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Neurobehavioral Outcomes Among Farm and Nonfarm Rural Ecuadorians

DONALD C. COLE,* FERNANDO CARPIO,† JIM JULIAN,‡ NINFA LEON,†
RAMONA CARBOTTE§ AND HIPATIA DE ALMEIDA†

** Environmental Health Program, McMaster University, Ontario, Canada*
† Fundacion NUESTRA, Quito, Ecuador
‡ Occupational Health Program, McMaster University, Ontario, Canada
§ Department of Psychiatry, McMaster University, Ontario, Canada

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COLE, D. C., F. CARPIO, J. JULIAN, N. LEON, R. CARBOTTE AND H. DE ALMEIDA. *Neurobehavioral outcomes among farm and nonfarm rural Ecuadorians.* NEUROTOXICOL TERATOL **19**(4) 277–286, 1997.—International researchers have urged greater use of simple neurobehavioral batteries in developing country settings where higher levels of exposure and a variety of cultural and demographic factors may both occur. We conducted a cross-sectional survey of 144 farm members and 72 age and education frequency-matched controls from rural Ecuador, using an amplified Neurobehavioral Core Test Battery. Farm members ranged from those with only indirect pesticide contact to applicators regularly applying organophosphate and carbamate insecticides by backpack sprayer. The distributions of scores showed those with less than 4 years of formal education and at the extremes of age (<16 or >65 years old) contributed sufficiently to nonnormality that they had to be excluded from subsequent analyses (resultant $n = 170$). After adjustment for age and education, language-based IQ test scores and farm membership were the most consistent determinants of neurobehavioral outcomes. Visual–spatial tasks were the most sensitive to the effects of farm membership. Gender (women better than men), alcohol problems, and solvent use were also important for some neurobehavioral tests. © 1997 Elsevier Science Inc.

Neuropsychological tests   Cross-cultural   Pesticides   Agricultural workers' diseases   Nervous system disorders   Ecuador

THE adverse health impacts of agricultural pesticide use has been an ongoing concern among health personnel over the last two decades (32). Although early case series clearly indicated psychiatric problems among those with chronic exposure, particularly to organophosphate compounds (14), and subsequent work has documented central nervous system sequelae of acute poisoning episodes (29), documentation of neurobevioral effects among those with usual exposures has been difficult (22). In developing countries, such as Ecuador, exposures are generally higher due to limited use of personal protective equipment while handling more toxic products (15). Assessments of neurobehavioral function might be expected to demonstrate impacts more easily in such exposure situations (18).

Yet the wide disparities in levels of education and socioeconomic status between general populations in developing countries and those of northern countries in which neurobehavioral tests were developed complicate their use (23). A cross-cultural assessment sponsored by the World Health Organization found significant differences between one Latin American country (Nicaragua) and other centres in a variety of tests potentially due to divergent levels of general education and familiarity with the kinds of tasks performed in neurobehavioral testing (4). It called for normative data from subjects with diverse levels of education and socioeconomic backgrounds, particularly from other Latin American countries.

An opportunity to carry out such research in another Latin American country was afforded by the interest of the Rockefeller Foundation and the International Agricultural Research Centers in assessing the sustainability of pesticide use among agricultural producers. Work in the Phillipines was followed by a project with the Potato Investigation Center in Ec-

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Requests for reprints should be addressed to Donald C. Cole, HSC 2C1, McMaster University, 1200 Main St. W., Hamilton, Ontario, Canada L8N 3Z5. Tel: (905) 525-9140, ext. 22037; Fax: (905) 577-0017; E-mail: coledon@fhs.mcmaster.ca

uador, which combined research on agricultural production, environmental contamination, and human health impacts. The human health project included a poisoning surveillance system, an exposure monitoring study, and a cross-sectional study among the farm population. This article reports on the neurobehaviorial outcomes across exposure groups in the cross-sectional study.

METHOD

Setting

Ecuador is classified as having a medium level of human development (31). The canton of Montufar, the study site, is in the northern province of Carchi on the central sierra, near the Columbian border, and has an estimated population of 29,000. It has a dispersed rural population farming potatoes, grains, and dairy cattle around a small town, San Gabriel. Literacy in 1982 was estimated at 86% with an average schooling of approximately grade five (5). Prior to the initiation of the project, Carchi had the highest provincial rates of reported pesticide poisonings, 17 cases per 100,000 population (7).

The agricultural economics research team had randomly selected collaborating potato farmers from the municipal land registry within two watersheds with high potato production. Among those actively farming, they obtained collaborators who provided monthly production information. It became clear that potato production is a risky, high-cost venture, requiring many more labor days and purchased inputs than other field crops (12). The collaborating farmers used 38 different fungicides and 28 different insecticides, applying to each plot, on average, more than seven applications with 2.46 products in each application, almost all with backpack sprayers due to the hilly terrain. Forty-three different active ingredients (a.i.) were used but three compounds dominated: the dithiocarbamate fungicide, mancozeb, made up more than 80% of all fungicide a.i. applied; the carbamate, carbofuran, and the organophosphate, methamidophos, both restricted products in the US and Canada, made up 47% and 43% of all insecticide a.i. applied, respectively. Structured farm observations and interviews of the farmers revealed a number of practices likely to increase pesticide exposure: mixing pesticides with hands and a stick (36/40 farms), leaking backpack sprayers (28/40), no use of effective person protective equipment other than rubber boots (38/40), storage of pesticides in the farmhouse (19/40), and potentially unsafe pesticide disposal (35/40) (8).

