had possible exposure to methyl parathion plus other chemical exposures (except leptophos); Group II had possible exposure to leptophos plus other chemical exposures; and Group III had possible exposure to EPN (0-ethyl 0-4-nitrophenyl phenylphosphonothioate) and other chemical exposures (except leptophos). With this definition of exposure, the number of workers in each group is as follows:

	All study participants (n = 155)	Screened participants (n = 130)
Group I	21	17
Group II	119	101
Group III	15	12

The small number of workers in Groups I and III should be noted.

Styrene and/or n-hexane exposure at Velsicol and other than at Velsicol occurred (as reported by participants) across all three exposure groups (Table 1).

TABLE 1
Number of reported hexane and/or styrene exposed participants

Exposure \ Group	Exposure group I n = 21			II n = 119			III n = 15			Total (n = 155)		
	Yes	No	Dk*	Yes	No	Dk	Yes	No	Dk	Yes	No	Dk
Hexane exposure at Velsicol	4	9	8	73	22	24	2	4	9	79	35	41
Hexane exposure other than Velsicol	1	18	2	15	102	2	2	13	0	18	133	4
Styrene exposure at Velsicol	5	8	8	59	29	31	3	6	6	67	43	45
Styrene exposure other than Velsicol	4	15	2	21	95	3	3	12	0	28	122	5

*Dk = participant did not know.

A total of 79 subjects reported n-hexane exposure at Velsicol (four didn't know). It appeared that no participant was exposed only to a single compound and that all had multiple chemical exposures. Exposure to n-hexane is particularly important since some of the health effects due to exposure to this compound[16] are indistinguishable from those due to exposure to leptophos. Exposure to several other neurotoxic chemicals is also thought to cause similar health effects. Non-Velsicol related exposure to these other chemicals, as reported by the participants, is summarized in Table 2. In summary, the occupational work histories indicate a worker population that has been exposed to many chemicals at a wide range of jobs.

TABLE 2
Number of reported chemical (other than hexane and styrene) exposures.

Exposure \ Group	Exposure group I n = 21			II n = 119			III n = 15			Total (n = 155)		
	Yes	No	Dk*	Yes	No	Dk	Yes	No	Dk	Yes	No	Dk
1. Metallic mercury	2	18	1	7	108	4	0	15	0	9	141	5
2. Methyl mercury	0	18	3	0	114	5	0	15	0	0	147	8
3. Methyl chloride	4	14	3	5	108	6	1	13	1	10	135	10
4. Arsenic	0	19	2	4	113	2	0	15	0	4	147	4
5. Thallium	0	19	2	0	117	2	0	15	0	0	151	4
6. Acrylamide	0	19	2	1	116	2	0	15	0	1	150	4
7. Trichloroethylene	3	17	1	13	99	7	1	13	1	17	129	9
8. Methyl bromide	0	19	2	2	114	3	1	14	0	3	147	5
9. Carbon monoxide	4	16	1	15	102	2	2	13	0	21	131	3
10. Lead	5	15	1	12	104	3	2	13	0	19	132	4
11. Solvents other than n-hexane (e.g. benzene)	9	11	1	37	80	2	5	10	0	51	101	3
12. Pesticides (other than leptophos, methyl parathion, or EPN)	2	18	1	10	108	1	1	14	0	13	140	2

*Dk = participant did not know.

Age

The average of the population is 32.2 years (Table 3). The mean ages of the exposure groups were found to be significantly different (using the analysis of variance technique). The mean age of Group I (37.9 years) is significantly higher

TABLE 3
Summary of age by exposure group.

Age \ Group	Exposure group I n = 21 n	(%)*	II n = 119 n	(%)	III n = 15 n	(%)	Total (n = 155) n	(%)
< 20 years	1	(5)	0	(0)	1	(7)	2	(1)
20–40 years	14	(67)	98	(82)	13	(87)	125	(81)
> 40 years	6	(28)	21	(18)	1	(6)	28	(18)
X ± S.D. (years)	37.9 ± 8.8		32.0 ± 9.3		27.8 ± 6.7		32.3 ± 8.6	

*% of exposure group in age category

than that of Group III (27.8 years). Therefore, for statistical analyses involving variables that are thought to be age dependent, age was used as a covariate or an age-adjustment was made.

Educational level

Because educational level is thought to affect the outcome of four of the psychological tests administered, educational level was used as a covariate when appropriate. However, as can be seen in Table 4, the educational level among groups was not significantly different.

TABLE 4
Descriptive statistics of educational level by group.

Group / Educational level	Exposure group I n (%)	II n (%)	III n (%)	Total (n = 155) n (%)
Level ≤ 8 years (elementary)	2 (9)	4 (4)	0 (0)	6 (4)
8 < Level ≤ 12 years (secondary)	11 (52)	70 (59)	10 (67)	91 (59)
12 < Level ≤ 16 years (college)	8 (38)	37 (31)	5 (33)	50 (32)
Level > 16 years (graduate work)	0 (0)	7 (6)	0 (0)	7 (4)
X ± S.D. (years)	12.0 ± 2.1	12.4 ± 2.6	12.3 ± 2.0	12.4 ± 2.4

Blood and urine tests

The descriptive statistics (mean and standard deviation) for blood and urine tests results are shown in Table 5. These statistics are given for each exposure group and for the total sample population. The normal ranges provided by the processing laboratory were used to determine the number of out-of-range values (Table 6). The association of the number of out-of-range values and exposure group was tested for each variable with the chi-square statistic. The tests of association were non-significant for each variable. The number of out-of-range non-fasting triglyceride values (31%) appears to be in excess of what one would expect in the general population.

In the sub-population of 130 (which excluded both males with confounding factors and all females), the hypothesis of equal means among exposure groups was tested by means of analysis of variance (ANOVA) for the following variables: SGOT, SGPT, BUN, cholesterol, triglycerides, LDH and cholinesterase. The results show no statistically significant difference among groups for any of the variables tested.

The summary statistics for blood count values by exposure group are shown in Table 7. There is no statistically significant difference among group means and the means were found not to differ significantly from the "normal" mean values provided by the laboratory.

TABLE 5
Summary by exposure group of results of biochemical measurements.

Variable \ Group	Exposure group I (n = 21) $\bar{X}$	S.D.	II (n = 119) $\bar{X}$	S.D.	III (n = 15) $\bar{X}$	S.D.	Total (n = 155) $\bar{X}$	S.D.
Glucose (mg/100 ml)	106.7	24.7	102.3	34.6	99.8	17.6	102.6	32.0
Sodium (mmol/liter)	139.7	1.4	139.8	2.4	139.1	2.1	139.8	2.2
Potassium (mmol/liter)	4.2	0.3	4.2	0.3	4.3	0.3	4.2	0.3
Chloride (mmol/liter)	104.0	1.7	103.2	3.3	102.7	2.3	103.3	3.0
CO_2 (mmol/liter)	26.4	1.3	27.1	1.9	26.2	1.7	26.9	1.8
BUN (mg/100 ml)	12.7	3.5	12.9	4.1	12.3	2.1	12.9	3.8
Creatinine (mg/100 ml)	1.0	0.1	1.0	0.2	1.0	0.2	1.0	0.2
Calcium (mg/100 ml)	9.9	0.5	10.0	0.4	10.1	0.5	10.0	0.4
Phosphorous (mg/100 ml)	3.1	0.4	3.3	0.4	3.8	1.6	3.4	0.6
Uric acid (mg/100 ml)	5.9	1.1	5.9	1.2	5.8	0.8	5.9	1.1
Total protein (g/100 ml)	7.2	0.3	7.3	0.4	7.4	0.3	7.3	0.4
Albumin (g/100 ml)	4.4	0.2	4.4	0.2	4.5	0.2	4.4	0.2
Iron (μg/100 ml)	110.2	42.2	103.6	33.6	110.7	41.3	105.2	35.4
Total bilirubin (mg/100 ml)	0.7	0.2	0.6	0.3	0.7	0.2	0.6	0.2
Alkaline phosphatase (U/liter)	68.9	18.0	74.6	19.0	80.4	22.2	74.3	19.3
SGOT (U/liter)	27.9	12.8	27.4	11.1	29.7	9.6	27.6	11.2
SGPT (U/liter)	29.8	22.0	25.8	18.0	25.3	15.1	26.3	18.2
LDH (U/liter)	161.4	30.1	161.0	24.0	170.1	23.9	161.9	24.8
Cholesterol (mg/100 ml)	200.3	35.0	203.1	54.4	204.9	36.6	202.7	50.3
Triglycerides (mg/100 ml)	147.2	88.9	156.0	105.9	125.1	86.5	151.3	101.9
Globulin (g/100 ml)	2.8	0.3	2.9	0.3	2.9	0.2	2.9	0.3
A/G	1.6	0.1	1.6	0.2	1.6	0.2	1.6	0.2
Cholinesterase–RBC ($\triangle$pH)	0.9	0.1	0.9	0.1	0.9	0.1	0.9	0.1

TABLE 6
Summary of out-of-normal range biochemical values.

Variable \ Group	Exposure group I (n = 21) n	(%)	II (n = 119) n	(%)	III (n = 15) n	(%)	Total (n = 155) n	(%)
Glucose (mg/100 ml)	1	(5)	8	(7)	1	(7)	10	(6)
BUN (mg/100 ml)	0	(0)	1	(<1)	0	(0)	1	(<1)
SGOT (U/liter)	3	(14)	8	(7)	2	(13)	13	(8)
SGPT (U/liter)	3	(14)	11	(9)	2	(13)	16	(10)
Cholesterol (mg/100 ml)	1	(5)	3	(2)	0	(0)	4	(3)
Triglycerides (mg/100 ml)	7	(33)	37	(32)	4	(27)	48	(31)
LDH (U/liter)	2	(9)	8	(8)	2	(13)	12	(8)

n = number of out-of-normal-range values
% = percent of out-of-range values within group

TABLE 7
Summary of blood count values.

