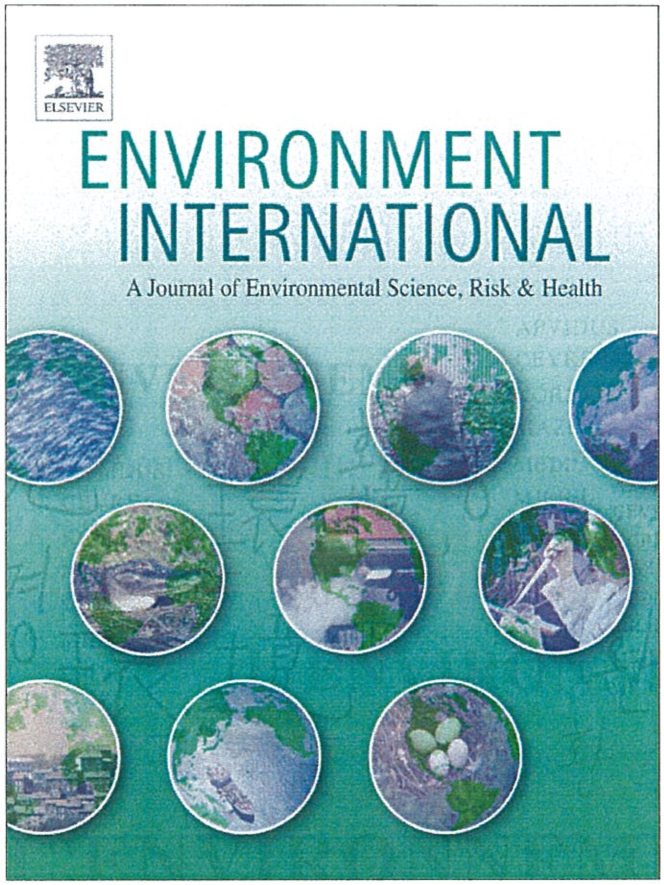
ELSEVIER
ENVIRONMENT
INTERNATIONAL
A Journal of Environmental Science, Risk & Health

Environment International 47 (2012) 28–36

Contents lists available at SciVerse ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Predictors of exposure to organophosphate pesticides in schoolchildren in the Province of Talca, Chile

María Teresa Muñoz-Quezada [a,b,*], Verónica Iglesias [b], Boris Lucero [a,c], Kyle Steenland [d], Dana Boyd Barr [d], Karen Levy [d], P. Barry Ryan [d], Sergio Alvarado [b], Carlos Concha [e]

[a] Faculty of Health Sciences, Catholic University of Maule, Avda. San Miguel 3605, Talca, Región del Maule, Chile
[b] School of Public Health, Faculty of Medicine, University of Chile, Avda. Independencia 939, Independencia, Santiago, Región Metropolitana, Chile
[c] Department of Psychology, Faculty of Social Sciences, University of Chile, Avda. C. Ignacio Carrera Pinto, 1045, Ñuñoa, Santiago, Región Metropolitana, Chile
[d] Department of Environmental Health, Rollins School of Public Health, Emory University, 1518, Clifton Road, Atlanta, GA 30322, USA
[e] Occupational Health Unity, Regional Secretary of Ministry of Health, Maule Region, Government of Chile, 2 Oriente, 1260, Talca, Región del Maule, Chile

ARTICLE INFO

Article history:
Received 30 December 2011
Accepted 5 June 2012
Available online xxxx

Keywords:
Dialkylphosphate metabolites
Organophosphate pesticide residues
Schoolchildren

ABSTRACT

Background: Few data exist in Latin America concerning the association between organophosphate (OP) urinary metabolites and the consumption of fruits and vegetables and other exposure risk variables in schoolchildren.

Methods: We collected samples of urine from 190 Chilean children aged 6–12 years, fruits and vegetables, water and soil from schools and homes, and sociodemographic data through a questionnaire. We measured urinary dialkylphosphate (DAP) OP metabolites and OP pesticide residues in food consumed by these 190 children during two seasons: December 2010 (summer) and May 2011 (fall). We analyzed the relationship between urinary DAP concentrations and pesticide residues in food, home pesticide use, and residential location.

Results: Diethylalkylphosphates (DEAP) and dimethylalkylphosphates (DMAP) were detected in urine in 76% and 27% of the samples, respectively. Factors associated with urinary DEAP included chlorpyrifos in consumed fruits ($p<0.0001$), urinary creatinine ($p<0.0001$), rural residence ($p=0.02$) and age less than 9 years ($p=0.004$). Factors associated with urinary DMAP included the presence of phosmet residues in fruits ($p<0.0001$), close proximity to a farm ($p=0.002$), home fenitrothion use ($p=0.009$), and season ($p<0.0001$).

Conclusions: Urinary DAP levels in Chilean school children were high compared to previously reported studies. The presence of chlorpyrifos and phosmet residues in fruits was the major factor predicting urinary DAP metabolite concentrations in children.

1. Introduction

Organophosphates (OP) are a group of synthetic pesticides used to control various insects on crops and in homes (Levine, 2007; Tadeo et al., 2008), and are widely used in agriculture. These pesticides are highly toxic cholinesterase-inhibiting compounds, but tend to degrade in the environment with exposure to sunlight and water. The lack of knowledge about how OPs should be applied and poor monitoring of their use have been associated with various human health problems, and environmental pollution by OP residues has accumulated over time (CDC, 2009; Levine, 2007; MINSAL, 2007; WHO, 2005).

There is ample evidence of adverse health outcomes associated with OP pesticide exposure in children and adults (Alavanja et al., 2004; Jurewicz and Hanke, 2006, 2008; Rosas and Eskenazi, 2008). Studies have linked OP pesticide exposure with adverse physiologic effects, increased frequency of cancer, neurobehavioral and cognitive abnormalities, teratogenicity, endocrine modulation and immunotoxicity (Alavanja et al., 2004; Bouchard et al., 2010, 2011; Engel et al., 2011; Handal et al., 2007; Jurewicz and Hanke, 2006, 2008; Marks et al., 2010; Rauth et al., 2006; Rosas and Eskenazi, 2008).

Human exposure to OP insecticides is widespread. Occupational use of OP insecticides, primarily in agriculture, represents the largest class of exposure. However, many populations, including children, have been shown to be widely exposed to OP insecticides from their diet, residential use, by living close to farms and from paraoccupational exposures via parents who work in agriculture (Barr et al., 2004; Bradman et al., 2005; Coronado et al., 2006; Kissel et al., 2005; Koch et al., 2002; Lu et al., 2004, 2008; Naeher et al., 2010; Valcke et al., 2006; Vida and Moretto, 2007).

In exposed populations, OP insecticides tend not to persist for extensive periods of time, with half-lives not exceeding one week in the

* Corresponding author at: Avda. San Miguel 3605, Talca, Región del Maule, Chile. Tel.: +56 71 203164; fax: +56 71 413553.
E-mail address: mtmunoz@ucm.cl (M.T. Muñoz-Quezada).

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doi:10.1016/j.envint.2012.06.002

human body (CDC, 2009; MINSAL, 2007). Therefore, short-term OP pesticide exposure has often been assessed by measuring urinary metabolites of OP pesticides (Egeghy et al., 2011). Most biomonitoring studies have focused on measuring six dialkylphosphate (DAP) metabolites that are common to most OP insecticides currently in use (Wessels et al., 2003). Other more selective metabolites for assessing exposure to specific OP insecticides have also been used; however, they provide information for only a limited number of OP pesticides (Wessels et al., 2003). Although there are limitations associated with measuring these six non-specific metabolites (e.g., exposure to preformed metabolites and exposure to multiple OPs giving rise to the DAP), they have been useful tools in estimating exposure to OP insecticides as a class.

To date, almost no research has been conducted in South America investigating pesticide exposure and potential predictors of these exposures. Chile, a country located on the western coastline of South America, is a large producer of agricultural crops. The region that has the highest percentage of rural population engaged in agriculture and livestock husbandry is the Maule Region, with 34% of people living in rural areas (INE, 2002). The Maule Region, is located 254 km south of capital Santiago in central Chile, and is divided into 4 Provinces: Talca, Linares, Curico and Cauquenes. The Province of Talca, has 10 counties. 4 counties were included in this research: San Clemente, Talca, Maule and Empedrado (see Fig. 1). According to 2008 sales data, Maule used over 5 million kg of pesticides, making it the third highest pesticide-consuming region in Chile, representing about 10% of all national sales (SAG, 2008). OP pesticides comprise 30% of all insecticide, acaricide and rodenticide use in Maule, surpassing the national rate (25.5%). The widespread use of OP insecticides in agriculture, their largely unrestricted sale, and insufficient knowledge of their proper application and risks have resulted in acute intoxications in Chile (Concha, 2010; MINSAL, 2007, 2010a), primarily in the occupational setting.

We have conducted a pesticide exposure assessment study involving children in urban and rural Regions in Talca Province, Chile. We used biological and environmental monitoring coupled with questionnaire data, as has been done in other studies (Melnyk et al., 2012), to help us ascertain the predominant pathways of exposures to children in these areas. To date, no data exist on OP pesticide exposures in Chile and only a few exist in Latin America, but none that have examined several potential pathways for exposure in the general population.