Populations

The health team conducted a census of all those capable of doing farm work, including family members and various kinds of contract labour. The farm population included those not doing direct farm work (consumers), those primarily performing work in the fields (exposed), and those primarily applying pesticides (applicators). Because of the flexible nature of work assignments among these small producers, applicators would also conduct other work in the fields and exposed workers would also be present during applications. The health team included all applicators, one-half the exposed and all consumers in the sampling frame, thereby oversampling the extremes of likely exposure to achieve greater contrast within the farm population. Changes between the initial sampling frame and the final participants arose because of farmers who died (two) or moved (one), contract labourers who were absent for more than 1 month or family members who were reluctant to participate in the extensive testing required (both the latter two groups accounted for <20% of the initial census population). Replacements for contract labourers had to have worked on the farm for more than 4 months and have carried out similar tasks. Age, sex, and formal education matched controls were obtained from the local nonfarm population through community groups and the municipal government, with one control for every two exposed or applicator farm members on a frequency match basis. Occupations of the controls included housewife, student, labourer, skilled worker, small business person, and professional. Incentives to participation included the equivalent of one-half the average daily local wage as well as a snack during the assessment (overall length approximately 4 h). All participants provided informed verbal consent prior to testing and were provided with immediate feedback on important clinical examination findings, with referrals by the field physician as appropriate.

Exposures

Individual exposure measures were obtained by an interviewer-administered questionnaire. All groups were asked about current household potato consumption and the number of persons in the household (to facilitate calculation of kg/person estimated weekly intakes), as a potential route for pesticide ingestion via the main constituent of the local diet. (Piped water for the area came from sufficiently high up the mountain to likely preclude pesticide exposure.) A record of prior pesticide poisonings by year was made. Work exposures targeted included solvents, metals, and pesticides across all groups. Among the exposed and applicator farm population, information regarding past pesticide use, by name and years, and current use, in hours during the last month, was obtained from the participant. The agricultural research team provided farm level information on recent pesticide applications in a representative 6-month period for dithiocarbamate fungicides, carbamate and organophosphorus insecticides, in general, and methamidophos, in particular. Pilot testing of the questionnaire in a similar rural area resulted in modifications of wording and order. In addition, hemoglobin-adjusted red cell cholinesterase was measured on all participants as a biological effect marker of current and recent anticholinesterase insecticide exposure using EQM kit base on an adapted Ellman method (24).

Neurobehavioral Measures

The neurobehavioral battery used built on the Neurobehavioral Core Test Battery (NCTB), developed and tested during a World Health Organization collaborative endeavour (9). Detailed descriptions of the tests and administration procedures are in standard reference tests (21). The NCTB comprises: Digit Span, Benton Visual Retention, Digit Symbol, Simple Reaction Time, Santa Anna, Pursuit Aiming Test, and the Profile of Mood States (POMS). The first five tests have been shown to be sensitive to the effects of known neurotoxins across a variety of exposed populations (4). The Benton Visual Retention test we used included 15 figures rather than the 10 in the NCTB to reduce ceiling effects. We added several other tests that were found to be sensitive to the effects of previous poisoning by methamidophos: Digit Vigilance, Trails A & B, and Block Design (29). We also included several of the language-based tests from the Weschler Adult Intelligence Scale (WAIS-verbal): Information, Similarities, and Vocabulary. These latter three had been specifically adapted from the standard Latin American translation by the Ecuadorean clinical psychologist (H de A) during her clinical work in Quito and prior studies in the Carchi area, substituting words and phrases more common in highland Ecuador. These language-based tests were viewed as relative control variables, primarily tapping capacities unlikely to be affected by neurotoxic exposures (21).

Procedures were based on the WHO manual for the NCTB, as translated into Spanish by Ecuadorean members of the research team and reviewed by one Nicaraguan-based WHO collaborator, Matt Keifer. Non-NCTB Spanish language procedures came from the Nicaraguan team's translations. Matt Keifer of the WHO international collaborative group also conducted training sessions with the supervising clinical psychologist (H de A) and the sole neurobehavioral examiner (a school teacher from San Gabriel). Field trials occurred first with patients of the clinical psychologist in Quito and second with agricultural workers from Carchi who were not part of the study group. These pilot studies permitted adjustments in ordering and instructions prior to application. The neurobehavioral examiner conducted the testing in a 2 hour block, unaware of the participants' exposure status, questionnaire responses, or clinical examination findings (all carried out separately by the field physician). Testing of farm participants was done in community centers located close to agricultural areas whereas controls were tested in the San Gabriel high school, community center, or municipal building, depending on their occupation. Field staff aimed to provide adequate lighting and limit distractions in order to optimize test conditions within the constraints posed by the rural, developing country setting. At the end of each day, the neurobehavorial examiner reviewed the neurobehavioral test forms for completeness and calculated scores on those tests requiring them, according to standardized methods. The supervising clinical psychologist reviewed coding, recalculated scores to check for consistency, and transferred final results to a summary sheet used for data entry.

Covariates

All participants completed a brief medical history, concentrating on those diseases or injuries that could independently affect outcomes (concomitant problems such as a history of head injury). Information on the potential effects of alcohol use was obtained using a 10-item Ecuadorian questionnaire from the Alcoholic Rehabilitation Center (CRA). Similar to the brief MAST (28) but adapted to Ecuadorean conditions, questions deal predominantly with social disruption (e.g., trouble at work because of drinking) with additional items on drinking behaviors (e.g., needing a drink to feel all right), medical treatment, and others' comments on one's drinking. Also similar to the brief MAST, some questions are weighted higher than others (e.g., receiving medical treatment scores 9, missing work scores 3) to result in an overall score (potential range 0–31) where increasing values reflect greater degrees of life disruption.