Variable \ Group	Exposure group I (n = 21) $\bar{X}$ (S.D.)	II (n = 119) $\bar{X}$ (S.D.)	III (n = 15) $\bar{X}$ (S.D.)	Total (n = 155) $\bar{X}$ (S.D.)
WBC (x 10^3)	7.8 (1.9)	7.8 (2.0)	9.0 (3.0)	7.9 (2.1)
RBC (x 10^6)	5.1 (0.4)	5.2 (0.3)	5.2 (0.5)	5.2 (0.3)
HCT (%)	45.8 (2.5)	45.5 (2.5)	45.9 (2.0)	45.5 (2.4)
Hgb (g)	16.0 (2.8)	15.9 (0.9)	16.0 (1.0)	15.9 (0.9)

Ophthalmological examination

The descriptive statistics for three visual function tests – Critical Flicker Frequency, Aimark Visual Perimetry, and Farsnworth Dichotomous – are shown by exposure group in Table 8. The means of the exposure groups for the Critical Flicker Frequency and Aimark Visual Perimetry tests were found not to be

TABLE 8
Summary of results of visual function tests.

Test \ Group	Exposure group I (n = 21) $\bar{X}$ (S.D.)	II (n = 119) $\bar{X}$ (S.D.)	III (n = 15) $\bar{X}$ (S.D.)	Total (n = 155) $\bar{X}$ (S.D.)	Total (n = 130) $\bar{X}$ (S.D.)
Critical flicker frequency test	43.4 (3.6)	42.3 (3.1)	42.3 (2.6)	42.5 (3.2)	42.5 (3.0)
Aimark visual perimetry test					
horizontal field	152.7 (11.1)	152.1 (9.7)	152.6 (11.3)	152.2 (9.7)	152.4 (10.0)
vertical field	117.2 (14.8)	114.8 (11.1)	117.2 (12.1)	115.3 (12.1)	115.3 (12.0)
	n (%)	n (%)	n (%)	n (%)	n (%)
Farnsworth dichotomous					
No of pass	21 (100%)	106 (91%)	14 (93%)	141 (92%)	118 (92%)
No of failure	0 (0%)	11 (9%)	1 (7%)	12 (8%)	10 (8%)

significantly different according to analysis of covariance with age as a covariate. The number of failures for the Farnsworth Dichotomous was not associated with exposure groups (as determined with a chi test of association).

When the results of the visual function tests were compared to existing values for an unexposed population[17], the following results were observed. For the Critical Flicker Frequency test a significant difference was seen, with a t-test, between the unexposed population ($\bar{X}$ = 50.0, S.D. = 4.5, n = 46) and the

study population. No difference was seen for the horizontal field means of the Aimark Visual Perimetry; however, the unexposed group mean (X = 124.8, S.D. = 12.3, n = 35) was found to be significantly higher than the study population mean. The 8% failure rate seen in the Farnsworth was not statistically significantly different from the 5.5% seen in published literature[4] for an unexposed population.

Other ophthalmological tests revealed several cases of abnormal extraocular movement, pupillary shape and position, reaction to light (direct and consensual) and accommodation reaction. Several other types of abnormalities were reported, such as eyelid ptosis, eye muscle disorder, conjunctivitis, corneal and lens changes, choroidal pigmentation and other retinal findings, and abnormal non-contact tonometry for glaucoma screening. In some cases a participant was found to have more than one of these ophthalmological abnormalities.

Chest X-ray examination

One-hundred and six of the 155 participants were considered to have a normal chest X-ray. Of the remaining 49, 29 had calcified granuloma. This type of shadow is most frequently a result of healed histoplasmosis or primary tuberculosis infection and frequently is seen among the general population. There were six cases of slight fibrotic changes with or without granuloma. None of the above was accompanied by active disease processes. Of the remaining 14, 5 showed increased vascularity, 3 small round opacity, 2 increased translucency, or 4 other changes.

Neurology examination

The results of four neurology tests of mental status – Serial 7's, 6 Digits Forward, 5 Digits Backward and Sentence Retention are shown in Table 9. Abnormal performance in these tests was not associated with the exposure groups.

Results of the reflexes and muscles tested, tremor observations, and tests of sensation are also shown in Table 9. There are no marked detectable differences between exposure groups for these results. There were four reported observed abnormalities for general motor survey or ataxia (all in Group II) and six observed cases of positive plantar reflex (Babinski) (one in Group I and five in Group II) and ten clonus (all in Group II). Hyperreflexia was observed in 15 cases for the upper limb reflexes and in 28 cases for the lower limb reflexes. Hyporeflexia was observed in 13 cases for the upper limb reflexes and 14 cases for the lower limb reflexes. Of particular interest is the number of clinically observed sensation abnormalities of the hand and foot. These are in keeping with the ENG findings discussed later.

Psychology tests

The descriptive statistics are given in Table 10 for the following psychological tests: Digit Symbol (WAIS), Digit Span (WAIS), Block Design

TABLE 9
Summary of neurological examination results.

Variable \ Group		Exposure group I (n=21)	Exposure group II (n=119)	Exposure group III (n=15)	Total (n=155)
I. Tests (Mental status)					
Serial 7's	Fail	4 (19)	25 (21)	2 (13)	31 (20)
6 Digits forward		0 (0)	2 (2)	0 (0)	2 (1)
5 Digits backward		1 (5)	6 (5)	1 (7)	8 (5)
Sentence retention		1 (5)	12 (10)	2 (13)	15 (10)
II. Reflexes					
Biceps or	Decreased	3 (14)	9 (8)	1 (7)	13 (8)
Brachioradialis or Triceps	Increased	2 (9)	13 (11)	0 (0)	15 (10)
Quadriceps or	Decreased	2 (9)	12 (10)	0 (0)	14 (9)
Gastrocnemius--Soleus	Increased	6 (28)	20 (17)	2 (13)	28 (18)
Plantar (Babinski)		1 (5)	5 (4)	0 (0)	6 (2)
Clonus (ankle)	Positive	0 (0)	10 (8)	0 (0)	10 (7)
III. General motor survey or Ataxia	Abnormal	0 (0)	4 (3)	0 (0)	4 (2)
IV. Muscle strength Iliopsoas or Toe extensor or Toe flexor	Abnormal	2 (9)	8 (7)	0 (0)	10 (7)
V. Tremor	Present	0 (0)	2 (2)	0 (0)	2 (1)
VI. Sensation					
Hand		2 (9)	8 (7)	2 (13)	12 (8)
Forearm		0 (0)	3 (3)	0 (0)	3 (2)
Upper arm	Abnormal	0 (0)	0 (0)	0 (0)	0 (0)
Foot		5 (24)	13 (11)	2 (13)	20 (13)
Calf		0 (0)	4 (3)	0 (0)	4 (3)
Thigh		0 (0)	0 (0)	0 (0)	0 (0)

% of group showing response are given in parentheses

(WAIS), Neisser Letter Search, Santa Ana Dexterity, Raven Progressive Matrices, and Choice Reaction Time (movement, perception).

The results of the Time-Shared Performance Test are not reported because more than half of the results were not retrievable due to malfunctioning equipment. The Digit Symbol, Digit Span, Block Design, and Raven Progressive Matrices test results were adjusted for age and education level and the Neisser

TABLE 10
Summary of psychology test results.

Group	Exposure group									Total (n = 130)		Total (n = 155)	
	I (n = 21)			II (n = 119)			III (n = 15)						
Test	$\bar{X}$	(S.D.)	$\bar{X}$ (Adj.)*	$\bar{X}$	(S.D.)	$\bar{X}$ (Adj.)*	$\bar{X}$	(S.D.)	$\bar{X}$ (Adj.)*	$\bar{X}$	(S.D.)	$\bar{X}$	(S.D.)
Digit symbol** (WAIS)	48.5	(11.7)	50.6	53.6	(11. 2)	54.0	58.2	(10.5)	55.6	53.7	(11.3)	53.5	(11.5)
Digit span** (WAIS)	11.1	(1.9)	11.3	11.3	(2.3)	11.3	11.8	(2.2)	11.6	11.4	(2.3)	11.3.	(2.2)
Block design** (WAIS)	34.7	(6.5)	35.9	36.4	(7.7)	36.5	38.9	(7.3)	37.8	36.5	(7.8)	36.4	(7.5)
Neisser letter search***	55.7	(10.9)	56.2	58.4	(11.9)	58.2	62.5	(10.8)	59.6	58.1	(11.7)	58.5	(11.7)
Santa Ana dexterity***	102.6	(20.2)	105.9	109.7	(17.4)	110.0	115.5	(12.5)	113.4	109.8	(18.)	109.3	(17.5)
Raven progressive matrices**	0.74	(0.14)	0.75	0.75	(0.15)	0.75	0.75	(0.16)	0.72	0.75	(0.13)	0.75	(0.15)
Choice reaction time (msec)													
Movement***	376.2	(69.0)	344.9	407.72	(98.0)	407.2	368.0	(64.6)	396.4	398.1	(93.2)	399.6	(92.5)
Perception***	277.6	(116.5)	283.6	252.6	(69.5)	247.8	225.0	(54.4)	214.4	249.7	(79.4)	253.6	(76.9)

*The adjusted means are based on the subpopulation (n = 130)
**Adjusted means adjusted for age and education.
***Adjusted means adjusted for age.

Letter Search, Choice Reaction Time, and Santa Ana Dexterity test results, for age only. This is in keeping with previously reported dependency of these tests on the variables, age and education level[10]. The appropriate adjusted means are shown in Table 10. Analysis of covariance was used to test for the equality of the adjusted means of the exposure groups for each of the seven psychological tests using age and educational level when appropriate. The statistical tests show no significant differences between means other than for Choice Reaction Time. The Choice Reaction Time test means were significantly different for perception ($p = 0.09$) and for movement ($p = 0.03$). Group I had the highest age-adjusted mean for perception and Group III, the lowest. Group II had the highest age-adjusted mean for movement and Group I, the lowest. The inconsistency of the results should be noted.