2. Materials and methods

We collected longitudinal data during two seasons (summer and fall) from children living in four counties (Empedrado, Talca, Maule, and San Clemente) in Talca Province, in south central Chile. These counties were selected to represent a range of geographic locations and demographic conditions. Within these counties, 14 public elementary schools with enrollment ≥ 60 students were selected through a stratified random sampling methodology assuring both rural and urban schools were represented in each county (see Fig. 2). Children from these schools were randomly selected for enrollment in the study. From a total of 2254 children attending the selected schools in Talca County, 180 (8%) were invited to a meeting to inform them about the study. We invited similar percentages of schoolchildren to participate from the remaining three counties: in Empedrado, 60 of 517 children (8%); in Maule, 90 of 918 children (10%); and in San Clemente, 75 of 592 children (12%). We invited a total of 405 parents to meetings in the schools to explain the study and request for the informed consent. Two hundred and fourteen parents finally attended

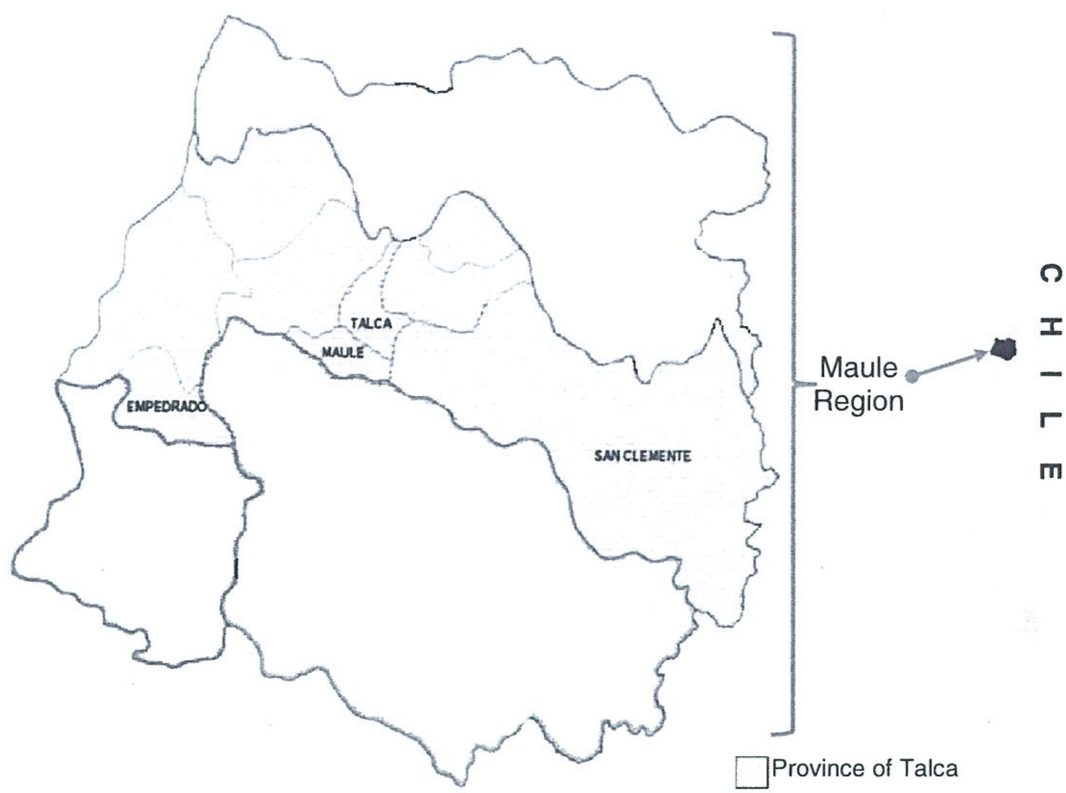

Fig. 1. Map of Chile with the Maule Region enlarged shows the participating counties from the Province of Talca. The shaded areas indicate the Talca Province and the individual participating counties are labeled.

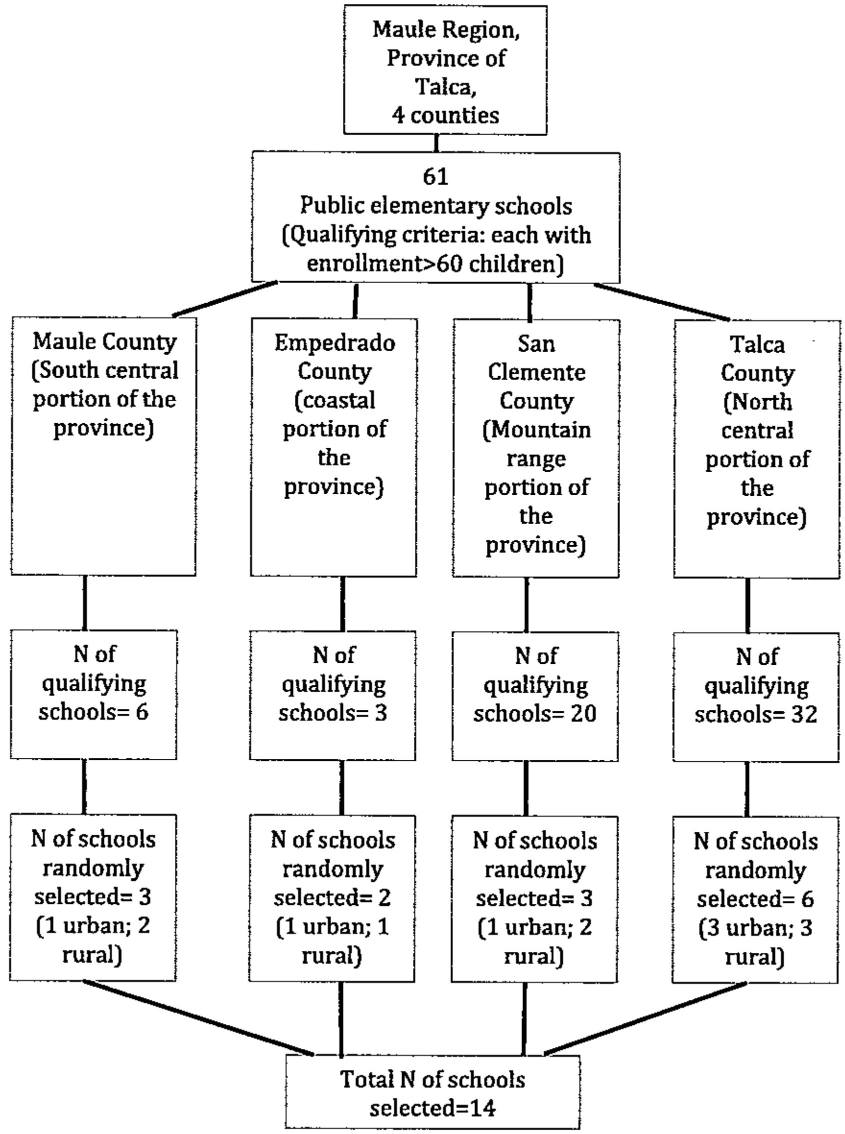

Fig. 2. Random sampling method of selection of schools from the Province of Talca.

the meetings and 100% agreed to participate. This study was approved by the ethics committee on human research of the Faculty of Medicine at the University of Chile, the ethics committee of the Catholic University of Maule, and the Institutional Review Board of Emory University. Informed consent was obtained from the parent of each minor child enrolled.

Data collection occurred during two seasons: once in December 2010 (summer) during the peak agricultural season and once in May 2011 (fall), the low agricultural production season. Questionnaires were administered during each season to collect information on general sociodemographic characteristics, proximity of residence to agricultural fields, home use of pesticides, and consumption of fresh fruit and vegetables over the prior four days. Additionally, in the fall, questions were included about the purveyor of the produce since no locally grown produce was available for consumption.

In Chile, free meals are given to children of low-income public schools; all schools in this study were low-income schools. In general, children consumed raw fruit supplied to them at school, usually one or two pieces of fruit per week. During the peak agricultural season of summer in Chile (December), we collected 2 kg of produce (orange or apples, based on the survey about what the children consumed) from the schools on Monday of the sampling week.

From the questionnaire information obtained in the summer, we found that children also ate produce at their homes on weekends. Therefore, during the fall (May) sampling, we identified the food suppliers through questionnaires (primarily a large market in Talca Province), and we collected 2 kg of produce (including either kiwi, lettuce, apple, orange, tangerine, pear, cabbage or tomatoes) from those suppliers on Tuesday of the sampling week and also 2 kg from the school on Monday of the sampling week. All produce were bagged and refrigerated at 4 °C, then transported by land for analysis the day after collection by the Laboratory Andes Control in Santiago, Chile. This laboratory operated under ISO/IEC 17025 accreditation. Both positive and negative controls were included in the analytic scheme. Sampling requirements for accurate measurement were that residues had to be measured in 2 kg of produce collected randomly, kept in good physical condition, avoiding exposure to high temperatures and sent for analysis within two days of collection.

More than 200 pesticides, including about 40 OP insecticides, were quantified in produce samples using the QuEChERS method for pesticide extraction (Lehotay et al., 2005; Schenck and Hobbs, 2004). Briefly, produce samples were homogenized separately in a blender then a 15-g aliquot was taken and spiked with surrogate internal standards. The produce was extracted with acetonitrile and dried with $MgSO_4$ to remove residual water. The extract was cleaned using dispersive primary secondary amine sorbent along with anhydrous $MgSO_4$. The extracts were concentrated and analyzed by gas chromatography–mass spectrometry. The limits of detection (LOD) for the pesticides were 0.01 mg/kg produce.

In addition, 2-L samples of drinking water that children consumed at schools and homes, and 2-kg samples of soil from the schools and public places within 500 m of the children's homes were collected during both seasons and were analyzed at the Laboratory Andes Control in Santiago, Chile, following the procedures described above for food analysis.

Spot urine samples were collected from each child in 100-mL sterile prepackaged bottles on the Tuesday of each sampling week during both December and May. Samples were kept frozen in a plastic container at −20 °C, and shipped to Pacific Toxicology Laboratories (Los Angeles, California, USA) for analysis of the six DAP metabolites of most OP insecticides: dimethylphosphate (DMP); dimethylthiophosphate (DMTP); dimethyldithiophosphate (DMDTP); diethylphosphate (DEP); diethylthiophosphate (DETP); and diethyldithiophosphate (DEDTP). Freeze-dried urine samples were derivatized with a benzyltolytriazine reagent to produce benzyl derivatives of alkylphosphate metabolites. A saturated salt solution was added to the tubes and the benzyl derivatives were extracted with cyclohexane and analyzed by gas chromatography with flame photometric detection. The quality control sample was made in-house by spiking a urine sample with two levels of OP metabolites. The assay was run with a reagent water blank and a urine blank. The recovery rate ranged from 80 to 120% of the expected value. The LOD of the method was 5 ng/mL for all metabolites except DEDTP and DMDTP, which had an LOD of 10 ng/mL. To assess the precision of the method, 20 duplicate analyses of unknown urine samples were performed. Further quality assurance measures included participation in proficiency testing of the German E-QUAS program.