Data Analysis

Each section of the questionnaire and the entire neurobehavioral score sheet were entered into separate FOXPRO data files by the Ecuadorian team. The Canadian research team conducted an audit of the entire record for 10% of the records. For those sections with deficiencies, all records were reviewed and corrected by comparison to the hard copy questionnaires. Data distributions were visualized using MINITAB analytic software (Windows version, 9.2 release). Such visualization facilitated a number of data analysis steps: identification of outliers, for further error checking; aggregation across variables (e.g., all concomitant medical conditions potentially affecting neurobehavioral scores together); collapse of categories within variables (e.g., pesticide poisonings to none vs. one or more); and identification of specific measures of neurobehavioral tests (e.g., number correct on Pursuit Aiming vs. incorrect or all completed). Flat files were then created for further analysis using MINITAB and SAS microcomputer versions.

Distributions of a number of the neurobehavioral outcomes were found to deviate considerably from normal (e.g., ceiling effects on Trail B times) with increasing variance noted at the extremes of age and educational level. Although fundamentally designed for an adult population, the presence of adolescent workers on the farms had led the Ecuadorean members of the research team to include younger participants. However, numbers were small for the control populations in both the <16 and 66+ age groups (see Table 3), leading the Canadian research team to restrict the populations to participants between the ages of 16 to 65. As well, the neurobehavioral tests used were primarily designed for schooled populations but considerable numbers of the population had 3 years or less of formal education with corresponding very low scores. Hence, it was also decided to only include those with at least 4 years of education for further analyses. Contrast coding was utilized to compare each farm group with the control population. Univariate regressions were conducted for each neurobehavioral outcome, including those variables that demonstrated bivariate differences between groups and their first-order interactions. The level of significance chosen for reporting was $p < 0.10$.

Individual tests were grouped into functional domains commonly sampled in neuropsychological studies of clinical populations (16). Similar clusters of tests had also emerged from a factor analysis of normative data using a 3 h neuropsychological test battery with healthy US blue collar workers (30). The five domains were: attention (Digit Vigilance and Digit Span); visuo-spatial (Block Design and Benton Visual Retention); psychomotor (Digit Symbol and Trails A & B); motor (Visual and Auditory Reaction Times, Santa Anna in the dominant hand, and Pursuit Aiming); and affective (POMS). For the affective domain, an overall summary mood score was used based on the standardized combination of values from the different subscales of the POMS. For each of the other four domains, aggregation across specific tests was required. Linear regression prediction equations based on age and education were developed for each test using the results for the age and education restricted control populations. A Z-score was then calculated for each farm participant by subtracting the age and education based predicted value for the test from the farm member's raw score and dividing the difference by the standard deviation of the controls. For some tests, a higher raw score indicated worse performance (e.g., reaction time). For these tests, the sign of the Z-scores were reversed, so that for all transformed values, high scores reflected better performance. The Z-scores were then averaged across those tests pertinent to a domain to obtain a summary Z-score for each functional domain for each farm participant. Finally, the arithmetic mean of these summary domain Z-scores provided an overall neurobehavioral score.

RESULTS

Table 1 presents the values of key demographic, language-based test, exposure, and health outcome variables across the

TABLE 1

EXPOSURE GROUP CHARACTERISTICS AND COMPARISONS

Variable	Control	Consumers	Exposed	Applicators	ALL	Group Effect p-Value
Group size (n)	72	23	28	123	246	
Gender						
Male	79%	0%	14%	96%	73%	<0.001
Female	21%	100%	86%	4%	27%	
Age	36.40*	37.04	34.74	37.99	37.06	0.81
	18.06	8.25	17.16	16.28	17.03	
Education (years)	6.31*	6.48	5.71	5.79	6.00	0.57
	3.41	3.44	2.73	3.02	3.14	
Language-based scores						
Information	6.97*	5.17	5.32	5.54	5.90	0.001
	3.07	1.67	2.51	2.47	2.68	
Similarities	7.29*	6.65	6.29	6.33	6.64	0.011
	2.30	1.90	1.49	1.92	2.03	
Vocabulary	7.24*	6.83	6.00	6.15	6.52	0.018
	2.67	2.29	2.31	2.43	2.52	
Relevant exposures						
Alcohol use (coeff)	9.06*	3.87	4.68	8.55	7.82	0.002
	8.53	4.68	6.46	7.12	7.49	
Solvent use (years)	1.22*	0.44	0.25	0.65	0.75	0.58
	4.89	2.09	1.00	3.39	3.64	
Pesticide poisonings						
One or more	3%	13%	7%	28%	17%	<0.001
Potato intake (kg/person)	4.27*	5.40	5.94	6.34	5.61	<0.001
	2.47	2.27	3.06	3.10	2.98	
Other outcomes						
Hemoglobin-adjusted red cell cholinesterase (IU/min/ml/g)	29.75*	25.58	25.25	26.56	27.25	<0.001
	3.63	6.31	5.95	4.06	4.72	
Concommitant neurobehavioral conditions						
One or more	17%	9%	5%	8%		0.005

*Top value represents the mean and bottom value represents the SD.

four exposure groups. A gender-based division of labour is apparent in contrasting the farm consumers (all women) and with the pesticide applicators (predominantly male). Considerable success was achieved in obtaining similar levels of age and education across the exposure groups (both nonsignificant group effects). However, WAIS verbal tests did show differences, with the farm groups scoring consistently lower than the controls. Among the relevant exposures, the controls reported more difficulties with alcohol but fewer lifetime pesticide poisonings than the farm groups, with male applicators showing greater difficulty with alcohol and former poisonings than the other farm groups. As expected estimated individual potato consumption was significantly higher in the farm groups, with applicators reporting the highest rate of consumption of over 6 kg per week, a clear indication of the role of potatoes as a staple in this region. Hemoglobin-adjusted red cell cholinesterase levels were also lower in the farm groups, consistent with ongoing organophosphate and carbamate exposure. Other medical conditions or past injuries that might have affected neurobehavioral performance were more prevalent among the controls. If those with such problems had participated in the study because they wanted more information on their functioning, the resulting selection bias would have tended to reduce any observed differences with the farm population.