Comparable mean values were available in the literature[10,17] for five of the tests (the Neisser Letter Search and Raven Progressive Matrices values were not comparable). Significant differences were found between the literature values and the study group values for Block Design (WAIS), Choice Reaction Time (movement) and Santa Ana Dexterity Test.

Electromyography tests

The results are shown in Table 11. The results indicate no significant patterns or differences due to exposure. It should be noted, however, that the extensor digitorum brevis, the abductor hallucis and the gastrocnemius muscles showed some type of muscle abnormality. For example, insertional activity was increased in the extensor digitorum brevis and the abductor hallucis. Additionally, for these two muscles abnormal motor unit potentials were observed and firing patterns were abnormal. The non-specific reduction in firing pattern of the gastrocnemius muscle is also of interest.

Electroneurography tests

Nerve conduction velocity and latency and amplitude (unadjusted) results are summarized in Table 12. Previous work (and results of this study) show a significant correlation of nerve conduction velocity with age. Therefore, analysis of covariance (age the covariate) was used to test mean differences between exposure groups by means of the nerve conduction velocities of the median, ulnar, peroneal, and posterior tibial motor nerves. No significant differences were found. Latency and amplitude value means were not significantly different among groups. Surface skin temperatures for both upper and lower limbs are comparable for all groups. A cooler temperature of the legs as compared to the arms should be noted and this difference is considered a factor in the lower conduction rates in the lower extremities.

TABLE 11
Summary of electromyography results (n = 155)

Muscle / Variable	Insertional activity			Positive wave					Fasciculations					Fibrillations					Abnormal motor unit potentials									Firing patterns					
	N	Dec	Inc	0	1+	2+	3+	4+	0	1+	2+	3+	4+	0	1+	2+	3+	4+	N	Ab+	Amplitude			Duration			Polyphasics			0	1	2	3	4	5
																					N	Dec	Inc	N	Dec	Inc	N	Dec	Inc						
Extensor digitorum brevis																																		
Group I	17	0	4	19	1	0	1	0	20	1	0	0	0	20	0	0	1	0	20	1	20	0	1	20	0	1	21	0	0	18	2	0	1	0	0
Group II	96	0	18	104	6	4	0	0	112	1	1	0	0	110	3	1	0	0	110	4	111	1	2	110	0	4	110	0	4	93	10	8	0	0	3
Group III	14	0	0	14	0	0	0	0	14	0	0	0	0	14	0	0	0	0	14	0	14	0	0	14	0	0	14	0	0	14	0	0	0	0	0
All	127	0	22	137	7	4	1	0	146	2	1	0	0	144	3	1	1	0	144	5	145	1	3	144	0	5	145	0	4	125	12	8	1	0	3
Abductor hallucis																																		
Group I	21	0	0	21	0	0	0	0	21	0	0	0	0	21	0	0	0	0	21	0	21	0	0	21	0	0	21	0	0	14	7	0	0	0	0
Group II	103	0	11	105	4	4	1	0	112	1	1	0	0	109	2	2	1	0	108	6	111	0	3	110	0	4	109	0	5	66	39	4	1	0	4
Group III	14	0	0	14	0	0	0	0	14	0	0		0	0	14	0	0	0	14	0	14	0	0	14	0	0	14	0	0	11	3	0	0	0	0
All	138	0	11	140	4	4	1	0	147	1	1	0	0	144	2	2	1	0	143	6	146	0	3	145	0	4	144	0	5	91	49	4	1	0	4
Tibialis anterior																																		
Group I	21	0	0	21	0	0	0	0	21	0	0	0	0	21	0	0	0	0	21	0	21	0	0	21	0	0	21	0	0	20	1	0	0	0	0
Group II	113	0	1	113	1	0	0	0	1113	1	0	0	0	114	0	0	0	0	114	0	114	0	0	114	0	0	114	0	0	104	7	0	0	0	3
Group III	14	0	0	14	0	0	0	0	14	0	0	0	0	14	0	0	0	0	14	0	14	0	0	14	0	0	14	0	0	14	0	0	0	0	0
All	148	0	1	148	1	0	0	0	148	1	0	0	0	149	0	0	0	0	149	0	149	0	0	149	0	0	149	0	0	138	8	0	0	0	3
Gastrocnemius																																		
Group I	21	0	0	21	0	0	0	0	21	0	0	0	0	21	0	0	0	0	21	0	21	0	0	21	0	0	21	0	0	17	4	0	0	0	0
Group II	113	0	1	114	0	0	0	0	113	1	0	0	0	114	0	0	0	0	113	0	113	0	1	113	0	1	113	0	1	98	10	1	0	0	5
Group III	14	0	0	14	0	0	0	0	14	0	0	0	0	14	0	0	0	0	14	0	14	0	0	14	0	0	14	0	0	12	2	0	0	0	0
All	148	0	1	149	0	0	0	0	148	1	0	0	0	149	0	0	0	0	148	0	148	0	1	148	0	1	148	0	1	127	16	1	0	0	5
Quadriceps																																		
Groups I	21	0	0	21	0	0	0	0	21	0	0	0	0	21	0	0	0	0	21	0	21	0	0	21	0	0	21	0	0	20	1	0	0	0	0
Group II	112	0	1	112	1	0	0	0	113	0	0	0	0	113	0	0	0	0			113	0	0	113	0	0	113	0	0	105	3	0	0	0	5
Group III	14	0	0	14	0	0	0	0	14	0	0	0	0	14	0	0	0	0	14	0	14	0	0	14	0	0	14	0	0	14	0	0	0	0	0
All	147	0	1	147	1	0	0	0	148	0	0	0	0	148	0	0	0	0	147	0	148	0	0	148	0	0	148	0	0	139	4	0	0	0	5
Abductor pollicis brevis																																		
Group I	20	0	0	20	0	0	0	0	20	0	0	0	0	20	0	0	0	0	20	0	20	0	0	20	0	0	20	0	0	19	1	0	0	0	0
Group II	109	1	2	110	1	1	00	0	112	0	0	0	0	111	1	0	0	0	109	3	111	0	1	111	0	1	110	0	2	106	3	0	1	0	2
Group III	15	0	0	15	0	0	0	0	15	0	0	0	0	15	0	0	0	0	15	0	15	0	0	15	0	0	15	0	0	15	0	0	0	0	0
All	144	1	2	145	1	1	0	0	147	0	0	0	0	146	1	0	0	0	144	5	146	0	1	146	0	1	145	0	2	140	4	0	1	0	2
First dorsal interosseous																																		
Group I	21	0	0	21	0	0	0	0	21	0	0	0	0	21	0	0	0	0	21	0	21	0	0	21	0	0	21	0	0	20	1	0	0	0	0
Group II	111	0	1	111	1	0	0	0	112	0	0	0	0	112	0	0	0	0	111	0	112	0	0	112	0	0	112	0	0	107	3	0	0	0	2
Group III	15	0	0	15	0	0	0	0	15	0	0	0	0	15	0	0	0	0	15	0	15	0	0	15	0	0	15	0	0	15	0	0	0	0	0
All	147	0	1	147	1	0	0	0	148	0	0	0	0	148	0	0	0	0	147	1	148	0	0	148	0	0	148	0	0	142	4	0	0	0	2

N = normal; Dec = decreased; Inc = increased
0 = Full Interference; 1 = Non-specific reduction; 2 = Diminished recruitment; 3 = Single Unit; 4 = No units under voluntary control; 5 = Pattern consistent with lack of voluntary effort; Ab = abnormal

TABLE 12
Summary of nerve conduction results (n = 155).

Nerve \ Variable	Skin temperature (°C)				Latency* (m/sec)				Amplitude**				Nerve conduction velocity (m/sec)			
	I $\overline{X}$ (S.D.)	II $\overline{X}$ (S.D.)	III $\overline{X}$ (S.D.)	All $\overline{X}$ (S.D.)	I $\overline{X}$ (S.D.)	II $\overline{X}$ (S.D.)	III $\overline{X}$ (S.D.)	All $\overline{X}$ (S.D.)	I $\overline{X}$ (S.D.)	II $\overline{X}$ (S.D.)	III $\overline{X}$ (S.D.)	All $\overline{X}$ (S.D.)	I $\overline{X}$ (S.D.)	II $\overline{X}$ (S.D.)	III $\overline{X}$ (S.D.)	All $\overline{X}$ (S.D.)
Upper limb	31.7 (1.0)	32.0 (0.8)	32.0 (0.8)	32.0 (0.8)												
Median motor					3.4 (0.4)	3.6 (0.7)	3.4 (0.3)	3.6 (0.7)	10.7 (3.0)	10.1 (3.4)	11.9 (3.1)	10.3 (3.4)	54.9 (5.2)	57.2 (6.0)	57.8 (3.4)	56.9 (5.8)
Median sensory (13 cm)					3.0 (0.5)	3.0 (0.3)	3.0 (0.3)	3.0 (0.4)	19.3 (11.4)	18.7 (7.7)	15.4 (5.9)	18.4 (8.1)				
Ulnar motor					2.7 (0.4)	2.7 (0.4)	2.6 (0.3)	2.7 (0.4)	10.3 (4.9)	8.5 (2.8)	8.3 (3.1)	8.7 (3.2)	56.9 (4.9)	58.3 (5.0)	57.9 (5.7)	58.1 (5.1)
Ulnar sensory (11 cm)					2.6 (0.3)	2.7 (0.3)	2.6 (0.3)	2.6 (0.3)	16.3 (8.2)	15.0 (6.4)	16.8 (7.1)	15.3 (6.7)				
Lower limb	30.8 (0.9)	30.9 (1.0)	30.7 (0.8)	30.8 (1.0)												
Peroneal motor					4.4 (0.7)	4.6 (0.9)	4.8 (0.9)	4.6 (0.9)	4.4 (2.0)	4.5 (2.2)	5.2 (2.4)	4.6 (2.2)	45.5 (5.9)	47.0 (6.3)	47.6 (3.7)	46.8 (6.0)
Posterior tibial motor					4.4 (0.8)	4.6 (1.1)	4.2 (0.6)	4.6 (1.0)	6.6 (3.2)	7.1 (3.3)	9.8 (4.0)	7.2 (3.4)	46.6 (4.9)	48.5 (6.2)	49.6 (4.7)	48.3 (5.9)
Sural sensory (14 cm)					3.1 (0.2)	3.3 (0.4)	3.0 (0.2)	3.2 (0.4)	17.4 (7.4)	15.4 (6.4)	17.0 (5.6)	15.8 (6.5)				

*Distal latency for motor nerves; latency for sensory nerves (orthodromic stimulation)
**Sensory nerve amplitudes are in μ (orthodromic stimulation) and motor nerve amplitudes are in mV (distal recording)

TABLE 13
Frequency of out-of-range ENG measurements (N = 130).

