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# Cognitive impairment in agricultural workers and nearby residents exposed to pesticides in the Coquimbo Region of Chile

Sebastián A. Corral[a,b,d,f], Valeria de Angel[e,f,g], Natalia Salas[c], Liliana Zúñiga-Venegas[a], Pablo A. Gaspar[e,f,g], Floria Pancetti[a,*]

[a] Laboratory of Environmental Neurotoxicology, Department of Biomedical Sciences, Faculty of Medicine, Universidad Católica del Norte, Coquimbo, Chile
[b] School of Psychology, Faculty of Social Sciences, Universidad Central de Chile, Santiago, Chile
[c] Facultad de Educación, Universidad Diego Portales, Santiago, Chile
[d] Department of Psychology, Faculty of Social Sciences, Universidad de Chile, Santiago, Chile
[e] Department of Psychiatry, Clinical Hospital, Universidad de Chile, Santiago, Chile
[f] Translational Psychiatry Laboratory, Physiology and Biophysics Department, Faculty of Medicine, Universidad de Chile, Santiago, Chile
[g] Biomedical Neuroscience Institute, Santiago, Chile

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ABSTRACT

Chronic exposure to organophosphate pesticides is a worldwide public health concern associated with several psychiatric disorders and dementia. Most existing studies on the effects of pesticides only evaluate agricultural workers. Therefore, this study sought to establish if individuals indirectly exposed to pesticides, such as residents in agricultural areas, also suffer cognitive impairments. Neuropsychological evaluations were carried out on three groups ($n$ = 102): agricultural workers directly exposed to pesticides ($n$ = 32), individuals living in agricultural areas indirectly (i.e. environmentally) exposed to pesticides ($n$ = 32), and an unexposed control group ($n$ = 38). The assessed cognitive processes included memory, executive functions, attention, language praxis, and visuoconstruction. The direct exposure group performed significantly lower in executive function, verbal fluency, and visual and auditory memory tests than the indirect exposure group, which, in turn, performed worse than the unexposed group. Even after adjusting for age, gender, and educational level, both exposure groups showed higher rates of cognitive deficit than control individuals. In conclusion, both direct and indirect chronic exposure to pesticides affects cognitive functioning in adults and, consequently, actions should be taken to protect the health of not only agricultural workers, but also of residents in agricultural areas.

## 1. Introduction

Worldwide pesticide use in the agricultural industry and for domestic purposes is associated with serious occupational health problems and deleterious environmental impacts (Suratman et al., 2015). Growth of the Chilean agricultural sector in recent decades has necessitated the expansion of areas used for crop production. Consequently, pesticide use has also increased, leading to acute intoxication outbreaks in agricultural areas, mainly during the spraying season (Pancetti et al., 2011; Zúñiga-Venegas et al., 2015).

In the Coquimbo Region, most of the applied agricultural pesticides belong to the organophosphate chemical family, which is used for insect management (Moretto, 1998). Acute organophosphate poisoning produces cholinergic symptoms resulting from the molecular inhibition of acetylcholinesterase, a key enzyme in central and peripheral synapses (Marrs, 1993). On the other hand, chronic exposure often goes unnoticed, with long-term consequences only becoming evident with the occurrence of neuropsychiatric and carcinogenic disorders, congenital malformations (Mostafalou and Abdollahi, 2013), and neurodegenerative diseases (Wang et al., 2014).

Abundant evidence supports that prolonged exposure to organophosphate and carbamate pesticides produces cognitive impairment that can be detected in exposed individuals through neuropsychological performance evaluations (Colosio et al., 2009; Rohlman et al., 2007). Indeed, exposure has been linked with impairments in intellectual functioning, academic skills, abstraction abilities, reasoning, and motor and social skills, among others. Furthermore, some studies specifically highlight psychomotricity, short-term memory, working memory, and attention as the most affected cognitive functions (Baldi et al., 2003; Kamel and Hoppin, 2004), and major impairments in planning abilities

*Abbreviations:* FAB, Frontal Assessment Battery; MANOVA, multivariate analysis of variance; MMSE, Mini-Mental State Examination; ROCF, Rey-Osterrieth Complex Figure

* Corresponding author at: Laboratory of Environmental Neurotoxicology, Faculty of Medicine, Universidad Católica del Norte, Larrondo 1281, 178-1421 Coquimbo, Chile.
*E-mail address:* pancetti@ucn.cl (F. Pancetti).

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and mood have also been described (Mackenzie-Ross et al., 2010).

Despite the notable impacts to human health, most studies focus assessments only on directly and chronically exposed individuals, such as agricultural workers. Indeed, little research has considered populations of environmentally, or indirectly, exposed individuals, and most of these studies center on environmentally-exposed children (Guillette et al., 1998; Rauh et al., 2011; Rohlman et al., 2005). One such study reported that children had a higher risk of cognitive impairment when the gestation period occurred while mothers lived in proximity to agricultural fields treated with pesticides (Shelton et al., 2014). Similarly, lower-than-expected IQ scores, as measured by the Wechsler Intelligence Scale (3rd Ed.), have been reported in Chilean children living near an important center for agricultural activity (Muñoz-Quezada et al., 2011).