Table 2 provides descriptive information on pesticide exposure data for the farm groups. An increasing gradient is apparent for cumulative past years and current hours of work with pesticides from the consumers through the generally work exposed to the applicators. The recent variable of numbers of pesticide applications in the last 6 months shows less distinction because it is derived from farm level information rather than being a measure of each individual's work with pesticides. Clearly, work exposure to organophosphate and carbamate insecticides is frequent enough in the farm population to be consistent with reductions in cholinesterase levels.

Table 3 presents raw summary statistics for the neurobehavioral outcomes across age and exposure groups, permitting comparison with results from other countries (4,9). Sample sizes for age/exposure cells tend to be small (see Table 3) but the numbers in the control and applicator populations are comparable to those in European groups involved in assessment of the NCTB (9). Nevertheless, wide ranges are apparent on all tests, demonstrating considerable interindividual variation. Various trends are apparent even in the raw data. The very young (<16) and very old (66+) generally had poorer scores than those in their middle years of life. Farm groups tended to do worse than the control group on the majority of tests.

TABLE 2

PESTICIDE EXPOSURE SUMMARY FOR FARM GROUPS

Variable	Consumers	Exposed	Applicators
Group size (n)	23	28	123
General pesticide use			
Past (cumulative years,	0.00*	10.26	15.96
individual measure)	0.00	8.44	10.73
Recent (# applications in last 6 months,	27.50*	23.60	24.49
farm measure)	13.75	15.60	13.25
Current (hours during last month,	4.52*	42.71	110.50
individual measure)	20.01	37.45	59.55
Dithiocarbamate fungicide use			
Past (years)	0.00*	10.46	15.14
	0.00	8.34	9.68
Recent (#app)	12.32*	11.08	12.18
	5.74	6.87	6.33
Current (h)	0.17*	1.29	24.59
	0.83	3.09	28.06
Insecticide use			
Past (years)	0.00*	10.89	16.59
	0.00	8.43	10.77
Recent (#app)	15.18*	12.52	12.31
	9.89	10.23	9.27
Current (h)	0.17*	4.00	29.38
	0.83	7.46	30.76

*Top values represent the mean and bottom value represents the SD.

Figures 1 and 2 provide scatter plots of scores against age for the control population, stratified by level of formal education. Digit Symbol Substitution scores decline markedly with lower levels of education and increasing age. Similarly, on Trails B many more older and lower education controls failed to complete the test within the 5-min maximum time allowed for completion (as indicated by the truncated distributions at the 300-s mark). The examiner observed considerable difficulty with these paper-and-pencil tests among those not generally writing in their daily work. The vertical lines indicate the cutoffs we adopted for age and the filled in circles denote those with grade 1–3 formal education who were excluded in subsequent analyses.

In subsequent univariate analyses ($n = 170$, Table 4), the relatively consistent effects of age and language related scores are apparent, whereas the effects of group and particular exposures are less apparent. The first-order interactions are also diverse and the range of variance accounted for (R^2) varies from only 14%, for the POMS, up to 64%, for the Pursuit Aiming test.

After normalization and standardization of direction across the tests, the reader can more easily note the effects and relative contribution of population groups and other variables on neurobehavioral functions (Table 5). Of note is that the intercept for each regression is substantially negative, indicating a farm population with general deficits in comparison to the controls. Consumers did worse in spatial, psychomotor, and motor functions and therefore did worse overall than controls. The generally exposed group did worse on spatial tests and the applicators did worse on attention tests. Gender, alcohol, and prior pesticide poisonings had no effect on overall score, although males did worse on spatial tests and those with problems with alcohol demonstrated decreased attention. As expected, superior performance in language functions resulted in higher scores, but not enough to compensate for the group differences. Finally, despite an inconsistent determinant of individual tests and no discernible effect on domain results, potato intake still accounted for some drop in overall neurobehavioral performance. The extent of the effect is similar to that observed for solvent use (small) among the nonfarm population but in the opposite direction. No interaction terms were found to be significant for the domain or mean scores.

DISCUSSION

The findings of this cross-sectional study add to the growing experience of using sensitive neurobehavioral tests in developing country settings, in general, and in detecting adverse impacts of agricultural life and work including pesticide use, in particular.

In a cross-cultural application, we have demonstrated that educational level is initially the most important variable to consider. This is consistent with the findings of Anger et al. (4), which showed considerably poorer scores among newly literate adult Nicaraguan males and subsequently among non-neurotoxicant-exposed Hispanic groups in the United States (3). Average raw scores, in our population with an average of 6 years of formal education, are intermediate between those observed in Nicaraguan males and those measured on developed country populations with average levels of education in the high school range. The scores of those with the lowest levels of education were sufficiently low to argue against their inclusion in modelling exercises.