Variable / Nerve	Latency* I n (%)	Latency* II n (%)	Latency* III n (%)	Latency* All** n (%)	Amplitude I n (%)	Amplitude II n (%)	Amplitude III n (%)	Amplitude All n (%)	Nerve conduction velocity I n (%)	Nerve conduction velocity II n (%)	Nerve conduction velocity III n (%)	Nerve conduction velocity All n (%)
Upper limb												
Median motor	0 (0)	3 (3)	0 (0)	3 (2)	0 (0)	2 (2)	0 (0)	2 (2)	2 (12)	8 (8)	0 (0)	10 (8)
Median sensory	2 (12)	18 (19)	1 (8)	21 (17)								
Ulnar motor	1 (6)	1 (1)	1 (8)	3 (2)	1 (6)	14 (15)	1 (8)	16 (13)	1 (6)	0 (0)	0 (0)	1 (1)
Ulnar sensory	1 (6)	14 (15)	1 (8)	16 (13)								
Lower limb												
Peroneal motor	0 (0)	1 (1)	0 (0)	1 (1)	3 (18)	11 (12)	3 (25)	17 (14)	2 (12)	8 (8)	0 (0)	10 (8)
Posterior tibial motor	1 (6)	11 (11)	0 (0)	12 (10)	10 (59)	36 (37)	3 (25)	49 (39)	2 (12)	4 (4)	0 (0)	6 (5)
Sural sensory	0 (0)	8 (9)	0 (0)	8 (7)								

*Distal latency for motor nerves; latency for sensory nerves (orthodromic stimulation)
**The number of reported results varied, % is base on number reported

n = number of out-of-normal range values

ENG normal values as provided by the two clinics involved in the study were used to develop a frequency count to identify out-of-range measurements (Table 13). The data in Table 13 show that the latency measurements for sensory median, ulnar and sural nerves were out-of range in 17, 13, and 7 percent, respectively, for the participants studied. Twenty-nine participants had either one or both sensory latencies abnormal (ulnar or median). Of special interest was the observation that 9 of these 29 (28 percent) showed impairment in both median and ulnar nerves. This finding should be considered in light of the numerous complaints by the participants of numbness or tingling in their hands or feet. A 10% abnormality rate was also seen for the posterior tibial motor nerve.

A review of Table 13 also shows that the amplitude of the muscle action potential (negative deflection) was out-of-range (smaller) in 13, 14, and 39 percent of the study participants for the ulnar, peroneal and posterior tibial nerves, respectively. Nerve conduction was out-of-range in 8, 8, and 5 percent of the participants for the median, peroneal, and posterior tibial motor nerves, respectively.

TABLE 14
Summary of reported health conditions.

Condition \ Group	Exposure group I n = 21		II n = 119		III n = 15		Total n = 155	
	Yes	%*	Yes	%	Yes	%	Yes	%
Asthma	1	5	6	5	0	0	7	5
Bronchitis	5	24	27	23	2	13	34	22
Tuberculosis	0	0	3	3	0	0	3	2
Cancer (any type)	1	5	3	3	1	7	5	3
Skin rash or disease	5	24	26	22	3	20	34	22
Heart disease	1	5	5	4	0	0	6	4
Stroke	0	0	1	1	0	0	1	1
Meningitis	0	0	1	1	0	0	1	1
High blood pressure	8	38	13	11	1	7	22	14
Migraine headaches	0	0	6	5	0	0	6	4
Head injury or concussion	5	24	18	15	2	13	25	16
Thyroid	1	5	3	3	0	0	4	3
Gall bladder	0	0	1	1	0	0	1	1
Kidney	6	29	20	17	0	0	26	17
Liver trouble	3	14	6	5	1	7	10	6
Diabetes	0	0	6	5	0	0	6	4
Anemia	0	0	7	6	0	0	7	5
Ulcers	4	19	5	4	0	0	9	6
Arthritis or rheumatism	3	14	7	6	0	0	10	6
Back trouble	9	43	21	18	5	33	35	23
Epilepsy	1	5	2	2	0	0	3	2
Poisoning	3	14	14	12	1	7	18	12
Nervous breakdown	0	0	6	5	1	7	7	5

*% of positive responses within group

TABLE 15

Response and rank by exposure group of symptoms reported within last five years and those presently reported (n = 155).

Symptom \ Group	Exposure group								
	I (n = 21)			II (n = 119)			III (n = 15)		
	n*	(%)**	Rank	n	(%)	Rank	n	(%)	Rank
Pain or stiffness in neck	8	(38)	6	45	(38)	6	5	(33)	11
	6	(29)	6	33	(28)	7	3	(20)	17
Changes in eyesight	14	(67)	1	52	(44)	2	7	(47)	7
	13	(62)	1	38	(32)	2	6	(40)	4
Drooping eyelids blurring or double vision	11	(52)	2	44	(37)	7	7	(47)	7
	8	(38)	3	33	(28)	7	6	(40)	4
Complete or partial loss of vision	2	(10)	24	4	(3)	30	2	(13)	25
	2	(10)	20	3	(3)	28	2	(13)	23
Changes in hearing	5	(24)	11	22	(18)	23	4	(27)	19
	5	(24)	9	20	(17)	17	4	(27)	12
Ringing or noise in ears	7	(33)	7	40	(34)	12	9	(60)	1
	6	(29)	6	31	(26)	11	8	(53)	1
Difficulty in speaking	0	(0)	31	26	(22)	21	3	(20)	23
	0	(0)	27	20	(17)	17	3	(20)	17
Difficulty in swallowing	4	(19)	13	19	(16)	24	1	(7)	27
	3	(14)	16	15	(13)	23	1	(7)	25
Spells of sickness to stomach	6	(29)	9	34	(29)	15	8	(53)	3
	6	(29)	6	20	(17)	17	5	(33)	9
Frequent vomiting	3	(14)	20	6	(5)	28	0	(0)	30
	2	(10)	20	3	(3)	28	0	(0)	29
Loss of balance or staggering	5	(24)	11	35	(29)	14	5	(33)	11
	2	(10)	20	20	(17)	17	4	(27)	12
Difficulty in walking	3	(14)	20	30	(25)	18	5	(33)	11
	2	(10)	20	19	(16)	21	4	(27)	12
Spells of dizziness	7	(33)	7	50	(42)	3	9	(60)	11
	3	(14)	16	30	(25)	12	8	(53)	1
»Black-outse or fainting	0	(0)	27	18	(15)	25	5	(33)	11
	0	(0)	27	5	(4)	26	1	(7)	25
Convulsion or seizure	0	(0)	27	3	(3)	31	1	(7)	27
	0	(0)	29	1	(1)	29	1	(7)	25
Nervousness or uncontrollable tension	10	(48)	3	41	(34)	11	5	(33)	11
	8	(38)	3	27	(23)	13	5	(33)	9
Difficulty in sleeping	9	(43)	4	48	(40)	4	6	(40)	10
	8	(38)	3	(36)	(30)	4	6	(40)	4
Drowsy or sleepy during day	4	(19)	13	47	(39)	5	8	(53)	3
	4	(19)	10	35	(29)	5	6	(40)	4
Decrease in memory or thinking ability	4	(19)	13	44	(37)	7	7	(47)	7
	4	(19)	10	37	(31)	3	6	(40)	4
Paralysis of any part of body	1	(5)	26	6	(5)	28	1	(7)	27
	1	(5)	25	5	(4)	26	0	(0)	29
Numbness or tingling in hands or feet	9	(43)	4	43	(36)	9	5	(33)	11
	9	(43)	2	33	(28)	7	4	(27)	12
Problems with coordination	3	(14)	20	31	(26)	17	5	(33)	11
	3	(14)	16	24	(20)	14	3	(20)	17
Muscle weakness	3	(14)	20	36	(30)	13	4	(27)	19
	3	(14)	16	32	(27)	10	1	(7)	25
Frequently feel fatigued	4	(19)	13	56	(47)	1	8	(53)	3
	4	(19)	10	41	(34)	1	5	(33)	9
Change in handwriting	4	(19)	13	26	(22)	21	4	(27)	19
	4	(19)	10	21	(18)	16	4	(27)	12
Unexplained sweating	4	(19)	13	27	(23)	19	3	(20)	23
	2	(10)	20	18	(15)	22	3	(20)	17
Difficulty with urination	1	(5)	26	15	(13)	26	4	(27)	19
	1	(5)	25	10	(8)	24	3	(20)	17
Unexplained weight change	0	(0)	27	33	(28)	16	5	(33)	11
	0	(0)	29	17	(14)	13	3	(20)	17
Decreased interest in sex	4	(19)	13	27	(23)	19	2	(20)	25
	4	(19)	10	22	(18)	15	2	(20)	23
Frequent headache	6	(29)	9	42	(35)	10	8	(53)	3
	4	(19)	10	34	(29)	6	7	(47)	3

*n = number of positive responses to participant having had symptom in last 5 yrs. (top line) and if he now has symptom (second line).