Creatinine was measured in the urine samples by a colorimetric method (Creatinine Procedure No 555; Sigma Diagnostics, St Louis, Mo). Its measurement was used to adjust results of OP metabolites (μg metabolite/g creatinine) to avoid the variable dilution caused by differing hydration states of the sample donor.

STATA 11.0 (StataCorp LP, College Station, TX) was used for all statistical analyses. Data from both December and May were combined in the analysis, and Generalized Estimated Equations (GEE) were used to account for the repeated measures on the same children during two seasons. DAP concentrations below the LOD were assigned a value equal to the LOD/√2 (Hornung and Reed, 1990). Concentrations were converted to SI units to create molar concentrations and all DEAP and DMAP metabolites were summed to create an aggregate exposure term (i.e., ΣDEAP and ΣDMAP) (Barr et al., 2004).

The frequency of detection (FOD) of at least one DEAP metabolite among children was 80%. The sum of DEAP metabolites was treated as a continuous variable after logarithmic transformation (the data were normalized by transformation, and data were considered normal by applying a studentized residual analysis). This variable was used as the outcome in a linear regression using GEE. The FOD of DMAP metabolites was much lower (25%) for any DMAP metabolite, and hence for the sum. Thus the sum of DMAP metabolites was dichotomized into two categories (i.e., below the LOD, above the LOD), and a logistic regression GEE was performed.

We first tested full models including all possible exposure variables and demographic covariates. Variables assessed for possible inclusion in the models were: pesticides in measured produce (present, not present); proximity of residence to farm (≤500 m, >500 m); home use of fenitrothion insecticide (yes, no); location (urban, rural) according to the Chilean Census; season (summer – December 2010, fall – May 2011); creatinine concentration (continuous); county (Talca, Empedrado, Maule, and San Clemente); parental occupation (agriculture, non-agriculture); parental education (≤8 years of study, >8 years of study); age (continuous); and sex (male, female). All variables with a *p*-value≤0.10 in the full model were retained in final models.

3. Results

Reliability testing to ensure precise urinary DAP measurement demonstrated good agreement among duplicate samples. Among the 20 duplicate pairs tested, a high correlation was found between duplicates of DEP metabolites ($r=0.99$, $p<0.0001$), DETP ($r=0.97$, $p<0.0001$), DMP ($r=0.86$, $p<0.0001$). DMDTP and DEDTP were consistently below the LOD so they could not be evaluated.

Of the 214 children initially enrolled in the study, the mean age was 8.6±1.7 years with almost equal numbers of males ($N=109$) and females ($N=105$). Twenty-four children were withdrawn from the study because they could not provide a urine sample ($N=22$) or a urine sample was of insufficient volume for laboratory analysis ($N=2$). The final sample size for the summer season (December 2010) was 190 children with a mean age of 8.6±1.6 years. For the fall season (May 2011), we evaluated 181 children, since 9 children were lost to follow-up, six moved residences and three declined to participate. The demographic characteristics of the participating children are shown in Table 1.

The majority of the demographic data remained consistent across seasons. Parental occupation changed in 14% of fathers and 18% of the mothers between the two seasons. More than half (58%) of the children lived within 500 m of a farm and less than 10% of the families used fenitrothion in the home.

Fig. 3 depicts the pesticide residues above the LOD in fruits or vegetables and the number of children exposed to these residues. OP pesticide residues were detected in produce samples taken during both summer and fall. Chlorpyrifos and diazinon were detected in 50% (n = 7) and 7% (n = 1), respectively, of 14 produce samples collected in December 2010. Based on the number of children who consumed produce in each school with detectable residues, 44% (n = 83) were exposed to chlorpyrifos residues and 8% (n = 16) were exposed to diazinon residues during the summer of 2010. Of the produce collected in May 2011, only phosmet was detected in 7% (n = 1) of 14 samples collected from school. Of the 40 samples collected from the local markets, chlorpyrifos was detected in 12% of the samples (n = 5), azinphos methyl was detected in 5% of the samples (n = 2); phosmet was detected in 8% of the samples (n = 3) and dimethoate was detected in 3% of the samples (n = 1). Multiple residues (i.e., chlorpyrifos and azinphos methyl) were detected in 5% of the samples tested (n = 2). During the fall of 2011, 52% of the children (n = 94) were exposed to chlorpyrifos residues, 19% of the children (n = 34) were exposed to phosmet residues, 8% of the children (n = 15) were exposed to azinphos methyl residues and 2% of the children (n = 3) were exposed to dimethoate.

Soil and drinking water were tested for the same OP pesticide residues. No pesticide residues were detected in any of the 36 drinking water or 28 soil samples taken.

Urinary DAP metabolite data are shown in Table 2. DEAP metabolite concentrations above the LOD were found in a greater proportion of children than those observed for DMAP metabolites both in December 2010 (72.6% versus 31.6%) and in May 2011 (80% versus 18.6%).

Table 3 shows the final GEE model for the sum of DEAP metabolites. According to the model, children who ate fruits or vegetables (at school or at home) with residues of chlorpyrifos above the LOD (either in December or May) had 2.8 ($=\exp^{1.03}$) times higher levels of DEAP metabolites than children who did not eat produce with chlorpyrifos residues above the LOD. Children with higher creatinine, children living in urban areas, children living in Talca County, and younger children had significantly higher levels of DEAP metabolites. Children who lived <500 m from a farm also had higher levels of DEAP metabolites, but this variable showed only marginal significance ($p=0.074$).

After running the GEE model with covariates we noted that the values of the DEAP metabolites within the same child were not correlated with each other across time periods. Hence the GEE results were equivalent to a simple linear regression. Running such a regression with the variable log ΣDEAP resulted in $R^2=0.42$. Chlorpyrifos residues were the biggest predictor, accounting alone for 33% of the variance. There was an interaction ($p<.05$) in the model with the variable season (summer/fall) for the covariate chlorpyrifos ($\beta=0.490$, $p=0.008$, 95% CI = 0.130–0.851). In reviewing the relationship of chlorpyrifos with the log of ΣDEAP separately for December 2010 (summer) and May 2011 (fall), we found a coefficient for chlorpyrifos of 0.56 in summer and 1.29 in fall, indicating that the presence of chlorpyrifos residues in produce had a more pronounced effect on DEAP metabolite levels for the second collection period, that is when we collected samples from both schools and homes.

Table 4 shows the final model for the DMAP metabolites. According to the model, children who ate produce that had detectable levels of phosmet were 60.6 (95% CI: 19.2–191.4) times more likely to have detectable urinary DMAP concentrations than those who did not. Children who lived closer to farms were 2.5 times more likely to

Table 1
Sociodemographic and exposure characteristics of 190 schoolchildren (aged 6–12 years) in Talca Province, Chile in December 2010 (summer) and May 2011 (fall).

Variable	December 2010		May 2011		*p* value
	N	%	*N*	%	
County					1
- Empedrado	28	14.7	28	15.5	
- Talca	68	35.8	64	35.4	
- San Clemente	53	27.9	49	27.0	
- Maule	41	21.6	40	22.1	
Location					0.98
- Urban	69	36.3	66	36.5	
- Rural	121	63.7	115	63.5	
Gender					0.79
- Female	94	49.5	92	50.8	
- Male	96	50.5	89	49.2	
Age of children					0.001[a]
- 6–8 years old	89	46.8	46	25.4	
- 9–12 years old	101	53.2	135	74.6	
Father's years of education					0.91
- <8 years	55	32.2	53	32.7	
- ≥8 years	116	67.8	109	67.3	
Mother's years of education					0.95
- <8 years	53	27.9	50	27.6	
- ≥8 years	137	72.1	131	72.4	
Father's occupation					0.33
- Farm worker	84	44.2	71	39.2	
- Non-farm worker	106	55.8	110	60.8	
Mother's occupation					0.047[b]
- Farm worker	31	16.3	17	9.4	
- Non-farm worker	159	83.7	164	90.6	
Distance of housing to farm					0.94
- ≤500 m	111	58.4	105	58.0	
- >500 m	79	41.6	76	42.0	
Use of OP pesticide fenitrothion at home					0.20
- Yes	17	9.0	10	5.5	
- No	171	91.0	171	94.5	

[a] The significant change in this sociodemographic variable is expectable since the children aged from one time point to the next in data collection.

[b] The mother's occupation likely achieves significance because more women typically work summer seasonal farm worker jobs in Chile.

have higher urinary DMAP concentrations than those who did not. Children whose homes were treated with fenitrothion were 3.5 times more likely to have higher urinary DMAPs than those whose homes were not. Finally, children living in Empedrado were 2.4 times more likely to have higher urinary DMAP concentrations than children living in Maule. Among all variables in the model, phosmet residues in fruit were the strongest contributor to the overall likelihood.

4. Discussion

We sought to evaluate pesticide exposure in schoolchildren living in Talca Province, Chile and to understand the factors predictive of these exposures. We collected samples in May and December to understand seasonal variation in pesticide exposure.

We found that, of the variables evaluated, dietary exposure was the predominant contributor to OP metabolites in urine during both high and low agricultural seasons. Because no pesticide residues were detected in drinking water or soil, these were not believed to be pathways of potential OP pesticide exposure.

We found that the major route of exposure to OP metabolites that we evaluated in the schoolchildren was ingestion, both for the period of greatest local agricultural productivity (summer) and for the period of lowest local agricultural productivity (fall), most likely due to consumption of fruits containing residues of OP insecticides. The origin of the vegetables consumed was primarily from a large market in the city of Talca, which provides agricultural products for the whole Province of Talca. Produce from this large market is normally derived locally during the summer but is transferred from farms in northern Chile during the fall months. In the summer 70%, and in the fall 77% of children, consumed vegetables from that market.