Of similar importance was age, with several neurobehavioral tests showing nonlinear relationships with age at the ex-

TABLE 3

NEUROBEHAVIORAL OUTCOMES BY EXPOSURE GROUP AND AGE GROUP: MEAN (STANDARD DEVIATION)

NB Outcome (Range)	Group	Age Group						
		< 16	16–25	26–35	36–45	46–55	56–65	66 +
Digit vigilance (s)	Ctl	521 (71)	361 (85)	361 (104)	450 (96)	490 (93)	552 (65)	581 (28)
(154, 623)	Con	453 (59)	378 (154)	479 (44)	398 (—)	498 (80)	600 (0)	— (—)
	Exp$_1$	526 (47)	415 (130)	476 (47)	421 (48)	499 (78)	559 (36)	600 (—)
	Exp$_2$	485 (72)	428 (105)	466 (84)	476 (107)	538 (64)	571 (47)	567 (46)
Digit span	Ctl	8.2 (0.8)	8.5 (1.0)	8.8 (1.1)	7.0 (1.6)	6.8 (1.1)	7.3 (1.2)	8.0 (0.0)
(number recalled)	Con	8.5 (0.6)	8.5 (0.6)	7.3 (2.2)	7.0 (—)	6.7 (2.4)	6.3 (2.1)	— (—)
(0,11)	Exp$_1$	8.0 (1.0)	8.7 (1.4)	8.5 (0.6)	7.5 (2.4)	7.0 (1.4)	5.3 (1.5)	7.0 (—)
	Exp$_2$	8.0 (1.3)	7.2 (1.8)	6.8 (1.8)	6.8 (2.0)	6.4 (1.4)	6.3 (1.9)	5.2 (2.7)
Block design	Ctl	8.8 (1.8)	10.4 (1.9)	10.4 (1.7)	9.3 (2.8)	9.3 (2.0)	9.3 (2.1)	7.0 (2.8)
(score)	Con	5.8 (1.0)	8.5 (3.1)	7.3 (1.9)	10.0 (—)	7.3 (2.7)	6.7 (0.6)	— (—)
(1, 18)	Exp$_1$	8.3 (3.2)	8.4 (2.5)	8.3 (2.9)	6.8 (4.6)	6.3 (0.5)	6.7 (1.5)	7.0 (—)
	Exp$_2$	8.2 (2.1)	7.7 (2.0)	8.8 (2.3)	8.2 (2.3)	6.6 (2.4)	6.3 (2.2)	6.4 (1.3)
Benton	Ctl	12.7 (0.8)	11.5 (2.0)	11.2 (2.3)	11.2 (2.3)	9.9 (3.1)	9.6 (2.3)	7.5 (0.7)
(figures recognized)	Con	11.0 (3.4)	10.0 (2.9)	9.3 (1.0)	12.0 (—)	6.7 (2.2)	6.3 (2.3)	— (—)
(3,15)	Exp$_1$	10.3 (1.5)	10.4 (3.9)	9.8 (2.2)	8.3 (2.2)	6.0 (2.2)	6.3 (0.6)	4.0 (—)
	Exp$_2$	10.8 (2.3)	9.4 (2.6)	8.7 (2.7)	8.7 (2.6)	6.8 (2.0)	6.7 (2.4)	5.8 (0.8)
Digit symbol	Ctl	30.7 (6.8)	39.8 (14.4)	37.7 (13.4)	26.6 (13.3)	15.9 (6.7)	13.8 (6.9)	12.5 (7.8)
(correct matches)	Con	31.8 (5.9)	42.0 (13.4)	27.0 (8.8)	32.0 (—)	18.9 (12.1)	5.7 (1.2)	— (—)
(3, 82)	Exp$_1$	36.7 (5.5)	37.7 (14.9)	30.8 (9.4)	22.3 (7.5)	14.0 (3.7)	14.0 (5.6)	8.0 (—)
	Exp$_2$	30.0 (4.6)	34.2 (9.6)	32.6 (12.6)	25.0 (12.4)	15.1 (6.5)	14.7 (6.5)	10.0 (2.6)
Trails A (s)	Ctl	65 (13)	43 (11)	48 (21)	87 (81)	80 (39)	120 (85)	131 (50)
(21, 300)	Con	71 (21)	79 (52)	79 (25)	63 (—)	139 (103)	241 (50)	— (—)
	Exp$_1$	81 (45)	78 (33)	72 (33)	102 (49)	136 (96)	154 (37)	197 (—)
	Exp$_2$	54 (14)	70 (29)	73 (32)	86 (53)	119 (65)	125 (50)	145 (60)
Trails B (s)	Ctl	155 (75)	107 (26)	122 (49)	181 (81)	223 (65)	226 (57)	300 (—)
(30, 300)	Con	132 (19)	197 (91)	184 (78)	123 (—)	227 (94)	300 (0)	— (—)
	Exp$_1$	143 (61)	179 (93)	151 (45)	186 (79)	228 (80)	300 (0)	300 (—)
	Exp$_2$	146 (29)	165 (68)	164 (68)	205 (78)	254 (77)	264 (55)	254 (51)
Visual reaction time	Ctl	363 (55)	287 (42)	316 (63)	313 (63)	309 (64)	344 (36)	354 (55)
(average ms)	Con	369 (78)	316 (82)	324 (45)	248 (—)	363 (98)	433 (96)	— (—)
(211, 1010)	Exp$_1$	351 (43)	303 (66)	300 (30)	345 (70)	422 (80)	330 (56)	385 (—)
	Exp$_2$	315 (44)	282 (48)	274 (32)	337 (121)	386 (182)	361 (94)	313 (60)
Auditory reaction time	Ctl	286 (38)	235 (28)	242 (24)	270 (45)	265 (18)	307 (43)	347 (96)
(average ms)	Con	297 (19)	246 (5)	250 (35)	237 (—)	291 (45)	387 (132)	— (—)
(176, 523)	Exp$_1$	318 (28)	244 (35)	264 (13)	283 (47)	361 (91)	280 (22)	309 (—)
	Exp$_2$	277 (47)	239 (34)	237 (23)	263 (51)	272 (31)	283 (49)	273 (19)
Santa Anna	Ctl	34 (4.2)	43 (5.6)	43 (6.3)	38 (9.0)	37 (6.7)	32 (7.7)	21 (9.2)
(dominant hand	Con	36 (8.5)	46 (7.9)	41 (6.7)	46 (—)	33 (9.5)	18 (4.2)	— (—)
pegs turned)	Exp$_1$	33 (7.1)	39 (6.8)	41 (3.9)	35 (6.1)	37 (6.2)	30 (4.5)	18 (—)
(13, 56)	Exp$_2$	34 (4.5)	37 (5.4)	37 (4.9)	34 (8.0)	28 (6.0)	29 (6.0)	27 (4.2)
Pursuit aiming	Ctl	95 (15)	143 (32)	143 (36)	120 (44)	80 (23)	73 (35)	51 (42)
(dots in circles)	Con	138 (28)	135 (32)	112 (17)	124 (—)	82 (25)	29 (13)	— (—)
(11, 218)	Exp$_1$	105 (25)	138 (39)	135 (29)	100 (29)	66 (31)	72 (26)	25 (—)
	Exp$_2$	113 (26)	125 (29)	129 (33)	104 (34)	76 (27)	66 (22)	57 (26)
POMS	Ctl	31.0 (20.9)	46.4 (29.9)	55.2 (27.9)	51.1 (30.5)	38.8 (29.4)	35.7 (27.7)	39.5 (7.8)
(−5, 114)	Con	31.0 (15.4)	43.7 (25.0)	41.8 (37.3)	47.0 (—)	63.3 (26.4)	78.0 (5.6)	— (—)
	Exp$_1$	35.0 (31.0)	42.9 (23.2)	35.8 (8.5)	65.8 (25.4)	36.5 (28.0)	50.0 (22.3)	22.0 (—)
	Exp$_2$	45.7 (25.2)	38.8 (23.0)	37.9 (24.6)	35.7 (23.5)	48.1 (24.6)	48.8 (32.4)	28.6 (8.8)
Sample size	Ctl	6	20	13	10	9	12	2
(by cell)	Con	4	4	4	1	7	3	0
	Exp1	3	9	4	4	4	3	1
	Exp2	6	30	23	23	15	21	5