**Percent responding positively within group.

Health history

The interviewer asked the participants a series of health history questions. The participants were asked to respond to the question "Have you ever been told by a doctor you had this health condition?". A list of the conditions and the frequency of positive responses are shown in Table 14. Bronchitis, skin rash or disease, and back trouble were the most frequently reported conditions(~ 22%) for the total group. High blood pressure (38%) and kidney problems (29%) were the most frequently reported by Group I. These problems were not seen in Group III and occurred to a lesser extent in Group II. It should be considered in interpreting these findings that Group I is an older group with considerably longer exposure to a variety of chemicals.

Physical examination

The results of the physical examination were in general, on a group basis, unremarkable. A few participants appeared to have overt functional impairment of the nervous system. This was discussed under the section on neurology examination. Thirteen were found to have out-of-range blood pressure values, and they were advised to seek further medical consultation.

Health symptoms

The interviewer asked the participants to respond (yes, no, or don't know), to a set of 30 questions related to health symptoms. These health symptoms and frequency of positive responses reported are listed in Table 15 by exposure groups, and in Table 19 for total sample population and subpopulation (those with confounding factors removed). The participant was first asked if he had experienced the symptom within the last five years (the top line for each symptom in Tables 15 and 19) and if the answer was positive, he was asked if he was experiencing the symptom presently (the second line for each symptom in Tables 15 and 19). The ranks of these positive responses within each group for each symptom are also shown in Tables 15 and 19. The two symptoms most often reported, both now and in last five years, are "changes in eyesight" and "feeling fatigued" – two non-specific complaints. It should be noted that 30 percent of the participants reported "numbness or tingling in hands or feet."

Sixteen of the health symptoms were thought to be particularly relevant to the neurology findings. They were:

- drooping eyelids, blurring or double vision
- decrease in memory or thinking ability
- difficulty in speaking
- *paralysis of any part of the body
- *loss of balance or staggering
- *numbness or tingling in hands or feet
- *difficulty in walking
- *problem with coordination
- spells of dizziness

- *muscle weakness
- nervousness or uncontrollable tension
- frequently feel fatigued
- difficulty in sleeping
- change in handwriting
- drowsy or sleepy during the day
- unexplained sweating

The six symptoms with asterisks are particularly relevant to the ENG findings. Of the sixteen neurology-related symptoms, six were among the ten most often reported. One of the six ENG-related symptoms "numbness or tingling in hands or feet" was among the ten most often reported.

The number of subjects who reported one or more of the neurology-related symptoms in the last five years is summarized by exposure group in Table 16. The association of symptom groups (as defined in Table 16) with exposure groups was tested using the chi-square statistic and rejected.

TABLE 16
Association of 16 neurology related symptoms* with exposure group.

Symptom group \ Group	Exposure group I n (%)	Exposure group II n (%)	Exposure group III n (%)	Total (n = 130) n (%)
I – One or more of 16 neurology related symptoms	14 (82)	81 (80)	11 (92)	106 (82)
II – Other than 16 symptoms only	2 (12)	8 (8)	0 (0)	10 (8)
III – No symptoms	1 (6)	12 (12)	1 (8)	14 (10)

Test of independence of symptom and exposure groups: $\chi^2 = 2.03$ ($p = 0.73$)
*Symptoms reported within last 5 years.

TABLE 17
Association of six ENG-related symptoms* with exposure groups.

Symptom group \ Group	Exposure group I n (%)	Exposure group II n (%)	Exposure group III n (%)	Total (n = 130) n (%)
I – One or more of 6 ENG related symptoms	8 (47)	56 (55)	8 (67)	72 (55)
II – Other than 6 symptoms only	8 (47)	33 (33)	3 (25)	44 (34)
III – No symptoms	1 (6)	12 (12)	1 (8)	14 (11)

Test of independence of symptom and exposure groups: $\chi^2 = 2.24$ ($p = 0.69$)
*Symptoms reported within last 5 years.

The results of the ENG-related symptoms reported for the last five years, are summarized by exposure group in Table 17. The association of symptom categories with exposure group was tested by means of the chi-square test and rejected.

Health status of study participants

The results of the preceding tests were used to classify each individual into one of three categories – "normal", "slightly abnormal", or "abnormal" – for each of the four batteries of tests (psychology, neurology, ENG and EMG). The criteria for classification were stated previously in the Methodology Section. An individual was classified as "abnormal" if he was "abnormal" in one or more of the test batteries (ENG, EMG, psychology, or neurology). He was classified as "slightly abnormal" if he was not classified as "abnormal" but was "slightly abnormal" in one or more of the test batteries. The criteria for classification into the abnormality categories within each battery of tests are stated in the Methodology Section.

TABLE 18
Results of tests of abnormalities by group and association.

Group / Abnormality group	Exposure group I n (%)	II n (%)	III n (%)	Total n = 130 n (%)	χ^2-value	p
EMG					3.71	0.45
Abnormal	1 (6)	3 (3)	0 (0)	4 (3)		
Normal	9 (53)	58 (57)	10 (83)	77 (59)		
Slightly abnormal	7 (41)	40 (40)	2 (17)	49 (38)		
ENG					5.67	0.23
Abnormal	8 (47)	35 (35)	2 (17)	45 (35)		
Normal	3 (18)	33 (33)	7 (58)	43 (33)		
Slightly abnormal	6 (35)	33 (33)	3 (25)	42 (32)		
Neurology					6.92	0.14
Abnormal	4 (24)	7 (7)	0 (0)	11 (8)		
Normal	8 (47)	63 (63)	9 (75)	80 (61)		
Slightly abnormal	5 (29)	31 (31)	3 (25)	39 (30)		
Psychology					1.60	0.81
Abnormal	3 (18)	11 (11)	1 (8)	15 (12)		
Normal	13 (76)	84 (84)	11 (92)	108 (83)		
Slightly abnormal	1 (6)	6 (6)	0 (0)	7 (5)		
One or more abnormalities					10.82	0.03*
Abnormal**	13 (76)	44 (44)	3 (25)	60 (46)		
Normal***	1 (6)	14 (14)	4 (33)	19 (15)		
Slightly abnormal****	3 (18)	43 (43)	5 (42)	51 (39)		

*Indicates we reject hypothesis that number of participants having one or more abnormalities is independent of exposure group at $p \leq 0.05$ level.
**Has one or more abnormality, may or may not have slight abnormality.
***Has no abnormality or slight abnormality.
****Has one or more slight abnormality but no abnormality.

TABLE 19

Response and rank by abnormality group of symptoms reported within last five years and presently reported.

Symptom \ Abnormality Group	Neurology n = 13		Psychology n = 17		ENG n = 57		EMG n = 8		One or more abnormality n = 73		Total n = 130		Total n = 155	
	n (%)	R	n (%)	R	n (%)	R	n (%)	R	n (%)	R	n (%)	R	n (%)	R
Pain or stiffness in neck	5 (38)	12	8 (47)	5	21 (37)	8	3 (38)	8	27 (37)	10	46 (35)	8	57 (37)	8
	4 (31)	10	7 (41)	5	17 (30)	8	2 (25)	9	21 (29)	10	31 (24)	11	42 (27)	10
Changes in eyesight	7 (54)	3	9 (53)	3	30 (53)	1	4 (50)	4	38 (52)	1	59 (45)	1	73 (47)	1
	6 (46)	3	8 (47)	4	28 (50)	1	3 (38)	3	34 (47)	1	45 (35)	1	57 (37)	1
Drooping eyelids	6 (46)	7	8 (47)	5	19 (33)	9	2 (25)	13	29 (40)	7	53 (41)	4	62 (40)	5
Blurring or double vision	5 (38)	4	7 (41)	5	18 (32)	4	1 (13)	13	26 (36)	4	40 (31)	2	47 (30)	4
Complete or partial loss of vision	1 (8)	26	3 (18)	25	3 (5)	28	0 (0)	26	6 (8)	27	7 (5)	28	8 (5)	29
	1 (8)	25	3 (18)	24	3 (5)	26	0 (0)	23	6 (8)	26	6 (5)	26	7 (4)	26
Changes in hearing	1 (8)	26	4 (24)	23	12 (21)	21	1 (13)	20	15 (21)	21	27 (21)	20	31 (20)	22
	1 (8)	25	4 (24)	19	11 (19)	17	0 (0)	23	14 (20)	19	25 (19)	14	29 (19)	16
Ringing or noise in ears	6 (46)	7	5 (29)	15	18 (32)	12	2 (25)	13	26 (36)	11	46 (35)	8	56 (36)	9
	4 (31)	10	4 (24)	19	15 (26)	11	1 (13)	13	20 (27)	12	36 (28)	7	45 (29)	7
Difficulty in speaking	3 (23)	22	3 (18)	25	8 (14)	22	1 (13)	20	10 (14)	26	24 (18)	23	29 (19)	23
	3 (23)	18	3 (18)	24	7 (12)	22	1 (13)	13	9 (13)	24	19 (15)	21	23 (15)	21
Difficulty in swallowing	3 (23)	22	2 (12)	27	8 (14)	22	1 (13)	20	12 (16)	23	19 (15)	24	24 (15)	24
	2 (15)	21	2 (12)	26	4 (7)	25	1 (13)	13	8 (11)	25	14 (11)	24	19 (12)	24
Spells of sickness to stomach	4 (31)	18	5 (29)	15	17 (30)	13	2 (25)	13	23 (32)	13	41 (32)	13	49 (31)	13
	2 (15)	21	5 (29)	14	10 (18)	20	1 (13)	13	15 (21)	17	24 (18)	16	31 (20)	14
Frequent vomiting	1 (8)	26	0 (0)	30	4 (7)	27	0 (0)	26	4 (5)	28	8 (6)	27	9 (6)	27
	1 (8)	25	0 (0)	30	2 (4)	28	0 (0)	23	2 (3)	29	3 (2)	29	5 (3)	29
Loss of balance or staggering	5 (38)	12	5 (29)	15	15 (26)	15	3 (38)	8	20 (27)	16	36 (28)	14	45 (29)	14
	4 (31)	10	5 (29)	14	11 (19)	17	1 (13)	13	15 (21)	17	21 (16)	18	26 (17)	19
Difficulty in walking	5 (38)	12	5 (29)	15	8 (14)	22	1 (13)	20	15 (21)	21	31 (24)	18	38 (24)	17
	4 (31)	10	5 (29)	14	7 (12)	22	1 (13)	13	13 (18)	20	20 (15)	19	25 (16)	20
Spells of dizziness	7 (54)	13	9 (53)	3	27 (47)	3	5 (63)	2	37 (51)	2	54 (42)	3	66 (42)	3
	4 (31)	10	9 (53)	2	18 (32)	4	3 (38)	3	25 (34)	6	32 (25)	10	41 (26)	11
"Black-outs" or fainting	2 (15)	25	5 (53)	15	6 (10)	26	1 (13)	20	11 (15)	25	19 (15)	24	23 (14)	25
	0 (0)	29	2 (12)	26	2 (4)	28	1 (0)	23	4 (5)	27	6 (5)	26	6 (4)	27