Urinary DAP concentrations were compared with those in other studies reported in the literature (Table 5). Neither of the two studies evaluating urinary DAP concentrations in Latin America reported actual urinary DAP concentrations for the populations studied; only frequencies of detection were given. The study of farm children in El Salvador had considerably lower frequency of detection than in our study but that is likely because of their higher LODs in this older work. The study by Grandjean et al. (2006) in Ecuador had higher frequencies of detection than most metabolites in our study, however, we cannot directly compare the magnitude of concentrations. Participants in this study had levels of urinary metabolites higher than those reporting actual metabolite concentrations in other research studies conducted in the United States. The laboratory which analyzed the urine samples have relatively higher LOD than the other studies mentioned in Table 5, which could explain a slight increase in the geometric means of the metabolites in this study compared with others, but these LOD differences are not greater than 5 μg/L for DEAP and 8 μg/L for DMAP. Despite this consideration, OP metabolite concentrations in Chilean children are still much higher than American children studied previously.

Phosmet residues were the biggest contributor to DMAP metabolites. However, the association was found only in May 2011 (fall). In December 2010 (summer), we did not find phosmet residues in fruits/vegetables measured in the school. However the fruit eaten at home was not measured in the summer, which is a limitation of the study.

The presence of DEAP metabolites in the urine of 80% of the schoolchildren is associated with dietary exposure to chlorpyrifos through fruits and vegetables. Chlorpyrifos is the OP pesticide most commonly sold in Chile (SAG, 2008). In both the Province of Talca, and throughout Chile, this pesticide is widely used because it is inexpensive and is easily accessible to the public. The pesticide phosmet, which produces DMAPs, is another best-selling pesticide in the Province of Talca, but only in the spring and summer seasons. However, in northern Chile, phosmet is sold in the fall due to better climatic conditions for agriculture. According to interviews, the fruits/vegetables eaten at school often originate not from local produce but from areas farther north than the Region of Maule.

Long-term health complications (e.g. neurological effects, cancer) have been associated with the use of the pesticide chlorpyrifos (Alavanja et al., 2004; Bouchard et al., 2010, 2011; Engel et al., 2011; Handal et al., 2007; Jurewicz and Hanke, 2006, 2008; Marks et al., 2010; Rauth et al., 2006; Rosas and Eskenazi, 2008). In the United States and Europe strict regulations govern their use and sale (CDC, 2009). The results presented here suggest the need for a review of policies to regulate the sale and application of chlorpyrifos in Chile, as well as some of the other harmful OP pesticides currently in use.

We observed that children living in urban areas have greater levels of diethyl-substituted OP metabolites than those who come from rural areas. This is seen also in some recent studies (Bradman et al., 2005; Lu et al., 2004) and can be explained because children in rural areas are more likely to consume fruits from their own orchards where no pesticides are used, in contrast to urban children who access produce purchased in markets or stores which may have higher levels of OP residues. The highest urine concentrations of DEAP metabolites were observed in Talca, where fruits and vegetables are provided by a large produce market. On the other hand, both diethyl- and dimethyl-substituted OP metabolites were increased in children living close to farms, suggesting that there is also a component of exposure from local agriculture. Furthermore, children had higher DMAP metabolite levels in urine in December 2010 than in May 2011, which may be associated with increased local application of DMAP-producing pesticides in the summer (SAG, 2008). Even though food that children ate at home was not collected in the first time point, which is a limitation of this study, it is noteworthy that the presence of DMAP metabolites in December 2010 was associated with the distance of farms ($OR = 1.9$; $p = 0.046$; $IC = 1.0–3.8$) and to

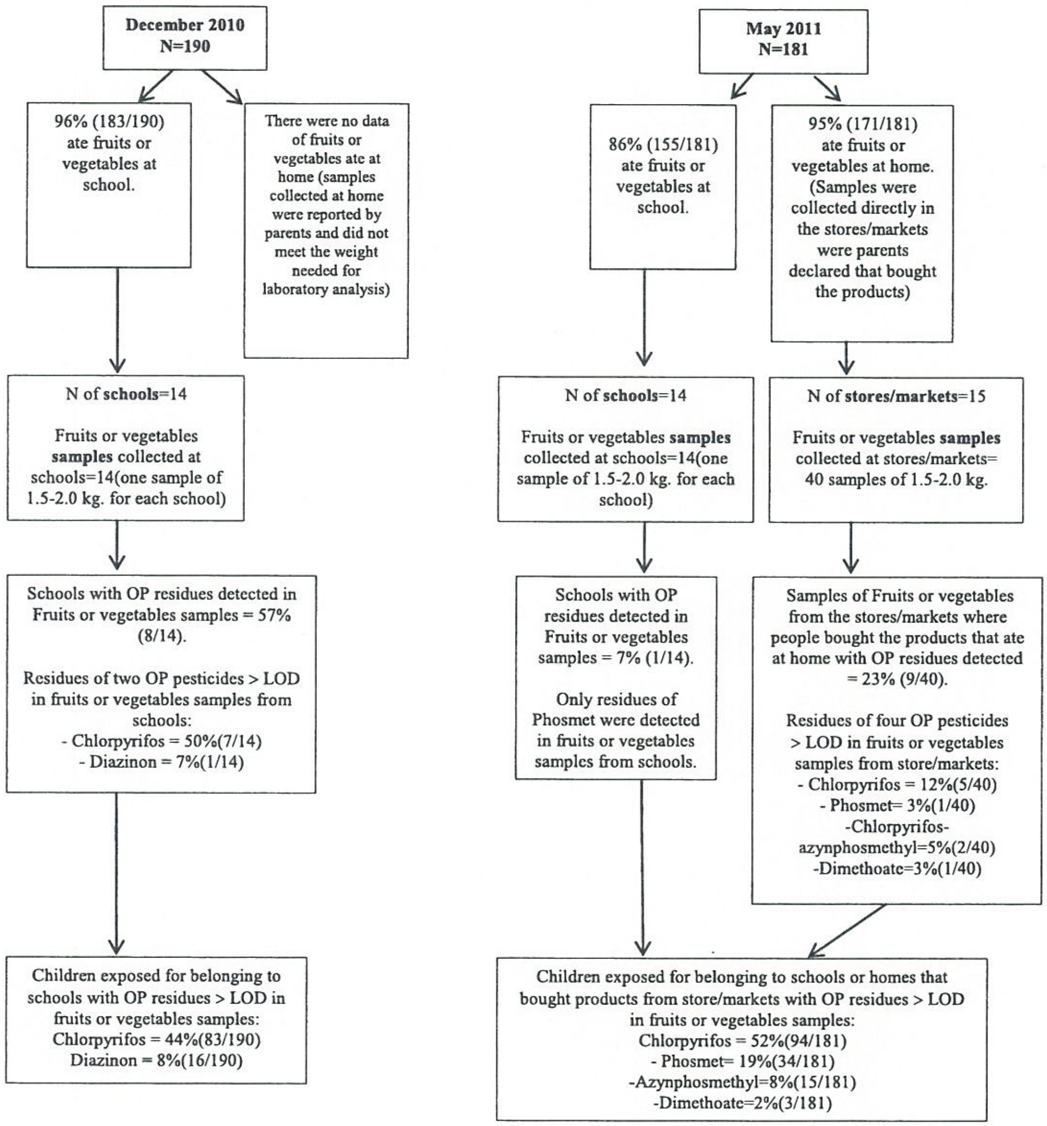

Fig. 3. Diagram of the results of OP residues on vegetables/fruits in summer (December 2010) and fall (May 2011) samplings, depicting the number of children that ate produce and the samples of food taken, the pesticide residues above the LOD on produce and the number of children estimated to be exposed to these residues.

the use of pesticides at home (OR = 3.7; $p = 0.014$; IC = 1.3–10.4). There were no differences in pesticide use in the homes between urban and rural children, or in proximity to farms in both periods (p value ≥ 0.05).

The presence of DEAP metabolites was also associated with younger age and higher creatinine levels, likely because of differences in the metabolism of younger children compared to older (Bouchard et al., 2010; Valcke et al., 2006), hygiene habits, such as inadequate washing of fruit or hands (Vida and Moretto, 2007), mouthing activity, greater ingestion of produce on a body weight basis (Cohen Hubal et al., 2000).

Few families apply OP pesticides in the home (Table 1). The only OP pesticide compound used in houses is fenitrothion. Children whose households applied that pesticide had higher levels of DMAP metabolites, which is consistent with the home application of this pesticide (CDC, 2009).

We found no association between schoolchildren of parents who work in agriculture and OP metabolites, and no association between the years of education of parents and metabolite levels. This differs from other studies, where employment in farm work and low level of education of parents were correlated with high levels of OP metabolites (Barr et al., 2004; Bouchard et al., 2010, 2011; Bradman et al., 2005; Coronado et al., 2006; Engel et al., 2011; Kissel et al., 2005; Koch et al., 2002; Lu et al., 2004, 2008; Marks et al., 2010; Naeher et al., 2010; Valcke et al., 2006; Vida and Moretto, 2007).

Our study has several associated limitations. The absence of pesticide residue data from the summer prevents us from fully understanding the pathways of exposure during that time period. Further, the produce sampling was taken from what the children were expected to consume but did not represent their actual dietary intake. We had similar limitations with our urinary metabolites. The DAPs measured are non-specific metabolites and can be derived from a

Table 2
Descriptive statistics of five organophosphate metabolites (OP) in the urine of schoolchildren (geometric mean, minimum and maximum values of metabolites concentration, and percentage of children above the limit of detection (LOD) for December 2010 (summer) and May 2011 (fall)).