Ctl = control, Con = consumers, Exp$_1$ = exposed nonapplicators, Exp$_2$ = applicators.

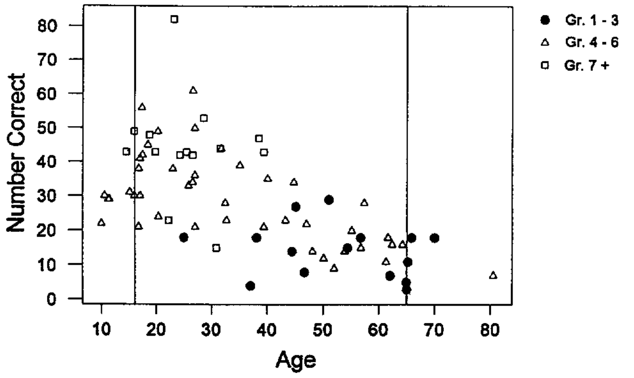

FIG. 1. Digit Symbol scores by age and education (72 controls).

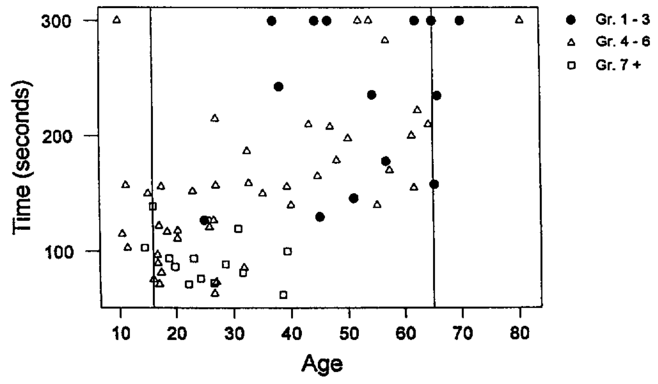

FIG. 2. Trail B times by age and education (72 controls).

tremes. For the Digit Vigilance, Reaction Times, and Santa Anna tests, scores at the extremes of age were generally poorer than those during the middle ages. The age range of the population in this study was wider than that used in NCTB Cross-Cultural Assessment, because the farm work-force included a number of young teenagers and older people who actively contribute to production. Hence, the difficulties in application of the tests arose because of the social composition of the population in a rural developing country setting, rather than properties of the test apparent in earlier cross-cultural comparisons.

Similar exercises in cross-cultural comparisons have been initiated buy the WHO to research neuropsychiatric aspects of HIV infection (23) and the epidemiology of dementia (10). The latter raise a number of potential explanations for the fact that poorer scores on neurobehavioral tests are associated with lower levels of education, similar to the results reported here. Lower premorbid levels of intellectual functioning may be important as may a range of other "deprivations" such as poorer nutrition, health care, or quality of education. Absence of functional literacy or motor habituation despite formal education may be occurring, as exemplified by the seeming unfamiliarity with pencil and paper use, particularly among the older age group with low levels of education. Of additional interest here may be that functional illiteracy may result in greater pesticide exposure due to inadequate understanding of toxicity and precautions, information available on pesticide labels. Exclusion of those with the lowest education may thus reduce the observed neurotoxic effects associated with farm membership.