Convulsion or seizures	0	(0)	30	1	(6)	28	1	(2)	30	0	(0)	26	2	(3)	30	4	(3)	31	4	(2)	30
	0	(0)	29	1	(6)	28	1	(2)	30	0	(0)	23	2	(3)	29	2	(2)	30	2	(1)	30
Nervousness or uncontrollable tension	7	(54)	3	7	(41)	8	19	(33)	9	4	(50)	4	29	(40)	7	44	(34)	12	56	(36)	9
	5	(38)	4	6	(35)	10	14	(24)	12	3	(38)	3	21	(29)	10	30	(23)	12	40	(26)	12
Difficulty in sleeping	10	(77)	1	11	(65)	1	23	(40)	5	4	(50)	4	33	(45)	5	51	(39)	5	63	(41)	4
	8	(61)	1	10	(59)	1	16	(28)	10	3	(38)	3	25	(34)	6	39	(30)	5	50	(32)	2
Drowsy or sleepy during day	5	(38)	12	7	(41)	8	23	(40)	5	5	(63)	2	29	(40)	7	48	(37)	7	59		6
	3	(23)	18	6	(35)	10	17	(30)	8	5	(63)	1	22	(30)	9	35	(27)	9	45		7
Decrease in memory or thinking ability	5	(38)	12	7	(41)	8	19	(33)	9	3	(23)	8	26	(36)	11	45	(35)	11	56	(38)	9
	5	(38)	4	6	(35)	10	18	(32)	4	2	(25)	9	23	(32)	8	37	(28)	6	47	(30)	4
Paralysis of any part of body	1	(8)	26	1	(6)	28	3	(5)	28	0	(0)	26	4	(5)	28	6	(5)	29	9	(6)	27
	1	(8)	25	1	(6)	28	3	(5)	26	0	(0)	23	4	(5)	27	5	(4)	28	6	(4)	27
Numbness or tingling in hands or feet	8	(61)	2	10	(59)	12	25	(44)	4	2	(25)	13	35	(48)	3	51	(39)	5	58	(37)	7
	7	(54)	2	9	(53)	2	21	(37)	2	1	(13)	13	29	(40)	2	40	(31)	2	46	(30)	6
Problems with coordination	6	(46)	7	5	(29)	15	13	(23)	19	2	(25)	13	21	(29)	15	33	(25)	16	39	(25)	16
	4	(31)	10	5	(29)	14	12	(21)	15	1	(13)	13	18	(25)	15	25	(19)	14	30	(19)	15
Muscle weakness	5	(38)	12	6	(35)	13	15	(26)	15	3	(38)	8	20	(27)	16	36	(28)	14	43	(28)	15
	5	(38)	4	6	(35)	10	14	(24)	12	3	(38)	3	19	(26)	14	30	(23)	12	36	(23)	13
Frequently feel fatigued	7	(54)	3	8	(47)	5	23	(40)	5	6	(75)	1	33	(45)	5	56	(43)	2	68	(44)	2
	5	(38)	4	7	(41)	5	18	(32)	4	5	(63)	1	26	(36)	4	40	(31)	2	50	(32)	2
Change in handwriting	6	(46)	7	5	(29)	15	13	(23)	19	2	(25)	13	19	(26)	18	25	(19)	22	34	(22)	19
	5	(38	4	5	(29)	14	12	(21)	15	2	(25)	9	17	(23)	16	20	(15)	19	29	(19)	16
Unexplained sweating	6	(46)	7	6	(35)	13	15	(26)	15	2	(25)	13	19	(26)	18	28	(22)	19	34	(22)	19
	4	(31)	10	4	(24)	19	11	(19)	17	0	(0)	23	13	(18)	20	19	(15)	21	23	(15)	21
Difficulty with urination	4	(31)	18	4	(24)	23	7	(12)	25	3	(38)	8	12	(16)	23	17	(13)	26	20	(13)	26
	2	(15)	21	4	(24)	19	7	(12)	22	2	(25)	9	10	(14)	23	11	(8)	25	14	(9)	25
Unexplained weight change	3	(23)	22	5	(29)	15	16	(28)	14	0	(0)	26	19	(26)	18	33	(25)	16	38	(24)	17
	2	(15)	21	4	(24)	19	10	(18)	20	0	(0)	23	13	(18)	20	18	(14)	23	20	(13)	23
Decreased interest in sex	4	(31)	18	7	(41)	8	15	(26)	15	4	(50)	4	22	(30)	14	27	(21)	20	33	(21)	21
	3	(23)	18	7	(41)	5	13	(23)	14	3	(38)	3	20	(27)	12	22	(27)	17	28	(18)	18
Frequent headache	4	(31)	18	7	(41)	8	28	(49)	2	1	(13)	20	34	(47)	4	46	(35)	8	56	(36)	19
	4	(31)	10	7	(41)	5	21	(37)	2	1	(13)	13	27	(37)	3	36	(28)	7	45	(29)	7

*n = number of positive responses to participant having had symptom in last 5 years (top line) and if he now has symptom (second line)
**Percent responding positively within group
***Rank within group

The number found for each of the three types of abnormality categories is shown in Table 18 by exposure groups. The number having one or more "abnormalities" is also shown in Table 18. There were 60 of the 130 member subpopulation with one or more abnormality, 51 with one or more slight abnormality, and 19 with no abnormal finding. The association of the number of abnormalities within each abnormality category with exposure groups was tested. No association was found except when the abnormality groups having the classification of one or more abnormality, one or more slight abnormality, or no abnormality were tested with exposure groups. The association was statistically significant ($p \leq 0.03$) according to the chi-square test of association. Group I had a 76% rate of abnormalities; Group II, 44%, and Group III, 25%. This grouping reflects age differences and length of exposure to chemicals, perhaps explaining the trend we see. This trend also appears to be present in each of the individual battery of tests.

The relationship of the health symptoms to the abnormality categories was explored. Table 19 shows the frequency and rank of each symptom within an abnormality category. The expected relationship of selected symptom to a particular type of abnormality is seen in these results.

In the results previously discussed, 7 of the 12 workers who had been reported as having had a diagnosed chemical poisoning were included. Of these seven, five were found to have a neurology abnormality: two, psychology; two, ENG; and one, EMG abnormality.

CONCLUSIONS

The study population was a relatively young (mean age-32.3 years) group of 155 workers with those having possible occupational exposure to leptophos comprising most of the group. Each worker reported multiple exposure to chemicals other than pesticides, with n-hexane being the most often reported.

The ophthalmology examination showed few abnormalities; however, the visual function tests indicated a population with significantly lowered Critical Flicker Frequency test results and lowered vertical peripheral field measurements for the Aimark Visual Perimetry Test. Results from chest X-ray, blood, and urine tests revealed no unusual findings.

Considering the occupational histories of the study participants, the number of abnormal reflexes observed and the presence in four persons of the Babinski Sign were not unexpected. Noteworthy was the high number of participants showing abnormal sensation in the neurological testing of the hands and feet. The psychological performance measurements indicated no significant differences among exposure group means for the Choice Reaction Time test. However, the Choice Reaction Time results, as well as those from the Santa Ana Dexterity and Block Design (WAIS), were significantly different from the results from an unexposed comparison population. This suggests an impairment of psychomotor performance of the study population. The non-significant test results suggest no detectable differences in cognitive and perceptual functions, as measured by the other psychological tests and the neurological evaluation of mental status.

Few workers showed significant EMG abnormalities. Three muscles (extensor digitorum brevis, abductor hallucis, and gastrocnemius) accounted for most of the abnormalities noted. The extensor digitorum brevis and abductor hallucis muscles are very susceptible to injury since they are located in the foot and the abnormalities noted could, in part, be due to local trauma. There are no data on the frequency of abnormalities of these two muscles in a "normal" population.

A substantial number of participants, fifty-seven, were classified as abnormal based on the ENG results. Of considerable interest are the number of out-of-range latency measurements for the sensory (median, ulnar, and sural) nerves (17, 13, and 7%), respectively. Of special significance was the observation that of the 29 workers showing abnormal latency findings, eight of them showed abnormal findings for both the median and ulnar nerves. It is of interest to note these findings in light of the previously discussed psychomotor performance impairment and complaints of numbness or tingling in hands or feet. The number of out-of-range values for muscle action potentials and nerve conduction velocities of motor nerves was greater than expected.