Metabolite	December 2010 (summer)			May 2011 (fall)		
	Geometric mean and geometric SD	Min–max	%> LOD	Geometric mean and geometric SD	Min–max	%> LOD
Creatinine g/L	1.07 (1.03)	0.26–2.70	100	0.96 (1.04)	0.12–2.70	100
DEP μg/L	9.1 (1.10)	3.5–417.1	40.5	19.5 (1.09)	3.5–383.8	80.1
DEP μg/g cr	8.7 (1.09)	3.5–268.0		18.6 (1.09)	3.5–237.0	
DEP nmol/L[a]	59.3 (1.10)	22.9–2708.4		126.4 (1.09)	0.0–2492.0	
DETP μg/L	8.3 (1.09)	3.5–691.4	43.2	3.7 (1.01)	3. 5–25.1	2.8
DETP μg/g cr	7.7 (1.08)	3.5–843.0		3.7 (1.01)	3. 5–24.0	
DETP nmol/L[a]	48.9 (1.09)	20.8–4067.1		21.8 (1.02)	0. 0–147.6	
SUM DEAP nmol/L	155.8 (1.08)	43.8–4090.5	72.6	160.7 (1.07)	43.8–2609.0	80.0
DMP μg/L	5.2 (1.06)	3.5–115.8	20.5	4.5 (1.05)	3.5–72.6	14.9
DMP μg/g cr	5.1 (1.06)	3.5–146.0		4.4 (1.05)	3.5–74.0	
DMP nmol/L[a]	41.3 (1.06)	28.1–919.1		36.0 (1.05)	0.0–576.2	
DMTP μg/L	5.5 (1.06)	3.5–94.6	25.8	4.5 (1.05)	3.5–139.2	13.8
DMTP μg/g cr	5.3 (1.06)	3.5–121.0		4.4 (1.06)	3.5–120.0	
DMTP nmol/L[a]	38.8 (1.06)	24.9–666.2		32.0 (1.06)	0.0–980.3	
DMDTP μg/L	8.9 (1.04)	7.1–146.4	16.3	7.1 (1.0)	7.1–7.1	0.0
DMDTP μg/g cr	8.7 (1.04)	7.1–126.0		7.1 (1.0)	7.1–7.1	
DMDTP nmol/L[a]	56.1 (1.04)	44.8–926.6		44.75 (1.0)	0.0–44.8	
Sum DMAP nmol/L	147.7 (1.10)	97.8–1662.5	31.6	120.5 (1.08)	97.7–1195.7	18.6

DEP = diethylphosphate; DETP = diethylthiophosphate; DEAP = diethylalkylphosphates; DMP = dimethylphosphate; DMTP = dimethyldithiophosphate; DMDTP = dimethyldithiophosphate; DMAP = dimethylalkylphosphates; LOD = limit of detection.
[a] Samples below the LOD were defined as LOD/√2.

multitude of OP pesticides or their preformed metabolites. Given the importance of chlorpyrifos exposure in our study, the measurement of a more specific metabolite, namely 3,5,6-trichloropyridinol (TCPy) may have provided a more compound-specific exposure assessment. However, since our initial goal was to evaluate class exposure and we had no a priori evidence that chlorpyrifos would be such an important pesticide to assess, we did not measure TCPy. Clearly, given the evidence produced in this study, future studies should include the measurement of TCPy.

The findings of this study provide some of the first data on pesticide exposure in children in Latin America and their potential exposure risk factors. The consumption of produce, both in school and at home, and living close to farms were the main predictors of pesticide exposure in children. Our data show higher levels of urinary OP pesticide metabolites in children than that found in other studies. It is notable that the levels of OP pesticide residues found in vegetables meet the standards required by regulatory agencies in Chile (MINSAL), which are regulated under the Codex Alimentarius (MINSAL, 2010b). However, several studies suggest that exposure to OP residues in low doses over a long period of time can lead to health consequences such as those mentioned above, plus attention span difficulties, and behavioral and cognitive deficits (Bouchard et al., 2010, 2011; Engel et al., 2011; Handal et al., 2007; Marks et al., 2010).

We generated evidence that in the province of Talca, Chile, there is continual exposure for schoolchildren to low doses of OP pesticides, mainly through the dietary pathway. A suggested use of these data is the reconsideration of regulations of pesticide food tolerances, since little control exists over the sale or use of OP pesticides rendering them one of the most widely used groups of pesticide in Chile.

Funding

This work was supported by NIH Fogarty grant D43 TW 05746-02, USA, and through the National Commission for Scientific and

Table 3
Linear regression model (GEE) for the logarithmic transformation of the sum of diethyl-substituted metabolites (DEAP) in the urine of schoolchildren in Talca Province, Chile in December 2010 (summer) and May 2011 (fall) combined.

DEAP[a]	Coef.	Std. err.	*p*-value
Chlorpyrifos[b]	1.03	0.088	0.000
Creatinine[c]	0.50	0.088	0.000
Location[d]	−0.21	0.901	0.018
Distance from farms[e]	0.15	0.086	0.074
Age[f]	−0.24	0.083	0.004
Empedrado[g]	0.00	0.135	0.984
Talca[g]	0.25	0.110	0.021
San Clemente[g]	−0.04	0.118	0.712
Constant	4.1	0.170	0.000

n of observations = 371; n of groups = 190.
[a] Logarithmic transformation of the sum of DEAPs in schoolchildren urine.
[b] Exposed = 1, unexposed = 0, to chlorpyrifos residues in fruits/vegetables from either homes or schools.
[c] Continuous measure of creatinine in urine of children (g/L).
[d] Geographic location (urban = 1, rural = 0).
[e] Distance of housing to farms that applied pesticides (less than 500 m = 1, greater than 500 m = 0).
[f] Age of children categorized as 6–8 years old (= 1) or 9–12 years old (= 0).
[g] County (reference = Maule).

Table 4
Logistic regression (GEE) model of the variable sum of dimethyl-substituted metabolites (DMAP) below vs. above the limit of detection in the urine of schoolchildren in Talca Province Chile in December 2010 (summer) and May 2011 (fall).

DMAP[a]	Coef.	Std. error	Odds ratio	[95% conf. interval]		*p*-value
Phosmet[b]	4.12	0.59	60.61	19.19	191.37	<0.0001
Distance from farms[c]	0.9	0.29	2.48	1.38	4.45	0.002
Pesticide at home[d]	1.44	0.48	3.48	1.37	8.85	0.009
Empedrado[e]	0.87	0.42	2.37	1.04	5.39	0.04
Talca[e]	−0.38	0.37	0.66	0.31	1.36	0.26
San Clemente[e]	−0.45	0.41	0.64	0.29	1.41	0.27
Time[f]	−2.16	0.43	0.12	0.05	0.27	<0.0001
Constant	0.74	0.59				

n of observations = 369; n of groups = 190.
[a] Sum of dimethyl-substituted metabolites (DMAP) in the urine of schoolchildren dichotomized as below vs. above the limit of detection.
[b] Variable related with exposure/not exposure to eating of vegetables/fruits with phosmet residues.
[c] Distance of housing to farms that apply pesticides (less or equal to 500 m).
[d] Use of OP pesticide fenitrothion at home.
[e] County (reference = Maule).
[f] Summer = 1 (December 2010) or fall = 0 (May 2011).

Table 5
Comparison of urinary concentrations of dialkylphosphates with the results of other similar studies.

	No. of subjects (area)	Age	Diethylphosphate metabolites[a]						Dimethylphosphate metabolites							
			>LOD[b] (%)	DEP (nmol/L)[c]	>LOD[b] (%)	DETP (nmol/L)[c]	>LOD[b] (%)	Sum DEAP nmol/L[d]	>LOD[b] (%)	DMP (nmol/L)[c]	>LOD[b] (%)	DMTP (nmol/L)[c]	>LOD[b] (%)	DMDTP (nmol/L)[c]	>LOD[b] (%)	Sum DMAP nmol/L[d]
Current Chilean study																
Dec 2010 samples (spray month)	190 (Talca, Chile)	6–11	40.5	59.3 (49.1–75.5)	43.2	48.9 (41.4–57.6)	72.6	155.8 (133.4–182.0)	20.5	41.3 (36.6–46.5)	25.8	38.8 (34.5–43.7)	16.3	56.0 (51.6–60.8)	31.6	147.7 (133.3–163.6)
May 2011 samples (nonspray month)	181 (Talca, Chile)	7–12	80.1	126.4 (107.1–149.2)	2.8	21.8 (20.9–22.7)	80.0	160.7 (140.1–184.4)	14.9	36.0 (32.9–39.4)	13.8	32.0 (28.8–35.6)	<LOD	44.7 (44.7–44.7)	18.6	120.5 (111.7–129.9)
Comparison studies																
Azaroff (1999)[e]	136 (El Salvador, farm children)	8–17		–[f]	–	–	14	–	–	–		–	–	–	35	–
Koch et al. (2002)[g]	44 (Seattle)	2–5	–	–	53.0		–	0.03 (1.56)[h]	–	–	73.0	–	–	–	–	0.080 (2.51)[h]
Barr et al. (2004)[i]	471 (US population)	6–11	–	1.73[i] (1.06–2.83)	–	–	–	17.4[i] (11.1–27.3)	–	–	–	3.08[i] (1.9–4.9)	–	–	–	72.8[i] (54.3–97.5)
Grandjean et al. (2006)[e]	72 (Ecuador)	5–9	82	–	58	–	89	–	85	–	17	–	28	–	85	–
Marks et al. (2010)[j]	290	3.5	–	–	–	–	–	7.0 (5.8–8.3)	–	–	–	–	–	–	–	62.5 (52.5–74.7)
	320 (Salinas Valley, California)	5	–	–	–	–	–	7.2 (6.0–8.7)	–	–	–	–	–	–	–	72.4 (61.0–86.0)
Bouchard et al. (2010)[j]	1139 (US population)	8–15	53.1	4.7 (0.9–28.1)	57.2	2.0 (0.4–7.6)	77.8	11.0 (2.1–35.0)	49	10.7 (2.8–39.0)	64.3	13.7 (1.9–58.8)	41.7	1.7 (0.4–7.3)	81.7	41.3 (10.1–130.7)

DEP = diethylphosphate; DETP = diethylthiophosphate; DEAP = diethylalkylphosphates; DMP = dimethylphosphate; DMTP = dimethyldithiophosphate; DMDTP = dimethyldithiophosphate; DMAP = dimethylalkylphosphates; LOD = limit of detection.

[a] Diethyldithiophosphate (DEDTP) is not presented in this table because its values were lower than the LOD in almost all the children.

[b] Samples below the LOD were assigned a value of LOD/√2 (Hornung and Reed, 1990). The limit of detection was 10.0 μg/L for dimethyl dithiophosphate (DMDTP) and 5.0 μg/L for all other alkylphosphate metabolites measured.

[c] Values correspond to geometric means and confidence interval (95%).

[d] Diethyl and dimethyl phosphate metabolites were summed as nmol/L. Values correspond to geometric mean and confidence interval.

[e] Neither of these two studies evaluating urinary DAP concentrations in Latin America reported actual urinary DAP concentrations for the populations studied; only frequencies of detection were given.

[f] An en-dash (–) indicates LOD % or analyte not reported.