Despite these difficulties, we were able to demonstrate poorer performance in the farm population relative to healthy controls, independent of age and education. Attentional problems (as reflected in performance on Digit Vigilance and Digit Span) were also found among Nicaraguan farm workers previously suffering a hospitalization for organophosphate poisoning compared to controls who had not been poisoned (29). The same workers showed poorer performance on visuo-spatial tests (Benton Visual Retention Test and Block Design) as did our farm population but the latter also did worse on psychomotor tests (Trails A and Digit Symbol Substitution). Examples of other groups with difficulties on visuospatial tests include Indian DDT sprayers (25) and a group of Cuban farm workers exposed to organophosphates and carbamates who both faired poorly on the Bender test for visuospatial functions and visual dexterity. As well, Maizlish and colleagues (22) found poorer performance on the Digit Symbol Substitution test among diazinon applicators compared to nonapplicators but it was not statistically significant. The Santa Anna dexterity tests and the Pursuit Aiming II test, both tapping motor ability, showed decrements among both previously poisoned Nicaraguan workers and our farm population. Anger et al. (4), in summarizing the rate of significant results in worksite studies, indicated that the Santa Anna was among the most sensitive to adverse neurobehavioral effects among the exposed (62% of studies) with the Benton (50%), Digit Symbol (45%), and Digit Span (44%) not far behind.

In contrast to Anger at al.'s summary but similar to Nicaraguan work, we did not find significant decrements in reaction time latencies in the farm population except in relation to potato consumption for visual reaction time. In fact, the decrements in neurobehavioral function (reaction time, Trails A & POMS) as the result of greater ongoing consumption of a potentially pesticide-contaminated food have not been previously reported. Nervous system symptoms do form part of the clinical picture in acute pesticide food poisoning outbreaks (20). Potatoes have been shown to harbour residues of organochlorines in China (11) and carbamates, both aldicarb (13) and carbofuran (26), in Canada. Potatoes may also contain naturally occurring toxic glycoalkaloids (17) or harbour mycotoxins due to common fungal infections. Hence, a route of chronic exposure to a range of toxins could exist. Alternatively, potato consumption may be capturing other unmeasured characteristics of the farm population, such as lower household socioeconomic status or lower consumption of other essential foods required for nervous system function.

Not only the source but also the timing and reversibility of the neurobehavioral effects observed must be considered. The "natural history" of human exposure and adverse health effects are not clear. For example, the latency (time from first exposure to appearance of the effects), dose–response relations, and duration of carbamate or organophosphate neurobehavioral effects are not known. When exposure is ongoing, acute (short term, hours to days), subacute (longer but still reversible, weeks), and chronic (long term, often irreversible, months to years) effects are all superimposed. Consistent with lower hemoglobin-adjusted red cell cholinesterase levels among the farm population, are the observed effects a combination of acute and subacute exposures to the current pesticides? Are some of the effects residual from earlier organophosphate, carbamate, or even organochlorine usage? Protracted behavioral neurotoxicity has been recently related to structural pest control

TABLE 4

NEUROBEHAVIORAL TEST SCORES STATISTICALLY SIGNIFICANT* REGRESSION COEFFICIENTS (SE)

Predictors	Digit Vigilance	Digit Span	Block	Benton	Digit Symbol	Trails A	Trails B	Visual RT	Auditory RT	Santa Anna	Pursuit Aiming	POMS
Intercept	553.599 (46.431)	6.894 (0.569)	5.061 (0.414)	8.260 (0.608)	24.150 (3.195)	−29.728 (35.357)	224.151 (20.287)	300.272 (33.396)	240.913 (13.725)	33.598 (2.180)	91.703 (12.628)	30.238 (4.471)
Group1 CON vs. CTL†	35.276 (11.617)	—	—	—	—	−27.807 (14.792)	—	—	—	—	−7.987 (3.619)	—
Group 2 EXP_1 vs. CTL†	—	—	−2.322 (0.561)	−0.977 (0.289)	—	—	—	—	—	—	—	—
Group 3 EXP_2 vs. CTL†	—	−0.510 (0.137)	−0.601 (0.204)	—	—	—	—	—	—	−1.532 (0.541)	—	—
NBC Any vs. None†	—	—	−1.375 (0.602)	—	—	—	—	—	—	—	—	—
Information	—	—	0.335 (0.062)	0.361 (0.092)	—	—	−8.625 (2.126)	—	3.777 (1.650)	0.560 (0.222)	10.077 (2.106)	—
Similarities	—	0.158 (0.071)	—	—	1.009 (0.513)	8.891 (4.869)	−9.726 (3.054)	−9.568 (3.139)	−5.033 (2.200)	1.115 (0.320)	—	—
Vocabulary	−20.604 (7.162)	—	—	0.189 (0.099)	1.164 (0.385)	−2.707 (1.451)	—	—	−4.365 (1.880)	—	—	—
Age	−0.138 (1.238)	−0.016 (0.008)	—	−0.074 (0.011)	−0.491 (0.048)	3.173 (0.702)	2.205 (0.303)	2.064 (0.432)	1.844 (0.225)	−0.225 (0.032)	−0.413 (0.327)	—
Gender Male vs. Female†	—	—	—	−0.483 (0.201)	—	−6.459 (3.084)	—	—	10.250 (8.020)	—	−9.022 (2.903)	−9.925 (2.317)
Education	−8.587 (2.603)	0.078 (0.046)	0.223 (0.058)	—	1.097 (0.275)	—	—	—	—	—	1.895 (0.808)	—
Solvent Use	—	—	—	0.097 (0.056)	—	—	−3.173 (1.468)	—	—	0.307 (0.154)	—	—
Alcohol Coefficient	1.702 (0.908)	−0.044 (0.016)	—	—	—	—	—	−1.652 (0.836)	—	—	−1.355 (0.381)	0.854 (0.276)
Potato Intake	—	—	—	—	—	10.146 (3.439)	—	3.782 (2.104)	—	—	—	1.948 (0.650)
First-order Interactions	Age*Vocab 0.3753 (0.181)	—	Educ*Group2 0.252 (0.074)	—	—	Age*Group1 0.544 (0.288) Age*Similar −0.267 (0.104) PotInt*Group1 5.757 (1.882) PotInt*Similar −0.878 (0.435)	—	—	Gender*Age −0.704 (0.221)	—	Gender*Alcohol 1.275 (0.378) Gender*Group1 6.851 (3.456) Age*Inform −0.140 (0.052)	—
R^2 (%)	40.24	26.06	48.03	49.21	62.58	52.20	47.70	19.95	39.36	47.32	64.09	14.06
MSE	6759.12	2.19	3.24	4.40	73.35	1041.99	3156.07	6174.10	1305.05	34.08	571.63	609.22