Initially a number of Velsicol workers had been diagnosed by local physicians as having encephalitis or multiple sclerosis because their symptoms and clinical examinations were thought to be consistent with these disorders (see Part II – Case Studies of Alleged Leptophos Poisoning). Although there are some subtle differences the symptoms and type of nerve damage seen in encephalitis or multiple sclerosis could mimic those caused by neurotoxic chemicals encountered in the workplace. Since the sick workers had been seen by different physicians who may not have been able to elicit a good occupational history and since appropriate toxicologic information about the relevant workplace chemicals might not have been immediately available to the attending physicians, it is not surprising that the diagnosis of encephalitis or multiple sclerosis was considered rather than pesticide poisoning. The clustering of three relatively rare cases of suspected multiple sclerosis in a small group of workers alerted the medical consultant to the company to the possibility of pesticide poisoning. It is the opinion of NIOSH medical officers that the signs and symptoms presented by these workers are compatible with organophosphate poisoning. Nonetheless, in view of the stated history of concurrent exposure to n-hexane and other neurotoxic chemicals, it is difficult to exclude the role played by these other chemicals.

In summary, NIOSH's medical evaluation of the workers showed that a substantial number of those examined were found to have neurological, electromyographic, electroneurographic, and psychological performance abnormalities ranging from slight to serious. A causal association of the medical findings with worker exposure to leptophos is difficult to establish in individual cases because of the possibility of exposure to other neurotoxic agents that were present. Our investigation does lead us to conclude that workers in this plant were adversely affected by conditions that could have been prevented by more careful medical surveillance, work practices, and engineering controls.

II – CASE STUDIES OF ALLEGED LEPTOPHOS POISONING

FACILITY AND PROCESS DESCRIPTION

The Velsicol Chemical plant at Bayport, Texas, has manufactured a number of phosphate-based agricultural insecticides. Before 1970, the plant produced methyl parathion. After that time, PHOSVEL (trademark) (leptophos) was manufactured. A total of 13,953,550 pounds of this insecticide was produced and subsequently exported from 1971 until production of leptophos was terminated in 1976.

Bulk chemicals used in the process were delivered to the plant by rail or tank truck and piped into storage tanks. Formulations and chemical reactions took place within a closed system. Leptophos was made by first reacting benzenephosphorusthiochloride (BPT) with methanol in the presence of trimethylamine. The intermediate product, 0-methylphenyl-thiophosphonyl-chloride, was reacted with 4-bromo-2,5-dichlorophenol in the presence of potassium carbonate to give technical leptophos. Upon removal of toluene, the final product is a waxy solid which decomposes at a temperature of 180 °C.

From 1970 until September, 1974, the molten leptophos was poured into shallow trays for overnight cooling. This procedure resulted in significant splashing of leptophos and created a potentially high dermal exposure. After a solidification, the trays were conveyed overhead and manually dumped into a pulverizer.

After September, 1974, the molten product was put into fiber drums where it cooled and solidified at ambient temperatures. The drums, each containing approximately 220 pounds of Phosvel, were then split with an axe. The solid Phosvel was next broken into smaller pieces with an axe before being manually placed on a conveyor belt which led to the pulverizer. Although it was estimated that the use of drums reduced handling by 40%, industrial surveys and accident reports indicated that significant, potential exposure to leptophos occurred during filling and again during removal of the product.

The pulverized product was fed by gravity into lined metal drums. This procedure required the assistance of one or two operators to package leptophos. The operation usually involved chopping and grinding for 4 to 5 hours and then cleaning the area by scraping, sweeping, and steam cleaning. There is evidence that solvents such as n-hexane were used during cleaning operations. The packaging personnel also transferred the drums to the warehouse for storage.

Protective clothing for both the operators and maintenance personnel included a uniform, gloves, safety glasses, and hard hat. In January, 1975, production of leptophos was increased to 3 shifts for 5 days a week. Additional workers were obtained from area labor pools for several weeks, but they were not supplied with protective clothing. MSA respirators were supplied to the employees in April, 1975. Employees were also advised to follow plant hygiene programs and told not to re-use the gloves before they were decontaminated.

Cholinesterase determinations were made from 1969 to 1975 with the Unopette method. This monitoring was completed monthly unless overexposure was suspected. The procedure was revised early in 1975.

CASE STUDIES OF ALLEGED CHEMICAL POISONING

It has been estimated that nearly 300 people were potentially exposed to leptophos at the Bayport plant. The National Institute for Occupational Safety and Health completed an investigation of 155 present and former industrial employees, office, and subcontract workers. Results of the extensive neurological examinations, physicals, laboratory and psychological tests were reported in Part I – Medical Examination of this report. This epidemiologic study involved nine employees whose medical records at Velsicol Chemical Corporation and the Texas Industrial Accident Board suggested the possibility of chemical intoxication. All of the employees except one were classified as warehousemen or packagers (Table 20). Accident reports, medical records, and industrial hygiene surveys indicated that each of the latter employees were potentially exposed to substantial levels of leptophos. Further review of records also indicated the possibility of exposure to a variety of solvents including n-hexane.

TABLE 20
General characteristics concerning employment and symptoms of the 9 workers with alleged chemical poisoning.

Characteristics	Employee								
	A	B	C	D	E	F	G	H	I
Age	19	46	26	21	23	27	22	31	22
Job classification	W	L/P	PO	W	W/P	P	W	W	W
Onset of symptoms									
a) Months employment	2	1.5	7	4	5	9	1	10	3
b) Date of onset	9–74	6–75	5–75	3–74	5–74	4–75	9–74	5–74	5–75

W = Warehouseman
L = Laborer
P = Packager
PO = Process operator

The employees studied were generally, relatively young with an average age of 26.7 years at the onset of symptomatology. The onset of complaints took place between March, 1974, and June 1975, which in most instances was within 6 months of employment. Medical records indicated that the workers generally presented to physicians as anxious, confused, weak and in some instances with early evidence of peripheral and/or central nervous system involvement. As shown in Table 21, five of the workers were disoriented and also had impaired judgement and memory; three employees had auditory or visual hallucinations; and four of the nine workers initially presented to physicians with anxiety.

TABLE 21
Clinical findings associated with employee illnesses, psychological disturbances of 9 workers with alleged chemical poisoning.

Psychological disturbances	Employee								
	A	B	C	D	E	F	G	H	I
Disoriented	+*	+			+	+			+
Impaired memory and judgement	+	+			+	+			+
Visual/auditory hallucinations	+	+					+		
Anxiety	+	+					+	+	

*+ = Positive finding

A number of the early complaints appeared to be related to diffuse parasympathetic stimulation. This included six workers with nausea and vomiting, four with profuse perspiring, and two employees with diarrhea (Table 22).

TABLE 22
Clinical findings associated with employee illness, signs and symptoms for 9 workers with alleged chemical poisoning.

Signs and symptoms	Employee								
	A	B	C	D	E	F	G	H	I
Slurred speech	+								+
Visual acuity (↓)	+	+		+				+	+
Nystagmus	+			+			+	+	+
Ataxia	+	+		+	+	+		+	+
Clonus				+		+	+	+	
Babinski	P*			P				P	P
DTR's (↑)	+			+		+		+	+
Motor function extremities (↓)	+	+		+	+			+	+
Muscle tone (↓)	+	+		+	+			+	+
Altered pain/vibration/position	+	+			+	+		+	+
Dysmetria	+							+	+
Paresthesias	+	+	+	+	+	+		+	+
Dizziness	+	+	+	+		+			+
Nuchal rigidity	+		+	+					+
Tremulousness	+			+				+	+
Headache	+	+	+			+			
Drowsiness	+	+	+		+	+			+
Nausea/vomiting	+	+	+			+	+		+
Profuse perspiring		+			+			+	+
Diarrhea				+					+
Weight loss			+	+	+				+
Chest tightness/wheezing									+

*P = present

Headaches, drowsiness, tremulousness, dizziness and decreased visual acuity were also generally present during initial visits to company or local physicians. Miosis was not noted in any of the medical records. Significant weight loss was indicated by four employees.

These findings were sometimes followed by recovery, but in most instances they progressed to more serious peripheral and central nervous system involvement. This sequence often included considerable cerebellar dysfunction in the most serious cases (Table 22). Nystagmus was present in five employees, clonus was elicited in four workers, and marked ataxia was exhibited by seven of the nine employees. Dysmetria was present in three instances.

Paresthesia of the extremities, which was present in eight of nine workers, constituted the most prevalent abnormality found in the medical records. A Babinski was present in four employees and six exhibited increased deep tendon reflexes. Altered pain, vibration and position sense, decreased motor function and decreased muscle tone were found in six employees. Results of routine laboratory tests (Table 23) consistently fell within normal limits. Only one

TABLE 23
Clinical findings associated with employee illnesses, laboratory tests for 9 employees having alleged chemical poisoning.

Laboratory tests	Employee								
	A	B	C	D	E	F	G	H	I
WBC	N	N	N	N		N		N	N
RBC	N	N	N	N		N		N	N
Electrolytes	N	N	N	N		N		N	N
Urinalysis	N	N	N	N	N	N		N	N
VDRL	NR	NR		NR	NR	NR		NR	NR
RBC cholinesterase	→		N	N	N	N	N	N	N
Serum protein electrophoresis	N			N				N	
RA-latex	–					–			
ANA	–	–				–		–	–
Heavy metal screen	–								–
Viral screen	N/–							N/–	N/–
Spinal fluid	N	N		N	N	N		N	N
Spinal fluid electrophoresis	N	N		N		N		ABN	N

N = normal; NR = nonreactive; – (negative findings; + = positive results

abnormal erythrocyte cholinesterase determination was observed. This determination was completed shortly after the employee was hospitalized and decreased cholinesterase activity was reported by two independent laboratories. Tests for antinuclear antibodies, rheumatoid factors, heavy metals, and viruses were nonrevealing. Examinations of spinal fluid proved to be within normal limits for the six individuals who received lumbar punctures. One specimen revealed an elevated γ-globulin level in conjunction with a normal spinal fluid protein.