[g] LOD are 7.4 (μg/L) for DMP, 1.1 for DMTP, 0.7 for DMDTP, 6.6 for DEP, 1.2 for DETP, and 1.1 for DEDTP.

[h] Geometric mean and SD.

[i] LOD were 0.58 (μg/L) for DMP, 0.18 (μg/L) for DMTP, 0.08 (μg/L) for DMDTP, 0.2 (μg/L) for DEP, 0.09 (μg/L) for DETP, and 0.05 (μg/L) for DEDTP. Geometric means were adjusted for age, sex, race/ethnicity, and concentrations of serum cotinine and urinary creatinine. GMs were calculated for metabolites with detection frequencies of ≥60%.

[j] Values for LOD of metabolites were not reported.

Technological Investigation (CONICYT) of the Chilean government through a FONIS grant SA10I20001.

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Rev Esp Salud Pública. 2018; Vol. 92; 22 de marzo e1-e10. www.msc.es/resp

ORIGINAL BREVE

Recibido: 25 de abril de 2017
Aceptado: 23 de febrero de 2018
Publicado: 22 de marzo de 2018

EXPOSICIÓN A PLAGUICIDAS ORGANOFOSFORADOS Y POLINEUROPATÍA PERIFÉRICA EN TRABAJADORES DE LA REGIÓN DEL MAULE, CHILE (*)

Ángela Grillo Pizarro (1), Eduardo Achú Peralta (1), María Teresa Muñoz-Quezada (2,3), Boris Lucero Mondaca (2,3).

(1) Departamento de Kinesiología, Facultad de Ciencias de la Salud, Universidad Católica del Maule, Talca. Chile.
(2) Departamento de Psicología, Facultad de Ciencias de la Salud, Universidad Católica del Maule, Talca. Chile.
(3) Centro de Investigación en Neuropsicología y Neurociencias Cognitivas, Universidad Católica del Maule. Chile.
Los autores declaran que no existe conflicto de intereses

(*) Financiación: El siguiente estudio fue financiado por el proyecto del Fondo Nacional de Investigación en Salud de la Comisión Nacional de Ciencia y Tecnología (CONICYT) de Chile, FONIS SA13I20019 y por el proyecto FONDECYT de iniciación 11150784 y por la Universidad Católica del Maule.

RESUMEN

Fundamentos. Los plaguicidas organofosforados (OP) se usan de manera masiva, por su bajo costo y por su baja persistencia, en el medio ambiente y su alta efectividad en el control de plagas de insectos, sin embargo, los trabajadores agrícolas, cuando se exponen a OP, presentan consecuencias negativas en su salud, principalmente de caracter neurológico. Por primera vez se reporta una investigación en población latinoamericana que estudió la asociación entre exposición laboral a OP y presencia de polineuropatía periférica en trabajadores agrícolas. El objetivo del estudio fue estimar la relación entre exposición laboral a plaguicidas organofosforados (OP) y presencia de polineuropatía periférica en trabajadores de la Región del Maule, Chile.

Método. Se realizó un estudio transversal analítico con 55 trabajadores agrícolas expuestos a OP y 58 trabajadores no agrícolas no expuestos. Se aplicó una prueba para la detección de polineuropatía periférica a través de la evaluación del umbral palestésico por método on-off. Para estimar la relación entre exposición a plaguicidas OP y polineuropatía periférica se realizó un modelo de regresión logística múltiple (intervalo de confianza del 95%).

Resultados. Un 26% del total de la muestra padecía de polineuropatía, con un 38% de casos positivos para el grupo expuesto y un 14% para el grupo no expuesto. El riesgo de desarrollar polineuropatía periférica fue 3,6 veces mayor en los trabajadores expuestos a OP que en los trabajadores no expuestos.

Conclusiones. Existe una asociación positiva entre la presencia de polineuropatía periférica y la exposición laboral crónica a OP, ajustando por edad y sexo.

Palabras clave. Plaguicidas organofosforados, Neuropatías periféricas, Exposición laboral, Trabajadores.

Correspondencia
María Teresa Muñoz-Quezada
Avenida San Miguel 3605 Talca
Región del Maule, Chile
mtmunoz@ucm.cl

ABSTRACT

Exposure to organophosphate pesticides and peripheral polyneuropathy in workers from Maule Region, Chile

Background. Organophosphate pesticides (OP) are used massively for their low cost, low environmental persistence and high effectiveness in insect pest control, however, agricultural workers, when exposed to OP, have negative consequences on their health mainly neurological. For the first time, a research is reported in a Latin American population that studied the association between labor exposure to OP and the presence of peripheral polyneuropathy in agricultural workers. The aim of the study was to estimate the relationship between occupational exposure to organophosphate pesticides (OP) and presence of peripheral polyneuropathy in workers in the Maule Region, Chile.

Method. We conducted a cross-sectional study with 55 agricultural workers exposed to OP and 58 non-agricultural workers not exposed. It was applied a test for the detection of peripheral polyneuropathy through pallesthetic threshold assessment by on-off method. To estimate the relationship between exposure to OP pesticides and peripheral polyneuropathy, we used a multiple logistic regression model (95% confidence interval).

Results. 26% of the total sample had polyneuropathy, with 38% positive cases for the exposed group and 14% for the non-exposed group. The risk of developing peripheral polyneuropathy was 3.6 times higher in workers exposed to OP than in non-exposed workers.

Conclusions. There is a positive association between the presence of peripheral polyneuropathy and chronic occupational exposure to OP, adjusting for age and sex.

Key words. Organophosphate, Pesticides, Peripheral Nervous System Diseases, Occupational exposure, Workers.

Cita sugerida: Grillo Pizarro A, Achú Peralta E, Muñoz-Quezada MT, Lucero Mondaca, B.Exposición a plaguicidas organofosforados y polineuropatía periférica en trabajadores de la región del Maule, Chile. Rev Esp Salud Pública.2018;92:22 de marzo e201803006.

INTRODUCCIÓN

Los organofosforados (OP) son plaguicidas que se utilizan masivamente en la agricultura para el control principalmente de insectos desde las restricción de los organoclorados[1]. Son neurotóxicos, su uso inadecuado puede afectar la salud, derivando en una sintomatología diversa expresada, por lo general, en intoxicación aguda y crónica[2,3,4, 5,6]. Los signos clínicos pueden perdurar varios años y afectan al sistema nervioso central y periférico, con predominio del primero, encontrándose dentro de los síntomas más representativos las alteraciones neuroconductuales y el aumento de umbral vibrotáctil[3,4,5,6,7,8,9].

La polineuropatía es una enfermedad que afecta a los nervios periféricos por diferentes causas y tiene una prevalencia mundial de 2% en la población general y aumenta a un 8% en adultos mayores de 55 años[10]. Existen pocos estudios que evalúen el efecto de la exposición crónica a OP en los nervios periféricos en humanos y que logren un consenso en sus resultados[11,12,13,14,15].

La neuropatías de origen tóxico, como es el caso de la exposición a OP, son predominantemente sensitivas y el cuadro clínico está estrechamente ligado con el tipo de fibra afectada[15]. En el caso de fibras pequeñas no mielinizadas presentan síntomas de hipoalgesia, disminución de la sensibilidad térmica, parestesia dolorosa, entre otros; y en fibras sensitivas largas mielinizadas se observa aumento del umbral palestésico, ataxia sensorial, parestesia con adormecimiento o picazón, y arreflexia osteotendinosa[10,13,14]. Es importante detectar la neuropatía de manera precoz, para poder prevenir y disminuir al mínimo las complicaciones futuras.

En los últimos años, nuevos estudios han encontrado disminución en el grupo de expuestos a plaguicidas OP en la actividad motora[11,14], síntomas claros de parestesia en guante[12] y presencia de polineuropatía[13].

Chile, como gran parte del mundo, utiliza ampliamente los plaguicidas[15,16,17, 8], lo que ha generado el aumento de la exposición en la población, especialmente en los trabajadores del sector agropecuario que son los que más utilizan estos compuestos, por lo tanto, presentan mayores consecuencias negativas en su salud[3,4,5,6,7,8,19].

La población agrícola representa el 13% de todos los ocupados en el país, concentrados principalmente en la Región del Maule, región que cuenta con una superficie de 30.296 km^2 y una población cercana a los 910.000 habitantes, principalmente residentes de la zona de los valles centrales. Está compuesta de cuatro provincias (Curicó, Talca, Linares y Cauquenes) y 30 comunas. La capital regional es la ciudad de Talca, durante el año 2015, poseía el índice de ruralidad más alto del país (33,6%). Su actividad principal es la silvoagropecuaria, que representa el 16% del Producto Interno Bruto. Aproximadamente el 30% del universo de los trabajadores de la región se dedican al sector agropecuario[20,21], siendo la actividad vitivinícola la más importante, con un 40% de viñedos en la superficie regional.

La región del Maule es la segunda del país con mayor venta de plaguicidas con 10.310.633 kg/l[18] y la venta de los insecticidas asciende a 2.962.137 kg/l. Los organofosforados son los más vendidos (52%), siendo el diazinon, clorpirifos, metidation, fosmet, metamidofos, clorpirifos/dimetoato, azinfos-metilo, profenofós, cadusafós y dimetoato, los organofosforados más utilizados (1.519.279 kg/l). Por otro lado, existen registros del año 2012 que señalan que las intoxicaciones agudas por plaguicidas en el Maule corresponden a un 25% de todo el país[16,17], siendo los insecticidas OP los más frecuentes en estas intoxicaciones. En esta región, se ha encontrado evidencia de altos niveles urinarios de metabolitos diaquilfosforados en escolares de escuelas básicas municipales, señalándose que la principal vía de exposición para este grupo son los alimentos que consumen[9], y encontrándose además una mayor proporción de estudiantes con discapacidad intelectual en escuelas municipales cercanas a predios agrícolas[6,19]. Un estudio que se realizó en esta zona, que evaluó la exposición a OP a través de un cuestionario de exposición y el desempeño neuropsicológico y motor de trabajadores agrícolas y no agrícolas, reveló que los trabajadores agrícolas expuestos a OP tuvieron un menor desempeño en la sensibilidad discriminativa (p= 0,009) ajustada por años de educación y edad en comparación con los controles[17]. A partir de estos antecedentes, se escogió la región del Maule para el desarrollo del estudio con trabajadores agrícolas.