Ages 16 to 65, at least 4 years of education; $n = 170$.

*$p < 0.10$.

†Contrast coding (+1, −1) used for X vs. Y.

TABLE 5

NEUROBEHAVIORAL FUNCTIONAL DOMAIN AND OVERALL SCORES (CONTROL ADJUSTED AND NORMALIZED) STATISTICALLY SIGNIFICANT* REGRESSION COEFFICIENTS (SE)

Predictors	Attention	Spatial	PsychoMotor	Motor	Overall NB
Intercept	−0.971 (.2097)	−2.257 (.1879)	−2.504 (.2857)	−1.325 (.2089)	−1.793 (.2119)
Group CON vs. CTL†	—	−0.384 (.1556)	−0.477 (.1374)	−0.241 (.0991)	−0.370 (.0845)
Group EXP_1 vs. CTL†	—	−0.306 (.1459)	—	—	—
Group EXP_2 vs. CTL†	−0.345 (.0786)	—	—	—	—
Pest. poisonings Any vs. None†	—	—	—	—	—
Information	—	0.133 (.0383)	0.118 (.0378)	—	—
Similarities	—	—	0.142 (.0534)	0.140 (.0289)	0.101 (.0352)
Vocabulary	0.106 (.0263)	0.0787 (.0383)	—	—	0.0885 (.0270)
Gender Male vs. Female†	—	−0.179 (.0762)	—	—	—
Solvent use	—	—	—	—	0.0279 (.0160)
Alcohol Coefficient	−0.0219 (.0091)	—	—	—	—
Potato Intake	—	—	—	—	−0.0273 (.0165)
R^2 (%)	22.104	46.237	32.621	17.633	42.327
MSE	0.745	0.637	0.984	0.525	0.374

Ages 16 to 65, at least 4 years of education; $n = 170$.
*$p < 0.10$.
†Contrast coding (+1, −1) used for X vs. Y.

use of chlordane (19). Such considerations may be clarified with further exposure modelling work.

Given that the causation of neurobehavioral outcomes is multifactorial, we have made every effort to account for the effects of important covariates in addition to language-based intelligence measures. As expected, reported problems with alcohol were associated independently with impaired performance on a number of neurobehavioral tests (27), likely due to the high consumption associated with social drinking in this population. In contrast, reported solvent exposure at work had mixed effects, perhaps indicating problems with our simple questionnaire-based method of assessing frequency and duration of exposure alone. Medical conditions (such as prior head injury) were only important for Block Design. Significant gender differences were observed with men consistently doing worse than women on several tests, unlike the usual pattern of small and inconsistent relationships reported elsewhere (4). Nutritional status was not fully assessed, nor the potential effects of fatigue from harder physical agricultural work.

Yet cross-sectional studies such as ours have a number of inherent limitations (2). Those people who participate are survivors who have not succumbed to a lethal or debilitating pesticide poisoning. Nonfamily farm members have stayed working with pesticides and are hence less likely to show the adverse effects of pesticides than those who have left for health reasons. On the other hand, those remaining on the farms may be selected from a larger population, the more enterprising and intelligent of which head off farm and work elsewhere, leaving a population with systematically poorer neurobehavioral scores. As well, individuals very over time, making measurements at only one point in time a potentially poor reflection of their ongoing exposure or health status, generating imprecision that could also lead to underestimates of the effects of exposure. All these factors limit the conclusiveness of evidence from cross-sectional studies. .

Ideally, studies of cohorts of workers and/or community members in high exposure situations in the developing world or among different immigrant groups in developed countries would deal with some of these limitations. Participants should be more judiciously selected to avoid some of the extremes of education and age that we faced. Exposures should be more fully characterized across a wider range of nutritional and occupational factors. Adaption of test batteries that have been further refined with experience (1) with sequential measurements both to increase precision and document temporal relationships would improve our confidence in our inferences. Although such further research may clarify the reasons for the neurotoxic effects we observed, we should not let the call for more research obscure the glaringly lower neurobehavioral scores we observed in our potato farming populations. Reductions in clear overexposure to pesticides should not be stalled pending further exploration of other potential contributors.

To this end, our association with an integrated agricultural project may facilitate the introduction of nonchemical pest control methods as a priority for farm policy.

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