Although frequent cases of acute intoxications occur when spraying crops with pesticides, there are very few studies in Chile that assess the impact of exposure on cognitive performance. This information gap continues to persist even despite evidence linking low cognitive performance with severe, lifelong consequences, including dementia (Meyer-Baron et al., 2015). Therefore, the aim of this study was to determine the cognitive impacts of pesticide exposure in directly (i.e. agricultural workers) and indirectly (i.e. agricultural area residents) exposed individuals. For this, cognitive assessments of memory, attention, executive function, and language and visuoconstruction praxis were performed in three groups with different degrees of pesticide exposure: direct, indirect, and unexposed.

## 2. Methods

### 2.1. Study design

This was an exploratory cross-sectional study that simultaneously ascertained information regarding exposure and outcome. Due to the pilot nature of the study, non-probability convenience sampling was carried out. The following three groups, with different degrees of pesticide exposure, were assessed: direct exposure, corresponding to agricultural workers with occupational and daily exposure to organophosphate pesticides; indirect exposure, corresponding to residents living in proximity to agricultural activities and that would therefore be environmentally exposed to pesticides; and non-exposure (controls), corresponding to individuals living far from agricultural activities. Exposure levels were estimated from a questionnaire completed by the volunteers (see supplementary Fig. S1). Informed written consent was obtained from voluntary participants prior to recruitment.

### 2.2. Study groups

The direct-exposure group included 32 individuals living in proximity to and directly working with agricultural pesticides. This group included pesticide mixers and sprayers, as well as crop harvesters, that performed agricultural work within the study area, which included the Elqui Valley (Montegrande, Pisco Elqui, and Pan de Azúcar villages) and Limarí Valley (Chañaral Alto village), Chile. The indirect-exposure group included 32 residents of the above-cited villages. Finally, the unexposed group consisted of 38 individuals recruited from coastal areas lacking agricultural activities. The studied geographical locations are depicted in Fig. 1. Group recruitments and evaluations took place between November 2009 and January 2011.

### 2.3. Inclusion and exclusion criteria

Men and women between the ages of 18 and 55 were considered. Inclusion criteria of the direct-exposure group were at least three years of daily contact with and direct manipulation of pesticides within a context of work. Inclusion criteria of the indirect-exposure group were at least three years of living in proximity to agricultural areas that applied pesticides, but without direct manipulation. For the direct and indirect exposed groups, individuals that reported an episode of acute intoxication during the study period were also included. Inclusion criteria of the unexposed group were not living in proximity to, coming into contact with, or directly manipulating pesticides.

Exclusion criteria included alcoholism, drug addiction, diagnosis of a psychiatric disease, and neurodegenerative/neurological disorders. Individuals under treatment with drugs affecting the central nervous system were also excluded since these drugs can alter neuropsychological outcomes, therefore affecting study results. Finally, left-handed individuals were also excluded to discard the bias produced by the laterality of neuropsychological functions.

### 2.4. Volunteer recruitment

Study locations were chosen based on the expected levels of pesticide exposure based on the agricultural activity carried out in that locations (mainly grapes and citrics farming). Direct-exposure individuals were recruited from three different locations. In Pisco Elqui, agricultural workers were interviewed and evaluated at a village office. In Pan de Azúcar, initial contact was through the Rural Health Service and Residents' Association, while subject evaluations took place at the local health center. Finally, in Chañaral Alto, volunteers were evaluated in the outbuildings of a local farm company.

Indirect-exposure individuals were recruited from four locations. In Montegrande, initial contact and volunteer evaluations took place at the Gabriela Mistral School. In Pisco Elqui, participants were contacted through home visits and were evaluated in their own homes. In Pan de Azúcar, volunteers were evaluated at the Rural Health Center. Finally, in Chañaral Alto, subjects were assessed at the administrative buildings of a farm company.

Unexposed subjects were recruited from the towns La Serena and Coquimbo. In an attempt to homogenize the groups and standardize educational levels, subjects in the control group were employed in manual labor jobs, mostly in construction or service areas such as cleaning, maintenance, and security. It is important to mention that the educational curriculum at every grade level is regulated by the Ministry of Education; therefore a lack of homogeneity among schools does not constitute a bias in this study.

### 2.5. Neuropsychological evaluations

Subjects who met the inclusion criteria were evaluated individually through seven neuropsychological tests that assessed general mental state, memory, attention, visuoconstruction praxis, and executive functions. All tests were administered by the same trained psychologist. Following is a brief summary of the applied neuropsychological tests and of the cognitive areas evaluated by each:

- Mini-Mental State Examination (MMSE) (Folstein et al., 1975): Brief evaluation of spatial and temporal orientation, short-term memory, attention, calculation, language, and praxis (Peña-Casanova et al., 2005).
- Digit span test, applying the Wechsler Adult Intelligence Scale in its revised version (WAIS-R) (Hermosilla, 1982). For further information about this version see also Rosas et al. (2014). Briefly, digit span test consists of forward and backward digits and is used to evaluate memory and attention, respectively. This test has been used in neuropsychological batteries to assess people exposed to pesticides (Rohlman et al., 2007; Roldán-Tapia et al., 2005).
- Rey-Osterrieth Complex Figure Test (ROCF) (Rey, 2003): Determines visuoconstruction skills and visual memory. The ROCF test also helps determine cognitive performance in different areas, such as planning, organizing, problem solving strategies, and motor functions (Lezak et al., 2012; Peña-Casanova et al., 2005). This test has also been found sensitive to cognitive impairment induced by