El objetivo del estudio consistió en estimar la relación entre exposición laboral a plaguicidas organofosforados (OP) y presencia de polineuropatía periférica en trabajadores de la Región del Maule, Chile. Evaluar la relación entre exposición OP y el riesgo de sufrir polineuropatía periférica permitiría reconocer esta problemática en poblaciones expuestas a estos plaguicidas y centrar esfuerzos en detectar a los afectados y prevenir futuras complicaciones. Cabe resaltar que en Latinoamérica y en Chile no existen estudios con estas características.

SUJETOS Y MÉTODOS

Se realizó un diseño transversal analítico con trabajadores agrícolas que debían tener mínimo un año ininterrumpido de desempeño en el área y trabajadores no agrícolas sin historial de exposición laboral que fuesen de la Región del Maule. El estudio se realizó durante los años 2014 a 2016. La población correspondió a 441.172 trabajadores de la Región del Maule, de los cuales 146.688 trabajaban en el área agrícola[21]. Se realizó una estimación del tamaño de muestra utilizando un estudio en el que se encontró presencia de neuropatía perifèrica sensorial en trabajadores aplicadores de plaguicidas con respecto a trabajadores no agrícolas[13]. Para realizar los cálculos se consideró una comparación de proporciones entre 2 grupos, con un test de significancia de 0,05 (dos colas), con una proporción esperada del grupo 1 de 0,40 y una proporción del grupo 2 de 0,09 y un poder del 80%. Con estos parámetros, la estimación muestral fue de 36 trabajadores por grupo. Además se consideró un sobre-muestreo de 20% en caso de abandono de los participantes o información incompleta, estimando finalmente un tamaño de muestra aleatorio mínimo n=88. Para contactar a los trabajadores se contó con el apoyo del Instituto de Desarrollo Agropecuario de Curicó, Servicio de Salud del Maule y el Hospital Regional de Talca, que entregaron los listados de los trabajadores que fueron seleccionados de forma aleatoria y contactaron con ellos por medio de los encargados de cada área de las instituciones mencionadas.

Una vez contactados los trabajadores, se les explicó en qué consistía la investigación, se les pidió que firmaran el consentimiento informado, se les otorgó un código de identificación, y finalmente debieron responder una ficha breve donde se les preguntaba su edad, sexo, lugar de trabajo, provincia donde vivían y trabajaban, para caracterizar su exposición, y conocer sus antecedentes de salud para aplicar los criterios de exclusión y decidir si participaban o no en el estudio. Los criterios de exclusión consistieron en el padecimiento previo de enfermedades neurológicas, psiquiátricas, metabólicas, un consumo excesivo de alcohol y/o de drogas, antecedentes de intoxicación aguda con OP e historial de familiares con alteraciones del sistema nervioso, ya que podían llevar a confundir el origen real de la polineuropatía. Finalmente, fueron evaluados en grupos de cinco personas, ubicadas cada una en una estación de evaluación dentro de los laboratorios de la Escuela de Kinesiología de la Universidad Católica del Maule.

La variable de interés correspondió a la presencia o ausencia de polineuropatía periférica, la cual que se midió a través del método on-off para el que se utilizó un diapasón de 128 Hz. La variable fue medida en la prominencia ósea situada en el dorso del primer ortejo, justo proximal a la uña, entregando dos estímulos para el primer ortejo derecho y dos para el izquierdo. Para cada uno de los estímulos se puntuaba el ingreso o cuando se posaba el diapasón y el cese del estímulo o cuando dejaba de vibrar, otorgándose un punto por cada estímulo percibido inadecuadamente, ya fuera al inicio (on) o al cese (off), pudiendo obtener un máximo de cuatro puntos por pie y un máximo de 8 en toda la evaluación. El punto de corte para determinar la presencia de la patología fueron 5 puntos[22], para luego ser dicotomizada esta variable como trabajadores con polineuropatía, que correspondió a los que tenían una cantidad igual o superior a 5 respuestas percibidas inadecuadamente, y trabajadores sin polineuropatía, que fueron aquellos que tenían menos de 5 puntos.

La variable de exposición fue medida a través de la aplicación de un cuestionario, consultando a los trabajadores si trabajaban o no en faenas agrícolas, si estaban expuestos o no a plaguicidas organofosforados y hace cuantos años que estaban expuestos. Se analizaron estas 3 variables y fueron dicotomizadas en trabajadores agrícolas expuestos a pesticidas OP y trabajadores no agrícolas no expuestos. Otras variables que se controlaron fueron la edad, el sexo, la provincia de los trabajadores y los años de exposición a plaguicidas OP en los trabajadores.

Para el análisis estadístico, las variables dicotómicas y categóricas se expresaron como proporción y las variables continuas como medidas de tendencia central y de dispersión. En el análisis binario, se utilizó la prueba regresión logística simple.

Para estimar la relación entre exposición a plaguicidas OP y polineuropatía periférica ajustada por las variables de control (edad, sexo, provincia y años de exposición), se realizó un modelo de regresión logística múltiple (intervalo de confianza del 95%) con la variable de interés de polineuropatía periférica aplicando el método de eliminación backward.

Para la selección de las covariables se consideraron criterios teóricos y estadísticos quedando en los modelos de regresión logística las variables con un valor en la prueba z de $p \leq 0,10$. Para todos los análisis, se utilizó el programa estadístico STATA 12.0.

El protocolo de investigación y el consentimiento informado del estudio se aplicó voluntariamente a los participantes y contó con la aprobación del Comité de Ética Científico de la Universidad Católica del Maule.

RESULTADOS

De los 159 trabajadores reclutados, 113 cumplieron con los criterios de selección o lograron ser evaluados con la totalidad de las pruebas de medición. De este grupo, el número de los trabajadores agrícolas expuestos a plaguicidas OP correspondió a 55 (49%) y de los trabajadores no expuestos a OP correspondió a 58 (51%).

Los trabajadores expuestos a plaguicidas OP poseían una edad promedio de 50 años, con una desviación estándar de 14,3 años, un mínimo de 29 y un máximo de 75 años. En el caso de los trabajadores no expuestos, presentaron una edad promedio de 49 años, con una desviación estándar de 12 años, con un mínimo de 18 años y un máximo de 68 años. Un 52% de la muestra fueron hombres, 52% menores de 50 años y 81% de los trabajadores agrícolas provenían de la Provincia de Curicó.

Los trabajadores expuestos a plaguicidas OP presentaron la mayor cantidad de participantes que obtuvieron más de 5 errores en la prueba de cribado para neuropatía, dando positivo 21 (38%) de los trabajadores expuestos, mientras que 8 (14%) de la muestra no expuesta obtuvo un resultado positivo para polineuropatía los que suman un total de 29 trabajadores, lo que equivalió a un 26% de la población estudiada.

En el grupo de trabajadores agrícolas la mediana de años de exposición a plaguicidas OP fue de 18 años, con un mínimo de 1 año de exposición laboral y un máximo de 60 años. Al revisar los años de exposición según la presencia o ausencia de polineuropatía, se observó una mediana de 0 en los trabajadores sin neuropatía y una mediana de 5 en los trabajadores con polineuropatía.

Con respecto al rendimiento en la prueba de polineuropatía periférica (tabla 1) asociada a las variables sexo, edad, provincia, trabajador expuesto a plaguicidas OP y años de exposición, se observaron asociaciones significativas en todas las variables. De los trabajadores que presentaron polineuropatía periférica, un 76% eran hombres y un 24% mujeres, un 83% tenía la edad de 50 años o más, el 90% con polineuropatía pertenecía a la provincia de Curicó, un 72% de los trabajadores estaba expuesto a plaguicidas OP y un 52% de los trabajadores con polineuropatía (n = 14), había estado expuesto durante 5 años o más a plaguicidas OP.

En la tabla 2 se observa una asociación estadísticamente significativa entre trabajadores expuestos a plaguicidas OP y un menor rendimiento en el examen sensitivo con respecto a la percepción del primer estímulo vibratorio de entrada en el primer ortejo derecho, el segundo estímulo vibratorio finalizado en el primer ortejo derecho, en el primer estímulo de entrada del primer ortejo izquierdo y en el segundo estímulo finalizado del primer ortejo izquierdo.

Al realizar el modelo de regresión logística (tabla 3) con la variable respuesta polineuropatía y la variable exposición a OP ajustado por edad, sexo, provincia y años de

Tabla 1
Características de los trabajadores de la Región del Maule que participaron en la medición del umbral palestésico

Variables		Sin polineuropatia (N=84) N (%)	Con polineuropatía (N=29) N (%)	OR (IC 95%)
Sexo	Hombre	37 (44)	22 (76)	0.25 (0.09-0.64)
	Mujer	47 (56)	7 (24)	
Edad	< 50 años	55 (65)	5 (17)	9.10 (3.14-26.36)
	> 50 años	29 (35)	24 (83)	
Provincia donde vive y trabaja	Talca	28 (33)	3 (10)	4.33 (1.20-15.55)
	Curicó	56 (67)	26 (90)	
Exposición a plaguicidas organofosforados en trabajadores	Trabajadores no expuestos	50 (60)	8 (28)	3.86 (1.53-9.72)
	Trabajadores expuestos	34 (40)	21 (72)	
Años de exposición a plaguicidas organofosforados	< de 5 años de exposición	57 (70)	13 (48)	2.45 (1.00-5.97)
	≥ de 5 años de exposición	25(30)	14 (52)	