Records indicated that one hospitalized employee had decreased nerve conduction. Table 24 also shows that there were two abnormal electroencephalograms and one abnormal electromyogram.

Hospital records showed that physicians entertained the possibility of organophosphorus intoxication. The bizarre peripheral and central nervous system involvement, absence of depressed cholinesterase activity, and lack of overt parasympathetic overstimulation appeared to make organophosphorus intoxication unlikely. Physicians felt that the clinical picture was more compatible with diseases of demyelination or encephalitis. Table 25 indicates that four employees were diagnosed as having multiple sclerosis, two were thought to

TABLE 24
Results of other diagnostic procedures used to evaluate illness of 9 alleged chemically poisoned workers.

Diagnostic tests	Employee								
	A	B	C	D	E	F	G	H	I
Pneumoencephalogram	N	N							
Brain scan	N	N						N	N
Nerve conduction	→					N		N	
Skull X-rays	N	N			N			N	N
EEG	N		N		N			ABN	ABN
EMG						N		ABN	

N = normal
ABN = abnormal

TABLE 25
Working and final diagnoses by local physicaens of workers having an alleged chemical poisoning.

Diagnosis	Employees								
	A	B	C	D	E	F	G	H	I
Encephalitis			F			W			W
Encephalomyelitis	F			W					
Multiple sclerosis			F	F	F			F	
Anxiety neurosis	W	F					F		
Dissociative rxn	W								
Nonpsychotic OBS		F					F		
Undefined schizophrenia		W			W				
Post-infectious encephalomyeloradiculitis					W				F

W = Working diagnosis
F = Final diagnosis

have psychiatric disorders, and the remaining three employees considered to have encephalitis, encephalomyelitis, or postinfectious encephalomyeloradiculitis.

DISCUSSION

It was established from Velsicol's records, Industrial Accident Board files, and medical records that the nine individuals involved in this survey were employed in the manufacture of leptophos. Although formulating, mixing, and chemical reactions took place within a closed system, subsequent manufacturing processes and hygiene did not minimize the hazards associated with organophosphorus compounds. There was significant dermal exposure resulting from pouring of the molten pesticide and manually transferring the solid product. The fiber drums often contained liquid cores which contaminated the worker as the drums were split. Exposure was further increased by recycling contaminated gloves and not strictly enforcing personal hygiene such as washing before eating, showering, and changing clothes.

The Velsicol Chemical Corporation instituted changes in their plant safety program in April, 1975. Workers were then supplied with MSA respirators and strongly urged to follow strengthened hygiene practices designed to reduce exposure to leptophos. Unfortunately, at least six of the workers did not directly benefit from the new practices since the onset of their symptomatology was recorded before April, 1975. It was also during 1974 and 1975 that the Velsicol Chemical Corporation reached its highest export quotas of leptophos, 4.9 million and 3.1 million pounds, respectively. Quantitative measurements of airborne leptophos are not available for these peak periods of production. However, the industrial hygiene survey conducted by Environmental Labs just before termination of leptophos production showed evidence of airborne leptophos reaching levels of 383 $\mu g/m^3$[9].

It is known that in addition to substantial exposure to leptophos, the workers received concurrent exposure to high levels of n-hexane and toluene. The neurotoxic effects of n-hexane constitute an important factor in this study. Atmospheric concentrations of n-hexane ranging from 500 to 2500 ppm have been associated with polyneuropathies[6,15]. Workers who had experienced a severe neuropathy from exposure were examined recently by a neurologist who found spasticity and Babinski signs of central nervous system damage[14]. Quantitative measurements for n-hexane vapor are not available, but reports indicate that workers used large volumes of n-hexane during clean-up operations. Narcosis and high dermal exposure to n-hexane have been reported by two workers with other workers listing only exposure to "solvents" or "chemicals" on their medical records. Workers were reportedly contaminated with leptophos and toluene when the cooled product was broken into smaller pieces before pulverization. Literature indicates that subjects have experienced paresthesias of the skin, changes in muscular coordination and mental confusion at 200 ppm exposure levels to toluene vapors[11,12,13]. Recent evidence in the literature suggests that chronic toluene exposure may be associated with persistent cerebellar ataxia[1].

CONCLUSIONS

In retrospect, the employees in this study generally presented symptoms of organophosphorus intoxication (Table 26). These included muscarinic manifestations such as nausea, vomiting, diarrhea, increased sweating, and blurred vision. Central nervous system manifestations such as anxiety, hallucinations, drowsiness, tremulousness, depression, and psychotic reactions were also

TABLE 26
Clinical manifestations of poisoning by organophosphorus compounds.

A. Nicotinic manifestations	
1. Muscular twitching	4. Pallor
2. Fasciculation	5. Tachycardia
3. Weakness	
B. Muscarinic manifestations	
1. Increased sweating	6. Blurred vision
2. Increased salivation	7. Urinary incontinence
3. Nausea and vomiting	8. Wheezing
4. Diarrhea	9. Chest tightness
5. Miosis	
C. Central nervous system manifestations	
1. Anxiety	7. Confusion
2. Giddiness	8. Drowsiness
3. Tremulousness	9. Nightmares
4. Emotional lability	10. Slurred speech
5. Depression	11. Inability to concentrate
6. Psychotic reactions	12. Hallucinations

TABLE 27
Profile of neuropathies associated with exposure to n-hexane and organophosphorus compounds.

n-Hexane neuropathy	Organophosphorus toxicity and neuropathy
Insidious onset	Insidious onset (abrupt ante toxicity)
Progressive distal weakness	Progressive distal weakness
Sensory loss in extremities	Sensory loss in extremities
Ataxia and slapping gait	Ataxia and slapping gait
Altered pain, vibration and position sense	Altered pain, vibration and position sense
Altered deep tendon reflex (at high concentrations)	Altered deep tendon reflexes
Muscle weakness	Muscle weakness
Normal clinical laboratory tests	Normal clinical laboratory tests
	Depression, psychotic reactions, anxiety, hallucinations, increased sweating and salivation, miosis and blurred vision, nausea, vomiting, and diarrhea, tremulousness

evident. Table 27 compares the clinical profile of neuropathies associated with n-hexane and organophosphorus compounds. Clinical presentation of the neuropathies is apparently identical at high levels of exposure. Manifestations often seen with acute toxicity to organophosphate pesticides are shown at the bottom of the column in Table 24. These clinical changes were often present in the Velsicol employees. This does not exclude the possibility that the clinical presentations of the Velsicol employees were a result of n-hexane or even toluene intoxication. It was more likely that excessive dermal exposure with solvents increased the total body burden of leptophos. Prolonged toxic effects of this thiophosphonate could be anticipated, based on its high potential for deposition in fat[2].

Progression of the toxic manifestations resulted in a pattern resembling that of encephalitis and/or multiple sclerosis. Medical evaluations produced strikingly similar patterns among Velsicol employees, with laboratory tests failing to show an illness of viral, connective tissue or heavy metal etiology. Of the four individuals diagnosed as having multiple sclerosis, only one showed an elevated γ-globulin fraction in spinal fluid. This is not pathognomonic for multiple sclerosis, but approximately 70% of the cases do show an elevated immunoglobulin-G level when spinal fluid is within normal limits.

The prevalence of multiple sclerosis in the southern states ranges from six to fourteen per 100,000. It seems doubtful that seven out of 300 Velsicol employees handling similar materials could by chance exhibit multiple sclerosis or other diseases of demyelination. This survey indicated the possibility of axonopathy secondary to chemical exposure. Literature is replete with evidence concerning the neurotoxic effects of certain chemicals. There is evidence that these employees received substantial exposure to n-hexane and leptophos. Toxicological studies and epidemiological evidence presently implicates these compounds as prime suspects in producing neuropathies in the Velsicol employees. The possibility exists that the effects from leptophos and n-hexane could be additive.

Of the nine employees whose records at Velsicol Chemical Corporation and the Texas Industrial Accident Board suggested the possibility of leptophos poisoning, five were found in NIOSH's Medical Examination to have a neurology abnormality; two psychology; two ENG; and one, EMG abnormality.

III – RECOMMENDATIONS

Prevention and early detection

All worker safety and health programs should be directed to prevention and early detection of problem areas. This means current awareness and communication among federal agencies, manufacturers, formulators, and users of toxic chemicals.

Industrial hygiene practices

Adequate engineering controls, improved work practices, and effective worker protective equipment should be implemented where workers in their job--environment may be exposed to known toxic chemicals. This requires knowing what is hazardous at the work site, how specifically to prevent or control the hazards, and active surveillance to effect control and prevention.

Medical surveillance and monitoring

Medical surveillance and monitoring should be initiated to assure the adequacy of worker protection. This should include the use of functional tests and the development of baseline medical data for each worker for comparison with subsequent medical examinations. Worker awareness of toxic effects should be insured through use of educational programs focusing on signs and symptoms associated with exposure to specific toxic chemicals in the work environment. Local physicians should be directly and specifically alerted to the need for emphasis on occupational histories to evaluate the potential for job-related chemical poisoning. Those responsible for protecting the worker's health should provide the detailed specific information necessary to effect these programs.

Medical examination for evaluating reversibility of effects

Since the medical findings in this study may reflect slow or incomplete recovery and in some instances permanent damage of serious consequence to the worker, medical follow-up examinations should be undertaken in appropriate cases to determine the reversibility of the observed effects and to better understand the significance of any diminished functional capacity to the demands of the worker's current and potential job opportunities.

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