Tabla 2
Examen sensitivo y medición del umbral palestésico

Exámen sensitivo		Trabajadores no expuestos a OP (n=58) N (%)	Trabajadores expuestos a OP (n=55) N (%)	OR (IC 95%)
Primer ortejo derecho primer estímulo de entrada	Percibido	55 (56)	44 (44)	4.58 (1.20-17.44)
	No percibido	3 (21)	11 (79)	
Primer ortejo derecho segundo estímulo de entrada	Percibido	50(53)	44 (47)	1.56 (0.57-4.23)
	No percibido	8 (42)	11 (58)	
Primer ortejo derecho primer estimulo finalizado	Percibido	31(56)	24 (44)	1.48 (0.70-3.11)
	No percibido	27 (47)	31 (53)	
Primer ortejo derecho segundo estimulo finalizado	Percibido	50 (60)	34 (40)	2.68 (1.25-5.75)
	No percibido	8 (28)	21 (72)	
Primer ortejo izquierdo segundo estímulo de entrada	Percibido	54 (55)	44 (45)	3.37 (1.01-11.33)
	No percibido	4 (27)	11 (73)	
Primer ortejo izquierdo primer estímulo de entrada	Percibido	52 (54)	45 (46)	1.92 (0.64-5.71)
	No percibido	6 (38)	10 (62)	
Primer ortejo zquierdo segundo estímulo finalizado	Percibido	30 (51)	29 (49)	0.96 (0.45-2.01)
	No percibido	28 (52)	26 (48)	
Primer ortejo izquierdo primer estímulo finalizado	Percibido	38 (60)	25 (40)	2.28 (1.06-4.86)
	No percibido	20 (40)	30 (60)	

OP: plaguicidas organofosforados

Tabla 3
Modelo de regresión logística en trabajadores agrícolas y no agrícolas, ajustado por edad y sexo

Polineuropatía[a]	Odd Ratio	Intervalo de confianza (95%)	
Trabajadores expuestos a plaguicidas organofosforados[b]	3,60	1,22	10,5
Edad[c]	9,32	3,02	28,7
Sexo[d]	0,4	0,13	1,19

[a]Polineuropatía: Presenta polineuropatía = 1; No presenta polineuropatía = 0
[b]Trabajadores expuestos a plaguicidas organofosforados (OP) = 1; Trabajadores no expuestos a OP= 0.
[c]Edad: < 50 años = 0; > 50 años = 1
[d]Sexo: Hombre = 0; Mujer = 1

exposición, se observó que el modelo final consideró un ajuste significativo con las variables edad y sexo.

En la tabla 3 se puede observar que existe una asociación positiva entre la presencia de polineuropatía y la exposición a OP en los trabajadores, existiendo un riesgo 3,6 veces mayor de presentar polineuropatía periférica en trabajadores expuestos a plaguicidas OP con respecto a los trabajadores no expuestos, ajustado por edad y sexo. Además, dentro de esta muestra, los trabajadores agrícolas que tenían una edad igual o mayor a 50 años tuvieron un riesgo 9,3 veces mayor de presentar polineuropatía que los trabajadores menores de 50 años. Las variables provincia y años de exposición quedaron fuera del modelo final al presentar un valor $p > 0,1$.

DISCUSIÓN

Este estudio confirma que la exposición a plaguicidas OP se relaciona con la presencia de polineuropatía periférica en trabajadores de la Región del Maule, controlando por edad y sexo. Los resultados muestran que existe una mayor presencia de polineuropatia distal de extremidad inferior en los trabajadores agrícolas con exposición crónica laboral a OP comparado con trabajadores sin exposición, presentando un riesgo 3,6 veces mayor de presentar esta enfermedad con respecto al grupo control (ajustado por edad y sexo), considerando que fueron excluidos todos aquellos participantes que presentaban factores confundentes para el origen de esta neuropatía, como son el consumo de alcohol y drogas, antecedentes de enfermedades neurológicas y diabetes mellitus, entre otros.

Si bien en el ajuste del modelo se incluye la variable sexo, la influencia de ésta es más bien marginal ($p = 0,100$), resultando de mayor significancia la variable de exposición anteriormente mencionada y la edad. La importancia de la variable edad es consistente en este caso con lo observado en otros estudios respecto al desarrollo de la neuropatía, cuya sintomatología es esperable que aparezca a mayor edad. Por ende, se ajustó por edad en el presente estudio, observando que de todos modos se mantenía el efecto de la exposición respecto a sintomatología de neuropatía, esto quiere decir que el grupo de expuestos a OP con mayor edad, similares a los no expuestos, presentan una mayor presencia de síntomas de polineuropatía (ver tabla 3).

Los resultados obtenidos en este trabajo son similares a los datos arrojados por un estudio en la India[13] donde un 40% de los aplicadores de plaguicidas presentaron síntomas de neuropatía versus solo un 9,1% en la población no expuesta (OR = 6,6; IC95%= 2,53-17,51) y un 21,4% de los aplicadores versus un 3% del grupo control dieron resultados positivos para polineuropatía. Los datos presentados en este estudio sumado a los antecedentes recién mencionados constituyen por tanto evidencia de la existencia de una asociación entre la exposición crónica a plaguicidas organofosforados y la presencia de síntomas de neuropatía sensorial.

La determinación de presencia de polineuropatía en el presente trabajo fue realizada mediante el método on-off que evalúa el umbral palestésico mediante la utilización de un diapasón de 128 Hz. Se optó por este método ya que numerosos estudios al mencionar las alteraciones encontradas en población expuesta a plaguicidas y que suponían presencia de polineuropatía como posible alteración de la exposición crónica de bajo nivel, mencionaban la elevación del umbral vibratorio[22,23], además de ser la herramienta disponible para estas evaluaciones con buena sensibilidad y especificidad[24,25], aunque este mismo estudio tuvo también buenos resultados para la prueba del monofilamento, prueba que es sugerida en la guía clínica de diabetes mellitus tipo 2 del Gobierno de Chile para detectar la polineuropatía diabética[26], la que junto a la de origen neurotóxico son clasificadas como polineuropatías de carácter crónico y en las que hay un compromiso inespecífico y simétrico del sistema nervioso periférico[10]. Podría considerarse para futuros estudios, complementar ambas pruebas, como es sugerido en la guía clínica para el diagnóstico de la polineuropatía diabética, con el fin de identificar a tiempo y con una evaluación integral, las alteraciones asociadas al sistema nervioso periférico en población ocupacional agrícola[26].

Una limitación importante que se podría mencionar respecto al presente estudio, se refiere a que la exposición fue caracterizada a partir de un cuestionario ocupacional. Lo recomendable para poder obtener una medición más eficaz de la exposición a plaguicidas OP es la utilización de biomarcadores (como por ejemplo, muestras de orina para la detección de residuos a partir del análisis de metabolitos dialquilfosfatos). Sin embargo, en estudios a nivel latinoamericano el uso de biomarcadores resulta difícil, principalmente por su alto costo, ya que los laboratorios que cuentan con la tecnología y los estándares de calidad para realizar análisis de este tipo de residuos específicos de muestras orgánicas humanas se encuentran en Estados Unidos y Europa.

Este estudio tuvo limitaciones asociadas a las diferencias sociodemográficas observadas entre trabajadores expuestos y no expuestos, que podría dificultar la comparación entre grupos, específicamente en cuanto al sexo y la provincia de origen en el caso de los expuestos. En este sentido cabe consignar que la mayor frecuencia de casos de polineuropatía que presenta la provincia de Curicó (90%) podría guardar relación más bien con la distribución de la muestra, la cual incluyó fundamentalmente participantes de esta zona (73%), debido a su mayor accesibilidad, siendo reclutados desde un programa gubernamental de apoyo a pequeños productores agrícolas. A su vez, en el caso del sexo existe una mayor cantidad de expuestos de sexo masculino (65%), lo cual es representativo de las condiciones propias de distribución de acuerdo al sexo del trabajo agrícola, donde quienes desempeñan labores asociadas a contacto más directo con plaguicidas y su aplicación son mayoritariamente hombres.

Otra limitación que es importante señalar, y que puede influir en la baja presencia de sintomatología asociada a la polineuropatía en la muestra, observada en la tabla 1, se refiere al efecto del trabajador sano, fenómeno frecuente en los estudios de salud ocupacional que apunta a la exclusión del trabajo de aquellos trabajadores que poseen una discapacidad o enfermedad o al ausentismo laboral por licencias médicas[27]. Este aspecto se debería considerar en futuros estudios ya sea a través de la consulta a través de cuestionarios a las empresas o instituciones públicas encargadas de los trabajadores o a partir del seguimiento de un estudio prospectivo.

Finalmente, es importante advertir que el diseño transversal del estudio no apunta a predecir o inferir relaciones causales entre la exposición a organofosforados y presencia de polineuropatía, aspecto que se podría probar con un estudio longitudinal, sin embargo, este estudio aporta evidencia para plantear que la exposición ocupacional a plaguicidas OP se asocia con polineuropatía periférica ajustadas por las otras variables de interés vinculadas a dicha sintomatología. A partir de esto se propone fortalecer las "buenas prácticas" en el ámbito de la salud laboral, basada en la calidad de la evidencia científica, la legislación y la bioética[28], generando propuestas de políticas públicas en el ámbito de la salud de los trabajadores agrícolas enfocadas en mejorar los conocimientos, prácticas de manejo y uso de equipos de protección, restringiendo la venta de los plaguicidas OP más peligrosos (exigiendo que solo puedan acceder a estos plaguicidas trabajadores capacitados en su uso y certificados por materia), y educar a la población sobre las consecuencias de un manejo inadecuado. Los estudios previos realizados con escolares y trabajadores agrícolas en la región, demuestran que existen factores de riesgo ambientales, vinculados a la exposición laboral por la aplicación de plaguicidas, a vivir cerca de predios agrícolas y a la permanencia de residuos de plaguicidas en los vegetales que consume la población[6,9,16,17]. En este sentido, la fiscalización estatal es clave para reducir la exposición ocupacional y que indirectamente afecta a la población general que consumen vegetales y que viven en comunidades rurales.

Se debe examinar este grupo poblacional como un foco de preocupación para el área de la prevención y rehabilitación neuromotora, con el propósito de prevenir las complicaciones en el desempeño funcional de estos trabajadores, interviniendo a través de la educación, enfocada en informar las consecuencias de esta exposición en la salud física y mental, y en enseñar a detectar algunos síntomas que pudiesen ser indicios o señales de alerta para esta enfermedad, así como medidas de cuidado cuando ya esté diagnosticada junto con la promoción de programas de ejercicios terapéuticos que ayuden a remediar sus secuelas, y orientar a reducir la exposición laboral a los agrotóxicos en los pacientes activos laboralmente.

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